



Oman National Formulary for Ministry of Health Institutions



**Third Edition
2016**



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Third Edition 2016

Produced by the Directorate of Rational Use of Medicine

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HIS MAJESTY SULTAN QABOOS BIN SAID

Foreword

It is my great pleasure to introduce the Omani National Formulary (ONF) in its third edition to all health providers in the Sultanate. There have been several changes and additional material which readers are encouraged to study. The formulary contains detailed and updated monographs of all of the drugs approved by the Central Drug Committee (CDC) for use in Ministry of Health facilities today. Deleted preparations are listed at the front. This formulary is the effort of the Directorate of Rational Use of Medicine and I thank them for the high standard of their efficient work. The new edition is smaller for easier carriage and ready reference. The nature of therapeutics today means that the ONF is a dynamic work and will be subject to regular revision as and when significant changes in policy occur and therapies are added or deleted. I hope that the use of this formulary will have the desired benefit for all health workers and ultimately for our patients.

Dr. Ahmed bin Mohammed bin Obaid Al-Saidi
Minister of Health

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Preface

The Omani National Formulary (ONF) is a publication of the Ministry of Health (MOH) for all medicines/ indications approved by the Central Drug Committee (CDC). It is a joint effort between the Directorate of Rational Use of Medicine and different reviewers from consultants at hospitals and senior pharmacists. It is intended as a guide to the medicines approved for use in public health facilities; it does not cover all the items available in the private sector. The information stated in the ONF is meant to provide prescribers, dispensers and drug administrators with guidance to make a rational selection and ultimately achieve rational use of medicines.

Kindly note that not all indications for drug use internationally are listed in this edition.

Layout of the ONF

The first part of the ONF contains guidance on how to write appropriate prescription, and how to effectively prescribe drugs in special conditions and cases such as paediatric, pregnant, breast-feeding and geriatric patients, and in the presence of renal or hepatic impairments. Notes on adverse drug reactions and how to report important clinical observation resulting from such interactions are also detailed.

The second part of the ONF contains the main text where major therapeutic categories are listed with drug information for each individual drug. The notes preceding each therapeutic subcategory or group are meant to help the reader in making rational drug selection for individual patients. Drug entries are arranged in the sequence of; generic drug name, indications, contra-indications, cautions, side-effects and doses. The approved dosage forms, strengths and pack sizes (if known) are stated under preparations. Sometimes indications, contra-indications and cautions are stated in the introductory notes for the main therapeutic category or group, and referred to when individual drug are discussed.

The third part of the ONF includes 8 appendices; appendix 1 includes an introduction to drug interactions and an alphabetical list of most of the clinically important drug interactions for the drugs discussed in the ONF. Appendix 2 and appendix 3 give information about the different mechanisms of injury to liver and kidney caused by hepatotoxic and nephrotoxic drugs respectively in addition to some formulas for creatinine clearance calculation. Appendix 4 highlights the drugs that should be stopped for some days prior to blood donation according to the Central Blood Bank in Oman. Appendix 5 involves a list of drugs that should be avoided in patients with

G6PD deficiency. Appendix 6 contains child-BSA-nomogram. Appendix 7 concerns therapeutic drug monitoring, the reference ranges are from the Royal Hospital. Finally, appendix 8 explains and illustrates the different methods for drugs administration.

The fourth part of the ONF is the index. The ONF is meant to be an easy and rapid reference; it does not contain all possible information for prescribing. For more detailed information, other references should be consulted.

Aims and objectives

The abundance of the drugs available in the pharmaceutical world is beyond full comprehension nowadays. Health authorities are encouraged all over the world to establish national drug policies to avoid confusion created by the diversity of resources and to cost-effectively manage their drug supplies. The Central Drug Committee (CDC) is the concerned body that observes drug policies and maintains vigilance on current development. The CDC had successfully produced a national drug list that covers the national need for drugs to tackle major health problems. This third edition of the ONF is supplementary and complementary to the national list where necessary information and policy issues are discussed and advocated. One of the fundamental objectives of the ONF is to unify the prescribing patterns in the Sultanate; as a good proportion of the service providers have various degrees of experience and backgrounds. The ONF will also be of particular value to medical and pharmaceutical teaching to promote the rational use of the approved drugs. To achieve such goals, the formulary is set for regular review and updating.

A great deal of time and effort was spent in preparing the ONF and a large number of references and experts were consulted. The Formulary Committee will be pleased to receive any recommendations, suggestions or corrections that would enrich any future editions. Please bear in mind that this guide is meant to be a quick reference for users. The editorial body has tried to include most of the reviewers' suggestions and an apology is extended if some of these suggestions do not appear in this edition.

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Additions and Deletions

New in the 2016 edition

Section	Additions	Deletions
Section 1 Gastrointestinal	- Atropine sulphate 1mg /10ml prefilled disposable injection - Esomeprazole granules, 10 mg/sachet - Sodium acid phosphate enema, 5 mL enema	Antispasmodic drop
Section 2 Cardiovascular	- Argatroban injection, 100 mg/ mL, 2.5 mL vial - Atorvastatin tablet, 40 mg tab. - Bisoprolol tablet, 5mg tab. - Captopril suspension, 1 mg/ml - Fondaparinux sodium injection, 5 mg/ mL, 0.3 mL pre-filled syringe - Fondaparinux sodium injection, 5 mg/ mL, 0.5 mL pre-filled syringe - Glyceryl trinitrate 0.4mg / dose 200 dose spray - Ivabradine tablets, 5 mg tab. - Metoprolol 1mg/ml - Micronized fenofibrate tablet, 145mg – 200mg tabs - Nifedipine suspension - Phytomenadione injection, 2 mg/0.2 mL ampoule - Rivaroxaban tablet, 15 mg tab. - Rivaroxaban tablet, 20 mg tab. - Spironolactone syrup, 2.5 mg/ mL - Valsartan tablet, 160 mg tab.	- Cilazapril tablets, 2.5mg tab. - Fenofibrate capsules, 300 mg cap. - Furosemide tablets, 500 mg tab. - Phytomenadione tablets, 10 mg tab. - Terazosin capsules, 5 mg cap.
Section 3 Respiratory	- Budesonide/ Formoterol powder for inhalation, 160/4.5 micrograms/ blister - Fluticasone/Salmeterol powder for inhalation, 500/50 micrograms/ blister - Montelukast sachets, 4 mg/ sachet - Omalizumab 150mg/ml - Pirfenidone capsules, 200 mg cap.	- Beclometasone dipropionate metered aerosol inhaler, 250 microgram/ metered inhalation - Beclometasone dipropionate metered aerosol inhaler, 50 microgram/ metered inhalation - Salbutamol syrup 2mg/5ml - Salbutamol tablet, 4 mg tab.

Additions and Deletions

		Terbutaline sulphate tablets, 2.5 mg
Section 4 CNS	- Aprepitant capsules, 125 mg cap. - Aprepitant capsules, 80 mg cap. - Carbidopa with Entacapone and Levodopa tablets, 100/25/200 mg tab. - Carbidopa with Entacapone and Levodopa tablets, 150/37.5/200 mg tab. - Donepezil tablets, 5 mg tab. - Duloxetine tablets, 120 mg tab. - Duloxetine tablets, 30 mg tab. - Ethosuximide syrup, 250 mg/ 5 mL - Fentanyl transdermal patches, 12.5 micrograms/ hour for 72 hours - Galantamine tablets, 8 mg tab. - Levetiracetam tablets, 1 g tab. - Methylphenidate tablets, 10 mg tab. - Methylphenidate tablets, 20 mg tab. - Methylphenidate tablets, 5 mg tab. - Midazolam syrup - Morphine sulphate slow release tablets, 40 mg S.R. tab. - Risperidone depot injection, 25 mg inj. - Risperidone depot injection, 50 mg inj. - Rivastigmine capsules, 3 mg cap. - Rivastigmine capsules, 6 mg cap.	- Ergotamine tartrate + caffeine tablets, 1 mg + 100 mg tab. - Lorazepam Injection, 4 mg/ ml
Section 5 Infections	Anidulafungin injection, powder for reconstitution, 100 mg vial	Ketoconazole tablets, 200 mg tab.

Additions and Deletions

• Artemether/ lumefantrine tablets, 20 mg/ 120 mg tab. • Artesunate injection, 60 mg inj. • Caspofungin injection, powder for reconstitution, 50 mg vial • Clarithromycin injection, powder for reconstitution, 500 mg vial • Clarithromycin suspension, 250 mg/5 mL • Clindamycin suspension, 75 mg/ 5 ml • Cloxacillin injection, powder for reconstitution, 500 mg vial • Darunavir tablets, 300 mg tab. • Efavirenz capsules, 200 mg cap. • Efavirenz capsules, 50 mg cap. • Efavirenz 600mg + Emtricitabine 200mg + Tenofovir disoproxil 300mg • Ertapenem injection, powder for reconstitution, 1 g vial • Lamivudine solution, 10 mg/mL • Linezolid injection, 600 mg inj. • Linezolid suspension, 100 mg/ 5 ml susp . • Linezolid tablets, 600 mg tab. • Lopinavir / Ritonavir oral solution, 80 mg/ 20 mg/ mL • Lopinavir / Ritonavir tablets, 100 mg/ 25 mg tab. • Lopinavir / Ritonavir tablets, 200 mg/ 50 mg tab. • Meropenem trihydrate injection, powder for reconstitution, 1 g vial • Nevirapine suspension, 10 mg/mL sus. • Pentamidine isethionate, solution for inhalation, 300 mg vial • Rifabutin tablets, 150 mg tab.	• Sodium Fusidate injection, powder for reconstitution, 500 mg vial • Tetracycline hydrochloride tablets/ capsule, 250 mg tab/cap.

Additions and Deletions

	• Tigecycline injection, 50 mg inj. • Voriconazole injection, powder for reconstitution, 200 mg vial • Voriconazole tablets, 200 mg tab. • Zidovudine syrup, 10 mg/mL	
Section 6. Endocrine	• Cabergoline tablets, 500 microgram tab. • Carbimazole tablets, 20 mg tab. • Denosumab injection, 60 mg/mL, 1 mL prefilled syringe • Denosumab injection, 70 mg/mL, 1.7 mL (120-mg) vial • Estradiol pessary, 10 microgram • Estradiol pump, 750 microgram pack • Exenatide Injection, 5 microgram/dose (60 doses) in prefilled pen • Insulin Aspart injection, 100 units/ mL, prefilled pen • Insulin Detemir injection, 100 units/ mL, prefilled pen • Insulin Glargine injection, 100 units/ mL, prefilled pen • Insulin Lispro injection, 100 units/mL, prefilled pen • Levothyroxine oral solution, 100 microgram/5 mL • Levothyroxine sodium tablets, 100 micrograms tab. • Octreotide acetate injection, powder and solvent, 20 mg vial • Sitagliptin phosphate tablets, 100 mg tab. • Thyrotropin Alfa injection, 1.1 mg inj. • Triptorelin injection, powder for reconstitution, 11.25 mg vial	• Glipizide tablets, 5 mg tab. • Strontium ranelate granules, 2 g/sachet

Additions and Deletions

	• Vildagliptin tablets, 50 mg tab.	
Section 7. Ob/Gyn	• Etonogestrel 68 mg intradermal implant • Hydroxyprogesterone hexanoate injection, 250 mg inj. • Solifenacin succinate tablets, 5 mg tab	• Indometacin neonatal injection, powder for reconstitution, 1 mg vial • Oxybutynin hydrochloride tablets, 5 mg tab.
Section 8. Malignant diseases & immunosuppressant	• Azacitidine injection, , powder for reconstitution, 100 mg/vial • Bendamustine injection, powder for reconstitution, 100 mg vial • Bendamustine injection, powder for reconstitution, 25 mg vial • Bicalutamide tablets, 150 mg tab. • Clofarabine injection, 20 mg vial • Dasatinib tablets, 50 mg tab. • Everolimus tablets, 0.75 mg tab. • Everolimus tablets, 10 mg tab. • Everolimus tablets, 5 mg tab. • Fingolimod hydrochloride capsules, 500 microgram caps. • Fulvestrant injection, 250-mg prefilled syringe • Gefitinib tablets, 250 mg tab. • Imatinib tablets, 400 mg tab. • Lapatinib tablets, 250 mg tab. • Lenalidomide capsules, 10 mg & 25 mg cap. • Methotrexate sodium injection, 20 mg in pre-filled syringe • Mycophenolate Sodium tablets, 360 mg tab. • Oxaliplatin injection, 100 mg vial • Panitumumab injection, 100 mg vial • Sorafenib tablets, 200 mg tab. • Sunitinib capsules, 12.5 mg cap. • Sunitinib capsules, 50 mg cap.	

Additions and Deletions

	• Tacrolimus sachets, 1 mg per sachet. • Tacrolimus sachets, 200 micrograms per sachet • Thalidomide tablets, 100 mg & 200 mg tab.	
Section . 9 Nutrition & blood	• Calcium syrup, 100 mg/ 5 mL • Cinacalcet tablets, 30 mg tab. • Colecalciferol capsules, 50,000 units cap. • Colecalciferol drops 10,000 IU / mL • Colecalciferol drops 400 IU / mL • Darbepoetin Alfa injection, 10 micrograms prefilled syringe • Deferasirox tablets, 125 mg , 250 mg & 500 mg tab. • Glutamine injection, 200 mg inj. • Nitisinone capsules, 2 mg cap. • Plerixafor injection, 24 mg in 1.2 mL vial • Romiplostim injection, powder for reconstitution, 250 microgram vial • Sevelamer powder, 800 mg per sachet • Sodium bicarbonate tablets, 500 mg tab. • Sodium Phenylacetate and Sodium Benzoate 100 mg/mL (of sodium phenylacetate) and 100 mg/mL (of sodium benzoate) in a concentration for injection • Sodium phenylbutyrate tablets, 500 mg tab. • Vitamine D3 drops, 10,000 IU • Zinc syrup, 20 mg/ 5 mL, 50-75 mL	

Additions and Deletions

Section 10. MSK	• Celecoxib tablets, 200 mg tab. • Diclofenac sodium suppositories, 25 mg tab. • Etanercept injection, 50 mg prefilled syringe • Etoricoxib tablets, 120 mg tab. • Etoricoxib tablets, 90 mg tab. • Ibuprofen injection, 10 mg / mL • Leflunomide tablets, 20 mg tab. • Naproxen tablets, 250 mg tab • Rasburicase injection, powder for reconstitution, 1.5 mg vial • Rasburicase injection, powder for reconstitution, 7.5 mg vial • Tocilizumab Injection, 20 mg/ mL, 4 or 10 mL vial	
Section 11. Eye	• Apraclonidine eye drops, 0.5% • Apraclonidine eye drops, 1.0% • Cyclopentolate eye drops, 0.5% ; 5 mL/bottle • Cyclopentolate eye drops, 1% ; 5 mL/bottle • Latanoprost with Timolol eye drops, 50 microgram latanoprost and 5 mg timolol per mL • Moxifloxacin eye drops, 0.5% • Ranibizumab injection, 10 mg/ 1 mL in prefilled syringe	• Dipivefrine eye drops , 0.1%; 10 mL/bottle • Hypromellose injection, 2%, 1.5 mL (single use syringe for intra-ocular injection) • Natamycin eye drop, 5%, 15 mL/bottle • Prednisolone eye drops, 0.125 %; 5 mL/bottle • Rose Bengal eye drops, 1%
Section 12. ENT	• Budesonide nasal spray, 64 micrograms/metered spray, 120 doses/ metered spray	
Section 13. skin	• Calcipotriol/ betamethasone dipropionate cream • Calcipotriol/ Betamethasone gel • Heparinoid cream, 0.3% • Heparinoid gel, 0.3%	• Calcipotriol cream, 50 microgram/ g cream, 30 g tube

Additions and Deletions

	• Tretinoin 0.05% cream	
Section 14. Immunological products & vaccines		• Tetanus antitoxins injection, 1,500 units injection in 1mL ampoule
Section 15. Anaesthesia	• Dexmedetomidine injection, 100 micrograms/ mL • Ketorolac Injection, 30 mg/ mL. 1 mL ampoule • Levobupivacaine injection, 25 mg / 10 ml ampoule • Levobupivacaine injection, 50 mg / 10 ml ampoule	• Ketamine hydrochloride injection, 10 mg (preservative free injection)
Section 16. Contrast media	• Barium sulfate suspension, 0.1%, 750 mL	

Guidance on appropriate prescribing

General remarks

Medicines should be prescribed only when improvement of the clinical condition is possibly achieved with the minimum risk to the patient. Drug therapy sometimes is unnecessary, unsuitable or ineffective. It is the prescriber's duty to explain to the patient in a simple, convincing way that some ailments are self limiting and drugs are not always necessary.

Great care should be practiced when prescribing during pregnancy to avoid any harmful drug effect to either the mother or the foetus. Cautious prescribing is retained for paediatric and geriatric patients, in patients with renal or hepatic impairment or in the immunocompromised and also for breast feeding mothers.

Rational use of medicines (RUM) as defined by WHO is “**All patients should receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to themselves and their community.**” RUM should be highly encouraged and promoted at all levels of the health services. The concept of RUM should not be mistaken as only rationing medication or reducing cost. RUM aims to:

- Avoid over prescribing
- Minimise adverse drug effects
- Select the right drug for the right clinical condition
- Increase awareness about drug costs
- Establish national drug policies

Irrational or non-rational use is the use of medicines in a way that is not compliant with the definition above. Worldwide more than 50% of all medicines are prescribed, dispensed or sold inappropriately, while 50% of patients fail to take them correctly.

Drugs in Oman are categorized for **administrative** purposes into the following:

- **Restricted drugs:** to be prescribed by consultants and specialists or to be used by specialized units.

- **Controlled drugs:** to be prescribed on a special prescription and these include three classes: a- *Narcotics* as classified according to International Narcotic Control Board (INCB) to be prescribed using **red prescription**; b- *Psychotropics* to be prescribed using **green prescription**; c- *Other drugs* that may pose a special threat of misuse as decided by local health authority, e.g., tramadol, these agents are prescribed using the green prescription.
- **Complementary drugs as per complementary drug list (CDL)** for rare disorders or in exceptional circumstances to be made available on demand by specialists
- **General drugs:** are prescribed by doctors without any specific limitation.

Primary health doctors are permitted to prescribe a limited number of the general drugs (see Primary Health Care Formulary, circular MH/DGMS/DGO/4/C/5/ 472 of 31 July 2002) and these are noted in separate formulary published by the Directorate General of Medical Supplies

Prescription writing

A prescription is a medico-legal document, which should be legibly written in ink. The Doctors name and professional title should clearly appear with the signature on the prescription. The prescription should contain full information about the patient such as, patient's name, registration number, sex, age or the date of birth, and body weight (if appropriate). Drug related information must carefully be written and these include the following:

- **Drug name:** drugs should be prescribed in their generic names wherever possible. This will minimise the confusion caused by the many trade names given to one single generic molecule. When a combined preparation is prescribed, it is advisable that acceptable terminology is used to describe such a preparation; e.g., *cough syrup*, for cough mixture; *oral decongestants* for antihistamine and sympathomimetics etc. Never invent a drug name or use non standard abbreviations.
- **Strengths or volumes** should be stated using the metric system (see table below). Doses less than 1 g should be stated in mg

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(e.g. 250 mg or 500 mg and not as 0.25 g or 0.5 g). Doses less than 1 mg should be stated in micrograms (e.g. 250 or 500 micrograms and not as 0.25 mg or 0.5 mg). When decimals are unavoidable, a zero should appear before the decimal point where there is no other figure, e.g. 0.5 mL and not .5 mL

Measure Unit	Symbol	Incorrect symbol
Gram	g	G or gm
Milligram	mg	mgm
Microgram	microgram	mcg
Millilitre	mL or ml	cc or cm ³
Litre	l	L, lr or lt

- **Dose regimen:** always state dose strength, dose frequency, duration of treatment, and quantity to be dispensed. Avoid using abbreviations as they may cause confusion. However, it may be convenient to use some internationally recognized Latin abbreviations such as bid, tid and qid for 2, 3 and 4 times daily respectively. Preferably, time intervals should be mentioned for example, every 6 hours, every 8 hours etc. Avoid using abbreviations as PRN or SOS alone or phrases such as “*as directed, as required or on need*”; frequency of dosing should be clearly mentioned, such as “PRN, one tablet three times daily” or “as required, 3 times daily”.

Prescribing at the two extremes of age

Most drugs are developed and tested in young to middle aged adults. At the two ends of the age spectrum, individuals differ both in their pharmacodynamic and pharmacokinetic characteristics. These differences may impose critical adjustments in the dose or dose regimen to produce the desired effect with the minimum of harmful or unwanted effects.

Paediatric prescribing

Drug clearance pathways are limited in the newly born, and develop variably in the first year and keep showing variations until puberty. Apart from immaturity of physiological processes, the reaction of infants and young children to drugs is influenced indirectly through complications such as fever, dehydration, and acid-base disturbances. Pharmacodynamic differences between children and adults have led to unexpected outcomes of therapy

and adverse effects. For example, while antihistamine and barbiturates generally sedate adults, these drugs cause many children to become hyperactive. It remains very difficult to work out a reliable method to determine the dose in children based on adult dose. Many formulas have been suggested using body weight, surface area or age as indicators to convert adult doses of drugs into a safe and effective dose in children. In the ONF children's doses are mentioned in the drug entries unless the drug is not recommended for paediatric use. The following table is an approximate guide to paediatric doses. The doctor should make a rational assessment to decide on the dose regimen that is suitable for each individual patient.

Age/weight table

Age	Weight (kg)	Surface area (m ²)	% of adult dose
Neonate (term)	3.5	0.23	12.5
1 month	4	0.25 - 0.26	14 - 14.4
3 months	6	0.32 - 0.34	15 - 18
6 months	8	0.38 - 0.40	20 - 22
1 year	10	0.46 - 0.49	25 - 27
2 years	12	0.54 - 0.58	30 - 32
3 years	14	0.61 - 0.64	33 - 35
4 years	16	0.67 - 0.71	36 - 39
5 years	18	0.72 - 0.77	40 - 43
7 years	22	0.86 - 0.90	47 - 50
10 years	30 - 32	1.04 - 1.11	58 - 62
12 years	38 - 40	1.21 - 1.30	70 - 75*
14 years	48 - 50	1.46 - 1.50	80 - 87*

** Doses might be 100% of adult dose dependent on individual and drug*

To calculate Body surface area (BSA) by using child-BSA-nomogram see appendix 6

Geriatric prescribing

In the general population, functional capacity of most of the major organ systems shows a decline with advancing age. This may be reflected in absorption, distribution, metabolism and elimination of drugs. In addition, it is believed that geriatric patients are more "sensitive" to the action of many drugs, implying a change in the pharmacodynamic interaction of drugs

Prescribing Guidance

with their sites of action. Such changes could also be attributed to diminished homeostatic responses. Drug usage patterns in the elderly also change due to an increasing incidence of disease with age. Among other changes are, the increasing incidence of multiple diseases, nutritional problems, reduced financial resources, and decreased compliance for a variety of reasons. Because of an increasing risk of adverse effects when prescribing in the elderly, the following precautionary measures are recommended:

- Drugs are prescribed only when highly indicated
- Start low and go slow every time a new drug is prescribed
- Avoid polypharmacy
- It is advisable some times to use paediatric formulations (such as liquids, suppositories or effervescent tablets) instead of oral tablets or capsules; the former preparations offer a better dose adjustment and improve compliance.
- Do not rush to treat a new symptom or complaint; it could be attributed to an adverse effect of an already used drug.

Drugs with greater risk in the elderly include, sedatives and hypnotics, analgesics, antipsychotics, antidepressant drugs, cardiovascular drugs, antimicrobials, long acting antidiabetic drugs and anti-inflammatory drugs. For individual drugs see drug entries in the ONF.

Prescribing in renal impairment

Drugs that are entirely or partially eliminated by the renal system may produce toxicity in the presence of renal impairment. Such toxicity is more serious with drugs that have a narrow safety margin. Problems arising from use of drugs in renal impairment can be avoided by reducing the dose, or the use of alternative drugs, or by increasing the dosing time interval. Dose reduction depends on whether the drug is entirely or partially eliminated by the renal system and on how toxic it is. For many drugs with only minor dose-related toxicity very strict modification of the dose regimen is unnecessary and a simple scheme for dose reduction is sufficient.

For drugs with toxic dose-related side-effects, the dose reduction is dependent on the glomerular filtration rate. However, glomerular filtration rate (GFR) is only used to initiate the dose regimen, but for maintenance, the judgement is based on clinical response and the drug-plasma concentration. The practical way of determining glomerular filtration rate is by measuring creatinine clearance. For creatinine clearance calculations, *see appendix 3*

Nephrotoxic drugs should be avoided in patient with renal disease because the consequences of nephrotoxicity are likely to be more severe when the renal reserve is already reduced. *See appendix 3* for lists of common drugs associated with nephrotoxicity. The state of renal function must be determined not only before but also during the treatment, since some drugs may cause further deterioration of renal function. Caution should be taken in elderly patients as renal function might be reduced even in the presence of normal serum urea or creatinine. For dosing reduction regimen, consult drug literature. In the ONF, relevant cautionary notes about individual drug and renal impairment are mentioned in the drug entries.

Prescribing in hepatic impairment

Reduced liver function may alter responses and lead to adverse drug reactions. This depends mainly on the severity of liver disease and on the extent of drug hepatic metabolism. Drugs that are entirely metabolised are more affected than those partially subjected to liver metabolism or excreted unchanged by the renal system.

It is not simple to determine the degree of liver impairment, and hence it is difficult to come out with a standard dose reduction regimen. The liver has a great reserve capacity and only very severe impairment will effectively decrease the rate of metabolism of some drugs leading to adverse effects. This is more frequent with drugs of low margin of safety. Drugs may induce hepatotoxicity, which aggravates existing liver impairment. Therefore, hepatotoxic drugs should be avoided in the presence of hepatic impairment and should only be used after assessing their benefit versus their risks. For more information about drug induced hepatotoxicity, *see appendix 2*

As a general rule, to avoid drug adverse reactions in the presence of hepatic impairment, avoid drugs that are extensively metabolised in the liver, or reduce the dose and closely observe the clinical response and the development of adverse effect. In the ONF, relevant cautionary notes about individual drug and hepatic impairment are mentioned in the drug entries.

Prescribing during pregnancy

Most drugs taken by pregnant women can cross the blood-placental barrier and expose the developing embryo and foetus to their detrimental effects. Many factors contribute to the occurrence of congenital malformation (teratogenesis), such as the genetic susceptibility of the embryo, pathological

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and nutritional status of the mother, as well as exogenous factors; drugs are one of the exogenous factors involved. The occurrence is also dependent on the following drug related factors:

- The physicochemical properties of the drug
- The rate at which the drug crosses the placenta and the amount reaching the foetus
- The duration of exposure
- Distribution characteristics in foetal tissues
- The stage of foetal development at the time of exposure

During the first 2 weeks following conception (pre-implantation period), the embryo is probably resistant to drugs because there is no direct circulatory link between the mother and the embryo. The period of greatest risk is from the 3rd to the 11th week of pregnancy. During this period cellular division and differentiation is most sensitive to harmful drug effects. All drugs should be avoided as much as possible during this period (1st trimester). After the first trimester most organs are formed, although the genital apparatus, teeth, and the nervous system continue to mature. Thus drugs administered during the second and third trimesters may affect growth and functional development of the foetus. Drugs given towards the end of pregnancy or during labour may have adverse effects on the neonate.

As a general rule, drugs should be avoided during pregnancy and especially during the first trimester, unless there is a clear indication and the expected benefit is greater to the mother than the risk to the foetus. If medication is a necessity, drugs of well tested safety should be used in the smallest effective dose and for the shortest possible therapeutic duration.

Doctors should always consider (1) the possibility of pregnancy when prescribing for women of childbearing age, (2) Pregnancy results in profound physiological changes, which may alter the pharmacokinetics of many drugs. In the ONF, relevant cautionary notes about individual drug use during pregnancy are mentioned in the drug entries.

Prescribing during breast-feeding

Drugs taken by lactating mother may be passed to the breast-fed infant through the milk. Some drugs appear in the milk in a pharmacologically significant concentration to cause adverse effect in the breast-fed infants. However, some drugs have inhibitory or stimulatory action on lactation such as bromocriptine or phenothiazines.

Breast-feeding should be maintained in women who need drug therapy provided that the infant is closely observed for possible adverse effects. However, some times it becomes necessary to avoid some drugs and occasionally to stop breast-feeding when:

- a drug is harmful to the infant even when it appears in small concentration in the milk
- a drug is liable to accumulate in the nursing mother circulation due to the presence of renal or hepatic impairment.

In the ONF, relevant cautionary notes about individual drug use during breast-feeding are mentioned in the drug entries.

Adverse drug reactions (ADR)

The use of drugs is often associated with the risk of adverse reactions: Severe adverse reaction to marketed drugs are uncommon as most of such reactions are noted during the various phases of clinical trials and upon their occurrence usually the manufacture is deterred from marketing the drug.

The mechanisms of adverse reactions fall into two main categories. Those in the first group are often extension of the pharmacological effects and thus are predictable by researchers and clinicians. In the second group, which may be immunological or of unknown mechanisms, are unexpected and may not be encountered unless the drug is put for use for many years; clinicians usually discover these toxicities. It is therefore of utmost importance, that an adverse reaction reporting system is actively brought up by practicing clinicians. A drug reaction may occur as early as the first dose, such as anaphylaxis or haemolytic anaemia. Serious toxic effects may occur during prolonged treatment as with corticosteroids. Other reactions may well occur long after cessation of treatment. The incidence of adverse effects increases with the number of drugs used by the patient. Some of these adverse reactions may be due to drug interactions. In the elderly, particular vigilance is required. Confusion, falls or severe constipation may be signs of adverse reactions. All drugs taken during pregnancy should be reported when an infant is born with congenital abnormalities or there is a malformed aborted foetus, as an adverse drug reaction might have been the cause. Adverse reactions may be prevented as follows:

Prescribing Guidance

- Drugs should only be used when evidently indicated.
- Great caution should be experienced in prescribing to pregnant or breast-feeding women.
- Ask your patient about any previous allergy or other adverse reactions.
- Be aware of any other drugs taken by the patient before prescribing new one. Make sure to ask about over the counter (OTC or self-purchased) medicines.
- Prescribe as few drugs as possible and clearly instruct the patient in their appropriate use.
- More attention is given to newly introduced drugs. Caution the patient to report any undesirable effect.

Reporting of adverse drug reactions

Medical staff are requested to report any adverse reaction encountered with new drugs. However, unusual, unexpected or serious reactions to established drugs or biological products should also be reported. In case of congenital abnormalities or deformities in aborted foetus, all drugs taken by the mother during pregnancy should be reported. The reported information is processed with a high degree of confidentiality. The attached format (see the yellow forms at the back of this publication) should be used for reporting purposes.

Report ADR to:

***Directorate General of Pharmaceutical Affairs and Drug Control
Muscat***

How to use the ONF

How the material is organised

There are 17 main sections, 8 appendixes. Each main section represents a particular body system or an aspect of medical care. Within each section there are introductory notes about each group of drugs. These notes are intended for the use of doctors, dentists, nurses, pharmacists and other health care providers to assist in the selection of suitable treatments. The notes are followed by details of the available drugs and preparations (*as per template below*).

DRUG CLASS

Notes

DRUG NAME – approved generic name

Indications:

Contraindications:

Cautions:

Side effects:

Dose:

Preparations

Guidance on Prescribing

There are notes on appropriate prescribing including the principles of rational prescribing and drug use; prescription writing; controlled drugs including psychotropics and narcotics; restricted drugs; prescribing at the extremes of age; prescribing in renal failure and hepatic impairment. There are additional notes on prescribing in pregnancy and breast feeding and reporting of adverse drug reactions (ADRs). In the text are examples of the different prescription forms found in Oman and the ADR reporting forms.

Appendixes

There are total of 8 appendixes. For more details, see under the preface/layout of the ONF

Emergency Treatment of Poisoning

Section 17 is devoted to the management of acute poisoning both accidental and self-administered. General aspects of management are included as well as details of specific antidotes where appropriate.

Index

The general index is placed at the back of the book and is often the first point of contact for most practitioners. Major key words have also been included to allow searches based on a particular condition or disease.

Example Prescriptions

SULTANATE OF OMAN
MINISTRY OF HEALTH
HOSPITAL



سلطنة عمان
وزارة الصحة
مستشفى

وصفة للمرضى الخارجيين OUT - PATIENT PRESCRIPTION

Department القسم Date التاريخ
Name الاسم
Age العمر Weight الوزن Sex الجنس
Registration No. رقم التسجيل

Rx :

FOR PHARMACY USE ONLY (PACK & QTY. ENDORSEMENT)

SPECIMEN

Dispensed by Signature
Checked by &
Name of Prescriber

MR - 6

Ministry of Health Out-Patient Prescription

Example Prescriptions

Ministry of Health
Directorate General of Pharmaceutical Affairs
and Drug Control



وزارة الصحة
المديرية العامة للصيدلانية
والرقابة الدوائية

Hospital Name : _____ № 0608 _____ اسم المستشفى

Out Patient Prescription for Oral Narcotics

Patient's Detailed Residence Location	Patient's Label

Diagnosis : _____

Rx

Name of Drug & strength	Dose & Frequency	Duration	Quantity in Hand	Quantity Dispensed

Date & quantity of last oral dose : _____

Doctor's Sign. : _____ Dispensed by : _____
& (name & sign.)

Stamp/Name : _____ Checked by : _____

Date : _____ Date : _____

***Please write in Capital Letters.**

Hospital Stamp

Patient's Copy

Example Prescriptions

No. 156601/2001

 **سلطنة عمان**
وزارة الصحة
المديرية العامة للمخازن

وصفة مخدرات
Narcotic Prescription

Name of Patient : Age :

Date : / / 20... Time :

Name of the Ward : I.P. No. :

Drug Prescribed & Dose :

Prescribed by & Sig. :

Given by & Sig. :

MOI/Head of the Unit :

Stamp of Hospital/H.C. :

No. 156601/2001

 **سلطنة عمان**
وزارة الصحة
المديرية العامة للمخازن

وصفة مخدرات
Narcotic Prescription

Name of Patient : I.P. No. :

Date : / / 20... Time :

Prescribed by :

Signature :

Stamp of Hospital/H.C. :

SPECIMEN

سلطنة عمان
المديرية العامة للمخازن

Example Prescriptions

SULTANATE OF OMAN MINISTRY OF HEALTH		سلطنة عمان وزارة الصحة	
HOSPITAL		مستشفى	
1225805	وصفة أدوية ذات مؤثرات نفسية وعقلية للمرضى الخارجيين PSYCHOTROPIC SUBSTANCES OUT-PATIENT PRESCRIPTION		
	Department	القسم	Date
	Name	الإسم	التاريخ
	Age	العمر	Weight
Registration No.		رقم التسجيل	
FOR PHARMACY USE ONLY (PACK & QUANTITY ENDORSEMENT)	R _x		
	SPECIMEN		
Dispensed by			
Checked by	& Name of Prescriber :		

Section 1: Gastro-Intestinal System

- Antacids
- Antispasmodics
- Ulcer healing drugs
- Antidiarrhoeal drugs
- Laxatives
- Ano-rectal preparations
- Drugs affecting gastrointestinal secretion

1 A: Antacids

Antacids neutralise the acid secreted by the gastric parietal cells. They help relieve symptoms of ulcer dyspepsia. Antacids should be used upon occurrence of symptoms, usually taken between meals and at bedtime 4 or more times daily. Healing of an ulcer might be achieved with additional doses up to one every hour, however healing of an ulcer is better achieved with antisecretory drugs (e.g. H₂-receptor blockers).

Aluminium hydroxide alone or in combination with magnesium salts (hydroxide or trisilicate) is commonly used. Antiflatulants, such as dimeticone are sometimes added to antacid preparations. Aluminium hydroxide tends to cause constipation while magnesium salts are laxative. Compound antacids have no advantage over single preparations in their neutralising capacity. Liquid preparations are more effective than tablets.

1 A.1: Aluminium Hydroxide

Dried aluminium hydroxide gel

Indications: dyspepsia, hyperphosphataemia.

Contraindications: hypophosphataemia.

Cautions: renal failure, porphyria, congestive heart failure, recent gastrointestinal haemorrhage.

Side-effects: constipation, faecal impaction, chalky taste, stomach cramps, nausea, vomiting.

Dose: One tab/cap 4 times daily and at bed time. Child not recommended for antacid therapy.

Preparations

Aluminium Hydroxide capsules, 475 mg cap.

1 A.2: Compound Antacid Preparations

Magnesium trisilicate or hydroxide with aluminium hydroxide

Indications: dyspepsia, gastritis, gastric and duodenal ulceration, reflux oesophagitis.

Contraindications: hypophosphataemia.

Cautions: patients with gastrointestinal haemorrhage, patient with CHF, oedema, hypertension, renal failure, cirrhosis.

Side-effects: constipation; large doses may cause osteomalacia, encephalopathy.

1: Gastro-intestinal system

Dose: 1-2 tablets or 10-20 mL suspension 4 times daily. Child under 12 years, not recommended.

Preparations

Compound antacid tablets, 505 mg tab

Compound antacid suspension, 100-200 mL/bottle

1 B: Antispasmodics

1 B.1: Antimuscarinics

Antimuscarinics reduce intestinal motility and gastric secretion. They can be useful in dyspepsia, irritable bowel syndrome and diverticular disease. Other indications include asthma, motion sickness, Parkinsonism, urinary incontinence and as antidote for organophosphorus poisoning. Atropine sulphate, hyoscine n-butylbromide, hyoscine hydrobromide, and homatropine are useful in gastrointestinal spasm. Atropine is more lipid soluble and hence is more likely to cross the blood-brain barrier and induce central effects such as confusion. These side-effects are less likely with hyoscine and homatropine.

Cautions: Due to the diversity of their actions, antimuscarinics should be used with caution in Down's syndrome, in children and in the elderly, in reflux oesophagitis, diarrhoea and ulcerative colitis. Greater caution should be taken when used in patients with acute

myocardial infarction, hypertension and in conditions characterized by tachycardia.

Contra-indications: Antimuscarinics are contraindicated in angle-closure glaucoma, myasthenia gravis, paralytic ileus, and prostate enlargement.

Side-effects: Constipation, dilatation of the pupil with loss of accommodation, photophobia, dry mouth, flushing and dryness of the skin, urinary retention and tachycardia. In the elderly, confusion may occasionally occur.

Atropine Sulphate

Indications: symptomatic relief of gastrointestinal disorders associated with smooth muscle spasm. In pre-medication, to prevent excessive salivation and bronchial secretion.

Contra-indications, cautions and side-effects: *see* notes above.

Dose: adult 400-600 micrograms every 4-6 hours. Child, with great caution, 10 micrograms/kg every 4-6 hours.

Preparations

Atropine sulphate injection, 600 micrograms/mL, 1 mL injection Atropine sulphate disposable syringe, 1 mg / 10 mL injection (Restricted)

Hyoscine n-Butylbromide

Indications: symptomatic relief of gastrointestinal or genito-urinary disorders characterized by smooth muscle spasm.

1: Gastro-intestinal system

Contra-indications, cautions and side-effects: *see* notes above.

Dose: orally, adult 10-20 mg 3-4 times daily. Child, 6-12 years, 10 mg 3 times daily.

Intramuscular or intravenous, 20 mg repeated as necessary (daily maximum dose 80 mg).

Preparations

Hyoscine n-butylbromide tablets, 10 mg tab

Hyoscine n-butylbromide injection, 20 mg/mL ampoule

1 B.2: Other antispasmodics and motility stimulants

Mebeverine is an antispasmodic which may be useful in irritable bowel syndrome. It should be avoided in paralytic ileus. Metoclopramide and domperidone are motility stimulants with dopamine antagonist actions. Motility stimulants stimulate gastric emptying, intestinal transit, and increase the strength of oesophageal sphincter contraction. They are of use in short term management of non-ulcer dyspepsia. Metoclopramide and domperidone are also used to control vomiting and nausea of non-specific nature or drug-induced (*see* section 4).

Mebeverine hydrochloride

Indications: adjunct in gastrointestinal disorders characterized by

smooth muscle spasm. Pain associated with irritable bowel syndrome and diverticular disease.

Cautions: Avoid in paralytic ileus, pregnancy, breast-feeding, porphyria.

Dose: orally, 135 mg tablet 3 times daily preferably before meal.

Preparations

Mebeverine hydrochloride tablets, 100 mg -135mg tab

Metoclopramide

Indications: gastro-oesophageal reflux disease, diabetic gastroparesis, nausea and vomiting, hiccups. (*see* section 4)

Cautions: hepatic and renal failure; elderly and young children.

Note: *Metoclopramide should be reserved only for severe, intractable vomiting of known cause in persons younger than 20 years of age.*

Side-effects: extrapyramidal effects especially in children and young adults; tardive dyskinesia may develop on chronic use.

Dose: Orally, adults over 15 years, 10 mg tablet 3 times daily; young adults 12-14 years; 5 mg (half a tablet) 3 times daily.

Preparations

Metoclopramide tablets, 10 mg tab
Metoclopramide injection, 10 mg/2 mL ampoule

1 C: Ulcer healing drugs

1: Gastro-intestinal system

Peptic ulceration is a self-limiting disorder of the digestive tract. It might involve the stomach (gastric ulcer), the duodenum (duodenal ulcer) or the oesophagus. Healing can be promoted by general measures such as stopping smoking, avoiding alcohol, spicy food or stressful life style. Healing can also be promoted by antacids or antisecretory drugs. *Helicobacter pylori* is the causative factor in all duodenal ulcers and most gastric ulcers that are not associated with NSAID use. Eradication of *H. pylori* infection can result in long term healing of duodenal and gastric ulcers.

Acid inhibition combined with antibacterial treatment is highly effective in the eradication of *H. pylori*; reinfection is rare. For initial treatment, a one-week triple therapy regimen that comprises a proton pump inhibitor, clarithromycin and either amoxicillin or metronidazole can be used. This regimen will eradicate *H. pylori* in about 85% of cases. Only if the ulcer is large or has complications does the proton pump inhibitor need to be continued. Two-week triple therapy regimens have a higher eradication rate compared to the one-week regimen, but adverse effects are common and poor compliance reduces the beneficial effects of the two-week treatment option. Two example dosing regimens are shown below:

Triple therapy example 1:

Esomeprazole 20 mg twice daily;
Amoxicillin 1 g twice daily;
Clarithromycin 500 mg twice daily.

Triple therapy example 2:

Esomeprazole 20 mg twice daily;
Clarithromycin 250 mg twice daily;
Metronidazole 400 mg twice daily.

1 C.1: H₂-receptor antagonists

The H₂-receptor antagonists reduce gastric acid secretion by virtue of their competitive inhibition of the H₂-receptors in the parietal cells. Ranitidine and nizatidine are used to heal gastric and duodenal ulcers and to relieve peptic oesophagitis. Although superseded by a new class of antisecretory drugs, H₂-receptor antagonists are still used to promote healing of NSAID induced ulcers and in Zollinger-Ellison syndrome. The long treatment course and the cost are disfavoured by these compounds against the new short treatment regimen with proton pump inhibitors. (PPI).

Cautions: should be used with caution in renal impairment, pregnancy and breast-feeding. They may mask symptoms of gastric cancer. Should be avoided in patients on warfarin, theophylline and phenytoin.

Side-effects: Gastrointestinal disturbances, headache, dizziness and tiredness. In the elderly, mental confusion and hallucination are more frequent. Cimetidine has

1: Gastro-intestinal system

been associated with gynaecomastia and impotence; such effects are less frequent in the new generation members of H₂-receptor antagonists.

Ranitidine

Indications: benign gastric, duodenal and NSAID induced ulcers, oesophageal reflux disease, Zollinger-Ellison syndrome and where reduction of gastric acidity is desirable.

Cautions: see notes above

Side-effects: see notes above; rarely tachycardia, agitation, visual disturbances, alopecia.

Dose: orally, for benign gastric, duodenal or NSAID induced ulcers treatment, 300 mg once at night, or 150 mg twice daily for 4-8 weeks. Maintenance, 150 mg once at night. Orally, for gastro-oesophageal reflux disease, 150 mg twice daily or 300 mg at night for 12 weeks. In moderate or severe cases, 150 mg 4 times daily or 300 mg twice daily for 8-12 weeks. Maintenance, 150 mg twice daily.

Orally, in Zollinger-Ellison syndrome, 150 mg 3 times daily. Doses can be increased according to patients' response up to 6g daily in divided doses.

Intramuscular injection or slow intravenous infusion, in surgical procedures 50 mg 45-50 minutes before induction of anaesthesia, may be repeated every 6-8 hours.

Preparations

Ranitidine tablets, 150 mg tab.

Ranitidine injection, 50 mg/2 mL ampoule

Ranitidine syrup, 75 mg/5 mL, 300 mL bottle (for paediatric gastroenterology only)

1.C.2: Proton pump inhibitors (PPI)

The hydrogen-potassium adenosine triphosphate enzyme system (proton -pump) is unique to the parietal cells. Inhibiting this system contributes to a reduction in gastric acid secretion. Proton pump inhibitors (PPI), such as omeprazole, can inhibit the acid secretion to any desirable limit. They are of particular benefit in patients with hypergastrinaemia, severe erosive oesophagitis and those not responding well to treatment with H₂-receptor antagonists. Eradication of *H. pylori* infection has been successfully achieved with omeprazole in combination with antibiotics.

Cautions: To be used with caution in presence of liver diseases, in pregnancy, breast-feeding. Gastric malignancy should be excluded before initiation of treatment. Can increase the risk of fractures particularly in the elderly

Side-effects: PPI can cause a number of side-effects including headache, diarrhoea, rashes, dizziness, nausea and vomiting, constipation, abdominal pain, flatulence, bronchospasm, blurred vision and dry

1: Gastro-intestinal system

mouth. Intensive decrease in gastric acidity increases the risk of gastro-intestinal infections.

Esomeprazole (Restricted)

Indications: NSAID induced ulcers, prophylaxis of NSAID-associated gastric ulcer in patients with an increase chance of gastro-duodenal complications, prophylaxis of stress ulceration, gastro-oesophageal reflux disease, duodenal ulcer associated with *H. pylori* infection, Zollinger-Ellison syndrome.

Cautions: see notes above

Side-effects: see notes above and Omeprazole below.

Dose: NSAID induced ulcer treatment, 20 mg once daily for 4-8 weeks.

Gastro-oesophageal reflux disease, 20 mg daily for up to 4 weeks then 20 mg when needed. Child 12-17 years, 20 mg once daily for up to 4 weeks. In the presence of erosive reflux oesophagitis, 40 mg for 4 weeks then maintenance of 20 mg daily. Child 12-17 years. Initially 40 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed or symptoms persist; maintenance 20 mg daily.

Ulcers associated with *H. pylori* infection, 20 mg twice daily.

Zollinger-Ellison syndrome, initial dose 40 mg twice daily adjusted to 80-160 mg daily

Gastric acid reduction during general surgical manipulation, 40 mg the night before surgery and then 40 mg 2-6 hours before surgery.

Preparations

Esomeprazole granules, 10 mg/sachet.

Omeprazole (Restricted)

Indications: benign gastric, duodenal and NSAID induced ulcers, oesophageal reflux disease, ulcers associated with *H. pylori* infection, Zollinger-Ellison syndrome, gastric acid reduction during surgical manipulations.

Cautions: see notes above

Side-effects: see notes above. Increased sweating, hallucination, insomnia, gynaecomastia, taste disturbance, paraesthesia

Dose: orally for benign gastric, duodenal or NSAID induced ulcers treatment, 20 mg once daily for 4-8 weeks. The dose can be increased to 40 mg in severe cases.

Ulcers associated with *H. pylori* infection, see treatment regimen above.

Zollinger-Ellison syndrome, initial dose 60 mg once daily, up to 120 divided into 2 daily doses.

Gastric acid reduction during general surgical manipulation, 40 mg the night before and then 40 mg 2-6 hours before surgery.

Preparations

Omeprazole capsules, 20 mg cap.

Omeprazole injection, powder for reconstitution, 40 mg vial (Restricted)

1 C.3: Chelates and complexes

Tripotassium dicitratobismuthate is a bismuth chelate that promotes healing of gastric and duodenal ulcer by selectively chelating with protein in the ulcer base, thus protecting it from the effects of acid and pepsin. It also stimulates the secretion of bicarbonate. It has antibacterial activity against *H. pylori* and this effect gives it a place in eradication therapy as mentioned above. Sucralfate is a basic aluminium salt of sulphated sucrose. It is viscous at acid pH and forms a protective paste that adheres to the ulcerated area. This paste protects the ulcer from the effects of acid, pepsin and bile salts. It is useful in gastric and duodenal ulcers and chronic gastritis.

Sucralfate (Restricted)

Indications: benign gastric and duodenal ulcer and chronic gastritis.

Cautions: Renal impairment, pregnancy and breast-feeding.

Side-effects: constipation, dry mouth, skin rash.

Dose: Benign duodenal and gastric ulcer, 2 g twice daily (on rising and at bed time) or 1 g four times daily (1 hour before meal and at bed time) for 4-6 weeks and can be extended to 12 weeks in resistant cases.

Preparations

Sucralfate tablets, 1 g tab.

1 D: Antidiarrhoeal drugs

Acute diarrhoea is defined as passing of 3 or more watery stools in any 24 hours, or any watery stool if accompanied by fever, abdominal pain and/or vomiting. Acute diarrhoea contributes significantly to the problem of malnutrition in infants and children and is more responsible for mortality than any other cause. The first line of treatment is the replacement of the lost water and electrolytes and prevention of dehydration. Oral rehydration therapy (ORT) can prevent and correct dehydration and prevent many diarrhoea-associated deaths. About 90-95% of all patients with watery diarrhoea can be treated with oral rehydration salt (ORS). No antibiotics are needed even in bacterial diarrhoea as in simple gastro-enteritis, as the condition will mostly resolve with oral rehydration. Not all acute diarrhoea is infectious. Toxins, anxiety, diet, drugs or microorganisms could cause diarrhoea. Viruses are the most important causative agent in children under the age of 5 years, especially during the drier, cooler months, whereas bacterial diarrhoea tends to peak during the warm rainy season in Oman. (*For the management and prevention of diarrhoea and dehydration in children under five years, see MOH guidelines*).

1: Gastro-intestinal system

1 D.1: Oral rehydration therapy (ORT)

Oral rehydration salt (ORS)

Indication: oral replacement of water and electrolyte in acute diarrhoea.

Cautions and Contraindications: ORS should be used with caution in patients with heart failure, hypertension and diabetes.

Side-effects: rarely hypernatraemia, which is very brief and clinically not very important. If puffiness of the eyes occurs, ORS should be stopped until it disappears.

Dose and content: ORS comes in sachets that are ready to be reconstituted, each in 200 ml of drinking water. Each sachet contains, anhydrous dextrose 2.70 g, sodium chloride 0.52 g, trisodium citrate dihydrate 0.58 g and potassium chloride 0.30 g.

The volume of the ORS to be taken is determined by the patient's body weight and degree of dehydration. The objectives are to replace lost fluids and salts and to compensate for subsequent losses. Mild to moderate dehydration requires the following ORT.

Rehydration phase

Mild dehydration: 50 mL/kg administered within 4-6 hr.

Moderate dehydration: 100 mL/kg administered within 4-6 hr.

Maintenance phase

Mild diarrhoea: 100 mL/kg/day until diarrhoea stops.

Severe diarrhoea: Replace stool losses volume for volume, or give 10-15 mL/kg/ hr.

Preparations

ORS sachets, 4.1 g/ sachet

1 D.2: Agents that reduce motility

Opioid derivatives and loperamide are drugs used to reduce intestinal motility and hence help in reducing the frequency of diarrhoea. **These drugs have no place in the management of diarrhoea in children under 5 years.**

Though they reduce stool frequency, these drugs do not prevent dehydration; in fact they obscure the size and seriousness of dehydration.

Loperamide hydrochloride

Indications: adjunct to rehydration in acute and chronic diarrhoea in adults and in acute diarrhoea in over 5 yrs. children.

Contraindications: hypersensitivity to loperamide products, in conditions such as active ulcerative colitis or antibiotic-associated colitis.

Side-effects: abdominal cramp, skin rash, drowsiness, dry mouth.

Dose: acute diarrhoea, adult 4 mg followed by 2 mg after each loose stool, do not exceed 16 mg daily; Child over 5 years only (6-8 yrs) 2 mg bid, (8-12 yrs) 2 mg 3 times daily.

1: Gastro-intestinal system

Chronic diarrhoea, 4-8 mg daily in 2 divided doses. Maintenance according response.

Preparations

Loperamide capsules, 2 mg cap

1 D.3: Treatment of chronic diarrhoea

Tumours should be excluded before managing chronic diarrhoea. Management includes appropriate diet or exclusion of certain foods, maintenance of adequate fluid intake and drug therapy. Conditions associated with chronic diarrhoea are among others, irritable bowel syndrome, ulcerative colitis, Crohn's disease, diverticular disease, mal-absorption syndrome, and Pseudo- membranous colitis. Aminosalicylate compounds, corticosteroids and cholestyramine are drugs of use in chronic diarrhoea-management.

1 D.3.1: Aminosalicylate compounds.

Mesalazine

Indications: treatment of mild to moderate ulcerative colitis and maintenance of remission.

Contra-indications: severe renal and hepatic impairment, salicylates hypersensitivity.

Cautions: elderly, pregnancy, breast-feeding, check blood count

(risk of blood dyscrasias), check renal function regularly.

Side-effects: headache, flatulence, abdominal pain, diarrhoea, nausea, alopecia, rash, blood disorders.

Dose: orally, dose is up to 4g in divided doses to control an acute attack. Maintenance dose is usually 1.5g daily in divided doses. By enema, 1g at bedtime.

Preparations

Mesalazine tablets, 500 mg tab.

Mesalazine enema, 1 g/100 mL pack

Olsalazine sodium (Restricted)

Indications: induction and maintenance of remission in ulcerative colitis.

Contraindications: salicylates hypersensitivity.

Cautions: avoid during pregnancy, breast-feeding. Blood should be regularly checked as blood disorders may occur.

Side-effects: diarrhoea, headache, nausea, exacerbation of colitis, haematological disorders.

Dose: 1 g daily in divided doses after meals. Increase, after one week, to a maximum of 3 g daily in divided doses (max single dose = 1 g).

Maintenance dose: 500 mg twice daily after meals.

Preparations

Olsalazine sodium capsules, 250 mg cap.

1: Gastro-intestinal system

Sulfasalazine (Sulphasalazine)

Indications: mild to moderate ulcerative colitis and maintenance of remission; colonic Crohn's disease.

Contraindications: Sulphonamide hypersensitivity, blood disorders.

Cautions: hepatic and renal failures; G6PD deficiency. There is a risk of haematological disorders, which necessitate a regular blood examination.

Side-effects: diarrhoea, headache, nausea, exacerbation of colitis, haematological disorders, tinnitus, rash, ocular complications, vertigo.

Dose: 1-2 g 4 times/day, maintenance dose 500 mg 4 times/day.

Preparations

Sulfasalazine tablets, 500 mg tab.

1 D.3.2: Corticosteroids

Local corticosteroids are applied in diarrhoea due to acute ulcerative colitis in the forms of enemas, suppositories or foam preparations.

Prednisolone sodium metasulphobenzoyate

Indications: ulcerative colitis, Crohn's disease.

Contra-indications, cautions, and side-effects: (see hydrocortisone sec. 6)

Dose: rectal, one rectal enema daily at bed time for 2-4 weeks.

Preparations

Prednisolone sodium metasulphobenzoyate retention enema, 20 mg/100 mL enema

1 E: Laxatives

Constipation is a condition in which the passage of hard stool is less frequently than the patients' own normal pattern. Constipation should be investigated to exclude being secondary to an underlying undiagnosed complaint. It can be prevented and treated with a combination of adequate exercise, a high fibre diet, and occasionally by appropriate laxative.

Laxatives are indicated when straining may be dangerous (as in angina), in painful anal conditions, in drug induced constipation, prior to GI surgery or radiology and other conditions. The abuse of laxatives could lead to atonic colon and dependence; dependence on laxatives is a common cause of constipation. Bowel movement habit varies among people and constipation should be considered when a patient's bowel movement deviate from normal.

Laxatives are classified, depending on their mechanism of actions, into:

- Bulk forming laxatives
- Stimulant laxatives
- Osmotic laxatives
- Faecal softeners

1: Gastro-intestinal system

1 E.1: Bulk forming laxatives

Bulk forming laxatives increase the faecal mass and hence stimulate peristalsis. They consist of hydrophilic colloids or indigestible vegetable fibres that promote large soft stool by holding water in the bowel lumen. Bran, methylcellulose, sterculia and ispaghula husk are bulk laxative preparations.

Indications: constipation due to inadequate dietary intake of fibre, in patients with colostomy, ileostomy, haemorrhoids. They are also of use in patients with chronic diarrhoea associated with irritable bowel syndrome (IBS), diverticular disease and ulcerative colitis.

Cautions: patients should be instructed to take adequate amount of fluids.

Contra-indications: in patients with intestinal obstructions, atony of the colon or faecal impaction.

Ispaghula husk

Indications: *see* notes above; hypercholesterolaemia.

Contraindications, cautions: *see* notes above.

Side-effects: flatulence, abdominal distension, GI obstruction or impaction. Hypersensitivity has been reported.

Dose: 3.5 g powder of 90% ispaghula husk once or twice daily with water preferably after meal.

For children above 6 years, one or half a 5 mL spoonful daily.

Preparations

Ispaghula husk powder, 3.5 g/sachets

1 E.2: Stimulant laxatives

This group of laxatives increases motility by stimulating the sensory nerves of the colon and promote the accumulation of water and electrolytes in the colonic lumen. Their main use is for constipation and for the evacuation of the bowel prior to surgery, X-ray and endoscopy. Bisacodyl, glycerol and sodium picosulphate are used in different dosage formulations.

They should be avoided in intestinal obstruction. Chronic use may lead to atonic non-functional colon and hypokalaemia.

Bisacodyl

Indication: constipation, colonic evacuation.

Contra-indications: abdominal pain, appendicitis, intestinal obstruction.

Side-effects: abdominal discomfort.

Dose: 5-10 mg at night. Avoid taking with milk or antacids. Tablets take 10-12 hours to act. Suppositories act within 30-60 min.

Preparations:

Bisacodyl tablets, 5 mg tab

Glycerin suppositories

Indications: constipation.

1: Gastro-intestinal system

Contra-indications: hypersensitivity to glycerin, severe dehydration.

Cautions: hypovolumic and elderly patients.

Side-effects: local irritation, abdominal pain.

Dose: suppositories are moulded for use in infants, children and adults. The suppository should be moistened with water before use. They contain 0.9-2.5 g of glycerin.

Preparations

Glycerin child suppository, 0.9-2 g supp.

Glycerin adult suppository, 1.8-2.5 g supp.

Sodium picosulfate (Sodium picosulphate) + Magnesium citrate (Restricted)

This laxative preparation contains sodium picosulphate, which is a stimulant laxative and magnesium citrate, which is an osmotic laxative that traps water and electrolytes to provide a wash-out effect.

Indications: constipation; bowel evacuation before surgery or endoscopy.

Contra-indications: GI obstruction; renal impairment.

Side-effects: headache, tiredness, nausea, griping and anal pain.

Dose: adult and child over 7 years, one sachet dissolved in water before breakfast one day prior to examination, repeat 6-8 hours later.

Preparations

Sodium picosulfate and magnesium citrate powder

1 E.3: Osmotic laxatives

Osmotic laxatives trap water in the bowel by osmosis. A phosphate enema is useful in bowel evacuation. Lactulose, a semi-synthetic disaccharide, is not absorbed from the gastro-intestinal tract. It causes osmotic diarrhoea with low pH due to lactic acid production, and inhibits the proliferation of ammonia-producing organisms. It is useful in hepatic encephalopathy.

Lactulose

Indications: constipation (it takes 2 days to show effect), hepatic encephalopathy.

Contra-indications: intestinal obstruction, galactosaemia.

Side-effects: flatulence, abdominal pain, bloating.

Dose: lactulose preparations contain 3.2-3.7 g/5 mL.

For constipation in adults, 15 mL twice daily adjusted according to patient's need.

Child, 5-10 yrs. 10 mL twice daily. For hepatic encephalopathy, 30-50 mL, 3 times daily, adjust to produce 2-3 soft stools daily.

Preparations

Lactulose syrup, 3.35 g/5 mL syrup

Sodium acid phosphate enema (Restricted)

1: Gastro-intestinal system

Indications: constipation; bowel evacuation before surgery or endoscopy.

Contra-indications: acute GI conditions; renal failure, congestive heart failure.

Side-effects: local irritation, oedema, hypotension.

Dose: sodium acid phosphate enema is prepared by dissolving 12.8 g sodium acid phosphate and 10.24 g sodium phosphate in 128 mL water.

Adult: 128 mL enema as needed

Child: 5 mL enema as needed

Preparations

Sodium acid phosphate enema, 128 - 133 mL enema

Sodium acid phosphate enema, 5 mL enema

Contra-indications: children.

Side-effects: anal irritation due to seepage of oil, granulomatous reactions, lipid pneumonia, and interference with fat-soluble vitamins absorption.

Dose: 10-30 mL at night as required.

Preparations

Liquid paraffin syrup, 100 mL syrup

1 E.5: Bowel cleansing solutions

Bowel cleansing solutions should not be routinely used as a laxative for constipation. They are used before colonic surgery, colonoscopy or radiological examination to ensure the bowel is free of solid contents.

1 E.4: Faecal softeners

Mineral oils such as liquid paraffin are indigestible and absorbed to a limited extent. They penetrate and soften the stool and may interfere with water absorption.

Adverse effects: leakage of oil past the anal sphincter leading to irritation, chronic use may lead to malabsorption of fat-soluble vitamins and drugs, lipid pneumonia consequent to aspiration of oil droplets can result after oral use.

Liquid Paraffin

Indications: constipation.

Caution: avoid prolonged use.

PEG 3350 + sodium chloride + sodium bicarbonate + potassium chloride + anhydrous sodium sulphate (Restricted)

PEG=polyethylene glycol

Indications: see notes above.

Contra-indications: GI obstruction, GI ulceration, perforated bowel, congestive cardiac failure.

Cautions: Pregnancy; heart diseases; ulcerative colitis, diabetes mellitus; reflex oesophagitis; in the presence of a possibility of regurgitation or aspiration.

Side-effects: nausea and vomiting; bloating.

1: Gastro-intestinal system

Dose: each powder sachet contains: PEG 3350 59 g, anhydrous sodium sulphate 5.68 g, sodium bicarbonate 1.685 g, sodium chloride 1.46 g, potassium chloride 743 mg. Each sachet is dissolved in water to one litre.

Adult, 250 mL of reconstituted solution every 10-15min. or by nasogastric tube 20-30 mL/min.

Child, not recommended.

Preparations

PEG 3350 59 g + anhydrous sodium sulphate 5.68 g + sodium bicarbonate 1.685 g + sodium chloride 1.46 g + potassium chloride 743 mg oral powder sachet

1 F: Ano-rectal preparations

Patients with haemorrhoids, fistula or proctitis may suffer from anal and perianal pruritis. These symptoms are best treated with plain ointment that contains astringents, local anaesthetics, lubricants, mild antiseptics or heparinoids. Local anaesthetics are useful in relieving pain but should not be used chronically as they may sensitise the anal skin. Diets with bulky residues are also helpful.

In proctitis, the above measures may supplement treatment with corticosteroids or aminosalicylates. Corticosteroid-containing ointments or creams are useful for the treatment of perianal regions provided that infections are excluded.

Corticosteroid suppositories are used to relieve inflammation of proctitis.

1 F.1: Local anaesthetic containing preparations

Lidocaine (lignocaine) 5% (Restricted)

Indications: to relieve pain associated with haemorrhoids and pruritus ani. It should be used before defaecation to relieve pain associated with anal fissure.

Cautions: excessive use should be avoided, as absorption is possible from rectal mucosa. In infants and children the use should be for a short (2-3 days) period.

Application: locally once or twice daily.

Preparations

Lidocaine ointment, 5%; 15-35 g/tube

1 F.2: Rectal Sclerosants

Oily phenol injection is administered into the tissue around internal haemorrhoids as an analgesic sclerosing agent.

Phenol 5% in almond oil (Restricted)

Indications: haemorrhoids.

Side-effects: irritation and tissue necrosis.

Preparations

Oily phenol injection, 5%, 5 mL ampoule

1F.3: Miscellaneous combinations

A variety of combinations made of corticosteroids, local anaesthetics and soothing agents are available for use in the treatment of haemorrhoids. They are suitable for occasional short-term use after exclusion of infections. Haemorrhoids in children are rare.

Anti-haemorrhoidal cream/ointment and suppositories

Preparations

Anti-haemorrhoidal ointments and suppositories

Contents: benzyl benzoate, bismuth oxide, bismuth subgalate, Peru balsam, zinc oxide

Or

Contents: Cinchocaine HCl and hydrocortisone

1 G: Drugs affecting gastrointestinal secretion

1 G.1: Digestive enzyme preparations

Pancreatin is orally supplemented to patients with total or partial absence of exocrine secretion in cystic

fibrosis and following pancreatectomy, total gastrectomy or chronic pancreatitis. Pancreatin assists in the digestion of fat, protein and starch. Pancreatin is inactivated by gastric acidity. Enteric-coated preparations are therefore used, or the drug can be taken alongside with antacids or immediately before meals. Pancreatin preparations should be protected from heat as they tend to be destroyed. Pancreatin has irritating effects on the buccal mucus, and should not be retained in the mouth for long. The most frequent side-effects are GI irritation including nausea, vomiting and abdominal discomfort.

Pancreatin (C.D.L)

It is a mixture of digestive enzymes, such as amylase, protease, and lipase. The preparations are of porcine origin.

Indication, cautions and side-effects: *see* notes above

Preparations

Pancreatin capsules containing, protease 430 unit, lipase 8000 unit, amylase 9000 unit in a capsule

Pancreatin capsules, 25,000 units cap. containing, protease 1000 unit, lipase 25000 unit, amylase 18000 unit in a capsule

pancreatin micro granules, providing: protease 200 units, lipase 5000 units, amylase 3600 units per 100 mg/20 g container

1: Gastro-intestinal system

1 G.2: Drugs affecting biliary composition and flow

Ursodeoxycholic acid

Indications: dissolution of the gallstones, primary biliary cirrhosis.

Contra-indications: radio-opaque stones, pregnancy, non-functioning gall bladder, inflammatory diseases and other conditions of the small intestine, colon and liver which interfere with entero-hepatic circulation of bile salts.

Cautions: liver disease.

Side-effects: nausea, vomiting, diarrhoea; gallstone calcification; pruritus.

Dose: Dissolution of gallstones, 8–12 mg/kg daily as a single dose at bedtime or in two divided doses, for up to 2 years; treatment is continued for 3–4 months after stones dissolve.

Primary biliary cirrhosis, 10–15 mg/kg daily in 2–4 divided doses.

Preparations

Ursodeoxycholic acid capsules, 250 mg cap.

Ursodeoxycholic acid suspension, 250 mg/5 mL, 250 mL bottle

Section 2: Cardiovascular system

- Positive inotropic drugs
- Diuretics
- Anti-arrhythmic drugs
- Beta-adrenoceptor blocking agents
- Antihypertensive therapy
- Nitrates and vasodilators
- Calcium channel blocking agents
- Sympathomimetics
- Coagulants
- Anticoagulants and protamine
- Antiplatelet drugs
- Fibrinolytic drugs
- Anti-fibrinolytics
- Lipid lowering drugs
- Local sclerosants
- Blood products

2 A: Positive inotropic drugs

Positive inotropic drugs increase the force of contraction of the myocardium.

2 A.1: Cardiac glycosides

All cardiac glycosides are selective and potent inhibitors of the active transport of Na^+ and K^+ across the cell membrane. They have a positive inotropic effect, which is the result of increased cytosolic Ca^{++} availability during systole. In addition, cardiac glycosides depress myocardial conductivity, slow

down heart rate and atrio-ventricular conduction, decrease ventricular response in atrial fibrillation, and potentiate vagal effect on the heart. Therapeutically, they are useful in heart failure to improve ventricular filling and increase cardiac output. Other uses include, slowing of the ventricular rate in AF (atrial fibrillation) and flutter, increasing vagal tone in PSVT (paroxysmal supra-ventricular tachycardia).

Digoxin is the most commonly used cardiac glycoside. It can be given orally and intravenously. Orally, it is well absorbed and mainly excreted unchanged. Renal impairment will prolong its plasma availability and hence its effect and toxicity. Most cases of heart failure do not require a loading dose; oral therapy is usually sufficient with a daily dose of 0.25 - 0.5 mg to reach a therapeutic plasma level within 1-2 weeks. When a rapid response is needed, digoxin may be given by intravenous infusion in a digitalizing dose of 0.5-1 mg, preferably in 50 mL over a period of 2 hours.

Maintenance doses need to be administered once daily since the digoxin half-life is long (36-48 hr). The plasma concentration of digoxin alone is not enough to predict toxicity, as the sensitivity of the myocardium and conducting system to digoxin varies among patients. A good knowledge of toxicity signs and careful monitoring are essential. In the elderly, care

2: Cardiovascular system

should be practiced in using digoxin since the susceptibility to digoxin toxicity is increased. Treatment of heart failure has been geared toward the use of vasodilators and in particular the ACE-inhibitors, and/or diuretics. Digoxin still has a role to play but its chronic inotropic effect in the presence of sinus rhythm has been debated.

Digoxin

Indications: heart failure and supraventricular arrhythmias especially atrial fibrillation.

Contra-indications: intermittent complete heart block, second degree AV block, supra ventricular arrhythmias caused by Wolff-Parkinson-White syndrome, hypertrophic obstructive cardiomyopathy.

Cautions: in hypokalaemia; recent infarction; thyroid dysfunction; elderly and renal impairment; avoid rapid IV administration; pregnancy.

Side-effects: are frequent and may be serious; mainly associated with over dosage; fatigue; visual disturbances; anorexia; nausea and vomiting; headache; arrhythmias; heart block.

Dose: oral, rapid digitalization, 1 - 1.5 mg over 24 hours in divided doses.

Slow digitalization, 250 - 500 microgram daily for 1-2 weeks.

Maintenance, 62.5-500 microgram daily according to renal function and, in atrial fibrillation, on heart-rate response.

Preparations

Digoxin tablets, 250 micrograms tab.

Digoxin tablets, 62.5 micrograms tab.

Digoxin paediatric elixir, 50 micrograms/mL elixir; 60 mL bottle

Digoxin injection, 250 micrograms/mL ; 2 mL ampoule

2 A.2: Phosphodiesterase Inhibitor

Milrinone (CDL)

Indications: treatment of patients with acute decompensated heart failure after failure of conventional maintenance therapy.

Contra-indications: hypersensitivity to the drug.

Cautions: obstructive valvular heart disease, monitor ECG, heart rate, blood pressure, central venous pressure, electrolytes and renal status, pregnancy, breastfeeding.

Side-effects: arrhythmias, hypotension, chest pain, tremor, bronchospasm and anaphylactic shock.

Dose: by intravenous injection, 50 microgram/kg over 10 minutes followed by intravenous infusion at rate of 375-750 nanogram/kg/minute. Dosage should not exceed 1.13 mg/kg/day and duration of therapy depends on patient responsiveness.

Preparations

Milrinone injection, 1 mg/mL, 10 mL ampoule

2 B: Diuretics

Diuretics are drugs employed to increase the output of water and sodium. They are useful in relieving oedema caused by cardiac, renal or hepatic diseases. They are also useful in treatment of hypertension either alone or in combination with other antihypertensive drugs. They are classified in this section into:

- Thiazide and related diuretics
- Potassium sparing diuretics
- Osmotic diuretics
- Carbonic anhydrase inhibitors

2 B.1: Thiazide and related diuretics

These are moderately potent diuretics that increase sodium excretion in urine due to inhibition of sodium re-absorption at the cortical part of the ascending loop of Henlé near the distal convoluted tubule.

Their chronic use may cause hypokalaemia and patients may show sign of glucose intolerance and hyperglycaemia. They interfere with urate excretion and may cause hyperuricaemia. Thiazide diuretics have an antidiuretic effect in patients with nephrogenic diabetes insipidus through an as yet unknown mechanism.

Indications: Thiazides and related compounds are indicated in the treatment of hypertension, mild car-

diac failure, mild oedema due to renal or hepatic disease, and in some cases of nephrogenic diabetes insipidus.

Contra-indications: Renal and hepatic impairment, pregnancy, hyperuricaemia, severe hypokalaemia

Cautions: May aggravate hypokalaemia, diabetes and gout. Pregnancy, breast-feeding, elderly, hepatic or renal impairment

Side-effects: The most important side effect of thiazides is hypokalaemia which can be prevented or minimized by intermittent use of the drug, increasing dietary intake of potassium, simultaneous use of potassium sparing diuretic. Other effects include, hyperuricaemia, aggravation of diabetes, allergic rashes, disturbances of plasma lipid levels, thrombocytopenia, postural hypotension, impotence (reversible).

Hydrochlorothiazide

Indications: oedema, hypertension
Contra-indications, cautions and side-effects: *see* notes above.

Dose: oedema; Initial dose 50-100 mg once daily, reduce for maintenance.

Hypertension: 25-50 mg daily. 12.5 mg in mild or moderate hypertension

Preparations

Hydrochlorothiazide tablets, 25 mg tab.

2: Cardiovascular system

Metolazone (Restricted)

Indication: oedema, hypertension

Contraindications and side-effects: see notes above.

Cautions: Excessive diuresis when combined with loop diuretics.

Dose: Orally for oedema: 5-10 mg daily, increase according to patients need. Maximum; 80 mg daily.
Orally for hypertension: Initially, 5 mg daily. Maintenance, 5 mg every other day.

Preparations

Metolazone tablets, 5 mg tab.

2 B.2: Loop diuretics

These are highly potent diuretics that increase sodium and water output in urine due to inhibition of sodium and chloride re-absorption at the medullary part of the ascending loop of Henlé. They are effective with as low glomerular filtration rate as 10 mL/min. Hypokalaemia, hypotension and severe dehydration may result from the unguarded use of loop diuretics. An effect will be seen after 1 hr with an oral dose and after 10 minutes with IV administration. Hearing loss may occur with prolonged use or during concomitant use with aminoglycosides. Due to its high potency and large volume of urine produced, frusemide should be administered during the day to avoid disturbing the patient's sleep.

Furosemide (Frusemide)

Indications: Oedema associated with left ventricular failure, congestive heart failure, cirrhosis of the liver and renal disease including nephrotic syndrome, oliguria due to renal failure.

Contra-indications: hypovolaemia, anuria, liver cirrhosis coma, renal failure due to nephrotoxic drugs.

Cautions: Hypotension; dehydration; pregnancy; breast-feeding; prostatic enlargement.

Side-effects: hyponatraemia, hypokalaemia, and hypomagnesaemia; hypotension; GI disturbances. It causes an increased excretion of calcium. Tinnitus and deafness may result from chronic use or with rapid parenteral administration.

Dose: orally, oedema, initially 40 mg daily, reduce to 20 mg daily or 40 mg every other day. Child, 1-3 mg/kg/day, maximum, 40 mg daily. Oliguria, initially 250 mg daily, increase gradually in steps of 250 mg; 250 mg 3-4 times daily, maximum 2 g daily.

By intramuscular or slow intravenous injection, initially 20-50 mg. Child, 0.5-1 mg/kg, maximum daily dose 20 mg.

By intravenous infusion in oliguria, 250 mg-1g at a rate not exceeding 4 mg/min.

Preparations

Furosemide tablets, 40 mg tab.

Furosemide sugar free paediatric liquid, 1 mg/mL, 100 - 150 mL bottle

Furosemide injection, 10 mg/mL, 2 mL ampoule (**Restricted**)
Furosemide injection, 10 mg/mL, 25 mL ampoule (**Restricted**)

2 B.3: Potassium sparing diuretics

These are weak diuretics that cause retention of potassium by interfering with the exchange of potassium with sodium at the distal convoluted tubule. Their action is in part aldosterone dependent.

Spirolactone, which is an aldosterone antagonist, and amiloride, which does not possess this action but acts directly on the tubules, are potassium sparing diuretics. They are used in combination with thiazides or loop diuretics to overcome hypokalaemia and as substitute for a potassium supplement regimen. Potassium sparing diuretics should not be used with ACE-inhibitors because of the danger of severe hyperkalaemia. Spirolactone is useful in hyper-aldosteronism (Conn's syndrome).

Spirolactone

Indications: Oedema and ascites in liver cirrhosis, nephrotic syndrome, primary hyper-aldosteronism

Contra-indications: Elderly; hepatic impairment; renal impairment;

Cautions: pregnancy; breast-feeding; hyperkalaemia; Addison's disease

Side-effects: GI disturbances; impotence; gynaecomastia; menstrual disturbances; headache; confusion; hyperkalaemia; blood disorders.

Dose: In ascites, hyperaldosteronism, and nephritic syndrome, 100-200 mg daily increased to 400 mg as required.

In hypokalaemia or hypertension, 25-100 twice daily

Preparations

Spirolactone tablets, 25 mg tab.
Spirolactone tablets, 100 mg tab.
Spirolactone syrup, 2.5 mg/mL (CDL)

Amiloride (Restricted)

Indications: oedema, in combination with thiazides or loop diuretics to avoid hypokalaemia.

Contra-indications: hyperkalaemia; renal impairment;

Cautions: pregnancy; breast-feeding; hyperkalaemia; elderly, diabetes mellitus

Side-effects: GI disturbances, dry mouth, rash, hyperkalaemia, hypotension.

Dose: If used alone: 5 mg twice daily or 10 mg once daily, adjust according to response, maximum 20 mg daily.

For combined diuretic therapy: 5-10 mg daily.

Preparations

Amiloride tablets, 5 mg tab.

2: Cardiovascular system

2 B.4: Osmotic Diuretics

These agents are freely filtered by the glomeruli with limited reabsorption by the renal tubules. The resultant increase of solute in the renal tubule will lead to an increase in urine volume. Mannitol is a widely used osmotic diuretic. Therapeutically, it is used to reduce intracranial or intraocular pressure. It is also used to promote diuresis in acute drug poisoning.

Mannitol

Indications: intracranial / intraocular hypertension, cerebral oedema, to induce diuresis in acute poisoning.

Contra-indications: pulmonary oedema, congestive heart failure.

Cautions: renal impairment; avoid extravasation (causes inflammation thrombophlebitis). Monitor urine output and electrolyte balance

Side-effects: chills, fever

Dose: Cerebral oedema, intracranial / intraocular hypertension: 1-2 g/kg intravenous infusion over 30-60 min.

Other uses: 1-2 g/kg IV infusion over 24 hr.

Preparations

Mannitol intravenous Infusion, 20% solution, 500 mL bottle

2 B.5: Carbonic anhydrase inhibitors

These are weak diuretics that are mainly used for the treatment of glaucoma and not used for their diuretic effect. They reduce the aqueous humor production through inhibition of the carbonic anhydrase enzyme. Acetazolamide, the main drug in this group, is administered orally or by injection. It is a sulphonamide derivative.

Acetazolamide

Indications: reduction of intraocular pressure in open-angle glaucoma, secondary glaucoma, and peri-operatively in angle-closure glaucoma.

Contra-indications: Electrolyte disturbances; severe hepatic impairment; renal impairment; sulphonamide sensitivity

Cautions: Avoid prolonged use; elderly; pregnancy; breast feeding, avoid extravasation at injection site (danger of necrosis), pulmonary obstruction

Side-effects: taste disturbances, nausea, vomiting, diarrhoea, paraesthesia, flushing, headache, fatigue, depression, metabolic acidosis and electrolyte disturbances, blood disorders, skin disorders

Dose: 0.25-1 g daily in divided doses, oral or by intravenous injection

Preparations

Acetazolamide tablets, 250 mg tab.
Acetazolamide injection, powder
for reconstitution, 500 mg vial.

2 C: Anti-arrhythmic Drugs

Arrhythmias are abnormalities in the cardiac rate, rhythm, or site of origin and conduction of cardiac impulse. Management of an arrhythmia requires precise diagnosis of the type of arrhythmia, and electrocardiography is essential. Drugs that modify the cardiac electrophysiology have a narrow margin between the dose for a desired effect and those associated with the adverse effects. More over, the adverse effects from anti-arrhythmic drugs may include the induction of new arrhythmias with possibly fatal consequences. Non pharmacological treatments, such as cardiac pacing and electrical defibrillation are indicated for some arrhythmias; for other cases no therapy is required though an arrhythmia is detected (see below). Treatment depends on the rate of arrhythmia and the underlying cause.

2 C.1: Drugs used for supra-ventricular and ventricular arrhythmia

a) Supraventricular premature contractions (Ectopic beats) are frequently benign. If spontaneous with normal heart, no treatment is

required. Reassurance and abstinence from tobacco, caffeine, and alcohol is often all that is needed. If the condition is troublesome, small doses of beta-blockers can be used.
b) Paroxysmal supraventricular tachycardia (PSVT) is a common arrhythmia and may occur in the absence of any detectable cardiac disease. The fast heart rate tends to start and stop suddenly and may last anywhere from a few minutes to many hours.

Sedation, vagotonic manoeuvres or Valsalva manoeuvre can treat attacks. If these manoeuvres do not work, intravenous digoxin, verapamil, adenosine or beta-blockers may be used. If drug therapy fails, cardioversion (delivery of an electrical shock) can be tried. Prevention is more difficult than treatment and drugs such as beta-blockers, verapamil or digoxin are useful alone or in combination.

c) Atrial flutter and fibrillation are very fast electrical discharge patterns that the atria contract extremely rapidly, thus causing the ventricles to contract faster and less efficiently than normal.

Atrial flutter is usually caused by organic heart disease. Conversion to normal sinus rhythm is best achieved by low energy cardioversion. Alternatively, amiodarone may be used to restore, and amiodarone and sotalol to maintain sinus rhythm. Anticoagulant therapy should be considered if the condition is long-standing.

2: Cardiovascular system

Atrial fibrillation usually occurs in association with organic heart disease. It may be caused by thyrotoxicosis. The ventricular rate can be controlled with digoxin. If adequate control cannot be achieved readily a beta-blocker or verapamil can be added. Anticoagulants are indicated for patients at risk. Aspirin is less effective than warfarin at preventing emboli but may be appropriate if there are no other risk factors for stroke.

Adenosine (Restricted)

Indications: paroxysmal supra-ventricular tachycardia

Contra-indications: second and third degree AV block and sick sinus syndrome, asthma

Cautions: atrial fibrillation or flutter; heart transplant

Side-effects: arrhythmias, facial flush, dyspnoea, and bronchospasm, choking sensation

Dose: By rapid intravenous injection, 3 mg over 2 seconds with cardiac monitoring; if necessary followed by 6 mg after 1-2 minutes, and then by 12 mg after a further 1-2 minutes.

Preparations

Adenosine injection, 3 mg/mL, 2 mL ampoule.

Amiodarone hydrochloride (Restricted)

Indications: resistant cases of supraventricular and ventricular arrhythmias; Wolff-Parkinson-White

syndrome. Treatment should be initiated in hospital under specialist observation.

Contra-indications: sinus bradycardia, sino-atrial heart block, thyroid dysfunction; pregnancy and breast feeding; iodine sensitivity; Avoid intravenous injection in severe respiratory failure, circulatory collapse, severe arterial hypotension.

Cautions: heart failure; regular tests of liver and thyroid functions; renal impairment, elderly.

Regular check of the eye during long-term therapy.

Side-effects: reversible corneal microdeposits, peripheral neuropathy and myopathy, photosensitivity, hypotension, bradycardia, thyroid dysfunction, hepatitis, nausea and vomiting, metallic taste, tremor, vertigo, impotence, insomnia, fatigue

Dose: orally: 200 mg 3 times daily for one week reduce to 200 mg twice daily for further 1-2 weeks. Maintenance, 200 mg daily or titrated as needed to control arrhythmia.

Intravenous infusion via caval catheter 5 mg/kg over 20-120 minutes with ECG monitoring, maximum daily 1.2g

Preparations

Amiodarone HCl injection, 50 mg/mL, 3 mL ampoule

Amiodarone HCl tablets, 200 mg tab.

Flecainide acetate (Restricted)

Indications: supra ventricular and ventricular arrhythmias.

Contra-indications: heart failure; history of myocardial infarction; long standing atrial fibrillation.

Cautions: patients with pacemakers; avoid in sinus node dysfunction; elderly; hepatic and renal dysfunction.

Side-effects: Arrhythmia, dizziness, visual disturbances, dyspnoea, headache

Dose: orally, 50-100 mg twice daily
Intravenous injection, 2 mg/kg over 10-30 minutes with ECG monitoring

Preparations

Flecainide acetate tablets, 100 mg tab.

Flecainide acetate injection, 10 mg/mL, 15 mL ampoule

2 C.2: Drugs used for ventricular arrhythmias

a) Ventricular premature contraction (ventricular ectopic beats) is an extra heartbeat caused by electrical activation of the ventricles before the normal heartbeat. It does not indicate danger in people who do not have heart disease. On the other hand, if they frequently occur in a patient with heart failure or aortic stenosis, they may be followed by more dangerous arrhythmias such as ventricular fibrillation. Treatment can be carried out with lignocaine or procainamide. Other

drugs include disopyramide or beta-blockers.

B) Ventricular tachycardia (VT) is almost always associated with organic heart disease and is particularly common in acute myocardial infarction (MI). It requires urgent treatment with cardioversion followed by IV infusion of lignocaine. In less urgent cases, lignocaine alone in IV bolus dose of 50-100 mg which can be repeated if arrhythmia is not converted to sinus rhythm.

Lidocaine hydrochloride

Indications: ventricular arrhythmias especially after myocardial infarction.

Contra-indications: sino-atrial disorders, all grades of atrioventricular block.

Cautions: hypersensitivity, lower doses in hepatic impairment.

Side-effects: dizziness, hypotension, mental confusion.

Dose: IV injection: 50-100 mg as bolus dose, repeated after 10 minutes if necessary. Maintenance, intravenous infusion 2-4 mg/minute.

Preparations

Lidocaine hydrochloride injection, 2% prefilled 5 mL syringe (100 mg/syringe).

Lidocaine hydrochloride injection, 2% (20 mg/mL), 50 mL vial.

2: Cardiovascular system

2 D: Beta-adrenoceptor blocking agents (beta-blockers)

Beta-blockers have good efficacy in the treatment of hypertension, ischaemic heart disease, and certain types of arrhythmias. They are also useful in the management of thyrotoxicosis, phaeochromocytoma, somatic symptoms of anxiety and intraocular hypertension. Their main action is through the blockade of beta-receptors in various tissues. Many beta-blockers are available for therapeutic use; they are all equally effective. There are, however, differences between them which may affect choice in treating particular disease or individual patients. Beta blockers can be classified into non-selective and β_1 -selective blockers. Non-selective β -blockers antagonize the sympathomimetic effects of both β_1 and β_2 receptors in many tissues. Blockade of β_2 receptors in the bronchial smooth muscles results in bronchospasm, especially in patients with bronchial asthma. It is worth mentioning that β_1 -selective blockers are cardioselective but not cardiospecific, and they do not show absolute safety in asthmatic patients. Furthermore, Beta-blockers can also be classified according to their membrane stabilizing effects, presence or absence of intrinsic sympathomimetic activity and the extent of their lipid solubility (see table below).

Indications:

Hypertension: Beta-blockers are widely used and effective antihypertensives, but mechanism of action is not fully understood. They reduce cardiac output; alter baroreceptor reflex sensitivity and block peripheral adrenoceptors. It is possible that central effects may also be involved. Beta-blockers have the advantage of causing less postural and exercise induced hypotension.

Beta-blockers may be used in combination with thiazide diuretics to achieve better control of hypertension. This combination should not be initiated unless hypertension is not reasonably controlled by beta-blockers or thiazide alone. In phaeochromocytoma, beta-blockers are used to control heart rate. However, they should never be used alone since beta blockade without concomitant use of alpha-adrenoceptor blockers may lead to hypertensive crises.

Ischaemic heart disease: Beta-blockers cause a reduction in cardiac work, activity and oxygen consumption at rest and during exercise or stress. Thus beta-blockers improve exercise tolerance in angina pectoris and reduce the severity and frequency of attacks. The dose required depends on the agent used and the severity of disease. Therapy should always be initiated with small doses and increase it gradually until symptoms are controlled. Abrupt withdrawal could be dangerous as it may lead to exacerbation of angina. Beta-blockers have

also been applied in preventing re-infarction in patients who have suffered an acute myocardial infarction.

Arrhythmias: Beta-blockers are valuable agents in the management of cardiac arrhythmias principally by attenuating the sympathetic effects on conductivity and automaticity of the heart. These drugs are useful in slowing the ventricular rate in patients with paroxysmal supraventricular tachycardia (PSVT), atrial fibrillation and atrial flutter. They are also effective in treating digitalis induced arrhythmias and those occurring during general anaesthesia. Esmolol, a cardioselective, and sotalol, a nonselective, beta-blocker are mostly used for treatment of arrhythmias.

Thyrotoxicosis: Beta-blockers are used in pre-operative preparation for thyroidectomy. Propranolol can reverse clinical symptoms of thyrotoxicosis without altering the thyroid function.

Other uses: Beta-blockers have been used to reduce somatic symptoms of anxiety such as tremor, palpitation and tachycardia. In migraine, beta-blockers are used for prophylaxis. Topical application of some beta-blockers is effective in reducing raised intra-ocular pressure.

Contra-indications:

Beta-blockers should be avoided in patients with bronchial asthma, hypotension, sinus bradycardia, cardi-

ogenic shock, congestive heart failure (unless it is due to tachyarrhythmia treatable with beta-blockers), intermittent claudication, metabolic acidosis and allergic rhinitis.

Cautions:

Abrupt withdrawal should be avoided. When treatment is to be discontinued, it should be gradually done and the patient should be carefully monitored.

In patients with diabetes, cardioselective agents are preferred, as beta-blockers might mask the warning signs of hypoglycemia.

In the presence of renal or hepatic impairment, selection of a beta-blocker depends on the pharmacokinetics of the individual agent (*see table above*).

Side-effects:

GI disturbances, dizziness, fatigue, cold extremities, hypotension, bradycardia, congestive heart failure, bronchospasm, sleep disturbances, depression, hallucination and skin rash. Side-effects can be minimised by proper selection of patient, drug and the initiation of therapy with small doses.

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Pharmacological properties of beta-blockers

Compound	Daily dose frequency	Gut absorption	Liver metabolism	Relative Lipid solubility	MSA**	ISA*	CNS effects
<i>Non-selective beta-blockers</i>							
Propranolol	2-4	100%	100%	++	+	0	+
Labetalol ***	1-2	100%	80%	—	±	±	±
Sotalol	1-2	100%	1%	—	0	0	±
Carvedilol ***	1-2	100%	100%	++	±	0	+
<i>Selective beta-blockers</i>							
Atenolol	1	50%	—	—	0	0	±
Esmolol	IV only	—	—	—	0	0	—

* ISA = Intrinsic sympathomimetic activity

** MSA= Membrane stabilizing activity

*** Act as α and β -receptor antagonist

2 D.1: Non-selective beta-blockers

In this group, which is a large group, only four beta-blockers are approved for therapeutic use in government institutions in Oman. These are, Propranolol, labetalol, carvedilol and sotalol.

Carvedilol (Restricted)

Indications: hypertension; angina; adjunct to diuretics, ACE-inhibitors or digoxin in symptomatic chronic heart failure.

Contraindications and cautions: *see* notes above. Closely monitor at beginning of therapy or a new dose increase.

Side-effects: *see* note above. Occasionally diminished peripheral circulation, peripheral oedema, dry mouth, dry eye, impotence.

Dose: orally, for hypertension, 12.5 mg once daily increase after 2 days to 25 mg daily, maximum 50 mg in single or divided doses.

Angina: 12.5 mg twice daily, increase to 25 mg twice daily.

Heart failure, start with a very low dose of 3.125 mg twice daily. Increase to 6.25 mg twice daily within two weeks; further increase gradually if necessary to reach a maximum of 25-50 mg twice daily according to patient's body weight. Maximum 25 mg twice daily body weight <85kg; 50 mg twice daily body weight >85kg

Preparations

Carvedilol tablets, 6.25 mg tab.

Carvedilol tablets, 25 mg tab.

Labetalol hydrochloride (Restricted)

Indications: hypertension (including hypertension in pregnancy); hypertensive crises ; phaeochromocytoma

Contraindications and cautions: *see* notes above. .

Side-effects: postural hypotension, tiredness, headache

Dose: Orally, initially 50-100 mg twice daily. Increase to 200 mg twice daily or further at 14 days interval for each step increment. Max. 2.4g daily.

Intravenous injection: 50 mg over 1 minute, repeated if necessary after 5 minutes. Max. 200 mg

Intravenous infusion: 2 mg/minute, maximum 200 mg, higher doses could be used in phaeochromocytoma.

Preparations

Labetalol tablets, 100 mg tab

Labetalol injection, 5 mg/mL, 20 mL ampoule.

Propranolol hydrochloride

Indications: hypertension; angina; arrhythmias, thyrotoxicosis, prevention of re-infarction, migraine prophylaxis

Contraindications and cautions: *see* notes above. With caution in pregnancy, breast feeding, in renal

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and hepatic impairment. In pheochromocytoma, not to be used alone but with an alpha-blocker

Side-effects: *see* note above

Dose: orally, for hypertension, initially 80 mg twice daily, increase as necessary at weekly interval; maintenance 160-320 mg daily.

Angina, initially 40 mg 2-3 times daily; maintenance 120-240 mg daily

Arrhythmias, anxiety tachycardia and thyrotoxicosis, 10-40 mg 3-4 times daily

Anxiety with symptoms of palpitation, sweating, tremor, 40 mg once daily increased if necessary to 3 times daily.

Prophylaxis after myocardial infarction, 40 mg 4 times daily for 2-3 days, then 80 mg twice daily, beginning 5-21 days after infarction

Intravenous injection: In arrhythmias and thyrotoxic crises, 1 mg over a minute, repeat at 2 min. interval. Max 10 mg.

Preparations

Propranolol tablets, 10 mg tab.

Propranolol tablets, 40 mg tab.

Propranolol injection, 1 mg/mL, 1 mL ampoule

Sotalol hydrochloride (Restricted)

Indications: life threatening ventricular arrhythmias

Contra-indications and cautions: *see* notes above. Correct electrolyte imbalance.

Side-effects: *See* notes above

Dose: orally, for arrhythmias, 80 mg daily in 1-2 divided doses. Increase at 2-3 days interval to 160-320 mg daily in 2 divided doses.

Preparations

Sotalol tablets, 80 mg tab.

2 D.2: Selective beta-blockers

Atenolol

Indications: hypertension, angina and arrhythmias.

Contra-indications and cautions: *see* notes above. Reduce dose in renal impairment

Side-effects: *see* notes above.

Dose: orally, for hypertension, 25-50 mg daily (100 mg daily is no more considered necessary)

Angina, 100 mg daily in 1 or 2 divided doses

Arrhythmias, 50-100 mg daily

Preparations

Atenolol tablets, 25 mg tab (**Restricted**)

Atenolol tablets, 50 mg tab.

Atenolol tablets, 100 mg tab.

Bisoprolol (Restricted)

Indications: Hypertension. Angina. Adjunct in heart failure

Contra-indications: Acute or decompensated heart failure requiring intravenous inotropes; sino-atrial block; beta-blockers, including those considered to be cardioselective, should usually be avoided in patients with a history of asthma,

bronchospasm or a history of obstructive airways disease. However, when there is no alternative, a cardioselective beta-blocker can be given to these patients with caution and under specialist supervision. In such cases the risk of inducing bronchospasm should be appreciated and appropriate precautions taken.

Cautions: Ensure heart failure not worsening before increasing dose; Diabetes; first-degree AV block; history of obstructive airways disease (introduce cautiously); myasthenia gravis; portal hypertension (risk of deterioration in liver function); psoriasis; symptoms of hypoglycaemia may be masked; symptoms of thyrotoxicosis may be masked.

Side-effects: Cramp; depression; muscle weakness; alopecia; bradycardia; bronchospasm; coldness of the extremities; conduction disorders; dizziness; dyspnoea; exacerbation of intermittent claudication; exacerbation of psoriasis; exacerbation of Raynaud's phenomenon; fatigue; gastro-intestinal disturbances; headache; heart failure; hyperglycaemia (in patients with or without diabetes); hypoglycaemia (in patients with or without diabetes); hypotension; paraesthesia; peripheral vasoconstriction; psychoses; purpura; sexual dysfunction; sleep disturbances (with nightmares); symptoms of hypoglycaemia masked; thrombocytopenia; vertigo; visual disturbances

Dose: Hypertension. Angina 5–10 mg once daily; maximum 20 mg per day.

Adjunct in heart failure. Initially 1.25 mg once daily for 1 week, dose to be taken in the morning, then increased if tolerated to 2.5 mg once daily for 1 week, then increased if tolerated to 3.75 mg once daily for 1 week, then increased if tolerated to 5 mg once daily for 4 weeks, then increased if tolerated to 7.5 mg once daily for 4 weeks, then increased if tolerated to 10 mg once daily; maximum 10 mg per day.

Preparations

Bisoprolol fumarate tablets, 5 mg tab

Metoprolol (Restricted)

Indications: Hypertension, angina, arrhythmias, migraine prophylaxis, hyperthyroidism (adjunct), surgery, early intervention within 12 hours of infarction

Contra-indications: Asthma; cardiogenic shock; hypotension; marked bradycardia; metabolic acidosis; phaeochromocytoma (apart from specific use with alpha-blockers); Prinzmetal's angina; second-degree AV block; severe peripheral arterial disease; sick sinus syndrome; third-degree AV block; uncontrolled heart failure.

Cautions: Diabetes; first-degree AV block; history of obstructive airways disease (introduce cautiously); myasthenia gravis; portal hypertension (risk of deterioration

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in liver function); psoriasis; symptoms of hypoglycaemia may be masked; symptoms of thyrotoxicosis may be masked.

Side-effects: Dry eyes (reversible on withdrawal); rashes (reversible on withdrawal); Alopecia; bradycardia; bronchospasm; coldness of the extremities; conduction disorders; dizziness; dyspnoea; exacerbation of intermittent claudication; exacerbation of psoriasis; exacerbation of Raynaud's phenomenon; fatigue; gastro-intestinal disturbances; headache; heart failure; hyperglycaemia (in patients with or without diabetes); hypoglycaemia (in patients with or without diabetes); hypotension; paraesthesia; peripheral vasoconstriction; psychoses; purpura; sexual dysfunction; sleep disturbances (with nightmares); symptoms of hypoglycaemia masked; thrombocytopenia; vertigo; visual disturbances.

Dose: Hypertension, orally with immediate-release medicines, initially 100 mg daily, increased if necessary to 200 mg daily in 1–2 divided doses, high doses are rarely required; maximum 400 mg per day. Orally with modified-release medicines, 200 mg once daily. Angina, orally with immediate-release medicines, 50–100 mg 2–3 times a day. Orally with modified-release medicines, 200–400 mg daily.

Arrhythmias, orally with immediate-release medicines, usual dose 50 mg 2–3 times a day, then increased if necessary up to 300 mg

daily in divided doses. By intravenous injection, up to 5 mg, dose to be given at a rate of 1–2 mg/minute, then up to 5 mg after 5 minutes if required, total dose of 10–15 mg.

Migraine prophylaxis, orally with immediate-release medicines, 100–200 mg daily in divided doses. Orally with modified-release medicines, 200 mg daily.

Hyperthyroidism (adjunct), orally with immediate-release medicines 50 mg 4 times a day.

In surgery, by slow intravenous injection, initially 2–4 mg, given at induction to control arrhythmias developing during anaesthesia, then 2 mg, repeated if necessary; maximum 10 mg per course.

Early intervention within 12 hours of infarction, initially by intravenous injection, 5 mg every 2 minutes, to a max. of 15 mg, followed by oral doses of 50 mg every 6 hours for 48 hours. The first oral dose is to be taken 15 minutes after intravenous injection; oral maintenance dose is 200 mg daily in divided doses.

Preparations

Metoprolol tartrate 1 mg per 1 ml solution for injection, 5 mg ampoule

2 E: Antihypertensive therapy

Antihypertensive therapy has reduced the frequency of cardiovascular events associated with hypertension. In Oman, cardiovascular

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diseases are responsible for 30-40% of all deaths.

High blood pressure is a major cause of stroke and significantly contributes to coronary disease. The risk of death increases in proportion to the height of the blood pressure (B.P.) with no clear demarcation when lethal hypertension begins. It follows that early diagnosis and treatment of symptomatic and symptomless hypertension will reduce mortality and help prevent serious health consequences.

Most of the hypertension cases are of no identifiable cause (essential hypertension) and therefore require a life-long treatment regimen. A small percentage of cases can be correlated with a defined cause (secondary hypertension), treating the cause will bring the B.P. back to normal in most conditions.

Non-pharmacological intervention in hypertension should be considered in all cases and may be all that is needed in mild cases. These interventions include:

- weight reduction
- dietary salt restrictions,
- avoiding stress
- no smoking and alcohol
- regular mild exercise

The treatment objectives are to bring B.P. to normal and tolerable level and to reduce associated risk factors. Treatment objectives might be achieved with a single drug or

combination of drugs when necessary with minimal adverse effects. Antihypertensive drugs include:

- Diuretics
- Beta-blockers
- Centrally acting drugs
- Alpha-adrenoceptor blockers
- Angiotensin converting enzyme inhibitors (ACE-Inhibitors)
- Calcium channel blockers
- Vasodilator antihypertensives
- Angiotensin-II receptor antagonists (Angiotensin-II receptor blockers, ARB)

If a drug from the above major classes is ineffective in lowering blood pressure in a given patient, it is advisable to substitute a drug from a different class. If therapy with a single drug is only partly effective, it may be preferable to add a small dose of a second drug from another class rather than increase the dose. Contraindications and cautions to the use of the above drugs should be considered and a proper choice is made (see table on the next page).

2 E.1: Vasodilator antihypertensive Drugs

This group includes potent drugs. They are rarely used alone in the chronic management of hypertension. They are mainly used in cases of hypertensive emergencies where

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they are administered intravenously. Orally they are used as adjunct drugs with other antihypertensives in cases of severe or resistant hypertension. Drugs such as hydralazine, sodium nitroprusside and tolazoline are directly acting vasodilators. They cause reduction in peripheral resistance, increase in heart rate and cardiac output.

Hydralazine

Indications: hypertension, adjunct with other antihypertensive drugs; chronic heart failure, adjunct to long acting nitrates; hypertensive crises

Contra-indications: hypersensitivity to hydralazine, dissecting aortic aneurysm, severe tachycardia

Cautions: hepatic impairment; cerebrovascular disease, check for

acetylator status before increasing the dose.

Side-effects: tachycardia, flushing, palpitation, hypotension, fluid retention

Dose: orally, for hypertension, 25 mg twice daily, increase if necessary to 50 mg twice daily For heart failure, initial dose 25 mg 3-4 times daily, increase gradually to usual dose of 50-75 mg –4 times daily. Intravenous injection, in hypertensive crises with renal complications, 5-10 mg diluted with 10 mL saline, repeated after 20-30minutes.

Preparations

Hydralazine tablets, 25 mg tab.

Hydralazine powder for injection, 20 mg ampoule

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Guidelines for selecting first line drugs for hypertension

Type of drug	Benifical in the following co-morbiddities	Contra-indications	Cautions
Diuretics	Heart failure; Elderly patients; Systolic hypertension	Gout	Diabetes Hyperlipidaemia Pregnancy Sexually active males
Beta Blockers	Angina; After myocardial infarct; Tachyarrhythmias; Pregnancy in the third trimester	Asthma and chronic obstructive airway disease Peripheral vascular disease Heart block	Hypertriglyceridaemia Insulin-dependent diabetes Heart failure Athletes and physically active patients
ACE-inhibitors	Heart failure; Left ventricular hypertrophy; After myocardial infarct; Diabetes with micro-albuminuria	Pregnancy Bilateral renal artery stenosis	Patients on diuretics Idiopathic angioedema
Calcium channel blockers	Angina; Peripheral vascular disease; Elderly patients; Systolic hypertension; Glucose intolerance	Pregnancy Unstable angina	Congestive heart failure Atrio-ventricular heart block
Alpha blockers	Prostatic hypertrophy Glucose intolerance		Orthostatic hypotension
Centrally acting drugs	Asthma; Pregnancy	Depression	Blood disorders
ARB	Heart failure; Renal disease	Cholestasis Biliary cirrhosis	Afro-Caribbean patients; elderly; aortic or mitral valve stenosis; hypotrophic cardiomyopathy; pregnancy; breast feeding.

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Sodium nitroprusside

Indications: hypertensive crises

Contra-indications: severe hepatic impairment; severe vitamin B₁₂ deficiency.

Cautions: hypothyroidism, renal failure, excessive hypotension, methaemoglobinaemia

Side-effects: mainly related to the rapid effect on reducing B.P.; Dizziness, headache, nausea, palpitation

Dose: in hypertensive crises by IV infusion, 0.5-1.5 microgram/kg/minute, adjust by gradual increment of 0.5 microgram/kg/minute every 5 minutes within a range of 0.5-8 micrograms/kg/minute.

Preparations

Sodium nitroprusside injection, 50 mg ampoule

has the advantage of being safe in asthmatics, heart failure and pregnancy.

Methyldopa

Indications: hypertension; hypertension in asthmatics and during pregnancy.

Contra-indications: depression, active liver disease, phaeochromocytoma

Cautions: positive direct Coomb's test in 20% of patients; reduce initial dose in renal dysfunction; regular blood count and liver function test advised

Side-effects: sedation, dry mouth, postural hypotension, systemic lupus erythematosus-like syndrome, haemolytic anaemia

Dose: oral 125-250 mg 2-3 times daily. Gradually increase if necessary to a maximum of 3 g daily in divided doses.

Preparations

Methyldopa tablets, 250 mg tab.

2 E.2: Diuretics

See section 2 B.

2 E.3: Beta-blockers

See section 2 D.

2 E.4: Centrally acting antihypertensives

Methyldopa is a prototype of this group of antihypertensives. It acts centrally through inhibition of sympathetic outflow. It lowers B.P. and peripheral resistance and no effect on reflex vasoconstriction. It

2 E.5: Alpha- adrenoceptor blocking drugs

Alpha adrenoceptor blocking drugs antagonize the sympathomimetic effects on both alpha 1 and 2 receptors. The resulting effects, which are mainly on the cardiovascular system, vary among the different members of the group. Prazosin and related compounds such as alfuzosin, terazosin, doxazosin and tamsulosin have postsynaptic alpha

blocking and vasodilator properties and rarely cause tachycardia. They cause rapid reduction in B.P after the first dose (“the first dose effect”) and should therefore be introduced with caution. Phentolamine and phenoxybenzamine cause peripheral vasodilatation and lowering of B.P. Reflex tachycardia and postural hypotension are limiting factors for their use in the treatment of hypertension. Phenoxybenzamine is used in the treatment of benign prostatic hyperplasia and in the long duration management of hypertension caused by phaeochromocytoma.

Prazosin (Restricted)

Indications: hypertension, benign prostatic hyperplasia

Contra-indications: congestive heart failure due to mechanical obstruction

Cautions: first dose effect may cause serious postural hypotension (advisable to take first dose upon retiring to bed); renal impairment; elderly; pregnancy

Side-effects: drowsiness, headache, lack of energy

Dose: for hypertension, 500 micrograms 2-3 times daily, initial dose at bedtime. Increase after 3-7 days to 1 mg 2-3 times daily, maximum 20 mg daily

Benign prostatic hyperplasia, 500 micrograms twice daily for a week, adjust dose according to response

Preparations

Prazosin hydrochloride tablets, 1 mg tab.

Prazosin hydrochloride tablets, 5 mg tab.

Doxazosin (Restricted)

Indications: see Prazocin

Contra-indications and cautions: see Prazocin.

Side-effects: postural hypotension, vertigo, asthenia, oedema, somnolence

Dose : for hypertension, 1 mg once daily , increase after 1 week to 2 mg once daily and then to 4 mg once daily , if necessary

Preparations

Doxazosin tablets, 1 mg tab.

Doxazosin tablets, 4 mg tab.

Tamsulosin (Restricted)

Indications: See Prazocin Above.

Contra-indications: hypersensitivity to the drug

Cautions: see Prazocin above.

Side-effects: see Prazocin above.

Dose: 400 micrograms daily as a single dose.

Preparations:

Tamsulosin capsules, 400 micrograms cap.

Terazosin (Restricted)

Indications: see Prazocin

Contra-indications and cautions: see Prazocin

Side-effects: peripheral oedema, asthenia, dizziness

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Dose: for hypertension, 1 mg daily at bedtime, increase after 7 days to 2 mg daily, increase if necessary; do not exceed 10 mg daily

Preparations

Terazosin capsules, 2 mg cap.

Alfuzosin

Indications: *see* Prazosin

Contra-indications: *see* Prazosin; severe liver impairment.

Side-effects: flushes, chest pain

Dose: 2.5 mg three times daily, max 10 mg daily; Elderly initially 2.5 mg twice daily.

Preparations

Alfuzosin hydrochloride tablets; 2.5 mg tab

Note: MoH policy is that only one of the above alpha blockers will be purchased and supplied for use based on its cost effectiveness

Phentolamine mesylate (Restricted)

Indications: hypertension; hypertension crises due to pheochromocytoma; diagnosis of pheochromocytoma

Contra-indications: hypotension, history of myocardial infarction, angina

Cautions: blood pressure and heart rate to be monitored during use; renal impairment; peptic ulcer

Side-effects: postural hypotension, tachycardia, dizziness, nasal congestion, diarrhoea

Dose: by intravenous injection, 2-5 mg repeated if necessary

Preparations

Phentolamine mesylate injection, 10 mg/mL ampoule

2 E.6.1: Angiotensin converting enzyme inhibitors

The essential effect of angiotensin converting enzyme inhibitors (ACE inhibitors) on the renin-angiotensin system is to inhibit the conversion of the relatively inactive angiotensin I to the active angiotensin II. They are highly selective in this regard and do not interfere with other component of the rennin-angiotensin system.

There are a good number of ACE inhibitors for use that have similar therapeutic effects. There is no compelling reason to favor one ACE inhibitor over another; since all ACE inhibitors effectively inhibit the conversion of angiotensin I to angiotensin II and all have similar therapeutic indications, adverse effects profiles and contra-indications. With few exceptions, the majority of ACE inhibitors are predominantly cleared by the kidneys. Captopril is a short acting while lisinopril and enalapril are long acting ACE inhibitors approved for use in Oman.

Indications: hypertension, heart failure, myocardial infarction, diabetic nephropathy

Contra-indications: ACE inhibitors are contraindicated in patients with hypersensitivity to ACE inhibitors, and in known or suspected renovascular disease, aortic stenosis or outflow tract obstruction.

ACE inhibitors should not be used in pregnancy.

Cautions: ACE inhibitors should be used with great caution in patients receiving diuretics. The first doses may cause hypotension especially in patients taking diuretics, on a low-sodium diet, on dialysis, dehydrated or with heart failure. Renal function should be monitored before and during treatment. ACE inhibitors have to be avoided in patients with a history of idiopathic or hereditary angioedema. Use with caution in breast-feeding. Avoid using ACE inhibitors with antacids, as they may tend to reduce their bioavailability.

Adverse effects: ACE inhibitors can cause profound hypotension, angioedema; rash, persistent dry cough, upper respiratory symptoms such as sinusitis, sore throat and rhinitis. Hyperkalaemia, acute renal failure and blood disorders have also been reported.

Captopril

Indications: *see notes above*

Contra-indications and cautions: *see notes above*

Side-effects: *see notes above*; tachycardia; weight loss; photosensitivity

Dose: in hypertension, used alone, initial 12.5 mg twice daily (first dose at bedtime). Reduce to 6.25 mg twice daily in elderly or patients receiving diuretics. Maintenance, 25-50 mg twice daily

In heart failure as an adjunct therapy, initially 6.25-12.5 mg, maintenance, 25 mg 2-3 times daily

For prophylaxis after infarction, initially 6.25 mg starting as early as 3 days after infarction, increase as needed over several weeks to 150 mg daily in divided doses.

Preparations

Captopril tablets, 25 mg tab.

Captopril suspension 1 mg/ml (CDL)

Enalapril

Indications: *see notes above*

Contra-indications and cautions: *see notes above*

Side-effects: *see notes above*; tachycardia; cerebrovascular accidents; angina; chest pain; anorexia; confusion; mood changes; impotence; skin disorders; blood disorders

Dose: in hypertension, used alone, initial 5 mg once daily. Reduce to 2.5 mg daily in elderly or patients receiving diuretics. Maintenance, 10-20 mg once daily

Preparations

Enalapril maleate tablets, 5 mg tab.

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Enalapril maleate tablets, 20 mg tab.

Lisinopril

Indications: *see* notes above

Contra-indications and cautions:
see notes above

Side-effects: *see* notes above; tachycardia; cerebrovascular accidents; dry mouth; confusion; mood changes; impotence

Dose: for hypertension, used alone, initial 10 mg daily. Maintenance, 10-20 mg daily. Maximum, 40 mg daily, reduce the dose if used in addition to diuretic

In heart failure as an adjunct therapy, initially 2.5 mg. Maintenance, 5-20 mg daily

For prophylaxis after infarction, the B.P. is a determining factor for the dose regimen. Systolic B.P. over 120mmHg, 5 mg daily for 3 days and then 10 mg daily. Systolic B.P. 100-120mmHg, 2.5 mg daily increased to 5 mg daily

Preparation

Lisinopril tablets, 5 mg tab.

Lisinopril tablets, 10 mg tab.

Note: MoH policy is that only one of the above ACE I inhibitors, enalapril or lisinopril, will be purchased and supplied for use based on its cost effectiveness

2 E.6.2: Angiotensin II receptor antagonists (Angiotensin II Receptor Blockers {ARB})

Therapeutically, angiotensin II receptor antagonists are as effective as ACE inhibitors. They do not cause the persistent dry cough or dry mouth, which are common with ACE inhibitors.

Valsartan (Restricted)

Indication: hypertension

Contra-indications: hepatic impairment; biliary obstruction

Cautions: renal artery stenosis, renal impairment, pregnancy, breast-feeding.

Side-effects: hypotension; fatigue

Dose: usually 80 mg once daily. Reduce in elderly, renal and hepatic impairment or intravascular volume depletion to 40 mg once daily. Increase if necessary after 3-4 weeks to 160 mg daily (80 mg daily in hepatic impairment)

Preparations

Valsartan capsules, 80 mg caps

Valsartan capsules, 160 mg caps

2 F: Nitrates and other vasodilators

2 F.1: Nitrates

Nitrates are vasodilators that are useful in the management of angina. They induce vasodilatation of coronary arteries leading to increased coronary blood flow. In addition, they induce venodilatation that leads to reduced venous return which consequently reduces ventricular filling pressure, myocardial

work and oxygen consumption. Arteriolar dilatation reduces vascular resistance and myocardial work. Sublingual glyceryl trinitrate (GTN) tablets are no longer used in Oman. They are replaced by isosorbide dinitrate 5 mg tablets. Transdermal GTN preparations are used for a prolonged effect. Isosorbide dinitrate is a more stable nitrate for oral use. It has a slower onset and a longer duration that could last up to 12 hours in modified release preparations.

Tolerance.

Tolerance may develop to the effects of nitrates with the continuous use of long-acting preparations such as the transdermal patches.

If tolerance is suspected then patients should leave patches off for several hours in a 24 hour period or if on a modified release preparation of isosorbide dinitrate tablets patients should take the second of their two daily doses after about 8 hours rather than 12 hours.

Glyceryl trinitrate

Indications: prophylaxis and treatment of angina

Contra-indications: hypersensitivity to nitrates; hypotension; severe anaemia

Cautions: severe hepatic or renal impairment; malnutrition and hypothermia; recent history of myocardial infarction

Side-effects: postural hypotension, throbbing headache, flushing

Dose: intravenous infusion, 10 – 200 microgram / minute.

Patches, Apply one patch to lateral chest wall or upper arm. Replace after 24 hours on a different area.

Preparations

Glyceryl trinitrate injection, 5 mg/mL, 10 mL ampoule

Glyceryl trinitrate injection, 1 mg/mL, 50 mL ampoule

Glyceryl trinitrate transdermal patch, 25 mg patch

Glyceryl trinitrate spray, 0.4 mg / dose, 200 dose spray

Isosorbide dinitrate

Indications: prophylaxis and treatment of angina; left ventricular failure

Contra-indications, cautions and side-effects: see notes under glyceryl trinitrate

Dose: Oral in divided doses: for angina, 30-120 mg daily; for left ventricular failure, 40-160 mg up to 240 mg if necessary.

Preparations

Isosorbide dinitrate tablets, 5 mg sublingual tab.

Isosorbide dinitrate tablets, 10 mg tab.

Isosorbide dinitrate tablets, 40 mg S.R. tab.

2 F.2: Other vasodilators

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Papaverine (Restricted)

Indications: vasodilator, erectile dysfunction (see sec. 7D.4)

Side-effects: hypotension

Preparations

Papaverine injection, 30 mg/mL; 2 mL ampoule

Ivabradine (Restricted)

Indications: Treatment of angina in patients in normal sinus rhythm. Mild to severe chronic heart failure

Contra-indications: Acute myocardial infarction; cardiogenic shock; congenital QT syndrome; do not initiate for angina if heart rate below 70 beats per minute; do not initiate for chronic heart failure if heart rate below 75 beats per minute; immediately after cerebrovascular accident; patients dependent on pacemaker; second- and third-degree heart block; severe hypotension; sick-sinus syndrome; sinoatrial block; unstable angina; unstable or acute heart failure.

Cautions: Atrial fibrillation or other arrhythmias (treatment ineffective); elderly; in angina, consider stopping if there is no or limited symptom improvement after 3 months; intraventricular conduction defects; mild to moderate hypotension (avoid if severe); retinitis pigmentosa

Side-effects: Atrial fibrillation; blurred vision; bradycardia; dizziness; first-degree heart block; headache; phosphenes; ventricular extrasystoles; visual disturbance

Dose: Treatment of angina in patients in normal sinus rhythm. Initially 5 mg twice daily for 3–4 weeks, then increased if necessary to 7.5 mg twice daily; reduced if not tolerated to 2.5–5 mg twice daily, heart rate at rest should not be allowed to fall below 50 beats per minute. Elderly initially 2.5 mg twice daily, heart rate at rest should not be allowed to fall below 50 beats per minute.

Mild to severe chronic heart failure. Initially 5 mg twice daily for 2 weeks, then increased if necessary to 7.5 mg twice daily; reduced if not tolerated to 2.5 mg twice daily, heart rate at rest should not be allowed to fall below 50 beats per minute.

Preparations

Ivabradine tablets, 5 mg tab

2 G: Calcium channel blocking agents

Calcium channel blocking agents inhibit membrane transport of calcium. They affect the myocardial cells, the cells within the conducting system of the heart and the smooth muscle cells of the vasculature. Thus, resulting in depression of the myocardium and diminishing the coronary and systemic vascular tone. They should be avoided in heart failure because of a possible further depression of the cardiac function.

Calcium channel blocking agents come from different chemical groups. They can be classified as dihydropyridine, phenylalkylamine or benzothiazepine types.

Nifedipine and nimodipine are members of the dihydropyridine group. Nifedipine is a vasodilator with antianginal and antihypertensive effects. It has little or no depressant effect at the S-A or A-V node. It is also a more potent peripheral vasodilator with moderate antiplatelet activity. In clinically practical doses, nifedipine has no antiarrhythmic properties. Nimodipine has a preferential cerebrovascular vasodilatory action. It is indicated for prevention of neurological defects secondary to cerebral artery spasm. Nimodipine also appears to be effective in the prevention of migraine headaches.

Verapamil is a calcium channel blocking agent of phenylalkylamine group with vasodilatory and antiarrhythmic effects. Verapamil increases myocardial oxygen supply and reduces myocardial oxygen demand secondary to decreasing heart rate and afterload. Its efficacy in variant angina is secondary to its ability to increase myocardial oxygen supply, whereas in exertion angina, beneficial effects are secondary to reduced myocardial oxygen demand.

Diltiazem is a benzothiazepine derivative calcium channel blocker. Its mechanism of action is similar to that of verapamil with less effect

on AV node in equal doses and preferential vasodilatation of coronary vasculature. Diltiazem possesses less negative inotropic activity than Verapamil and only one-tenth the vasodilator potency of nifedipine.

Calcium channel blocking agents are mainly indicated in the treatment of angina, hypertension and arrhythmias (for other uses *see* individual agents). Sudden withdrawal of calcium channel blocking agents in patients with angina may exacerbate angina.

Amlodipine besilate (Restricted)

Indications: prophylaxis of angina; hypertension

Contra-indications: cardiogenic shock, unstable angina; pregnancy and breast feeding

Cautions: hepatic impairment

Side-effects: headache, oedema, fatigue, gum hyperplasia, rashes, dizziness

Dose: 5 mg daily, maximum 10 mg daily

Preparations

Amlodipine besilate tablets, 5 mg tab.

Diltiazem hydrochloride (Restricted)

Indications: prophylaxis and treatment of angina; hypertension

Contra-indications: severe bradycardia, left ventricular failure, heart block; pregnancy and breast feeding

2: Cardiovascular system

Cautions: reduce dose in renal or hepatic dysfunction

Side-effects: bradycardia, sinoatrial and AV block, dizziness, hypotension, GIT disturbances

Dose: angina, 60 mg 3 times daily; increased if necessary to 360 mg daily

Intravenous bolus, 0.25 mg/kg over 2 minutes, intravenous infusion, 5-15 mg/hour for up to 24 hrs.

Hypertension, 120 mg twice daily

Preparations

Diltiazem HCl tablets, 60 mg tab.

Nifedipine

Indications: prophylaxis and treatment of angina; hypertension

Contra-indications: cardiogenic shock, unstable or acute attack of angina,

Cautions: severe hypotension; reduce dose in hepatic dysfunction; pregnancy (may inhibit labour); severe heart failure

Side-effects: bradycardia; dizziness and headache; hypotension which could be very severe with short acting preparations; skin disorders; oedema

Dose: angina, initially 10 mg 3 times daily, increased to 20 mg 3 times daily if required.

Hypertension, initially 20 mg twice daily, increased to 40 mg twice daily when necessary.

Preparations

Nifedipine retard tablets; 20 mg tab.

Nifedipine suspension (CDL)

Nimodipine (Restricted)

Indications: prevention and treatment of neurological deficit following subarachnoid haemorrhage

Cautions: cerebral oedema, avoid concomitant administration of other calcium channel blocking agents or beta-blockers; reduce dose in renal impairment

Side-effects: hypotension, variation in heart rate, flushing, headache

Dose: prevention, orally, 60 mg every 4 hours, maximum 360 mg. Treatment, intravenous infusion, 1 mg /hour initially, then 2 mg/hour. Reduce dose in elderly or in patients with less than 70kg body weight

Preparations

Nimodipine tablets, 30 mg tab.

Nimodipine injection, 200 microgram/mL, 50 mL vial

Verapamil hydrochloride

Indications: supraventricular arrhythmias, hypertension, angina pectoris

Contra-indications: hypotension, heart block, bradycardia, heart failure

Cautions: not to be used in patients taking beta-blockers; acute phase of myocardial infarction; hepatic impairment; pregnancy and breast feeding

Side-effects: constipation; hypotension, bradycardia and asystole may follow an IV administration

Dose: orally, supraventricular arrhythmias 40-120 mg 3 times daily

Angina, 80-120 mg 3 times daily
Hypertension, 240-480 mg daily in 2-3 divided doses.

Slow intravenous injection, 5-10 mg over 2-3 minutes, repeated after 5-10 minutes if required.

Preparations

Verapamil tablets, 40 mg tab.

Verapamil 240 mg S.R tab.

Verapamil HCl injection, 2.5 mg/mL, 2 mL ampoule (**Restricted**)

2 H: Sympathomemtics

Drugs such as adrenaline, isoprenaline, and dobutamine are agonists for alpha and/or beta-receptors.

2 H.1: Direct sympathomemtics

In cardiac arrest, adrenaline in a concentration of 1 in 10,000 is recommended in a dose of 10 mL. Isoprenaline is used during cardiac surgery to resuscitate the heart. Anaphylactic shock necessitates a prompt action to treat laryngeal oedema, bronchospasm and hypotension. The first line treatment includes securing the airway, restoration of blood pressure and administration of adrenaline intramuscularly.

Adrenaline (Epinephrine)

Indications: anaphylactic shock; cardiopulmonary resuscitations, acute bronchial asthma.

Cautions: angle closure glaucoma, anaesthesia with cyclopropane or halothane, thyrotoxicosis, diabetes, pregnancy with maternal BP above 130/80, HTN or other cardiovascular disorders.

Side-effects: anxiety, tachycardia, tremor, headache, in high doses arrhythmias

Dose: cardiac arrest, intravenous injection of 10 mL of 1 in 10,000 (1 mg /10 mL)

Anaphylactic shock, intramuscular injection of 1 in 1,000 (0.5 mg/0.5 mL or 1 mg/mL) solution

Preparations

Adrenaline injection, 1 in 10000 (1 mg/10 mL) ampoule

Adrenaline injection, 1 in 1000 (0.5 mg/0.5 mL) ampoule

Isoprenaline Hydrochloride

Indications: heart block; severe bradycardia

Cautions: ischemic heart diseases, diabetes mellitus, hyperthyroidism

Side-effects: tachycardia, tremor, arrhythmias, hypotension

Dose: by intravenous infusion, 0.5-10 micrograms/minute

Preparations

Isoprenaline hydrochloride injection, 1 mg/mL, 2 mL ampoule

Isoprenaline hydrochloride injection, 0.2 mg/mL, 1 mL ampoule

2: Cardiovascular system

2 H.2: Vasoconstrictor sympathomimetics

These are vasoconstrictor drugs that act on the alpha-receptors in peripheral blood vessels resulting in a transient rise in blood pressure. They should only be used to raise blood pressure in cases of emergencies when other measures have failed.

Noradrenaline acid tartrate

Indications: acute severe hypotension,

Contra-indications: hypertension

Cautions: vascular thrombosis, hyperthyroidism, diabetes mellitus; extravasation may cause necrosis at site of injection

Side-effects: hypertension, arrhythmias, headache

Dose: acute hypotension, by intravenous infusion, of a solution containing 80 micrograms/mL at an initial rate of 0.16-0.33 mL / minute, adjusted according to response

Preparations

Noradrenaline acid tartrate injection, 2 mg / mL; 2 mL ampoule (equivalent to noradrenaline base 1 mg/mL)

Phenylephrine hydrochloride

Indications: acute hypotension

Contra-indications: cautions and side-effects: *see* noradrenaline above; phenylephrine has a longer

duration of action than noradrenaline, which may cause an excessive and prolonged rise in blood pressure

Dose: by subcutaneous or intramuscular injection, 2.2-5 mg

By slow intravenous injection, 1 mg/mL solution, 100-500 micrograms repeated after 15 minutes if necessary

By intravenous infusion, initial rate of 180 micrograms/minute, reduce according to response.

Preparations

Phenylephrine injection, 1% (10 mg/mL); 1 mL ampoule

2 H.3: Positive inotropics

Dobutamine and dopamine stimulate the heart and increase contractility with little effect on the rate. They act through stimulating the beta₁-receptors in the heart. Their main indication is in cardiogenic shock.

Dobutamine hydrochloride

Indications: inotropic support in infarction and cardiac surgery

Cautions: severe hypotension complicating cardiogenic shock

Side-effects: tachycardia and marked increase in systolic blood pressure indicate overdosage

Dose: by intravenous infusion, 2.5-10 micrograms/kg/minute, adjusted according to response

Preparations

2: Cardiovascular system

Dobutamine injection, 12.5 mg/mL, 20 mL vial for dilution and use as intravenous infusion

Dopamine hydrochloride

Indications: cardiogenic shock in infarction or cardiac surgery

Contra-indications: tachyarrhythmia, phaeochromocytoma

Cautions: correct hypovolaemia; low dose in shock due to acute myocardial infarction

Side-effects: tachycardia, hypotension, hypertension peripheral vasoconstriction,

Dose: by intravenous infusion, 2-5 micrograms/kg/minute initially

Preparations

Dopamine injection, 40 mg/mL, 5 mL ampoule

check the product literature for details.

Phytomenadione

Indications: haemorrhagic disorders of newborns, antagonist to the effect of oral coumarin anticoagulants

Cautions: intravenous injections should be given very slowly

Dose: see product literature

Preparations

Phytomenadione injection, 1 mg/0.5 mL ampoule,

Phytomenadione injection, 2 mg / 0.2 mL ampoule,

Phytomenadione injection, 10 mg/1 mL ampoule

2 I: Coagulants

Phytomenadione (vitamin K) is a fat-soluble vitamin essential for the complete hepatic synthesis of the plasma clotting factors, II (prothrombin), VII, IX and X, and proteins necessary for the calcification of bones.

Vitamin K is used for prophylaxis against haemorrhagic disease of newborn. It is also used to antagonise the effect of oral coumarin anticoagulants. The route and dose are determined by the urgency of the situation. Some of the solutions for infusion can be used orally,

2 J: Anticoagulants and protamine

This group of drugs includes:

- Parenteral anticoagulants
- Oral anticoagulants
- Protamine sulphate

2 J.1: Parenteral Anticoagulants

Heparin is a directly acting anticoagulant with an immediate effect when injected intravenously. It activates plasma antithrombin III, which in turn inhibits several clotting factors particularly factor X and thrombin. Inhibition of factor X requires low doses of heparin. This explains the need for small

2: Cardiovascular system

doses in the prophylaxis of thrombosis versus high doses for the treatment of pre-existing thrombosis. Heparin is not absorbed through the gastrointestinal mucosa and therefore is given parenterally. It is administered by intravenous infusion, intermittent intravenous injection or subcutaneous injection.

The most important adverse effect of heparins is bleeding from various sites. Protamine sulphate antagonizes the action of heparin and is used by slow intravenous injection. *(The table on the subsequent page shows a comparison between unfractionated heparin and low molecular heparin)*

Argatroban is a thrombin inhibitor. An oral anticoagulant can be given with argatroban, but it should be started once thrombocytopenia has been substantially resolved. Consult the product literature for the dosing regime details.

Fondaparinux is a synthetic pentasaccharide that inhibits activated factor X.

Heparin

Indications: treatment of deep-vein thrombosis, pulmonary embolism, prophylaxis in orthopaedic and general surgery, used in the management of coronary artery diseases and in the maintenance of extracorporeal circuits in cardiopulmonary bypass and haemodialysis.

Contra-indications: haemophilia and other haemorrhagic disorders, peptic ulcer, recent cerebral haemorrhage.

Cautions: hepatic and renal impairment; pregnancy; hypersensitivity to heparin; thrombocytopenia; hyperkalaemia.

Side-effects: haemorrhage, skin necrosis, hyperkalaemia, thrombocytopenia.

Dose: prophylaxis in general surgery, by subcutaneous injection, 5,000 units 2 hours before surgery, then every 8-12 hours for 7 days or until patient is ambulant.

Treatment of deep-vein thrombosis and pulmonary embolism, by intravenous injection, loading dose of 5,000 units, followed by continuous infusion of 1,000-2,000 unit/hour, or subcutaneous injection of 15,000 units every 12 hours.

Preparations

Heparin injection, 1,000 IU/mL, 5 mL vial

Heparin injection, 5,000 IU/mL, 5 mL vial.

Heparin injection, 25,000 IU/mL, 5 mL vials

Low molecular weight heparin injection of the type Dalteparin, Enoxaparin or Tinzaparin 15,000 - 20,000 IU multidose vial

Enoxaparin 4,000 and 8,000 IU vials

Dalteparin 5,000 and 10,000 IU vials

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	Unfractionated heparin	low molecular weight heparin
Average molecular weight	20,000 Dalton	3,000 Dalton
<u>APTT</u> monitoring	<u>APTT</u> monitoring is required	<u>APTT</u> monitoring not required but monitoring of anti-Factor Xa activity may be necessary in patients at increased risk of bleeding (e.g. in renal impairment and those who are underweight or overweight).
Route of administration	Intravenous, so hospitalization is required	Subcutaneous,, so possible to permit <u>outpatient</u> treatment
Frequency of administration	Continuous infusion of unfractionated heparin is needed	Has long duration of action so ,once-daily dosing might be enough
Cost	Low	High
Side-effects	Higher likelihood of bleeding, thrombo-cytopenia or osteoporosis.	Lower likelihood of bleeding, thrombo-cytopenia or osteoporosis.

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Argatroban

Indications: Anticoagulation in patients with heparin-induced thrombocytopenia type II who require parenteral antithrombotic treatment.

Cautions: Bleeding disorders; diabetic retinopathy; gastro-intestinal ulceration; immediately after lumbar puncture; major surgery (especially of brain, spinal cord, or eye); risk of bleeding; severe hypertension; spinal anaesthesia.

Side-effects: Haemorrhage; nausea; purpura.

Dose: Initially 2 micrograms/kg/minute, dose to be adjusted according to activated partial thromboplastin time, (by intravenous infusion) increased to up to 10 micrograms/kg/minute maximum duration of treatment 14 days.

An oral anticoagulant can be given with argatroban, consult the product literature for the dosing regime details.

Preparations

Argatroban injection, 100 mg/ml, 2.5 ml

Fondaparinux

Indications: See dose information below

Contra-indications: Active bleeding; bacterial endocarditis

Cautions: Active gastro-intestinal ulcer disease; bleeding disorders; brain surgery; elderly patients; low body-weight; ophthalmic surgery; recent intracranial haemorrhage; risk of catheter thrombus during

percutaneous coronary intervention; spinal or epidural anaesthesia (risk of spinal haematoma—avoid if using treatment doses); spinal surgery

Side-effects: Anaemia; bleeding; purpura

Dose: Prophylaxis of venous thromboembolism in patients after undergoing major orthopaedic surgery of the hip or leg, or abdominal surgery. Initially 2.5 mg by subcutaneous injection, dose to be given 6 hours after surgery, then 2.5 mg once daily.

Prophylaxis of venous thromboembolism in medical patients immobilised because of acute illness, 2.5 mg by subcutaneous injection once daily.

Treatment of superficial-vein thrombosis. Adult (body-weight 50 kg and above) 2.5 mg once daily by subcutaneous injection for at least 30 days (max. 45 days if high risk of thromboembolic complications), treatment should be stopped 24 hours before surgery and restarted at least 6 hours post operatively.

Treatment of unstable angina and non-ST-segment elevation myocardial infarction 2.5 mg once daily by subcutaneous injection for up to 8 days (or until hospital discharge if sooner), treatment should be stopped 24 hours before coronary artery bypass graft surgery (where possible) and restarted 48 hours post operatively.

Treatment of ST-segment elevation myocardial infarction. Initially 2.5

mg by intravenous injection or intravenous infusion daily for the first day, then (by subcutaneous injection) 2.5 mg once daily for up to 8 days (or until hospital discharge if sooner), treatment should be stopped 24 hours before coronary artery bypass graft surgery (where possible) and restarted 48 hours post operatively.

Treatment of deep-vein thrombosis and pulmonary embolism. Adult (body-weight up to 50 kg) 5 mg by subcutaneous injection every 24 hours, an oral anticoagulant (usually warfarin) is started at the same time as fondaparinux (fondaparinux should be continued for at least 5 days and until $\text{INR} \geq 2$ for at least 24 hours). Adult (body-weight 50–100 kg) 7.5 mg every 24 hours, an oral anticoagulant (usually warfarin) is started at the same time as fondaparinux (fondaparinux should be continued for at least 5 days and until $\text{INR} \geq 2$ for at least 24 hours). Adult (body-weight 101 kg and above) 10 mg every 24 hours, an oral anticoagulant (usually warfarin) is started at the same time as fondaparinux (fondaparinux should be continued for at least 5 days and until $\text{INR} \geq 2$ for at least 24 hours).

Preparations

Fondaparinux sodium injection
5mg/ml, 0.3 ml prefilled syringe

Fondaparinux sodium injection
5mg/ml 0.5 ml prefilled syringe

2 J.2: Oral anticoagulants

Warfarin is the most commonly used oral anticoagulant. It inhibits the hepatic synthesis of vitamin K-dependent clotting factors: II, VI, VII, IX and X. Warfarin is well absorbed orally and extensively bound to plasma proteins and metabolized by the liver. The full anticoagulant effect of warfarin is delayed for a few days. If an immediate effect is required, heparin can be used concomitantly.

It is essential that the INR (international normalised ratio) be determined daily or on alternate days in early days of treatment with Warfarin, then at longer intervals.

Haemorrhage is the main adverse effect of oral anticoagulants. They are also teratogenic and should not be used during the first trimester of pregnancy. Warfarin passes the blood-placental barrier and may cause placental and foetal bleeding, especially towards the end of pregnancy and at delivery.

Rivaroxaban is a direct inhibitor of activated factor X (factor Xa)

Rivaroxaban (Restricted)

Indications: Prophylaxis of venous thromboembolism following knee replacement surgery. Prophylaxis of venous thromboembolism following hip replacement surgery. Initial treatment of deep-vein throm-

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bosis. Initial treatment of pulmonary embolism. Continued treatment of deep-vein thrombosis (following initial treatment). Continued treatment of pulmonary embolism (following initial treatment). Prophylaxis of recurrent deep-vein thrombosis. Prophylaxis of recurrent pulmonary embolism. Prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation and with at least one of the following risk factors: congestive heart failure, hypertension, previous stroke or transient ischaemic attack, age ≥ 75 . Prophylaxis of atherothrombotic events in acute coronary syndrome (with aspirin alone or aspirin and clopidogrel)

Contra-indications: Active bleeding; in acute coronary syndrome—previous stroke; in acute coronary syndrome—transient ischaemic attack; malignant neoplasms; oesophageal varices; recent brain surgery; recent gastro-intestinal ulcer; recent intracranial haemorrhage; recent ophthalmic surgery; recent spine surgery; significant risk of major bleeding; vascular aneurysm

Cautions: Anaesthesia with post-operative indwelling epidural catheter (risk of paralysis—monitor neurological signs and wait at least 18 hours after rivaroxaban dose before removing catheter and do not give next dose until at least 6 hours after catheter removal); bronchiec-

tasis; prosthetic heart valve (efficacy not established); risk of bleeding; rivaroxaban should not be used as an alternative to unfractionated heparin in pulmonary embolism in patients with haemodynamic instability, or who may receive thrombolysis or pulmonary embolectomy; severe hypertension; vascular retinopathy

Side-effects: Abdominal pain; constipation; diarrhoea; dizziness; dyspepsia; haemorrhage; headache; hypotension; nausea; pain in extremities; pruritus; rash; renal impairment; vomiting; angioedema; dry mouth; malaise; syncope; tachycardia; thrombocythaemia

Dose: Prophylaxis of venous thromboembolism following knee replacement surgery 10 mg once daily for 2 weeks, to be started 6–10 hours after surgery.

Prophylaxis of venous thromboembolism following hip replacement surgery 10 mg once daily for 5 weeks, to be started 6–10 hours after surgery.

Initial treatment of deep-vein thrombosis. Initial treatment of pulmonary embolism. Initially 15 mg twice daily for 21 days, to be taken with food.

Continued treatment of deep-vein thrombosis (following initial treatment). Continued treatment of pulmonary embolism (following initial treatment). Prophylaxis of recurrent deep-vein thrombosis. Prophylaxis of recurrent pulmonary embolism

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20 mg once daily, to be taken with food.

Prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation and with at least one of the following risk factors: congestive heart failure, hypertension, previous stroke or transient ischaemic attack, age $\geq$ 75 years, or diabetes mellitus 20 mg once daily, to be taken with food.

Prophylaxis of atherothrombotic events in acute coronary syndrome (with aspirin alone or aspirin and clopidogrel) 2.5 mg twice daily usual duration 12 months.

Preparations

Rivaroxaban tablets 15 mg tab

Rivaroxaban tablets 20 mg tab

Warfarin Sodium (Restricted)

Indications: prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation; prophylaxis after introduction of prosthetic heart valve; prophylaxis and treatment of venous thrombosis and pulmonary embolism; transient ischaemic attacks

Contra-indications: haemorrhagic tendencies, pregnancy, blood dyscrasias, hypersensitivity to warfarin products, hypertension

Cautions: hepatic or renal disease, breast feeding, recent surgery, concomitant use of antiplatelet or ulcerogenic agents

Side-effects: haemorrhage, skin rash, alopecia, nausea and vomiting

Dose: initially, 10 mg daily for 3 days; reduce dose in elderly, liver disease and cardiac failure. Maintenance dose depends on prothrombin time, usually 3-9 mg daily taken at the same time each day.

Preparations

Warfarin tablets, 1 mg tab.

Warfarin tablets, 2 mg tab.

Warfarin tablets, 5 mg tab.

2 J.3: Protamine Sulphate

Protamines are low molecular weight, polycationic, strongly basic proteins used to neutralize the anti-coagulant effects of heparin.

Protamine sulphate

Indications: Overdosage of heparin

Cautions: allergy to protamine

Side-effects: hypotension, bradycardia, hypersensitivity reactions, flushing

Dose: by intravenous injection, over about 10 minutes, 1 mg neutralizes 80-100 units of heparin when given immediately after heparin administration, maximum 50 mg.

Preparations

Protamine sulphate injection, 10 mg/mL, 5 mL ampoule

2 K: Antiplatelet drugs

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Antiplatelet drugs are used to prevent arterial thrombus formation where thrombi are formed by platelet aggregation and anticoagulants have little effect. Injury to the wall of an artery initiates processes in which platelets play an essential role: (a) adhesion of platelets to exposed subendothelium followed by platelet aggregation, leading to the formation of a primary haemostatic plug, (b) enhancement of several reactions in the coagulation pathway leading to the formation of fibrin. The fibrin network reinforces the platelet aggregates to form a stable thrombus.

Aspirin 75-300 mg has been shown to reduce mortality after myocardial infarction, and as prophylaxis to prevent thrombus formation following bypass surgery, atrial fibrillation, stable angina or intermittent claudication.

Other drugs such as dipyridamole, anagrelide and ticlopidine have also been used to prevent platelet aggregation. Their mechanisms of action, somehow, differ from that of aspirin.

Aspirin

Indications: prophylaxis of cerebrovascular disease or myocardial infarction. (see also section 4. D 1)

Contra-indications, cautions and side-effects: see section 4. D 1

Dose: a controversy over the proper dose for the antiplatelet effect of aspirin has arisen from different studies conducted. A dose between 70-

300 mg has been suggested for secondary prevention.

Preparations

Aspirin tablets, 75-100 mg tab.

Aspirin tablets, 300 mg tab.

Anagrelide hydrochloride (C.D.L)

Indications: reduction of platelets in essential thrombocythemia

Cautions: renal and hepatic impairment; cardiovascular disease may be worsened

Side-effects: headache, palpitations, thrombocytopenia, orthostatic hypotension

Dose: initially, 0.5-1 mg twice daily for a week, maintenance dose is kept at minimum to maintain platelets below 600,000/mL, maximum 10 mg daily in 4 divided doses.

Preparations

Anagrelide tablets, 0.5 mg tab.

Anagrelide tablets, 1 mg tab.

Clopidogrel (Restricted)

Indications: thrombotic disorders prophylaxis in acute myocardial infarction, peripheral arterial disease, cerebrovascular accident.

Contra-indications: active bleeding (such as peptic ulcer or intracranial haemorrhage), breast-feeding.

Cautions: discontinue use 7 days prior to elective surgery if antiplatelet effect is not desired, patients at risk of increased bleeding from trauma, surgery, or other pathological condition, renal impairment, hepatic impairment, pregnancy,

concomitant use with drugs that increase risk of bleeding e.g. aspirin.

Side-effects: abdominal pain, constipation, diarrhoea, gastritis, bleeding disorders (including gastro-intestinal and intracranial), headache, rash, leucopenia, thrombocytopenia, duodenal ulcer, hypertension, hypercholesterolaemia.

Dose: acute coronary syndrome (with or without ST segment elevation), initially 300 mg then 75 mg daily (with aspirin). Prevention of atherosclerotic events in peripheral arterial disease or after myocardial infarction or ischaemic stroke, 75 mg once daily.

Preparations

Clopidogrel tablets, 75 mg tab.

Clopidogrel tablets, 300 mg tab.

Dipyridamole (Restricted)

Indications: prophylaxis in cardiac valve replacement, platelet aggregation prophylaxis

Cautions: hypotension, rapidly worsening angina

Side-effects: GIT disturbances, dizziness, headache, hypotension

Dose: 300-600 mg daily in 3-4 divided doses before meals

Preparations

Dipyridamole tablets, 75 mg tab.

Ticlopidine (Restricted)

Indications: prophylaxis during angioplasty

Contra-indications: active bleeding disorders, neutropenia / thrombocytopenia, severe liver impairment

Cautions: hepatic and renal impairment; monitor blood count

Side-effects: bleeding manifestation, blood disorders, diarrhoea, nausea and vomiting, myelosuppression, cholestatic jaundice

Dose: 250 mg twice daily

Preparations

Ticlopidine tablets, 250 mg tab.

Tirofiban

Indications: unstable angina and non-ST-segment elevation MI in high risk patients. Contra-indications: severe uncontrolled hypertension (systolic BP >180 or diastolic BP >110 mm Hg), active internal bleeding, recent significant GI or genitourinary bleeding (within 6 weeks), bleeding disorders; e.g. thrombocytopenia, haemophilia, Von Willebrand's disease, history of intracranial disease (neoplasm, arteriovenous malformation, aneurysm), history of haemorrhagic stroke, INR >2.0.

Cautions: concomitant drugs that may increase the risk of bleeding, pregnancy, breastfeeding, renal or hepatic impairment, anaemia, severe heart failure, major surgery or trauma (within 3 months), monitor platelet count, haemoglobin and haematocrit before treatment;

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within 6 hours after start of treatment and at least once daily thereafter.

Side-effects: bleeding, thrombocytopenia.

Dose: Intravenous infusion, 400 nanogram/kg/minute for 30 minutes, followed by 100 nanogram/kg/minute for 48–108 hours.

Preparations

Tirofiban injection, 250 micrograms/mL, 50 mL vial

2 L: Fibrinolytic drugs

Fibrinolytic drugs help dissolve clots that have already formed. Dissolving clots quickly may prevent the death of heart tissue deprived of its blood supply because of blocked blood vessels.

Fibrinolytic drugs such as streptokinase and plasminogen activators (e.g. alteplase or reteplase) have been shown to reduced mortality due to myocardial infarction.

Cautions: risk of bleeding is very high. Risk of allergic reaction

Contra-indications: recent haemorrhage, trauma or surgery, recent cerebrovascular events, recent symptoms of peptic ulcer, heavy vaginal bleeding, previous allergic reaction to streptokinase. Also, streptokinase should not be used again beyond 4 days of first administration. **Side-effects:** haemorrhage, which can be treated with an-

tifibrinolytic agents; fever, liver enzyme abnormalities; hypotension and arrhythmias may occur as a result of reperfusion.

Human tissue type plasminogen activator (Restricted)

Alteplase or reteplase

Indications: acute myocardial infarction; pulmonary embolism

Cautions, contra-indications and side-effects: see notes above

Dose: as for alteplase:

Myocardial infarction, accelerated regimen initiated within 6 hours; patients over 65kg total dose 100 mg intravenously, give 15 mg bolus, 50 mg over 30 minutes, then 35 mg over 60 minutes

Patients under 65kg intravenously, 15 mg bolus, then 0.75 mg/kg over 30 minutes, then 0.50 mg/kg over 60 minutes

Myocardial infarction initiated within 6–12 hours, intravenously 10 mg as bolus dose, 50 mg over 60 minutes, then four infusions each of 10 mg over 30 minutes, in patients over 65kg. Reduce dose in patients less than 65 kg.

Pulmonary embolism intravenously, 10 mg as bolus dose over 1–2 minutes, followed by 90 mg over 2 hours for patients over 65 kg.

Preparations

Alteplase injection, powder for reconstitution, 50 mg (29 mega units) vial

Reteplase injection, powder for reconstitution, 10 units vial

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Streptokinase (Restricted)

Indications: acute myocardial infarction, deep vein thrombosis, pulmonary embolism, central retinal venous or arterial thrombosis

Contra-indications, cautions and side-effects: *see* notes above

Dose: Myocardial infarction, by intravenous infusion, 1,500,000 units over 60 minutes

For other indications, by intravenous infusion, 250,000 units over 30 minutes then 100,000 units every hour for up to 12-72 hours depending on the patient's response

Preparations

Streptokinase injection, powder for reconstitution, 750,000 unit vials

2 M: Antifibrinolytics

Tranexamic acid inhibits plasminogen activation and impairs fibrin dissolution. It is used when haemorrhage cannot be controlled as in prostatectomy, dental extraction in haemophilic patient and menorrhagia; it can also be used in streptokinase overdose.

Tranexamic acid (Restricted)

Indications: *see* notes above

Contra-indications: thromboembolic disease

Cautions: reduce dose in renal impairment; massive haematuria; concomitant oestrogen therapy

Side-effects: nausea, vomiting, diarrhoea

Dose: oral, local fibrinolysis, 15 - 25 mg/kg 2 - 3 times daily

Menorrhagia, 1 - 1.5 g 3 - 4 times daily for 3 - 4 days

By intravenous injection, 0.5-1 g 3 times daily

Preparations

Tranexamic acid injection, 100 mg/mL, 5 mL ampoule

Tranexamic acid syrup, 500 mg/5 mL, 300 mL sugar free syrup

2 N: Lipid-regulating drugs

High lipid level has been associated with increased risk of coronary atherosclerosis. There is evidence that lowering LDL-cholesterol by 25-35% is effective in both the primary and secondary prevention of the clinical manifestation of coronary heart disease.

Patients with coronary heart disease, and those at high risk of having it because of multiple risk factors, are candidates for treatment with lipid-regulating drugs.

Presently, treatment with statins has proved to be effective in reducing myocardial infarction, coronary deaths and overall mortality.

Statins are the drugs of choice for treatment of hypercholesterolaemia or hyperlipidaemia in patients with high risk of coronary heart disease. Fibrates can be used for hypertriglyceridaemia.

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Nonpharmacological measures should go parallel with drug therapy such as strict dietary habits, stopping smoking and keeping near ideal body weight.

Lipid –regulating drugs include:

- Fibrates
- Bile acids binding resins
- Statins

2 N.1: Fibrates

Fibrates are broad-spectrum lipid-regulating drugs. Though they tend to reduce serum triglycerides they also tend to reduce LDL-cholesterol and to raise HDL-cholesterol

Bezafibrate

Indications: hyperlipidaemias

Contra-indications: severe renal or hepatic impairment, gall bladder disease, pregnancy and breast-feeding

Cautions: myotoxicity, renal and hepatic impairment

Side-effects: GI disturbances; skin disorders; impotence; headache; hepatotoxicity

Dose: 200 mg 3 times daily after food. Slowly released preparations, 400 mg once daily after food.

Preparations

Bezafibrate retard tablets, 400 mg tab.

Fenofibrate

Indications: hyperlipidaemias

Contra-indications: severe renal or hepatic impairment, gall bladder disease

Cautions: myotoxicity, renal and hepatic impairment, pregnancy and breast-feeding

Side-effects: GIT disturbances; skin disorders; impotence; headache; hepatotoxicity

Dose: Micronized preparations, 145-200 mg 1-2 times daily

Preparations

Fenofibrate (Micronized) tablets
145-200 mg tab.

Note: MoH policy is that only one of the above fibrates bezafibrate *or* fenofibrate, will be purchased and supplied for use based on its cost effectiveness

2 N.2: Bile acid binding resin

Colestyramine is a synthetic polyamine resin, which lowers plasma cholesterol by binding bile acids in the intestine and inhibiting their re-absorption and enterohepatic cycling and increasing their faecal excretion.

Its main side-effects are GIT disturbances. It should be avoided in complete biliary obstruction and during pregnancy. Fat-soluble vitamins absorption might be affected and supplementary vitamin A, D and K may be needed in patients taking high doses.

Colestyramine (Cholestyramine) *(Restricted)*

Indications:

hypercholesterolaemia, pruritus associated with partial biliary obstruction

Contra-indications: complete biliary obstruction

Cautions: check for fat-soluble vitamin deficiency, pregnancy and breast-feeding

Side-effects: constipation, abdominal discomfort/pain, flatulence, nausea, vomiting, bleeding tendencies due to hypoprothrombinaemia associated with vitamin K deficiency

Dose: oral for lipid reduction, 12-24 g daily in single or divided doses, max. 36 g daily.

For pruritus, 4-8 g daily

N.B: other drugs should be taken at least 1 hour before or 4-6 hours after colestyramine to reduce possible interference with absorption

Preparations

Colestyramine sachets, 4 g sachet

2 N.3: Statins

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a crucial enzyme in the synthesis of cholesterol by the liver. These compounds are more effective than the polyamine binding resins in lowering LDL-cholesterol, but less

effective than the fibrates in reducing triglycerides and raising HDL-cholesterol.

Lowering cholesterol levels produces an important reduction in coronary events, in all cardiovascular events, and in total mortality in patients aged up to 75 years with coronary heart disease and with total serum cholesterol concentration of 5 mmol/litre or greater.

Cautions: Statins should be used with caution in patients with liver diseases or with high alcohol intake. Liver function tests should be carried out before starting treatment with statins and regularly thereafter.

Contra-indications: active liver disease; pregnancy and breast-feeding

Side-effects: myositis, myopathy

Atorvastatin (Restricted)

Indications: primary hypercholesterolaemia or combined hyperlipidaemia in patients who have not responded to dietary restrictions and other measures

Contra-indications: *see* notes above

Cautions: *see* notes above

Side-effects: *see* notes above; also insomnia, angioedema, anorexia, asthenia, paraesthesia. peripheral neuropathy, pruritus, alopecia, impotence

Dose: primary hypercholesterolaemia and combined hyperlipidaemia, usually 10 mg once daily.

2: Cardiovascular system

Familial hypercholesterolaemia, initially 10 mg, increased at 4 weeks interval to 40 mg once daily

Preparations

Atorvastatin tablets, 10 mg tab.

Atorvastatin tablets, 40 mg tab.

Fluvastatin (Restricted)

Indications: primary hypercholesterolaemia, in patients with total cholesterol concentration of 6.5 mmol/litre or higher; adjunct to diet as preventive measure to retard the progression of coronary atherosclerosis.

Contra-indications: see notes above

Cautions: see notes above

Side-effects: see notes above; insomnia

Dose: initial 20-40 mg daily in the evening. Adjust up to 40 mg twice daily if necessary.

Preparations

Fluvastatin capsule, 40 mg cap

Fluvastatin capsule, 80 mg cap.

Pravastatin (Restricted)

Indications: primary hypercholesterolaemia, in patients not responding to diet restriction; adjunct to diet as preventive measure to retard the progression of coronary atherosclerosis; adjunct to diet in hypercholesterolaemia without clinically evident coronary heart disease

Contra-indications: see notes above

Cautions: see notes above

Side-effects: see notes above; rash, chest pain, fatigue

Dose: 10-40 mg daily in the evening. Adjust as necessary

Preparations

Pravastatin tablets, 20 mg tab.

Simvastatin (Restricted)

Indications: primary hypercholesterolaemia or combined hyperlipidaemia in patients who have not responded to dietary restrictions and other measures; adjunct to diet as preventive measure to retard the progression of coronary atherosclerosis.

Contra-indications: see notes above

Cautions: see notes above

Side-effects: see notes above; also rash, alopecia, dizziness, depression

Dose: 10 mg daily in the evening. Adjust up to 40 mg once daily if necessary.

Preparations

Simvastatin tablets, 20 mg tab

Note: MoH policy is that only one of the above statins will be purchased and supplied for use based on their cost effectiveness

2 O: Local sclerosants

Sodium tetradecyl sulphate

Indications: sclerotherapy of varicose veins.

Contra-indications: inability to walk, acute phlebitis, oral contraceptive use, obese legs.

2: Cardiovascular system

Cautions: extravasation may cause necrosis of tissues.

Side-effects: allergic reaction.

Dose: slow intravenous injection, 0.1-1 mL of 3% solution into empty isolated segment of the vein.

Preparations

Sodium tetradecyl sulphate injection, 3% solution, 5 mL ampoule

2 P: Blood products

Drotrecogin Alfa (Restricted)

(Recombinant Human Activated Protein C)

Indications: for adult patients with severe sepsis associated with acute multiple organ dysfunction who have a high risk of death.

Contra-indications: internal bleeding, intracranial neoplasm, low platelets count, not for children below 18 years, chronic severe liver disease.

Cautions: pregnancy, breastfeeding, concomitant use with drugs that increase risk of bleeding.

Side-effects: bleeding, ecchymosis.

Preparations

Drotrecogin Alfa injection, powder for reconstitution, 5 mg vial

Human coagulating factor VIII (Restricted)

Indications: control of haemorrhage in haemophilia A.

Cautions: intravascular haemolysis after large or frequent repeated doses.

Side-effects: allergic reactions.

Preparations

Factor VIII injection, 250-310 IU vial

Human fibrinogen factor IX (C.D.L)

Indications: congenital factor IX deficiency (haemophilia B).

Cautions: risk of thrombosis.

Side-effects: allergic reactions.

Preparations

Factor IX injection, 500-600 IU vial

3: Respiratory system

Section 3: Respiratory system

- Bronchodilators
- Corticosteroids
- Leukotriene receptor antagonists
- Allergic disorders
- Respiratory stimulants and pulmonary surfactants
- Aromatic inhalation
- Cough preparations
- Mucolytics

3 A: Bronchodilators

Various drugs including adrenoceptor stimulants, antimuscarinics and theophylline can produce bronchodilation.

3 A.1: Adrenoceptor stimulants

Adrenoceptor stimulants are either selective beta₂-adrenoceptor stimulants such as salbutamol and salmeterol, or nonselective adrenoceptor stimulants such as adrenaline and ephedrine.

3 A.1.1: Selective beta₂-adrenoceptor stimulants

Selective beta₂-adrenoceptor stimulants are available in various pharmaceutical formulations and can be effectively used in the management of mild to moderate types of asthma. Rapid response can be

achieved with pressurized aerosol inhalers. Oral preparations are reserved for children and patients who cannot tolerate inhalation; they have slower onset but longer duration of action than inhalers. It is more likely that side-effects such as tremor and headache are experienced more frequently with oral than inhalational preparations. Intravenous or subcutaneous injections are reserved for severe acute attacks when intense bronchospasm prevents the proper delivery of aerosol to the airways.

Use of inhalational preparations:

Administration by inhalation delivers the drug directly to the bronchi and is therefore required only in small doses.

Aerosols or pressurized inhalation is a convenient method for administration and drugs delivered can last for 3-5 hours for recommended doses of salbutamol and 12 hours for salmeterol or formoterol.

Patients should clearly be instructed and trained in the proper use of inhalers. Inadequate use should not be mistaken for drug ineffectiveness.

Respirator or nebuliser solutions are administered over a period of 5-15 minutes usually driven from an oxygen cylinder or a special electrical compressor.

For recommended management of different types of asthma *see* below.

3. Respiratory system

Salbutamol sulphate

Indications: asthma; premature labour

Contra-indications: hypersensitivity to salbutamol.

Cautions: hyperthyroidism, hypertension, serious cardiovascular diseases, diabetes mellitus; labour and delivery may be complicated; hypokalaemia may be exacerbated by high doses of salbutamol.

Side-effects: fine tremor, nervous tension, headache, muscle cramp.

Dose: oral (but use by inhalation preferred), 4 mg (maximum 8 mg) 3-4 times daily, reduce in elderly. Child, under 2 years 100 micrograms/kg 4 times daily (2-5 years 1-2 mg 3-4 times daily, 6-12 years 2 mg 3-4 times daily).

Subcutaneous or intramuscular, 500 microgram every 4 hours if necessary.

Slow intravenous injection, 250 microgram repeated if necessary.

Slow intravenous infusion, initially 5 microgram/minute adjusted to 3-20 microgram/minute according to response.

Aerosol inhalation, 100-200 microgram (1-2 puffs) 3-4 times daily, repeated every 4 hours when necessary for persistent symptoms. Child, 1 puff increased to 2 puffs if necessary, 3-4 times daily.

Inhalation of powder (salbutamol rotacap) 200 microgram 3-4 times daily.

Inhalation of nebulised solutions 2.5-5 mg up to 4 times daily when

necessary. Child, 2.5 mg repeated if necessary up to 4 times daily.

Preparations

Salbutamol sulphate rotacap, 200 microgram/rotacap (**Restricted**)

Salbutamol sulphate inhaler, 100 microgram/metered inhalation

Salbutamol sulphate nebules, 1 mg/mL, 2.5 mL nebules (**Restricted**)

Salbutamol sulphate nebuliser solution, 5 mg/mL solution, 15 - 30 mL (**Restricted**)

Salmeterol (Restricted)

Indications: asthma when long-term therapy is required.

Contra-indications Cautions and side-effects: see under salbutamol.

Dose: aerosol inhalation, 50 microgram (2 puff) twice daily, could be increased to 100 microgram twice daily.

Child, above 4 years 50 micrograms twice daily.

Preparations

Salmeterol aerosol inhaler, 25 microgram/ metered inhalation

Formoterol fumarate (Eformoterol fumarate) (Restricted)

Indications: asthma when long-term therapy is required.

Contra-indications Cautions and side-effects: see under salbutamol.

Dose: Powder inhalation, adult and child over 5 years, 12 microgram twice daily.

Preparations

3: Respiratory system

Formoterol powder for inhalation,
12 microgram/capsule

3 A.1.2: Other adrenoceptor stimulants

Ephedrine and adrenaline are non-selective adrenoceptor stimulants, which should be avoided in asthma since they are liable to cause cardiac irregularities. Adrenaline injection (*see* section 2) is used in the emergency treatment of acute allergic and anaphylactic reactions.

Ephedrine hydrochloride

Indications: asthma

Contra-indications: thyrotoxicosis; diabetes; pregnancy with maternal blood pressure above 130/80 mmHg; hypertension or other cardiovascular disorders.

Cautions: elderly, prostatic hypertrophy **Side-effects:** tachycardia, anxiety restlessness.

Dose: subcutaneous injection, 25-50 mg.

Intravenous injection, 5-25 mg /dose slowly, maximum 150 mg /day.

Preparations

Ephedrine SO₄ or HCl injection, 30-50 mg/mL, 1 mL ampoule

3 A.2: Antimuscarinics

Antimuscarinics, such as ipratropium, block acetylcholine from inducing bronchospasm or increasing the viscosity of mucous secretion.

Bronchodilation can be further induced by these drugs in patients already receiving beta2-adrenoceptor stimulants.

Ipratropium is more effective in relieving bronchoconstriction associated with chronic obstructive pulmonary diseases (COPD) than in relieving asthma.

Ipratropium bromide (Restricted)

Indications: bronchospasm, particularly in chronic bronchitis.

Contra-indications and Cautions: prostatic hypertrophy, glaucoma, pregnancy.

Side-effects: dry mouth; rarely urinary retention, constipation.

Dose: aerosol inhalation, 20-40 microgram, up to 80 microgram at a time, 3-4 times daily; child up to 6 years 20 microgram 2-3 times daily; 6-12 years 20-40 microgram 2-3 times daily.

Inhalation of nebulised solution, 250-500 microgram up to 4 times daily; child under 5 years 125-250 micrograms max. 1 mg daily; 6-12 years 250 micrograms, max. 1 mg daily.

Preparations

Ipratropium bromide aerosol inhaler, 20 microgram/metered inhalation

Ipratropium bromide nebuliser solution, 250 micrograms/mL vial

Ipratropium bromide nebuliser solution, 500 micrograms/2 mL vial

Tiotropium

Indications: Maintenance treatment in COPD.

Contra-indications, cautions and side-effects: *see* under ipratropium bromide

Dose: 18 micrograms inhaled once daily.

Preparations

Tiotropium inhaler powder, hard capsules, 18 micrograms/cap.

Note: each 18 micrograms capsule delivers 10 micrograms of tiotropium.

3 A.3: Theophylline

Theophylline and related compounds induce bronchodilatation by inhibiting phosphodiesterase enzyme and leading to increased intracellular cAMP which acts as a mediator for relaxation of smooth muscle and inhibition of histamine release from mast cells.

Theophylline derivatives are orally effective in less severe and more chronic asthma. Sustained release preparations are preferred to simple rapid release preparations.

Plasma concentration of theophylline can vary with serious consequences. There is a narrow margin between the therapeutic and toxic dose and therefore, the differences in half-life are very important. Theophylline is metabolized in the liver; there is considerable variation

in its half-life particularly in smokers, alcoholics, hepatic failure and when other drugs are used concurrently.

The use of injectable theophylline should be avoided in patients already receiving oral preparations; plasma level should be considered before administration in severe cases of asthma.

Intravenous aminophylline should be administered very slowly over a 20-30 minutes; intramuscular injection is painful.

Aminophylline

Note: aminophylline is a stable mixture of theophylline and ethylenediamine.

Indications: acute severe asthma.

Contra-indications: sensitivity to the drug.

Cautions: cardiac diseases, hypertension, epilepsy, hepatic impairment, slow administration (*see* notes above).

Side-effects: anxiety, confusion, nausea, insomnia, tachycardia; **rapid intravenous injection may cause severe hypotension and sudden death if given too rapidly.**

Dose: slow intravenous injection (over 20-30 minutes), 250-500 mg. Intravenous infusion, young patients, 750 mg /24 hours; adults, 1500 mg /24 hours.

Preparations

Aminophylline intravenous injection, 25 mg/mL, 10 mL ampoule

3: Respiratory system

Theophylline

Indications: chronic asthma.

Contra-indications: sensitivity to the drug.

Cautions: cardiac diseases, hypertension, epilepsy, hyperthyroidism, hepatic impairment, peptic ulcer.

Side-effects: anxiety, confusion, nausea, insomnia, tachycardia.

Dose: sustained release oral preparation, 200-300 mg twice daily. Children over 6 years, 125-250 mg twice daily.

Preparations

Theophylline sustained release tablets, 300 mg tab.

Theophylline syrup, 60 mg/5 mL

In patients with chronic continuing asthma, long-term therapy with oral steroids is used when other drugs fail to produce a response or patient relapses repeatedly into status asthmaticus. Concomitant use of inhalational steroids reduces the need for large oral doses. Oral steroids should be given as single morning dose to reduce interference with circadian secretion. Inhalational corticosteroids are better administered using large-volume spacer devices. These devices help by increasing airway deposition and reducing oropharyngeal deposition, which will contribute to a lesser incidence of oral candidiasis (thrush).

3 B : Corticosteroids

Inhalational corticosteroids are widely used for the treatment of less severe and more chronic asthma. Their use is associated with less frequent side-effects than systemic corticosteroids. The use of inhalational corticosteroids must be regularly maintained to achieve a therapeutic effect; 3-7 days are needed to get a maximum benefit. Patients are also advised to use salbutamol inhalation prior to the steroid inhalation for a better penetration of the steroid.

A short course of oral steroid such as prednisolone, or an injection of hydrocortisone is still used in the treatment of acute attacks of asthma (see treatment charts and sec.6 C.1).

Budesonide

Indications: prophylaxis of asthma.

Cautions: untreated severe respiratory infection; tuberculosis.

Side-effects: paradoxical bronchospasm; adrenal crisis (with prolonged high doses); adrenal suppression (with prolonged high doses); aggression (particularly in children); anxiety; behavioural changes (particularly in children); bruising; candidiasis of the mouth; candidiasis of the throat; cataracts; coma (with prolonged high doses); Cushing's syndrome (with moon face, striae and acne); depression; dysphonia; glaucoma (with prolonged high doses); hoarseness; hyperactivity (particularly in children); hyperglycaemia (usually only with high doses); irritability

3. Respiratory system

(particularly in children); lower respiratory tract infections in older patients with chronic obstructive pulmonary disease (with high doses); pneumonia in older patients with chronic obstructive pulmonary disease (with high doses); reduced mineral bone density (with long-term treatment of high doses); side-effects applicable to systemic corticosteroids may also apply if absorption occurs following inhaled use; sleep disturbances; throat irritation
Dose: inhalation of nebulised solutions, 1-2 mg twice daily, child 3 months-12 years, half the above doses.

Preparations

Budesonide nebuliser solution (Respules), 250 micrograms/mL, 2 mL ampoule

Budesonide nebuliser solution (Respules), 500 micrograms/mL, 2 mL ampoule

Budesonide/ Formoterol (Restricted)

For Indications, cautions and side-effects: see under individual drugs

Preparations

Budesonide / Formoterol powder for inhalation, 160/4.5 micrograms/blister

Fluticasone (Restricted)

Indications, cautions and side-effects: see under budesonide.

Dose: aerosol inhalation, adult, 125-250 microgram (1-2 puffs) twice daily, child 4-16 years, 50-100 microgram (1-2 puffs) twice daily. Dose can be adjusted according to severity of asthma.

Preparations

Fluticasone aerosol inhaler, 50 microgram/metered inhalation

Fluticasone aerosol inhaler, 100 microgram/metered inhalation

Fluticasone/ Salmeterol (Restricted)

For indications, cautions and side-effects: see under individual drugs

Preparations

Fluticasone/Salmeterol powder for inhalation, 100/50 micrograms/blister

Fluticasone/Salmeterol powder for inhalation, 125/50 microgram/blister

Fluticasone/Salmeterol powder for inhalation, 250/50 micrograms/blister

Fluticasone/Salmeterol powder for inhalation, 500/50 micrograms/blister

3 C: Leukotriene receptor antagonists

The leukotriene receptor antagonists including montelukast, block the effects of cysteinyl leukotrienes in the airways. They are effective in asthma when used alone or with

3: Respiratory system

an inhaled corticosteroid. Montelukast has not been shown to be more effective than a standard dose of inhaled corticosteroid but the two drugs appear to have an additive effect. The leukotriene receptor antagonists may be of benefit in exercise induced asthma and in those with concomitant rhinitis but they are less effective in those with severe asthma who are also receiving high doses of other drugs.

Montelukast

Indications: *see* notes above, prophylaxis of asthma, chronic asthma, symptomatic relief of seasonal allergic rhinitis in patients with asthma.

Cautions: pregnancy, breast-feeding.

Side-effects: abdominal pain, thirst; hyperkinesia (in young children), headache, dry mouth, diarrhoea, dyspepsia, nausea, vomiting, hepatic disorders, palpitation, oedema, increased bleeding, depression, tremor, asthenia, dizziness, hallucinations, paraesthesia, hypoesthesia, sleep disturbances, abnormal dreams, agitation, aggression, seizures, arthralgia, myalgia, pruritus, Churg-Strauss syndrome (medium and small vessel autoimmune vasculitis, leading to necrosis. It has occurred very rarely in association with the use of leukotriene receptor antagonists; in many of the reported cases the reaction followed the reduction or withdrawal of oral corticosteroid therapy. The prescribers should be alert

to the development of eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, or peripheral neuropathy).

Dose: prophylaxis of asthma, adult and child over 15 years, 10 mg once daily in the evening; child 6 months–6 years 4 mg once daily in the evening, 6–15 years 5 mg once daily in the evening; seasonal allergic rhinitis, adult and child over 15 years, 10 mg once daily in the evening.

Preparations

Montelukast chewable tablets, 5 mg tab.

Montelukast chewable tablets, 10 mg tab.

Montelukast sachet, 4 mg / sachet.

3 D: Monoclonal Antibodies

Omalizumab (Restricted)

Indications: Prophylaxis of severe persistent allergic asthma. Add-on therapy for chronic spontaneous urticaria in patients who have had an inadequate response to H1 antihistamine treatment

Cautions: Autoimmune disease; susceptibility to helminth infection—discontinue if infection does not respond to anthelmintic

Side-effects: Abdominal pain; arthralgia; headache; injection-site reactions; pyrexia; sinusitis; upper respiratory tract infection; bronchospasm; cough; diarrhoea; dizziness; drowsiness; dyspepsia; flushing; influenza-like illness; malaise;

3. Respiratory system

nausea; paraesthesia; pharyngitis; photosensitivity; postural hypotension; pruritus; rash; syncope; urticaria; weight gain.

Dose: Subcutaneous injection. Prophylaxis of severe persistent allergic asthma. Dose according to immunoglobulin E concentration and body-weight (consult product literature).

Add-on therapy for chronic spontaneous urticaria in patients who have had an inadequate response to H1 antihistamine treatment 300 mg every 4 weeks.

Preparations

Omalizumap solution injection, 150 mg/ml prefilled syringe

3 E: Allergic disorders

Drugs affecting allergic disorders of the upper respiratory tract, particularly antihistamines, are discussed in this section.

3 E.1: Antihistamines

These are H₁-receptor antagonists used for symptomatic relief of rhinorrhoea and sneezing associated with hay fever; they are less effective in relieving nasal congestion. Antihistamines are also used in prevention of urticaria, treatment of skin allergic reactions, insect bites, and drug-induced allergies.

Antihistamines have been classified according to their potential to induce sedation into sedating and non-sedating antihistamines.

Antihistamines differ in their duration of action, incidence of drowsiness and anticholinergic effects while no difference can be drawn on efficacy. Most of the non-sedating antihistamines have a long duration of action compared to the sedating agents. Promethazine may act for a long duration (10-12 hours).

3 E.1.1: Sedating antihistamines

3 E.1.1.1: Alkylamines

Chlorphenamine maleate
(*Chlorpheniramine*)

Indications: allergic disorders; emergency treatment of anaphylactic reactions.

Contra-indications and cautions: antihistamines should be used with caution in patients with glaucoma, prostatic hypertrophy, urinary retention and hepatic diseases. Elderly and children are more susceptible to side-effects.

Side-effects: drowsiness, headache, antimuscarinics effects; hypotension may be induced with injection

Dose: oral, 4 mg 3-4 times daily; Child under 1 year not recommended, 1-2 years, 1 mg twice daily, 2-5 years 1 mg 3-4 times

3: Respiratory system

daily, 6-12 years 2 mg 3-4 times daily.

Subcutaneous, intramuscular or slow intravenous injection, 10-20 mg; Child 1-6 years, 2.5-5mg, 6-12 years 5-10 mg (for all dose can be repeated up to four times in 24 hours).

Preparations

Chlorphenamine maleate tablets, 4 mg tab.

Chlorphenamine syrup, 2 mg/5 mL; 100 mL/bottle

Chlorphenamine maleate injection, 10 mg/mL ampoule

3 E.1.1.2 Phenothiazines

Promethazine hydrochloride

Indications: symptomatic relief of allergy; emergency treatment of anaphylactic reactions; sedation; motion sickness

Contra-indications, cautions and side-effects: as for chlorpheniramine

Dose: oral, 10-20 mg 2-3 times daily, or 25 mg at bed time, increased to 2 times daily; Child, under 2 years not recommended; 2-5 years 5-10 mg daily in 1-2 divided doses, 5-10 years 10-25 mg daily in 1-2 divided doses.

Deep intramuscular injection, 25-50 mg, maximum 100 mg; Child 5-10 years 6.25-12.5 mg

Slow intravenous injection in emergencies, 25-50 mg as a solution containing 2.5 mg/mL in water for injection, maximum 100 mg

Preparations

Promethazine hydrochloride tablets, 10 mg tab.

Promethazine hydrochloride tablets, 25 mg tab.

Promethazine hydrochloride syrup, 5-6 mg/5 mL; 100-125 mL/bottle

Promethazine hydrochloride injection, 25 mg/mL ampoule

3 E.2: Non-sedating antihistamines

Loratidine (Restricted)

Indications: symptomatic relief of allergy

Contra-indications and cautions: as for other antihistamines.

Side-effects: less antimuscarinics and sedative effects than other antihistamines; for other effects *see* chlorpheniramine.

Dose: orally, adult and child over 5 years 10 mg daily; Child 2-5 year 5 mg daily

Preparations

Loratidine tablets, 10 mg tab.

Loratidine syrup, 5 mg/5 mL; 75-100 mL/bottle

Cetirizine hydrochloride (Restricted)

Indications: symptomatic relief of allergy

Contra-indications and cautions: as for other antihistamines; reduce dose in renal impairment

3. Respiratory system

Side-effects: less antimuscarinics and sedative effects than other antihistamines; for other effects *see* chlorpheniramine.

Dose: 10 mg daily or 5 mg twice daily; Child 2-6 years 5 mg daily or 2.5 mg twice daily

Preparations

Cetirizine hydrochloride tablets, 10 mg tab.

Cetirizine hydrochloride syrup, 5 mg/5 mL; 75-100 mL/bottle

Note: MoH policy is that only one of the above non-sedating antihistamines, loratidine *or* cetirizine, will be purchased and supplied for use based on its cost effectiveness

3 E.3: Antihistamines and decongestants combinations

Oral antihistamines and sympathomimetic decongestants may be combined in one preparation to be used for the symptomatic relief of hay fever or vasomotor rhinitis. The decongestants may counter some of the sedative effects of antihistamine.

Antihistamine and decongestant preparations

Indications: symptomatic relief of allergy; hay fever and vasomotor rhinitis.

Contra-indications and cautions: *see* under antihistamines and sympathomimetics (*see* sec 2)

Side-effects: hypertension, palpitation, dizziness, psychiatric disturbances.

Dose: *see* under preparations

Preparations

Pseudoephedrine HCl 60 mg + triprolidine HCl 2.5 mg tablets

Dose: one tablet 3 times daily

Pseudoephedrine HCl 30 mg + triprolidine HCl 1.25 mg/5 mL syrup; 60-100 mL/bottle

Dose: adult 10 mL 3 times daily; Child 3-12 months 2.5 mL, 1-5 years 5 mL, 6-12 years 7.5 mL, 3 times daily

3 F: Respiratory stimulants and pulmonary surfactants

Respiratory stimulants (analeptics) such as doxapram are of doubtful value in treating respiratory failure induced by barbiturates or other CNS depressants. They are ineffective and may be harmful in asthma or in respiratory failure due to neurological or muscular disorders and in drug toxicity. However, analeptics are useful in acute ventricular failure in patients with chronic lung disease. These drugs have a narrow safety margin and can readily induce convulsion. Their use should be confined to inpatients under strict expert supervision. The use of analeptics has largely been replaced by ventilatory support. Surfactants have been used in the management

3: Respiratory system

of respiratory distress syndrome in preterm infants

Caffeine Citrate

Indications: neonatal apnoea; adjunct to extubation in preterm infants.

Cautions: necrotizing enterocolitis may occur, infants with cardiovascular disorders, hepatic or renal impairment and seizure disorders, other causes of apnoea should be eliminated before use, safety and efficacy in long-term treatment not established.

Side-effects: physical signs of withdrawal including irritability, lethargy; headache, tachycardia, raised serum glucose concentration.

Dose: orally or by intravenous injection, initially 20 mg/kg, then 5 mg/kg once daily starting 24 hours after initial dose (some neonates may require 10 mg/kg).

Preparations

Caffeine citrate oral solution injection, 20 mg/mL, 3 mL (single dose vial)

Caffeine citrate injection, 20 mg/mL, 3 mL vial

Doxapram hydrochloride

Indications: respiratory depression; acute respiratory failure

Contra-indications: severe hypertension, status asthmaticus, epilepsy.

Cautions: give with oxygen in severe irreversible airway obstruction; hyperthyroidism, hepatic impairment, pregnancy.

Side-effects: arrhythmias, nausea & vomiting, flushing, pruritus, tremors.

Dose: postoperative respiratory depression, intravenous injection 1-1.5 mg/kg or by intravenous infusion, 2-3 mg/minute adjusted according to response.

Acute respiratory failure, intravenous infusion 1.5-4 mg/minutes adjusted according to response.

Preparations

Doxapram injection, 20 mg/mL; 5 mL ampoule

Beractant

Indications: prevention and treatment of neonatal respiratory distress syndrome.

Cautions: continuous monitoring of blood gases.

Side-effects: pulmonary haemorrhage reported especially in more premature infants.

Dose: by endotracheal tube, 100 mg/kg equivalent to a volume of 4 mL/kg within 8 hours of birth, may be repeated within 48 hours at 6 hours interval.

Preparations

Beractant suspension, 25 mg/mL phospholipid suspension, 8 mL vial

Colfosceril

Indications: treatment and prophylaxis of respiratory distress syndrome.

Cautions: as beractant

Side-effects: as beractant

3. Respiratory system

Dose: by *endotracheal tube*, treatment, 67.5 mg/kg; if still intubated, may be repeated after 12 hours; prophylaxis, first dose soon after birth, if still intubated may be repeated 12 and 24 hours later.

Preparations

Colfosceril palmitate suspension 108 mg for reconstitution with 8 mL water for injections (when reconstituted contains 67.5 mg/5 mL) with *endotracheal tube connectors*

Note: Ministry of Health policy is that only one of the above pulmonary surfactants beractant *or* colfosceril will be purchased and made available for use

3 G: Oxygen

Oxygen should be considered as a drug. It is prescribed to hypoxaemic patients to increase alveolar oxygen tension and decrease the work effort of breathing to maintain a given arterial oxygen tension P_aO_2 . The concentration depends on the condition being treated; **an incorrect concentration could have serious or lethal effects.**

High concentration therapy up to 60% is safe in conditions like pneumonia, pulmonary thromboembolism and fibrosing alveolitis. In acute severe asthma the arterial carbon dioxide P_aCO_2 is subnormal but as asthma deteriorates it may rise steeply (especially in children).

These patients usually require high concentrations of oxygen and if the P_aCO_2 remains high in spite of other treatment, intermittent positive pressure ventilation needs to be urgently considered. Where blood gas measurements are not readily available a concentration of 35% to 50% oxygen delivered through a conventional mask is recommended. Exceptionally, asthma is diagnosed in patients with a long history of chronic bronchitis and probable respiratory failure; in these patients a lower concentration (24 to 28%) may be needed to limit oxygen-induced reduction of respiratory drive.

Low concentration oxygen therapy (controlled oxygen therapy) is reserved for patients with ventilatory failure due to chronic obstructive pulmonary disease (COPD) or other causes. The concentration should not exceed 28% and in some patients a concentration greater than 24% may be excessive. The aim is to provide just enough oxygen to correct the hypoxaemia without worsening pre-existing CO_2 retention and respiratory acidosis. Treatment should be carried out in hospital where facilities for blood gas measurements are available.

Oxygen gas

Re-fillable cylinders of 6, 12, 24, 48, 100 and 200 cubic feet (CF) are available.

3: Respiratory system

3 H: Aromatic inhalation

Inhalation of aromatic substances such as benzoin tincture compound or menthol added to warm water will facilitate the inhalation of moist warm air, which is useful and comforting in bronchitis. It can also help relieve nasal congestion in rhinitis or sinusitis.

Benzoin tincture compound, 4.5% solution.

Direction for use: add 5ml of tincture benzoin to 500 mL hot water (not boiling) and inhale the vapour.

3 I: Cough preparations

Cough preparations are generally of two classes; cough suppressants that help by ridding the patients of the distress of dry coughing, and cough expectorants, which help maintaining easy cough to expel mucous exudates.

3 I.1: Cough expectorants

These preparations have no advantage over warm steam inhalation to facilitate the expulsion of bronchial secretion; they may have some placebo effect.

These are compound preparation that may contain a number of ingredients often in sub-therapeutic doses of expectorant materials such as iodide, cough suppressants, antihistamines, sympathomimetics and sedatives.

Preparations

Cough expectorant for Children; 100-125 mL/bottle

Cough expectorant for Adults; 100-120 mL/bottle

3 I.2: Cough suppressants

Cough suppressants are used to stop unproductive cough and when cough is distressing. They may cause sputum retention and this may be harmful in patients with chronic bronchitis and bronchiectasis.

Codeine and dextromethorphan are commonly included in commercial cough preparations. Long-term use may lead to abuse and dependence problems. Sedating antihistamines are also found in many cough suppressant preparations and they tend to induce sedation and drowsiness. Codeine containing cough preparations are not recommended for use in children and are totally avoided in those under 1 year of age.

Preparations

Cough Suppressant (e.g. Butamirate citrate 15 mg/10 mL; 200 mL/bottle

3 J: Mucolytics

Bromhexine

Indications: for ICU patients to facilitate thin mucous secretion in bronchial obstruction caused by thick mucus.

Side-effects: nausea, diarrhoea

3. Respiratory system

Dose: with nebuliser, 2 mg/mL, 5 mL solution.

Preparations

Bromhexine nebulised solution, 2 mg/mL solution; 40 mL bottle

Dornase alfa (Restricted)

(Phosphorylated glycosylated recombinant human deoxyribonuclease 1 (rhDNase))

Indications management of cystic fibrosis patients with a forced vital capacity (FVC) of greater than 40% of predicted to improve pulmonary function.

Cautions: pregnancy, breast-feeding.

Side-effects: pharyngitis, voice changes, chest pain, laryngitis, rashes, urticaria, conjunctivitis.

Dose: adult and child over 5 years, by inhalation of nebulised solution (by jet nebuliser), 2.5 mg (2500 units) once daily (patients over 21 years may benefit from twice daily dosage).

Preparations

Dornase alfa nebuliser solution, 1 mg/mL (1000 units) solution, 2.5 mL vial

nary fibrosis by exerting both antifibrotic and anti-inflammatory properties.

Pirfenidone (Restricted)

Indications: Treatment of mild to moderate idiopathic pulmonary fibrosis

Contra-indications: Cigarette smoking

Cautions: Avoid exposure to direct sunlight—if photosensitivity reaction or rash occurs, dose adjustment or treatment interruption may be required (consult product literature). If treatment is interrupted for 14 consecutive days or more, the initial 2 week titration regimen should be repeated; if treatment is interrupted for less than 14 consecutive days, the dose can be resumed at the previous daily dose without titration.

Side-effects: Abdominal discomfort; anorexia; arthralgia; constipation; diarrhoea; dizziness; dry skin; dysgeusia; dyspepsia; erythema; flatulence; gastritis; gastro-oesophageal reflux disease; headache; hot flush; insomnia; malaise; myalgia; nausea; non-cardiac chest pain; photosensitivity reaction; pruritus; raised hepatic enzymes; rash; somnolence; upper respiratory tract infection; urinary tract infection; vomiting; weight loss

Dose: Initially 267 mg 3 times a day for 7 days, then increased to 534 mg 3 times a day for 7 days, then increased to 801 mg 3 times a

3 K: Antifibrotics

The exact mechanism of action of pirfenidone is not yet understood, but it is believed to slow down the progression of idiopathic pulmo-

3: Respiratory system

day. Concomitant use with ciprofloxacin requires a reduced dose of pirfenidone to 534 mg three times daily with high-dose ciprofloxacin (750 mg twice daily).

Preparations

Pirfenidone capsules, 200 mg cap

Section 4: Central nervous system

- Hypnotics and anxiolytics
- Drugs used in psychosis and related disorders
- Antidepressants
- Analgesics
- Antiepileptics
- Drugs used in Parkinsonism and related disorders
- Drugs used in nausea, vomiting and vertigo
- Drug used in substance dependence
- Drugs used for attention deficit hyperactivity disorder
- Dementia

4 A: Hypnotics and anxiolytics

4 A.1: Hypnotics

Insomnia should be considered an underlying symptom that has many causes including emotional and physical disorders or as a drug unwanted effect. Difficulty in falling asleep is common in the young and the elderly. It often occurs with emotional disturbances such as anxiety, nervousness, depression or fear. Sometimes people find it difficult to fall asleep simply because their body and brain are not tired. Insomnia may be transient, of short term or chronic.

Tolerance to the hypnotic effect may develop within 3-14 days of continued use. Prolonged use may

cause rebound insomnia and precipitate a withdrawal syndrome when treatment is discontinued. Hypnotics should be avoided in children and in the elderly who may become ataxic and confused. Caution should be observed when using the higher range of dose, which should only be used in the short term.

4 A.1.1: Hypnotic benzodiazepine derivatives

Midazolam (Controlled/restricted)

Indications: anaesthesia induction; conscious sedation.

Contra-indications: acute angle glaucoma.

Cautions: avoid intra-arterial injection, avoid extravasation; concomitant use of ketoconazole or itraconazole (syrup).

Side-effects: amnesia, respiratory depression.

Dose: intravenously, as induction agent, 0.15 - 0.35 mg / kg.

For conscious sedation, 0.05 - 0.1 mg / kg.

Preparations

Midazolam injection, 5 mg/mL, 3 mL ampoule

Midazolam tablets, 7.5 mg tab.

Midazolam syrup 2 mg/ml

4 A.1.2: Chloral and derivatives

Chloral hydrate

Indications: insomnia in children and the elderly (short-term use).

4. Central nervous system

Contra-indications: cardiac disease; gastritis; hepatic and renal impairment; pregnancy and breast feeding.

Cautions: respiratory diseases; avoid contact with skin and mucous membrane.

Side-effects: gastrointestinal disturbances, ataxia, nightmares, skin rash.

Dose: 0.5 - 1 g with plenty of water (30 minutes before bed time) maximum 2 g. Child 30-50 mg / kg, maximum 1 g.

Preparations

Chloral hydrate syrup, 500 mg/5 mL, 500 mL bottle

4 A.2: Anxiolytics

4 A.2.1: Benzodiazepine anxiolytics

Benzodiazepines are the most commonly used anxiolytics. They have replaced older generations of drugs such as barbiturates and meprobamate that used to have more adverse effects and interactions than benzodiazepines.

Benzodiazepine may show paradoxical effects such as increased aggression and hostility, increased anxiety and perceptual disorders. Patients on benzodiazepine should be advised not to drive or operate machinery that requires a high degree of attention as benzodiazepines impair psychomotor performance.

Both emotional and physical dependence may develop to benzodiazepines. Abrupt cessation may precipitate confusion, toxic psychosis, delirium or convulsion. Long-term use of benzodiazepines should be avoided. Withdrawal of benzodiazepine should be gradual to avoid withdrawal syndrome.

a) Long-acting benzodiazepine

Diazepam (Controlled)

Indications: anxiety or insomnia (short-term use); status epilepticus, febrile convulsion (see **Sec 4 E.4**), muscle spasm, perioperatively.

Contra-indications: respiratory depression; severe hepatic impairment, neuromuscular respiratory weakness, sleep apnoea syndrome.

Cautions: respiratory disease, muscle weakness and myasthenia gravis, simultaneous use of alcohol, pregnancy and breastfeeding, renal and hepatic impairment, avoid prolonged use and abrupt withdrawal.

Side-effects: drowsiness, light-headedness, confusion and ataxia, amnesia may occur.

Dose: oral, 2 mg 3 times daily for anxiety, increase to 5-10 mg 3 times daily when necessary. Insomnia, 5-10 mg at bedtime.

Intramuscular or slow intravenous in acute panic state, 10 mg repeated after 4 hours if necessary. By rectum, as rectal solution, acute anxiety 500 microgram/ kg repeated af-

ter 12 hours if required. As suppositories, when oral route is not appropriate, 10-30 mg.

For use in status epilepticus, *see* sec. 4.E.2

Preparations

Diazepam tablets, 5 mg tab.

Diazepam injection, 5 mg/mL, 2 mL ampoule

Diazepam suppository, 10 mg supp.

Diazepam rectal tube (rectal solution), 2.5-10 mg tube

b) Short-acting benzodiazepines

Bromazepam (Controlled /restricted)

Indications: anxiety (short-term use).

Contra-indications, cautions and side-effects: *see* diazepam.

Dose: 1.5 - 3 mg up to 3 times daily. Elderly and child, half the daily adult doses.

Preparations

Bromazepam tablets, 1.5 mg tab.

Lorazepam

Indications: anxiety or insomnia (short-term use). Also, in comparison to diazepam, it has less hang over effect.

Contra-indications, cautions and side-effects: *see* diazepam. Also, it carries greater risk of withdrawal syndrome than diazepam.

Dose: orally, 1-4 mg daily in divided doses for anxiety, 1-2 mg at

bedtime for insomnia. Elderly, half the daily adult doses.

Preparations

Lorazepam tablets, 1 mg tab.

4 A.2.2: Miscellaneous anxiolytics

Buspirone Hydrochloride (Controlled/restricted)

Indications: generalized anxiety disorders.

Contra-indications: epilepsy; severe hepatic or renal impairment, pregnancy and breast feeding.

Cautions: does not alleviate benzodiazepine withdrawal syndrome (a patients on benzodiazepine should still be gradually withdrawn). The dependence and abuse liability of buspirone has not yet been established.

Side-effects: dizziness, light-headedness, nausea.

Dose: 5 mg 2-3 times daily increase gradually. Usual maintenance dose 15-30 mg daily in divided doses. Long-term use may be indicated.

Preparations

Buspirone tablets, 5 mg tab.

Buspirone tablets, 10 mg tab.

Hydroxyzine hydrochloride

Indications: anxiety (short term), pruritus.

Contra-indications, cautions and side-effects: *see* notes under sedating antihistamines (sec.3.D.1.1)

Dose: anxiety, adult only 50-100 mg 4 times daily.

4. Central nervous system

Pruritus, 25 mg at night, increase as needed to 3-4 times daily. Child over 6 years, 15-25 mg daily, increase to 50 mg daily in divided doses.

Preparations

Hydroxyzine tablets, 10 mg tab.

4 B: Drugs used in psychosis and related disorders

Drugs used for the treatment of psychosis and manic conditions will be reviewed in this section.

4 B.1: Antipsychotics

Antipsychotics are of various chemical groups. Phenothiazines, butyro-phenones, thioxanthene derivatives and the newly introduced atypical antipsychotics are effectively applied in the management of psychotic disorders. They share the capability of blocking dopamine receptors in the brain. The new generation of atypical antipsychotics block both dopamine and serotonin brain receptors.

Antipsychotics improve mood and behaviour in schizophrenia. However, they treat delusion, hallucination, agitation and thought disorders in schizophrenia mania, dementia or acute intoxication with substances such as amphetamines. The typical antipsychotics produce emotional quieting, psychomotor slowing and indifference and may

seriously impair consciousness/alertness. They do not produce excessive sedation nor do they induce physical dependence. Antipsychotics are more effective in acute schizophrenia than in treating chronic symptoms.

Atypical antipsychotics reduce negative as well as positive symptoms of psychosis and do not seriously impair alertness and consciousness. Treatment with antipsychotics should continue for quite a long time after the first episode. Withdrawal requires careful supervision since acute relapse may follow cessation of therapy in some patients. Relapse, in others, appear after several weeks of stopping therapy.

The blockade of dopamine receptors in the brain is so widely distributed that the antipsychotic effects are hardly achieved without unwanted extrapyramidal (EP) effects.

EP effects are easily recognized but difficult to predict because they depend partly on the dose, type and duration of the antipsychotics; and partly on the susceptibility of the patient. Atypical antipsychotics rarely produce EP effects.

EP effects can be manifested as:

Acute dystonia, which is characterized by spasm of tongue, face, neck and back leading to abnormal movements. This could occur at a very early stage of treatment. It can be treated with antiparkinsonian drugs.

Akathesia (restlessness), which may resemble an exacerbation of

the condition being treated. This may appear after 5-60 days of therapy. It can be treated by reducing the dose or changing the drug.

Parkinsonian symptoms, which may develop gradually and can be treated with antiparkinsonian drugs of good anticholinergic effects.

Tardive dyskinesia, which develops as a delayed sequela of long-term antipsychotic use. It is difficult to treat but can be avoided by allowing the antipsychotic treatment course to be interrupted intermittently.

Other adverse effects associated with the use of antipsychotics include:

Hypotension and interference with temperature regulation which are dose related and could cause serious falls and hypothermia in the elderly.

Neuroleptic malignant syndrome manifested by hyperthermia, akinesia, muscle rigidity, autonomic imbalance and altered consciousness is a rare but lethal reaction to antipsychotics.

Hyperprolactinaemia has been associated with chronic use of antipsychotics. Effects such as galactorrhoea, amenorrhoea, gynaecomastia and impotence have been reported.

Choice of therapy from the available wide range of antipsychotics is a matter of suitability to a particular

patient, the degree of sedation required and susceptibility to EP effects. The atypical antipsychotics are better tolerated and show less serious EP effects.

4 B.1.1: Phenothiazines

Chlorpromazine hydrochloride

Indications: psychosis; antiemetic in palliative care; intractable hiccup.

Contra-indications: coma due to CNS depressants; bone marrow depression.

Cautions: epilepsy, parkinsonism, respiratory disease, pregnancy and breast-feeding.

Side-effects: dry mouth, constipation, EP effects, galactorrhoea, hypotension, sedation and drowsiness, headache, hypothermia.

Dose: For nausea, vomiting and agitation; 10-25 mg once or twice daily for a short period of time. Intramuscular injection 25-50 mg may be preferred in serious acute cases of agitation.

For excitement, restlessness, and violent behaviour control, 50-100 mg orally or deep intramuscularly. May be repeated every 3-4 hours up to 400 mg daily. In elderly one third or half the above dose. Child 6-12 years, half the adult dose (maximum 75 mg daily).

Intractable hiccup, 25-50 mg 3-4 times daily.

4. Central nervous system

Preparations

Chlorpromazine tablets, 25 mg tab.

Chlorpromazine tablets, 100 mg tab.

Chlorpromazine HCl injection, 25 mg/mL, 2 mL ampoule (**Restricted**)

Fluphenazine decanoate

Indications: maintenance in schizophrenia and other psychosis.

Contra-indications: *see* under chlorpromazine above. Do not use in children and in severely depressed.

Cautions: *see* under chlorpromazine. When transferring from oral to depot preparations, dosage by mouth should be gradually phased out.

Side-effects: EP effects may appear few hours after administration by injection and continue for two days and may be delayed. Others: *see* under chlorpromazine

Dose: deep intramuscular injection into the gluteal muscle, 12.5-25 mg at intervals of 2-5 weeks adjust according to response.

Preparations

Fluphenazine decanoate injection, 25 mg/mL, 1 mL vial

Trifluoperazine

Indications: Psychosis.

Contra-indications cautions and side-effects: *see* under chlorpromazine; less sedation and hypotension. EP effects are more frequent and may occur with low doses but more often with doses exceeding 6 mg daily.

Dose: schizophrenia and other psychotic disorders, adjunctive management of agitation, excitement and violent impulsive behaviour, 5 mg twice daily, or 10 mg modified release preparations. Increase as necessary. Child up to 12 years, 5 mg daily.

Preparations

Trifluoperazine tablets, 1 mg tab.

Trifluoperazine tablets, 5 mg tab.

Trifluoperazine retard capsules, 10 mg cap.

4 B.1.2 :Atypical antipsychotics

Clozapine (CDL)

Indication: is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia.

Contraindications: in patients with myeloproliferative disorders, uncontrolled epilepsy, paralytic ileus, history of agranulocytosis or neutropoenia, severe cardiovascular disorders, severe renal impairment, depression or comatose states from any cause.

Cautions: avoid abrupt withdrawal, monitor leucocytes and differential blood count, hepatic impairment, pregnancy, prostatic hypertrophy, susceptibility to angle closure glaucoma.

Side-effects: tachycardia, vomiting, constipation, nausea, headache, tremor, drowsiness, sweating, leucopenia, leucocytosis.

Dose: by mouth; initially, 12.5 mg once or twice on first day. If well tolerated, can be increased gradually, usual dose is 200–450 mg daily. Maximum dose 900 mg daily.

Preparations

Clozapine tablets, 25 mg tab.

Olanzapine (Restricted)

Indications: psychosis.

Contra-indications: angle closure glaucoma,; breast feeding.

Cautions: cardiovascular disease, epilepsy Parkinson's disease, prostatic hypertrophy, pregnancy, blood disease. Serum level may be slightly lowered by concomitant smoking or the use of carbamazepine.

Side-effects: weight gain, postural hypotension, mild EP effects, blood dyscrasias, hyperglycaemia.

Dose: initial, 10 mg daily, adjusted to 5–20 mg daily after assessment.

Preparations

Olanzapine tablets, 5 mg tab.

Olanzapine tablets, 10 mg tab.

Quetiapine

Indications: schizophrenia, treatment of episodes of mania either alone or with mood stabilisers.

Contraindications: breast-feeding.

Cautions: pregnancy, hepatic impairment, renal impairment, cerebrovascular disease, diabetes mellitus.

Side-effects: orthostatic hypotension, increased liver enzymes, agitation, drowsiness, dyspepsia, constipation, dry mouth, mild asthenia, rhinitis, tachycardia, leucopenia, neutropenia, eosinophilia, elevated plasma-triglyceride and cholesterol concentrations, reduced plasma-thyroid hormone concentrations, possible QT interval prolongation, oedema, priapism.

Dose: orally; Schizophrenia, 25 mg twice daily on day one, 50 mg twice daily on day two, 100 mg twice daily on day three, 150 mg twice daily on day four, then adjusted according to response, usual range 300–450 mg daily in 2 divided doses; max. 750 mg daily; elderly initially 25 mg daily as a single dose, increased in steps of 25–50 mg daily in 2 divided doses. Mania, 50 mg twice daily on day one, 100 mg twice daily on day two, 150 mg twice daily on day three, 200 mg twice daily on day four, then adjusted according to response in steps of up to 200 mg daily to max. 800 mg daily; usual range 400–800 mg daily in 2 divided doses; elderly initially 25 mg daily as a single dose, increased in steps of 25–50 mg daily in 2 divided doses.

Preparations

Quetiapine tablets, 25 mg tab.

Quetiapine tablets, 100 mg tab.

Quetiapine tablets, 200 mg tab.

4. Central nervous system

Risperidone (Restricted)

Indications: psychosis in which both negative and positive symptoms are prominent.

Contra-indications: breast-feeding.

Cautions: cardiovascular disease, pregnancy, renal and hepatic impairment.

Side-effects: insomnia, agitation impaired concentration, constipation, blurred vision, dry mouth, hyperprolactinaemia, sexual dysfunction, blood disorders.

Dose: initial dose 2 mg daily in divided doses, titrate gradually, usual dose range 4-6 mg daily in divided doses.

Preparations

Risperidone tablets, 2 mg tab.

Risperidone tablets, 4 mg tab.

Risperidone depot injection, 25 mg injection

Risperidone depot injection, 50 mg injection

out. It may have a mood elevating effect.

Side-effects: EP effects may appear 1-3 days after administration by injection and continue for 5-10 days and may be delayed. Others, *see* under chlorpromazine.

Dose: by deep intramuscular depot injection into the gluteal muscle, 20-40 mg at interval of 2-4 weeks. Adjust dose according to response; max. 400 mg weekly.

Preparations

Flupentixol decanoate oily injection, 40 mg/mL ampoule

Flupentixol decanoate oily injection,, 100 mg/mL ampoule

Zuclopenthixol acetate

Indications: maintenance in schizophrenia and other psychosis, particularly with aggression and agitation.

Contra-indications: *see* notes above

Cautions: *see* notes above

Side-effects: *see* notes above. Less sedation.

Dose: by deep intramuscular injection in the gluteal muscle, 50-100 mg at intervals of 2-3 days, adjusted according to response.

Preparations

Zuclopenthixol acetate injection, 50 mg/mL ampoule

4 B.1.3: Thioxanthene Derivatives

Flupentixol decanoate (Flupentixol decanoate)

Indications: maintenance in schizophrenia and other psychosis.

Contra-indications: *see* notes above, and under chlorpromazine

Cautions: *see* under chlorpromazine. When transferring from oral to depot preparation, dosage by mouth should be gradually phased

4 B.1.4: Butyrophenones

Haloperidol

Indications: schizophrenia and other psychosis, aggressive behaviour.

Contra-indications, cautions and side-effects: *see* under chlorpromazine; less sedation and fewer anti-muscarinics or hypotensive effects. EP effects are more frequent in thyrotoxic patients.

Dose: oral, 1.5-3 mg 2-3 times daily, or 3-5 mg 2-3 times daily in severe cases. Higher doses might be used in resistant cases.

Child, initially 25-50 microgram/kg daily in 2 divided doses; increase as necessary.

By intramuscular injection, 2-10 mg, repeated every 4-8 hours according to response.

For use in nausea and vomiting, intractable hiccup, orally 0.5-1.5 mg 3 times daily, adjusted according to response.

Preparations

Haloperidol tablets/capsules, 1.5 mg tab./cap.

Haloperidol tablets/capsules, 5 mg tab./cap.

Haloperidol tablets/capsules, 10 mg tab./cap.

Haloperidol liquid, 2 mg/mL, 100 mL bottle

Haloperidol liquid, 2 mg/mL, 15 mL drops

Haloperidol injection, 5 mg/mL ampoule

4 B.2: Anti-manic drugs

Lithium carbonate

Indications: prophylaxis and treatment of mania; prophylaxis of bipolar disorders; prophylaxis of recurrent depression.

Contra-indications: renal disease; cardiac disease, parkinsonism, potent sodium depleting diuretics, pregnancy, breast feeding.

Cautions: because of the narrow margin of safety, regularly monitor serum level; thyroid function test should be regularly performed; advise patient on adequate sodium and water intake; treatment to be discontinued when signs of toxicity appear such as ataxia, coarse tremor, dysarthria, blurred vision; severe toxicity is characterized by hyperextension of limbs, convulsion, circulatory failure and coma.

Side-effects: GI disturbances, nausea, diarrhoea, oedema, polyuria, polydipsia; hypothyroidism; hypokalaemia.

Dose: initially, 0.25-2g daily in divided doses; dose should be adjusted to give serum level 0.6-1.2mmol/litre in samples taken on empty stomach 12 hours after the last dose.

Preparations

Lithium carbonate tablets, 400 mg tab.

4. Central nervous system

4 C: Antidepressants

Older antidepressants such as the MAO inhibitors are presently of secondary role in the management of depression. Tricyclic and non-tricyclic compounds are widely used with the non-tricyclic compounds showing less incidence of adverse effects. However, a new group of selective serotonin re-uptake inhibitors (SSRIs) are progressively used which show fewer antimuscarinic side-effects than tricyclic compounds and also less cardiotoxic effects in high doses. Some neuroleptics in small doses may also have antidepressant effects though they do not fit into the above classification (e.g. flupenthixol which is used for the treatment of psychosis but has an antidepressant effect when used in small doses).

Patients with depression should be frequently assessed, especially in the early weeks of treatment, to detect any suicidal tendencies. Limited quantities of antidepressant drugs should be dispensed and made available to patients as antidepressants are highly toxic in overdosage. Newer drugs tend to be safer than tricyclic compounds. Treatment cannot be assessed before two weeks and thereafter should be maintained for about 6 months after the depression has resolved. In cases of relapses, patients may be in need for longer-term treatment.

The dose of antidepressants should be adjusted to obtain optimum response; optimum doses vary between individuals. Premature or sudden withdrawal of treatment may lead to recurrence of symptoms and increase risk of suicide.

4 C.1: Tricyclic and related antidepressant drugs

These drugs are effectively used for the treatment of moderate to severe depression. Psychomotor and physiological changes associated with depression are also affected; sleep normalization is the first benefit to be noticed. In most patients, due to the long half-life of tricyclic antidepressants, a single daily dose is sufficient, usually at night.

Tricyclic and related antidepressants can roughly be divided into sedative and less sedative. Agitated and anxious patients can be treated with sedative antidepressants such as, amitriptyline, maprotiline and clomipramine. Apathetic and withdrawn patients will benefit more from the less sedating antidepressants. The choice of antidepressant is governed by patient response and clinical assessment.

4 C.1.1: Tricyclic antidepressants

Amitriptyline hydrochloride

Indications: depression when sedative effect is particularly required; nocturnal enuresis in children.

Contra-indications: recent myocardial infarction, severe liver disease; arrhythmia.

Cautions: cardiac disease, epilepsy, pregnancy, breast feeding, thyroid dysfunction, urinary retention, angle closure glaucoma.

Side-effects: sedation, dry mouth, constipation, blurred vision, cardiovascular side-effects, behavioural changes, interference with sexual functions, weight gain and increased appetite.

Dose: depression, 75 mg daily in divided doses (reduce in elderly and young adult, 30-75 mg) or as a single dose at bed time. Increase gradually, if necessary, to maximum of 150 mg daily. Nocturnal enuresis, child 7-10 years 10-20 mg, 11-16 years 25-50 mg at night, for 3 months (gradual withdrawal).

Preparations

Amitriptyline HCl tablets, 25 mg tab.

Clomipramine hydrochloride

Indications: depression; obsessive-compulsive disorders.

Contra-indications, cautions and side-effects: *see* under amitriptyline

Dose: depression, 10 mg daily, increase as necessary to 30-150 mg daily in divided doses or as a single daily dose at bedtime. Reduce dose in elderly.

Obsessive compulsive disorders, 25 mg daily, increase over 2 weeks to 100-150 mg daily.

Preparations

Clomipramine HCl tablets, 10 mg tab.

Clomipramine HCl tablets, 25 mg tab.

Imipramine Hydrochloride

Indications depression when less sedative effects than amitriptyline are required; nocturnal enuresis in children.

Contra-indications, cautions and side-effects: *see* under amitriptyline but less sedation.

Dose: depression, initially up to 75 mg daily in divided doses increased gradually when necessary to 150-200 mg, reduced dose in elderly. Nocturnal enuresis in children, 7 years 25 mg, 8-11 years 25-50 mg, over 11 years 50-75 mg at bedtime for three months, (gradual withdrawal).

Preparations

Imipramine HCl tablets, 25 mg tab.

4 C.1.2: Related antidepressants

Maprotiline hydrochloride

Indications: depression, particularly when sedative effect is required

Contra-indications, cautions and side-effects: *see* under amitriptyline; antimuscarinics effects less frequent; skin rashes are common; risk of convulsions with higher dosage.

4. Central nervous system

Dose: initially 25-75 mg daily in divided doses or as a single dose at bedtime, increase gradually as necessary to maximum of 150 mg daily

Preparations

Maprotiline HCl tablets, 25 mg tab.

Maprotiline HCl tablets, 50 mg tab.

4 C.2: Selective serotonin re-uptake inhibitors (SSRIs)

SSRIs are found effective in depression with less antimuscarinic, sedative and cardiovascular effects than tricyclic compounds. They are of particular advantage in obsessive-compulsive disorders. Side-effects of their own such as anorexia and weight loss, abdominal pain, dyspepsia, constipation, diarrhoea, vomiting are also reported. Other side-effects include, nervousness, headache, anxiety, insomnia, tremor, sexual dysfunction, sweating and movement disorders.

SSRIs are contraindicated in epilepsy and in a patient entering a manic phase.

Citalopram (*Restricted*)

Indications: depression, panic disorder.

Contra-indications: *see* notes above

Cautions: concurrent electro-convulsive therapy, history of mania, history of bleeding disorders, hepatic and renal impairment, pregnancy and breast feeding.

Side-effects: *see* notes above, palpitation, tachycardia, postural hypotension, coughing, amnesia, migraine.

Dose: depression, 20 mg daily as a single dose, increase as necessary, maximum 60 mg daily.

Panic disorder, initially 10 mg daily gradually increased to 20 mg daily.

Preparations

Citalopram tablets, 20 mg tab.

Fluoxetine hydrochloride (*Restricted*)

Indications: depression, bulimia nervosa, obsessive-compulsive disorder.

Contra-indications: *see* notes above

Cautions: *see* notes above

Side-effects: *see* notes above; hypersensitivity reactions; insomnia, asthenia, tremor, headache, lupus-like syndrome, abnormal bleeding.

Dose: depression, 20 mg daily.

Bulimia nervosa, 60 mg daily.

Obsessive-compulsive disorder, initially 20 mg daily.

Preparations

Fluoxetine HCl capsules, 20 mg cap.

Paroxetine (*Restricted*)

Indications: depression, obsessive-compulsive disorder, social phobia, panic disorder.

Contra-indications: *see* notes above

Cautions: *see* notes above

Side-effects: *see* notes above; extrapyramidal side-effects have been reported; postural hypotension.

Dose: depression, 20 mg daily at morning, increase gradually when necessary to maximum of 50 mg daily.

Compulsive obsessive disorder, initially 20 mg at morning, increase gradually to a maximum of 60 mg daily.

Social phobia, 20 mg in the morning, increase gradually if response is not adequate after 2 weeks.

Preparations

Paroxetine tablets, 20 mg tab.

4 C. 3: Other antidepressant drugs

Duloxetine (Restricted)

Indications: Major depressive disorder. Generalised anxiety disorder. Diabetic neuropathy. Moderate to severe stress urinary incontinence

Cautions: Bleeding disorders; cardiac disease; elderly; history of mania; history of seizures; hypertension (avoid if uncontrolled); raised intra-ocular pressure; susceptibility to angle-closure glaucoma.

Side-effects: Abdominal pain; abnormal dreams; anorexia; anxiety; constipation; decreased appetite; diarrhoea; dizziness; drowsiness; dry mouth; dyspepsia; fatigue; flatulence; headache; hot flush; insomnia; nausea; nervousness; palpitation; paraesthesia; pruritus; sexual

dysfunction; sweating; tremor; visual disturbances; vomiting; weakness; weight changes; Bruxism; cold extremities; dysphagia; gastritis; halitosis; hepatitis; hypertension; hypothyroidism; impaired attention; impaired temperature regulation; movement disorders; muscle twitching; musculoskeletal pain; photosensitivity; postural hypotension; raised cholesterol; stomatitis; syncope; tachycardia; taste disturbance; thirst; urinary disorders; vertigo.

Dose: Major depressive disorder 60 mg once daily.

Generalised anxiety disorder. Initially 30 mg once daily, increased if necessary to 60 mg once daily; maximum 120 mg per day.

Diabetic neuropathy 60 mg once daily, discontinue if inadequate response after 2 months; review treatment at least every 3 months, maximum dose to be given in divided doses; maximum 120 mg per day.

Moderate to severe stress urinary incontinence 40 mg twice daily, patient should be assessed for benefit and tolerability after 2–4 weeks, alternatively initially 20 mg twice daily for 2 weeks, this can minimise side-effects, then increased to 40 mg twice daily, the patient should be assessed for benefit and tolerability after 2–4 weeks.

Preparations

Duloxetine tablets, 30 mg tabs

Duloxetine tablets, 120 mg tabs

4. Central nervous system

Flupentixol dihydrochloride (*Flupenthixol dihydrochloride*)

Indications: short term management of depression; psychosis (*see* section 4. B.1.3)

Contra-indications and cautions: cardiovascular disease, senile confusional state, parkinsonian disorders.

Side-effects: restlessness, insomnia, extrapyramidal effects.

Dose: initially 1 mg in the morning increased after 7 days to 2 mg when necessary, discontinue if no adequate response after one week of maximum dose (3 mg daily).

Preparations

Flupentixol dihydrochloride tablets, 1 mg tab.

Flupentixol dihydrochloride tablets, 3 mg tab.

4 D: Analgesics

4 D.1: Non-opioid analgesics

Mild to moderate pain can be treated with non-opioid analgesics such as aspirin or paracetamol. Headache, mild musculoskeletal pain or dysmenorrhoea can be managed with paracetamol or aspirin. Aspirin is contraindicated in children less than 12 years of age and in breast-feeding unless specifically indicated because of the possibility of developing Rye's syndrome. It is also contraindicated in patients

with peptic ulceration and in patients with a history of hypersensitivity to aspirin or other NSAIDs. Paracetamol is less irritant to the GI and has no association to Rye's syndrome when used in children. However, paracetamol overdosage causes hepatotoxicity.

Acetyl salicylic acid (Aspirin)

Indications: pyrexia, mild to moderate pain, antiplatelet (sec. 2.K.) and rheumatoid arthritis (sec. 10)

Contra-indications: children under 12 years and in breast feeding, GI ulceration, haemophilia.

Cautions: asthma, allergic disease, pregnancy.

Side-effects: generally highly tolerated, but high incidence of GI irritation. Asthma and skin rash in hypersensitive patients.

Dose: orally 300-900 mg every 4-6 hours when necessary. Maximum 4g daily.

By intravenous or intramuscular injection, 500-1000 mg repeated every 4-6 hours when needed.

Preparations

Aspirin tablets, 75-100 mg tab.

Aspirin tablets, 300 mg soluble tab.

Paracetamol

Indications: pyrexia, mild to moderate pain.

Contra-indications: hepatic and renal impairment, alcohol dependence.

Cautions: high doses may cause hepatic damage, which might not be apparent for 4-6 days.

Side-effects: rare when used for short period within recommended dosage ranges; rash and blood disorder.

Dose: adult, 0.75-1g 3-4 times daily, maximum 4 g daily in divided doses.

Child, 2 months old 60 mg for post immunization fever.

Under 3 months 10 mg / kg, 3-4 times daily.

3-12 months 60-120 mg, 3-4 times daily.

1-5 years 120-250 mg, 3-4 times daily.

6-12 years 250-500 mg, 3-4 times daily.

Preparations

Paracetamol tablets, 500 mg tab.

Paracetamol syrup, 120 mg/5 mL syrup, 50 - 75 mL/ bottle

Paracetamol paediatric drop, 100 mg/mL 15 mL drop

Paracetamol suppositories, 125-150 mg /supp.(for infants)

Paracetamol suppositories, 200-300 mg /supp (for children)

Paracetamol injection, 10 mg/mL, 100 mL vial

(Restricted) Caution to be used in children under 11 years old, consult product literature for further information

4 D.2: Opioid analgesics

Opioid analgesics are used for moderate to severe pain that is mainly of visceral origin. The main concern

over the use of opioids is the tendency of developing tolerance and dependence over repeated use. However this is not a deterrent from using them during terminal illnesses. Opioids dispensing is strictly controlled and restricted. The control measures require the writing of a special prescription by authorized doctors. All responsible staff must maintain proper records. Opioids, in addition to analgesia and to some extent euphoria, may induce sedation, constipation respiratory depression; cough suppression, urinary retention, nausea and vomiting. They produce these effects with some qualitative and quantitative variations.

Opioids are **contraindicated** in patients with asthma (avoid during attack), hypotension, head injury, intestinal obstruction, in patients with a history of drug abuse, raised intracranial pressure, during pregnancy or breast-feeding. Morphine remains the most commonly used drug of this group for severe pain and it is the standard against which other opioid analgesics are compared.

Morphine is the drug of choice for oral therapy of severe pain in palliative care. Phenothiazines in addition to their antiemetic effect, can be used concomitantly with morphine to improve the analgesic, sedative and euphoric effects.

Pethidine produces rapid but short lasting and less potent analgesic ef-

4. Central nervous system

fects than morphine. It has been applied during labour and pre-medication due to its weaker respiratory depressant effect.

Alfentanil and other related compounds are used by injection for intra-operative analgesia.

Methadone has a longer duration than morphine and has the advantage of being orally administered and less sedative.

Tramadol has fewer of the opioid side-effects and is thought to act by two different mechanisms; as an opioid and as enhancer of the serotonergic and adrenergic pathways.

Morphine (Narcotic)

Indications: moderate to severe pain of visceral origin; euphoria in terminal illnesses; pre-medication.

Contra-indications: *see* notes above

Cautions: hepatic and renal impairment, reduce dose in elderly, convulsive disorders, urinary retention.

Side-effects: nausea and vomiting (keeping patient at rest reduce side-effects) constipation, large doses produce respiratory depression, urinary retention, biliary spasm, headache, sweating, some patients may experience dysphoria and mood changes.

Dose: Acute pain, intramuscular or subcutaneous injection 10-15 mg every 4-6 hours if necessary. Child, 1-5 years 2.5-5 mg, 6-12 years 5-10 mg.

Slow intravenous injection, quarter to half corresponding intramuscular dose.

Premedication, by intramuscular or subcutaneous injection, up to 10 mg 60-90 minutes before operation.

Post-operative pain by intramuscular or subcutaneous injection, 10 mg every 2-4 hours.

Chronic pain, by mouth or subcutaneous or intramuscular injection 5-20 mg regularly every 4 hours, dose may be increased according to need.

Preparations

Morphine sulphate injection, 10 mg/mL ampoule

Morphine sulphate preservative free injection, 10 mg/mL ampoule

Morphine sulphate oral solution, 10 mg/5 mL vial or 100 mg/5 mL vial

Morphine sulphate slow release tablets, 10 mg S.R. tab.

Morphine sulphate slow release tablets, 30 mg S.R. tab.

Morphine sulphate slow release tablets, 40 mg S.R. tab.

Morphine sulphate slow release tablets, 60 mg S.R. tab.

Morphine sulphate regular release tablets, 10 mg tab.

Morphine sulphate regular release tablets, 30 mg tab.

Morphine sulphate regular release tablets, 60 mg tab.

Codeine Phosphate (Controlled)

Indications: mild to moderate pain.

Contra-indications, cautions and side-effects: *see* under morphine and notes above

Dose: 30-60 mg every 4-6 hours when necessary max, 240 mg daily in divided doses. Child, 1-12 years, 3 mg / kg daily in divided doses.

Preparations

Codeine phosphate tablets, 30 mg tab.

Fentanyl (Narcotic)

Indications: adjunct analgesic in anaesthesia; severe pain in cancer cases.

Contra-indications, cautions and side-effects: *see* under morphine and notes above; local reactions such as rash, and itching have been reported; rapid injection may produce muscular stiffness, bradycardia. Monitor patients using patches for increased side-effects if fever present (increased absorption possible).

Dose: by intravenous injection with spontaneous respiration, 50-200 micrograms then 50 micrograms as required. Child, 3-5 microgram/ kg and then 1 microgram/ kg as required.

With assisted ventilation larger doses are used, 300-3500 micrograms (0.3-3.5 mg) then 100-200 micrograms as required. Child, 15 micrograms/ kg, then 1-3 micrograms/ kg as required.

Preparations

Fentanyl citrate injection, 50 microgram/mL, 2 mL ampoule
Fentanyl citrate injection, 50 microgram/mL, 10 mL ampoule

Fentanyl transdermal patches, 12.5 micrograms/hour for 72 hours
Fentanyl transdermal patches, 25 micrograms/hour for 72 hours
Fentanyl transdermal patches, 50 micrograms/hour for 72 hours

Hydromorphone hydrochloride

Indications: severe pain in cancer.

Contraindications: *see* notes above; also acute abdomen

Cautions: *see* under morphine; also pancreatitis; toxic psychosis

Side-effects: *see* under morphine; also paralytic ileus, seizures, asthenia, agitation, and myoclonus

Dose: orally, 1.3 mg every 4 hours, increased if necessary according to severity of pain; child under 12 years not recommended.

Preparations

Hydromorphone hydrochloride capsules, 1.3 mg cap.

Hydromorphone hydrochloride capsules, 2.6 mg cap.

Pethidine hydrochloride (Narcotic)

Indications: moderate to severe pain, obstetric analgesia, peri-operative analgesia.

Contra-indications: *see* under morphine and notes above

Cautions: *see* under morphine and notes above; avoid in renal impairment; not suitable for continuous severe pain; avoid with liver enzyme inhibitors.

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Side-effects: *see* under morphine and notes above; convulsions reported with over-dosage.

Dose: acute pain, intramuscular injection, 50-100 mg (1-1.5 mg / kg) repeated after 4 hours. Child 0.5-2 mg / kg.

Slow intravenous injection 25-50 mg (0.5-1 mg / kg) repeated after 4 hours.

Obstetric analgesia, by intramuscular injection 50-100 mg (1-1.5 mg / kg), repeated after 1-3 hours.

Premedication, by intramuscular injection 50-100 mg (1-1.5 mg / kg) one hour before operation.

Preparations

Pethidine HCl injection, 50 mg/mL ampoule

Pethidine HCl injection, 50 mg/mL 2 mL ampoule

Remifentanil (*Narcotic*)

Indications: supplementation of general anaesthesia during induction and maintenance.

Contra-indications cautions and side-effects: *see* under morphine and notes above; bradycardia.

Dose: induction, intravenous infusion of 0.5-1 microgram/ kg/minute.

Maintenance in ventilated patient, intravenous infusion 0.05-2 microgram/ kg/minute.

Maintenance in spontaneous ventilation, 40nanograms/ kg/minute.

Preparations

Remifentanil injection, 1 mg vial

Remifentanil injection, 5 mg vial

Tramadol hydrochloride (*Controlled*)

Indications: moderate to severe pain.

Contra-indications cautions and side-effects: *see* under morphine and notes above; also hypertension may occur, hallucination and convulsions, not useful for patient as substitute for opioid dependence.

Dose: oral, 50-100 mg, every 4-6 hours, maximum 400 mg daily. Not recommended in children.

By intramuscular or intravenous injections, or intravenous infusion 50-100 mg every 4-6 hours.

Preparations

Tramadol HCl capsules, 50 mg cap.

Tramadol HCl injection, 50 mg/mL, 2 mL ampoule

Tramadol drop, 100 mg/mL solution, 10 mL/bottle (*C.D.L*)

4 D.3: Anti-migraine drugs

Migraine headache is a common disorder that is characterized by throbbing sensation and association with nausea and vomiting, photophobia, and a positive family history. Acute attack may well respond to simple measures such as bed rest and simple analgesics such as aspirin and paracetamol.

Metoclopramide is of particular benefit when acute attack is associated with gastric stasis, as it will stimulate the absorption of analgesics and exerts an antiemetic effect.

Prophylactic therapy is not necessary in patients having one attack a month or less. If attacks occur more frequently, a prophylactic measure needs to be taken. A wide variety of drugs have been used including antidepressants, antihistamines or beta-blockers.

A selective 5HT₁ agonist such as sumatriptan has been found considerably effective in the management of acute attacks.

Flunarizine hydrochloride (Restricted)

Indications: prophylaxis of migraine.

Contra-indications: hypersensitivity to flunarizine or cinnarizine.

Side-effects: sedation and drowsiness.

Dose: doses of 10 mg daily as a single dose and doses up to 20 mg 3 times daily have been used.

Preparations

Flunarizine hydrochloride capsules, 5 mg cap.

Naratriptan

Indications: treatment of acute attack of migraine.

Contra-indications: peripheral vascular diseases, ischaemic heart diseases, previous history of stroke, uncontrolled hypertension.

Cautions: hepatic and renal impairment, pregnancy and breast-feeding, sensitivity to sulphonamides.

Driving: May cause drowsiness and affect performance of skilled tasks

Side-effects: vision changes, tingling sensations, tiredness or weakness, nausea, vomiting, dizziness.

Dose: by mouth, 2.5 mg as soon as possible after onset. Can be repeated after four hours. However, if there is no benefit from the first dose a second dose should not be given.

Maximum dose 5 mg in 24 hours.

Preparations

Naratriptan tablets, 2.5 mg tab.

Rizatriptan

Indication: treatment of acute attack of migraine.

Contra-indications: ischemic heart disease, uncontrolled hypertension, Concurrent administration of MAO inhibitors, another 5-HT₁ agonist, or an ergotamine-containing medication.

Cautions: renal impairment, hepatic impairment, elderly and children, patients taking propranolol, pregnancy.

Side-effects: palpitation, diarrhoea and vomiting, paraesthesia, decreased mental acuity, euphoria and tremor, dyspnea, hot flushes.

Driving: May cause drowsiness and affect performance of skilled tasks.

Dose: single dose of 10 mg tablet, can be repeated after at least 2 hours; no more than 20 mg in 24-hour period.

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Preparations

Rizatriptan tablets, 10 mg tab.

Similar drugs:

Almotriptan tablets, 12.5 mg tab.

Frovatriptan tablets, 2.5 mg tab.

Sumatriptan succinate (Restricted)

Indications: treatment of acute attack of migraine.

Contra-indications: ischaemic heart disease, uncontrolled hypertension.

Cautions: should not be used for prophylaxis; hepatic impairment; pregnancy and breast-feeding; not to be used with other migraine therapy.

Side-effects: sensation of tingling, heat, and heaviness, tightness that may be due to coronary vasoconstriction or anaphylaxis.

Dose: 50 mg up to 100 mg immediately after an attack, maximum daily dose is 300 mg.

Preparations

Sumatriptan succinate tablets, 100 mg tab.

Zolmitriptan

Indications: treatment of acute attack of migraine.

Contra-indications: peripheral vascular diseases, ischaemic heart diseases, previous history of stroke, uncontrolled hypertension, Wolff-Parkinson-White syndrome or arrhythmias associated with accessory cardiac conduction pathways.

Cautions: hepatic and renal impairment, pregnancy and breast-feeding, should not be taken concurrently with other therapies for acute migraine.

Driving: May cause drowsiness and affect performance of skilled tasks

Side-effects: *see* under Naratriptan; dry mouth, drowsiness.

Dose: orally, 2.5 mg as soon as possible after onset. If migraine persists, can be repeated after at least two hours. Maximum dose 10 mg in 24 hours.

Preparations

Zolmitriptan tablets, 2.5 mg tab.

4 D.4: Other analgesics

Clonidine

Note: *This drug is only used in Oman for its analgesic property*

Indications: adjunct in pain management, postoperative analgesia, essential hypertension.

Contraindication: anticoagulant therapy, bleeding diathesis, epidural administration above the C4 dermatome, injection site infection.

Cautions: cardiovascular disease, depressive illness, concurrent anti-hypertensive therapy, pain management for obstetrical, post-partum, or perioperative (risk of haemodynamic instability).

Side-effects: hypotension, dry mouth, sedation, dizziness, nausea, nocturnal restlessness, bradycardia, rashes.

Preparations

Clonidine injection, 150 micrograms/mL, 1 mL ampoule

4 E: Antiepileptics

Epilepsy is a disorder of the electrical activity in the brain (cerebral dysrhythmia) characterized clinically by recurrent transient fits or disturbance of consciousness or abnormal motor activity or autonomic functioning. The aim of therapy is to control fits without producing a serious impairment so that the patient can lead a normal life with minimal restrictions.

Therapy usually starts with the minimal dose and gradually increases until fits are controlled or side-effects dominate. Low frequency of administration should be maintained to ensure patient compliance. Most antiepileptics are given twice daily except for some long acting drugs such as Phenobarbital or phenytoin that might be given once daily.

Treatment should be initiated with a single drug. Drug combinations should not be tried unless alternating with single drugs is no more effective in spite of administering maximum doses.

Drug plasma concentration may need to be monitored to avoid fluctuation in response. Most antiepileptics have a narrow therapeutic index. Interactions with other

drugs are a main cause of fluctuation in response.

Once treatment has started and control of fits is achieved, it should be maintained for at least 2 years. Abrupt withdrawal may aggravate the condition and precipitate status epilepticus.

There is an increasing risk of teratogenicity associated with the use of antiepileptics during pregnancy. Women on antiepileptics who wish to be pregnant should be advised on the possible consequences. Adequate folate administration before and during pregnancy may lower the possibility of neural tube defects. Withdrawal of the treatment during pregnancy involves greater danger to the mother and the foetus. Choice of therapy depends on the type of epilepsy. Generalized tonic-clonic seizure is better treated with carbamazepine, phenytoin and sodium valproate. Phenobarbital is an alternative but is more sedating. For absence seizure (petit mal) ethosuximide and sodium valproate are the drugs of choice.

Myoclonic seizures are well treated with sodium valproate. Clonazepam, ethosuximide or lamotrigine may also be used.

4 E.1: Control of grand mal and partial seizures

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Carbamazepine

Indications: partial and generalized tonic-clonic seizures; trigeminal neuralgia.

Contra-indications: AV conduction abnormality; bone marrow depression.

Cautions: hepatic or renal impairment; blood disorders; pregnancy and breast feeding.

Side-effects: nausea and vomiting, dizziness, drowsiness, ataxia, blood disorders, skin rashes.

Dose: oral, 100-200 mg 1-2 times daily, increase gradually to maintenance dose of 0.8-1.2g daily in divided doses. Child up to 1 year 100-200 mg, 1-5 years 200-400 mg, 6-10 year 400-600 mg, 10-15 year 600 mg-1g, daily in divided doses.

Preparations

Carbamazepine tablets, 100 mg tab.

Carbamazepine tablets, 200 mg tab.

Carbamazepine tablets, 200 mg controlled release tab.

Carbamazepine syrup, 100 mg/5 mL (2%) syrup; 100 mL/bottle

Clonazepam (Controlled/restricted)

Indications: adjunct in all forms of epilepsy.

Contra-indications: severe liver disease, respiratory insufficiency.

Cautions: avoid abrupt withdrawal, reduce dose in elderly, renal and hepatic impairment, as benzodiazepine derivatives *see* under diazepam.

Side-effects: drowsiness, fatigue, muscle hypotonia, and hypersalivation in infants.

Dose: 1 mg initially at night for 4 nights, increased gradually to 4-8 mg daily in divided doses if necessary.

Child up to 1-year 250 microgram increased gradually to 0.5-1 mg, 1-5 years 250 microgram increased gradually to 1-3 mg, 6-12 years 0.5 mg increased gradually to 3-6 mg, daily in divided doses.

Preparations

Clonazepam tablets, 0.5 mg tab.

Clonazepam tablets, 2 mg tab.

Clonazepam oral drops, 2.5 mg/mL; 10 ml drops

Ethosuximide (Restricted)

Indications: Absence seizure.

Cautions: hepatic and renal impairment; regular blood counts for possible blood disorders.

Side-effects: nausea, abdominal pain, headache, fatigue, ataxia, hiccup, psychosis, and depression.

Dose: initially 500 mg daily increased gradually to patient's needs, maximum 2 g daily.

Child up to 6 year 250 mg daily, over 6 year 500 mg increased slowly to a maximum 1 g daily.

Preparations

Ethosuximide capsules, 250 mg cap.

Ethosuximide syrup 250 mg / 5 ml

Gabapentin (Restricted)

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Indications: monotherapy and adjunctive treatment of partial seizures with or without secondary generalisation, peripheral neuropathic pain, trigeminal neuralgia.

Cautions: avoid abrupt withdrawal, elderly; renal impairment, diabetes mellitus, false positive readings with some urinary protein tests, pregnancy, breast-feeding.

Side-effects: diarrhoea, dry mouth, dyspepsia, nausea, vomiting, constipation, abdominal pain, flatulence, appetite changes, gingivitis, weight gain; hypertension, vasodilation, oedema; dyspnoea, cough, rhinitis; confusion, depression, hostility, sleep disturbances, headache, dizziness, anxiety, amnesia, ataxia, dysarthria, nystagmus, tremor, asthenia, paraesthesia, hyperkinesia; influenza-like symptoms; impotence, urinary incontinence; leucopenia; myalgia, arthralgia; diplopia, amblyopia; rash, purpura, pruritus, acne, pancreatitis, hepatitis, jaundice, palpitation, hallucinations, movement disorders, thrombocytopenia, blood-glucose fluctuations in patients with diabetes, tinnitus, acute renal failure, Stevens-Johnson syndrome, and alopecia.

Dose: epilepsy and neuropathic pain, orally, 300 mg on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times daily on day 3 *or* initially 300 mg 3 times daily on day 1; then increased according to response in steps of 300 mg daily (in 3 divided doses) every 2–3 days;

usual dose 900 to 3600 mg/day in 3 divided doses.

Preparations

Gabapentin tablets, 300 mg tab.

Levetiracetam (Restricted)

Indication: monotherapy treatment mainly for partial seizures with or without secondary generalisation or as an adjuvant. **Cautions:** renal impairment and hepatic impairment; pregnancy; breastfeeding. Avoid sudden withdrawal.

Side-effects: dizziness, ataxia, convulsion, depression, weight changes, insomnia, tremor, visual disturbances, dyspepsia, nausea.

Dose: for monotherapy, initially 250 mg twice daily increased according to response; maximum 1.5 g twice daily. For adjuvant therapy 500 mg twice daily up to 1.5 g at same frequency. Child and adolescent (4–18 years), 10 mg/kg twice daily up to 30 mg/kg at same frequency.

Preparations

Levetiracetam tablets, 250 mg tab.

Levetiracetam tablets, 500 mg tab.

Levetiracetam tablets, 1 g tab.

Levetiracetam syrup, 100 mg/mL, 300 mL bottle

Phenobarbital (Phenobarbitone) (Controlled/restricted)

Indications: all forms of epilepsy except absence seizure; status epilepticus.

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Cautions: elderly, children, impaired hepatic or renal function, respiratory depression, pregnancy and breast feeding, potentiate other CNS depressants.

Side-effects: sedation, lethargy mental depression, ataxia, and allergic skin reactions.

Dose: oral, 60-180 mg at night. Child 5-8 mg / kg daily.

Intramuscular injection, 200 mg repeated after 6 hours if necessary.

Status epilepticus, by intravenous injection (dilute injection 1 in 10 mL of water for injection) 10 mg / kg at a rate not exceeding 100 mg /minute, maximum 1g.

Preparations

Phenobarbital tablets, 30 mg tab.

Phenobarbital elixir, 15 mg/5 mL elixir; 500 mL/bottle

Phenobarbital injection, 200 mg/mL, 1 mL ampoule

Phenytoin

Indications: all forms of epilepsy except absence seizure.

Cautions: hepatic impairment; pregnancy and breast feeding; avoid sudden withdrawal; blood count to be carried out regularly.

Side-effects: nausea and vomiting, mental confusion, headache, insomnia, and tremor occur commonly. Skin rash, coarse facies, acne and hirsutism, fever and hepatitis; epidermal necrolysis, lupus erythematosus, Stevens-Johnson syndrome, polyarteritis nodosa; gingival hypertrophy, and tenderness;

rarely haematological disorders including megaloblastic anaemia which responds to folic acid therapy; plasma calcium concentration may be lowered leading to rickets and osteomalacia.

Intravenous (rapid) administration may lead to heart block and cardiac arrhythmias particularly in patients with cardiac disease and the elderly; it may also cause hypotension and CNS depression.

Sign of overdose include slurred speech, nystagmus, blurred vision and ataxia.

Dose: orally 150-300 mg daily, gradually increased to 400 mg if necessary, as a single dose or 2 divided doses. Child 1 month-12 years, 1.5-2.5mg/kg twice daily adjusted to between 2.5-5mg / kg twice daily for maintenance. Intravenous (*see* section 4 E.2)

Preparations

Phenytoin sodium capsule, 50 mg cap.

Phenytoin sodium capsule, 100 mg cap.

Phenytoin sodium suspension, 30 mg/5 mL susp.; 500 mL /bottle

Sodium valproate

Indications: all forms of epilepsy.

Contra-indications: active liver disease, porphyria.

Cautions: monitor liver function; renal impairment; check for bleeding tendencies.

Side-effects: nausea, gastric irritation, reversible hair loss; oedema;

inhibition of platelet aggregation; weight gain and increased appetite.

Dose: orally, 600 mg daily in 2 divided doses after meal, increase at 3 days intervals by 200 mg to a maximum of 2.5g daily in divided doses if necessary, usual maintenance dose 1-2g daily.

Child under 20 kg, initially 20 mg / kg daily in divided doses. Child over 20kg, 400 mg daily in divided doses.

Preparations

Sodium valproate tablets, 200 mg tab.

Sodium valproate tablets, 500 mg tab. Sodium valproate syrup, 200 mg/5 mL syrup 100 – 150 mL /bottle

Sodium valproate injection, 400 mg vial

Topiramate (Restricted)

Indications: partial and generalized tonic-clonic seizures; adjunctive treatment of seizures in Lennox–Gastaut syndrome; prevention of migraine in adults.

Contra-indications: breast-feeding.

Cautions: history of psychiatric disorders, ensure adequate hydration (especially if history of nephrolithiasis and hypercalciuria), renal impairment and hepatic impairment.

Side-effects: headache, confusion, amnesia, impaired concentration, depression, nervousness, agitation,

hallucinations, paraesthesia, dizziness, fatigue, speech disorder, reduced serum bicarbonate (Metabolic acidosis), nephrolithiasis, weight loss, leucopenia. Also, has been associated with acute myopia with secondary angle-closure glaucoma.

Dose: In epilepsy: if used alone, initially, 25 mg once daily at bedtime; then increase daily dose at intervals of at least a week by 25–50 mg. Maintenance, 50 mg twice daily. Maximum dose is 400 mg daily, child 6-16, initially 0.5-1 mg/kg daily. Maintenance, 3–6 mg/kg daily in 2 divided doses. Maximum 15mg/kg daily. In adjunctive treatment, initially, 25 mg once daily as a single dose at bedtime then increase gradually. Usual dose, 100–200 mg twice daily. Maximum, 800 mg daily. Child 2-16, initially, 1–3 mg/kg daily (up to 25) mg daily as a single dose at bedtime; increase daily dose at intervals of at least a week by 1–3 mg/kg. Maintenance, 5–9 mg/kg daily in 2 divided doses. Maximum, 15 mg/ kg daily. Migraine prophylaxis: Initially, 25 mg daily as a single dose at bedtime; then increase daily dose at intervals of at least a week by 25 mg, according to response. Maintenance, 25–50 mg twice daily.

Preparations

Topiramate tablets, 25 mg tab.

Topiramate tablets, 50 mg tab.

Topiramate tablets, 100 mg tab.

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Topiramate sprinkle capsules, 15 mg cap.

Preparations
Diazepam injection, 5 mg/mL, 2 mL ampoule

4 E.2: Drugs for status epilepticus

The drug of first choice in the treatment of status epilepticus is intravenous diazepam. The possibility of respiratory depression should be kept in mind and **resuscitation facilities should be available**. Absorption from intramuscular injection is too slow to cater for the emergency situation. If status epilepticus continues or returns in short period then other drugs are tried.

Phenytoin is given by slow intravenous injection to prevent recurrence.

Clomethiazole (Chlormethiazole) is given by intravenous infusion and because of its short half life, the rate of infusion can be monitored to meet the patient's clinical condition.

Diazepam (Controlled/restricted)

Indications: status epilepticus, convulsion (*see* sec.4 A.2.1 for other indications)

Contra-indications, cautions and side-effects: *see* under diazepam; hypotension and apnoea may occur with intravenous administration.

Dose: intravenous injection, 10-20 mg at a rate of 5 mg / minute, repeated if necessary after 30-60 minutes.

Child 200-300 microgram / kg or 1 mg per year of age.

Phenytoin Injection (Restricted)

Indications: status epilepticus, seizure in neurosurgery (others *see* sec. 4E.1)

Contra-indications: heart block.

Cautions: hypotension, heart failure, resuscitation facilities should be available.

Side-effects: intravenous injection may cause cardiovascular and CNS depression.

Dose: intravenous infusion or slow injection, loading dose 10-15 mg / kg at a rate not greater than 50 mg / minute, followed by maintenance oral or intravenous dose of 100 mg every 6-8 hours.

Child, a loading dose of 15-20 mg / kg at a rate not greater than 1-3 mg / kg / minute.

Preparations
Phenytoin injection, 50 mg/mL, 5 mL ampoule

4 E.3: Adjunct therapy of epilepsy

Lamotrigine (Restricted)

Indications: monotherapy and adjunctive treatment of partial seizure and primary and secondary generalized tonic-clonic seizure.

Contra-indications: hepatic impairment.

Cautions: closely monitor for blood disorder, hepatic and renal

functions; skin rash, influenza like symptoms might call for early withdrawal. Avoid abrupt withdrawal; withdraw gradually over 1-2 weeks.

Side-effects: rash, fatigue, dizziness, headache, Steven's Johnson Syndrome, toxic epidermal necrolysis, hypersensitivity reactions.

Dose: monotherapy, 25-50 mg 4 times daily, increase as necessary to maximum 500 mg daily.

Adjunct therapy with other antiepileptics, adjust dose according to response.

Preparations

Lamotrigine tablets, 5 mg tab.

Lamotrigine tablets, 25 mg tab.

Lamotrigine tablets, 50 mg tab.

Vigabatrin (Restricted)

Indications: epilepsy not satisfactorily controlled by other antiepileptics, monotherapy for the management of infantile spasms.

Contra-indications: pregnancy, visual field defects.

Cautions: renal impairment; elderly; close monitoring of the neurological functions; history of psychosis and behavioural problems.

Side-effects: drowsiness, dizziness, behaviour changes, anxiety, weight gain.

Dose: 2-3 g daily in divided doses. Child 1-2 g daily in divided doses.

Preparations

Vigabatrin tablets, 500 mg tab

4 E.4: Febrile Convulsions

Brief febrile convulsions need only simple treatment such as antipyretics e.g. paracetamol. Prolonged febrile convulsions (15 minutes or more), recurrent febrile convulsions or those occurring in a child at risk need more active treatment as there is a possibility of brain damage. Diazepam is the drug of choice given either by slow intravenous injection or preferably, rectally in solution.

The rectal route is the preferred route in febrile convulsions using the rectal solution. Suppositories are not suitable for febrile convulsions as absorption is too slow. For preparations see under Diazepam Sec 4 A.2.1

4 F: Drugs used in Parkinsonism and related disorders

Parkinson's disease is a slowly progressing, degenerative disorder of the nervous system. It has several distinguished characteristics; tremor at rest, sluggish initiation of movement and muscle rigidity. The basal ganglia nerve cells help smooth movement and coordinate changes in posture through a balance between the cholinergic and dopaminergic systems. Degeneration of nerve cells in the basal ganglia will lead to a reduction in dopamine, the dopaminergic neuro-

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transmitter. There is no clear reason for this degeneration. Parkinson's disease can be of known cause as in case of late complications of viral encephalitis, or drug induced as in the case with antipsychotic drugs.

Treatment of Parkinson's disease centred on replenishing the depleted dopamine stores in the basal ganglia. Inhibiting the cholinergic activities can also help in treatment by using centrally acting antimuscarinic drugs.

4 F.1: Dopaminergic drugs

Levodopa is the drug of choice in severe Parkinsonism. It can reduce hypokinesia and rigidity and may benefit tremor. It is of no value in treating drug-induced or post-encephalitic parkinsonism.

Peripheral metabolism of levodopa will reduce the centrally available drug. It is therefore recommended that peripheral decarboxylase inhibitors be administered with levodopa. This, in addition to inhibiting peripheral metabolism, will lower the peripheral effects such as cardiovascular side-effects. Levodopa may some times lose its effectiveness after several months of therapy and the patient experiences marked change from mobility to immobility (known as on-off effect). These fluctuating disabilities may last from minutes to hours. The cause

of this fluctuation could be attributed to plasma level variation.

Levodopa + Carbidopa (Co-Careldopa)

Indications: parkinsonism (but not drug-induced).

Contra-indications: closed angle glaucoma.

Cautions: peptic ulcer, cardiovascular diseases, diabetes mellitus, open angle glaucoma, avoid abrupt withdrawal.

Side-effects: anorexia, nausea and vomiting, insomnia, agitation, postural hypotension reddish discoloration of urine and other body fluids, psychotic disorders.

Dose: levodopa 100 mg + carbidopa 25 mg, one tablet thrice daily increased according to response. Maximum 8 tablets daily in divided doses.

Levodopa 250 mg + carbidopa 25 mg one tablet twice daily increased according to response. Maintenance dose 3-6 tablets in divided doses.

Preparations

Levodopa + carbidopa tablets, 100 + 25 mg tab.

Levodopa + carbidopa tablets, 250 + 25 mg tab.

Carbidopa with Entacapone and Levodopa (Restricted)

Indications: Parkinson's disease

Contra-indications: History of neuroleptic malignant syndrome;

history of non-traumatic rhabdomyolysis, pheochromocytoma; also see co-careldopa.

Cautions: Excessive daytime sleepiness and sudden onset of sleep can occur with carbidopa with entacapone and levodopa. ischemic heart disease; also see co-careldopa.

Side-effects: Abdominal pain; abnormal dream; confusion; constipation; diarrhoea; dizziness; dry mouth; dyskinesia; dystonia; fatigue; hallucinations; insomnia; ischemic heart disease; nausea, sweating, reddish-brown urine, vomiting; myocardial infarction; also see co-careldopa.

Dose: See product literature.

Preparations

Carbidopa with Entacapone and Levodopa tablet 100/25/200 mg tabs

Carbidopa with Entacapone and Levodopa tablet 150/37.5/200 mg tabs

Amantadine hydrochloride

Indications: Parkinson's disease, antiviral.

Contraindication: epilepsy, history of gastric ulceration, pregnancy, breast-feeding.

Cautions: hepatic impairment; renal impairment, congestive heart disease, confused or hallucinatory states, elderly, avoid abrupt withdrawal in Parkinson's disease.

Driving: May cause drowsiness and affect performance of skilled tasks

Side-effects: anorexia, nausea, nervousness, inability to concentrate, insomnia, dizziness, convulsions, hallucinations or feelings of detachment, blurred vision, gastrointestinal disturbances, livedo reticularis, peripheral oedema, leucopenia, rashes.

Dose:

Parkinson's disease, 100 mg daily increased after one week to 100 mg twice daily, max. 400 mg daily; elderly 65 years and over, 100 mg daily adjusted according to response.

Preparations

Amantadine hydrochloride capsules, 100 mg cap.

Selegiline hydrochloride

Indications: Parkinson's disease, used alone or as adjunct to levodopa with dopa-decarboxylase inhibitor.

Contraindications: pregnancy, breast-feeding.

Cautions: avoid abrupt withdrawal; gastric and duodenal ulceration (avoid in active ulceration), uncontrolled hypertension, arrhythmias, angina, psychosis, side-effects of levodopa may be increased, concurrent levodopa dosage can be reduced by 10–20%.

Side-effects: nausea, constipation, diarrhoea, dry mouth; postural hypotension; dyskinesia, vertigo,

4. Central nervous system

sleeping disorders, confusion, hallucinations; arthralgia, myalgia; mouth ulcers with oral lyophilisate; arrhythmias, agitation, headache, micturition difficulties, skin reactions; chest pain.

Dose: 10 mg in the morning, or 5 mg at breakfast and midday, elderly; start treatment with a dose of 2.5 mg daily.

Preparations

Selegiline hydrochloride tablets, 5 mg tab.

4 F.2: Antimuscarinic drugs

Antimuscarinic drugs are less effective than levodopa in the treatment of parkinsonism although they may supplement its effects. They are more effective in reducing rigidity and tremor but do not affect hypokinesia. Mild cases of Parkinsonism can be managed with antimuscarinic drugs alone and in severe cases can be combined with levodopa or other drugs. They have a value in post-encephalitic parkinsonism.

Antimuscarinic drugs also reduce the symptoms of drug-induced Parkinsonism, but there is no justification on using them with antipsychotics unless parkinsonian side-effects appear. There is no place for antimuscarinic drugs in the therapy of tardive dyskinesia, they may even exacerbate the condition.

Procyclidine hydrochloride

Indications: parkinsonism; drug induced extrapyramidal symptoms (*see* notes above)

Contra-indications: untreated urinary retention, angle-closure glaucoma, GI obstruction.

Cautions: cardiovascular disease, hepatic and renal impairment.

Side-effects: dry mouth, dizziness, confusion, blurred vision, and light-headedness.

Dose: orally 2.5 mg 3 times daily gradually increase if necessary, maximum daily dose is 30 mg in divided doses. Intramuscularly in acute dystonia, 5-10 mg repeated if necessary after 20 minutes. Intravenously, 5 mg, which usually acts within 5 minutes.

Preparations

Procyclidine HCl tablets, 5 mg tab.
Procyclidine HCl injection, 5 mg/mL, 2 mL ampoule

4 F.3: Drugs used in essential tremor, chorea, tics, and related disorders

Botulinum Toxin Type A

Indications: blepharospasm, hemifacial spasm.

Contra-indications: generalized disorders of muscle activity like myasthenia gravis.

Cautions: pregnancy, breast-feeding, history of aspiration or dysphagia, specific cautions related to above indications; angle closure glaucoma, avoid injection in lower lid area to avoid ectropion.

Side-effects: excessive doses may paralyse distant muscles, influenza like symptoms, hypersensitivity reactions, specific side-effects related to above indications; keratitis, eye dryness, ptosis, facial oedema, photophobia.

Preparations

Botulinum Toxin Type A injection,
100 unit vial

4 G: Drugs used in nausea, vomiting and vertigo

Anti-emetic drugs should only be prescribed when the underlying cause of vomiting is well identified; otherwise symptomatic treatment may delay the diagnosis and therapy of the underlying disease. Knowing and treating the underlying cause, as with vomiting in diabetic acidosis, overdosage of digitalis or acute bacterial infection will mitigate the need for antiemetics. The possibility of drug-induced vomiting should be excluded; otherwise either the dose is reduced or the drug is changed. Antiemetics are more useful for prophylaxis than for treatment.

Drugs such as hyoscine and antihistamines can prevent **motion sickness**. The adverse effects of hyoscine may limit its use in motion sickness in spite of being the most effective.

Although drowsiness is common with most antihistamines, sedation

may contribute to their effectiveness.

Vertigo and nausea associated with Ménière's disease and middle-ear surgery can be reduced by betahistine, a histamine analogue that is claimed to improve the microcirculation. Drug therapy is not always effective.

Vomiting of pregnancy during the first trimester does not require drug therapy. If vomiting is very severe, antihistamines or phenothiazines may be used for a short period. If symptoms have not settled within 24-48 hours, a specialist opinion should be sought.

4 G.1: Antiemetics

Prochlorperazine

Indications: severe nausea and vomiting, vertigo.

Contra-indications and cautions: see under chlorpromazine (sec. 4.B1.1)

Side-effects: see under chlorpromazine.

Extrapyramidal effects may occur more frequently in children, elderly and debilitated.

Dose: orally, acute attack of nausea and vomiting, 20 mg initially followed by 10 mg after 2 hours.

Prophylaxis, 5-10 mg 2-3 times daily.

Child over 10kg, 250 microgram / kg 2-3 times daily oral route only.

Preparations

4. Central nervous system

Prochlorperazine tablets, 5 mg tab.

Metoclopramide

Indications: nausea and vomiting in adults, particularly in gastrointestinal disorders, and treatment with cytotoxic or radiotherapy; prophylaxis of migraine. *In patients under 20 years the use is restricted for intractable vomiting of known cause, vomiting of radiotherapy and cytotoxics, or for pre-medication.*

Cautions: hepatic and renal impairment, elderly, young adults and children; pregnancy and breast feeding.

Side-effects: Extrapyramidal effects, especially in children/young adults, restlessness, depression.

Dose: orally, 10 mg 3 times daily reduce to 5 mg in young adults 15-19 years.

Intramuscular and slow intravenous injections 10 mg 3 times daily if necessary, maximum 500 microgram/kg daily.

Restricted use in children. Titrate dose very carefully.

Preparations

Metoclopramide tablets, 10 mg tab.

Metoclopramide HCl injection, 10 mg ampoule

Domperidone hydrochloride

Indications: nausea and vomiting.

Cautions: renal impairment; pregnancy and breast feeding; not recommended for prolonged use, use cautiously in children.

Side-effects: dystonia, arrhythmia, galactorrhoea, sexual dysfunction, rashes.

Dose: orally for acute nausea and vomiting, 10-20 mg every 4-8 hours.

Child 200-400 microgram/kg every 4-8 hours.

By rectum in suppositories, 30-60 mg every 4-8 hours, not recommended for child under 15 kg.

Child over 2 years for severe nausea and vomiting induced by cytotoxic drugs or radiotherapy, according to body weight:

10-15 kg 15 mg twice daily

15.5-25 kg 30 mg twice daily

25.5-35 kg 30 mg three times daily

Preparations

Domperidone oral suspension, 0.1% suspension (5 mg/5 mL) ; 150-200 mL/bottle (Restricted)

Domperidone tablets, 10 mg tab.

Domperidone suppositories, 10 mg supp.

Domperidone suppositories, 30 mg supp.

4 G.2: Anti-vertigo drugs

Betahistine dihydrochloride

Indications: vertigo, Ménière's disease.

Contra-indications: phaeochromocytoma.

Cautions: asthma, history of peptic ulcer, pregnancy and breast-feeding.

Side-effects: GI disturbances, headache, pruritus, rashes.

Dose: 8-16 mg 3 times daily.
Maintenance 24-48 mg daily.

Preparations

Betahistine dihydrochloride tablets,
16 mg tab.

4 G.3: Specific serotonin receptor antagonist (5HT₃ antagonists)

Ondansetron (Restricted)

Indications: nausea and vomiting induced by chemotherapy or radiotherapy; prevention and treatment of postoperative nausea and vomiting.

Cautions: pregnancy and breast feeding, hepatic impairment.

Side-effects: constipation, headache, sensation of warmth or flushing; transient alteration of liver enzymes.

Dose: for moderate vomiting due to chemotherapy or radiotherapy, orally 8 mg 1-2 hours before treatment, 8 mg immediately before treatment. Intramuscular or slow intravenous injections, 8 mg immediately before treatment, then by mouth 8 mg every 12 hours for up to 5 days.

For severe nausea and vomiting due to chemotherapy and radiotherapy, 8 mg immediately before treatment followed by 8 mg at intervals of 2-4 hours when necessary for further two doses, then by mouth 8 mg every 12 hours for up to 5 days.

Child, by slow intravenous injection, 5 mg / m² immediately before

chemotherapy then 4 mg by mouth every 12 hours for up to 5 days.

For prevention of postoperative nausea and vomiting, orally 8-16 mg 1 hour before anaesthesia which may be followed by 8 mg at 8 hours intervals for further 2 doses, alternatively, intramuscular or slow intravenous injection 4 mg at induction of anaesthesia. Child, over 2 years, 100 microgram/ kg intravenously before, during or after induction.

Treatment of postoperative nausea and vomiting, intramuscular or slow intravenous injection 4 mg. Child over 2 years, 100 micrograms/ kg by slow intravenous injection.

Preparations

Ondansetron injection, 2 mg/mL, 2 mL ampoule

Ondansetron injection, 2 mg/mL, 4 mL ampoule

Ondansetron tablets, 4 mg tab.

Ondansetron tablets, 8 mg tab.

4 G4 : Neurokinin-receptor antagonists

Aprepitant (Restricted)

Indications: Adjunct to dexamethasone and a 5HT₃-receptor antagonist in preventing nausea and vomiting associated with moderately and highly emetogenic chemotherapy

Contra-indications: Acute porphyrias

4. Central nervous system

Side-effects: Anorexia; asthenia; constipation; diarrhoea; dizziness; dyspepsia; headache; hiccup

Dose: Initially a 125 mg dose taken 1 hour before chemotherapy, then 80 mg once daily for 2 days, consult product literature for dose of concomitant corticosteroid and 5HT₃-antagonist.

Preparations

Aprepitant capsules, 80 mg cap.

Aprepitant capsules, 125 mg cap.

4 H: Drugs for management of substance dependence.

Clomethiazole (Chlormethiazole) *(Controlled/restricted)*

Indications: alcohol dependence; others *see* sec. 4 E.2.

Contra-indications, cautions and side-effects: *see* under sec. 4 E.2

Dose: orally, for alcohol withdrawal, initially 600-1200 mg repeated if necessary after few hours
Day 1, 2.4-3.6 g in 3-4 divided doses

Day 2, 1.8-2.4 g in 3-4 divided doses,

Day 3, 1.2-1.8 g in 3-4 divided doses, then reduce gradually over 4-6 days, total treatment period not more than 9 days.

Preparations

Clomethiazole edisylate capsule, 300 mg cap.

Atomoxetine

Indications: for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Contra-indications: narrow angle glaucoma, concomitant use with Monoamine Oxidase Inhibitors (MAOI).

Cautions: all paediatric patients being treated with should be monitored closely for suicide potential, clinical deterioration, and unusual changes in behaviour, liver impairment, cardiovascular disease, history of seizures, pregnancy and breast-feeding, monitor growth in children.

Side-effects: gastrointestinal disorders, headache, dermatitis, palpitations, sleep disorders, menstruation irregularity, sexual dysfunction, urinary retention, hot flushes.

Dose:

Children over 6 years and adolescents up to 70 kg body weight, initially 500 microgram/kg and increased after 7 days to a target total daily dose of approximately 1.2 mg/kg administered either as a single daily dose in the morning or as divided doses in the morning and late afternoon/early evening.

Children and adolescents over 70 kg body weight, should be initiated at a total daily dose of 40 mg and increased after 7 days to a target total daily dose of approximately 80 mg administered either as a single daily dose in the morning or as divided doses in the morning and late

4 I: Drugs used for attention deficit hyperactivity disorder

afternoon/early evening; the maximum recommended total daily dose is 100 mg.

Preparations

Atomoxetine capsules, 10 mg cap.

Atomoxetine capsules, 18 mg cap.

Atomoxetine capsules, 25 mg cap.

Methylphenidate (Restricted)

Indications: Attention deficit hyperactivity disorder (initiated under specialist supervision)

Contra-indications: Anorexia nervosa; arrhythmias; cardiomyopathy; cardiovascular disease; cerebrovascular disorders; heart failure; hyperthyroidism; phaeochromocytoma; psychosis; severe depression; severe hypertension; structural cardiac abnormalities; suicidal ideation; uncontrolled bipolar disorder; vasculitis.

Cautions: Agitation; alcohol dependence; anxiety; drug dependence; epilepsy (discontinue if increased seizure frequency); family history of Tourette syndrome; susceptibility to angle-closure glaucoma; tics.

Side-effects: Abdominal pain; aggression; alopecia; anorexia; arrhythmias; arthralgia; asthenia; changes in blood pressure; cough; depression; diarrhoea; dizziness; drowsiness; dry mouth; dyspepsia; fever; growth restriction; headache; insomnia; irritability; movement disorders; nasopharyngitis; nausea; nervousness; palpitation; pruritus;

rash; reduced weight gain; tachycardia; tics; vomiting; abnormal dreams; confusion; constipation; dyspnoea; epistaxis; haematuria; muscle cramps; suicidal ideation; urinary frequency

Dose: Child 6–17 years. Initially 5 mg 1–2 times a day, increased in steps of 5–10 mg daily if required, at weekly intervals, increased if necessary up to 60 mg daily in 2–3 divided doses, increased if necessary up to 2.1 mg/kg daily in 2–3 divided doses, the licensed maximum dose is 60 mg daily in 2–3 doses, higher dose under the direction of a specialist, discontinue if no response after 1 month, if effect wears off in evening (with rebound hyperactivity) a dose at bedtime may be appropriate (establish need with trial bedtime dose). Treatment may be started using a modified-release preparation; maximum 90 mg per day.

Preparations

Methylphenidate tablets 5 mg tab

Methylphenidate tablets 10 mg tab

Methylphenidate tablets 20 mg tab

4 J: Dementia

Donepezil (Restricted)

Indications: Mild to moderate dementia in Alzheimer's disease

Cautions: Asthma; chronic obstructive pulmonary disease; sick sinus syndrome; supraventricular

4. Central nervous system

conduction abnormalities; susceptibility to peptic ulcers.

Side-effects: Abnormal dreams; aggression; agitation; anorexia; diarrhoea; dizziness; fatigue; hallucinations; headache; insomnia; muscle cramps; nausea; pruritus; rash; syncope; urinary incontinence; vomiting; Bradycardia; duodenal ulcers; gastric ulcers; gastro-intestinal haemorrhage; seizures; AV block; extrapyramidal symptoms; hepatitis; potential for bladder outflow obstruction; sino-atrial block

Dose: Initially 5 mg once daily for one month, then increased if necessary up to 10 mg daily, doses to be given at bedtime

Preparations

Donepezil hydrochloride tablets 5 mg tab

Galantamine (Restricted)

Indications: Dementia in Alzheimer's disease

Cautions: Avoid in gastro-intestinal obstruction; avoid in urinary outflow obstruction; avoid whilst recovering from bladder surgery; avoid whilst recovering from gastro-intestinal surgery; cardiac disease; chronic obstructive pulmonary disease; congestive heart failure; electrolyte disturbances; history of seizures; history of severe asthma; pulmonary infection; sick sinus syndrome; supraventricular conduction abnormalities; susceptibility to peptic ulcers; unstable angina.

Side-effects: Abdominal pain; bradycardia; decreased appetite; depression; diarrhoea; dizziness; dyspepsia; fall; fatigue; hallucination; headache; hypertension; laceration; malaise; muscle spasm; nausea; syncope; tremor; vomiting; weight loss; Arrhythmias; blurred vision; dehydration; first-degree AV block; flushing; hypersensitivity; hypersomnia; hypotension; muscular weakness; palpitation; paraesthesia; retching; seizures; sweating; taste disturbance; tinnitus.

Dose: Immediate release tablets: mild to moderately dementia in Alzheimer's disease. Initially 4 mg twice daily for 4 weeks, increased to 8 mg twice daily for 4 weeks; maintenance 8–12 mg twice daily.

Preparations

Galantamine hydrobromide tablets 8 mg tab

Rivastigmine (Restricted)

Indications: Mild to moderate dementia in Alzheimer's disease. Mild to moderate dementia in Parkinson's disease

Cautions: Bladder outflow obstruction; conduction abnormalities; duodenal ulcers; gastric ulcers; history of asthma; history of chronic obstructive pulmonary disease; history of seizures; risk of fatal overdose with patch administration errors; sick sinus syndrome; susceptibility to ulcers

4. Central nervous system

Side-effects: Abdominal pain; agitation; anorexia; anxiety; bradycardia; confusion; diarrhoea; dizziness; drowsiness; dyspepsia; extrapyramidal symptoms; headache; increased salivation; insomnia; malaise; nausea; sweating; tremor; urinary incontinence; vomiting; weight loss; worsening of Parkinson's disease; Atrial fibrillation; AV block; depression; syncope; Angina; duodenal ulceration; gastric ulceration; rash; seizures.

Dose: Mild to moderate dementia in Alzheimer's disease. Initially 1.5 mg twice daily, increased in steps of 1.5 mg twice daily, dose to be increased at intervals of at least 2 weeks according to response and tolerance; usual dose 3–6 mg twice daily (max. per dose 6 mg twice daily), if treatment interrupted for more than several days, retitrate from 1.5 mg twice daily.

Mild to moderate dementia in Parkinson's disease. Initially 1.5 mg twice daily, increased in steps of 1.5 mg twice daily, dose to be increased at intervals of at least 2 weeks according to response and tolerance; usual dose 3–6 mg twice daily (max. per dose 6 mg twice daily), if treatment interrupted for more than several days, retitrate from 1.5 mg twice daily.

Rivastigmine hydrogen tartrate capsules 6 mg cap

Note: Ministry of Health policy is that only one of the above medicines for dementia will be supplied at any given time.

Preparations

Rivastigmine hydrogen tartrate capsules 3 mg cap

5. Infections

Section 5: Infections

- Antibacterial drugs
- Antifungal drugs
- Antiviral drugs
- Antiprotozoal drugs
- Anthelmintics

The antibiotics policy

The use of antibiotics in the Sultanate of Oman follows specific rules and guidelines. These guidelines should be referred to along side the information that is published in the ONF to ensure local up-to-date policies are being adhered to.

Selection of antimicrobial drugs

A thoughtful selection of antimicrobial agent for treatment of infectious diseases requires clinical judgement and detailed knowledge of pharmacological and microbiological factors and the cost. Unfortunately, the decision to use antibiotics frequently is made lightly by practicing medical staff, without regards to the potential infecting microorganism or the pharmacological characteristics of the antibiotic. The most expensive antibacterial drugs are often erroneously considered as most effective.

Antibiotics are used in 2 general ways, as empirical therapy and as definitive therapy. When used empirically a broad-spectrum antibiotic or a combination is used to

cover a wide possible range of infective microorganisms since the causative microorganism has not been identified. However, once the infective microorganism is identified, definitive antimicrobial therapy should be employed.

Before starting therapy, the first decision to be made is whether administration of an antibacterial agent is truly indicated. Many physicians reflexly associate fever with treatable infections and prescribe antibiotic therapy, without further evaluation. This practice is irrational and potentially dangerous; the diagnosis may be masked if appropriate culture is not taken prior to therapy; antibiotics can cause serious toxic effects.

To prescribe an antibiotic the following points should be considered:

- Which organism is the likely cause of the infection?
- What is the clinical diagnosis and what other measures are taken to increase diagnostic precision?
- Which antibiotics are effective and available? -Is their range of antimicrobial activity appropriate and what information is available about the likelihood of drug resistance?
- What are the undesirable effects of the selected antibiotic?
- What is the correct dose and dose interval, and what is the best route of administration?
- What is the duration of treatment?

Considering all the above, the treatment remains to be monitored to evaluate its effectiveness.

A rational choice of an antibacterial drug is judged through careful consideration of the patient and drug-related variables. Following is a general discussion of some of these variables.

Drug related variables

The **site of infection** may determine the choice of antibiotic, depending on its pharmacokinetic properties. For example, cephalosporins (except new third generation members), aminoglycosides and amphotericin B do not reach the cerebrospinal fluid in sufficient amount to counter infections in the brain or the meninges. Erythromycin is only partly excreted in the urine and therefore not useful in urinary tract infections. Ampicillin, amoxicillin, cefalexin and rifampicin are sufficiently concentrated in the bile and hence may be effective in biliary tract infections. The site of infection may also determine the dose and route of administration. Drugs poorly penetrate the eye, prostate and bone; therefore infections in such sites require higher dosage of antimicrobials. Parenteral administration is recommended for drugs of poor gastrointestinal absorption in serious systemic infections or in unconscious

patients. Penetration of antibiotic agents into infected areas such as abscess cavities is impaired, since the vascular supply is reduced; successful therapy of abscesses usually requires drainage.

When antibacterials are used to treat an infection, the success of the treatment depends on the concentration achieved at the site of infection that is sufficient enough to inhibit bacterial growth. When host defences are maximally effective, it might only be needed to achieve a minimal inhibitory effect, such as that provided by bacteriostatic agents. On the other hand when host defences are impaired the need arises for a more bactericidal effect to achieve complete antibiotic-mediated killing effects. The dose of the drug must be sufficient enough to produce the necessary effects on the microorganism without inducing toxic effects to the human cells. In such cases the microorganism is said to be susceptible to the antimicrobial. If the concentration of drug required to inhibit or kill the microorganism is greater than the concentration that can be safe to the patient, the microorganism is said to be resistant to the antimicrobial. Most *in vitro* sensitivity tests are standardized on the basis of the drug concentration that can safely be achieved in the plasma. They do not reflect concentrations that can be attained at site of infection; nor do they take into consideration the

5. Infections

local factors that may affect the activity of the drug. Such a limitation should always be kept in mind when reading laboratory results of culture and sensitivity tests.

The most frequent **adverse effects** of antibiotics are:

- hypersensitivity reactions (not dose related)
- toxic and irritative effects (dose related)
- superinfections

If a choice exists between drugs, the least toxic is to be selected.

Antibiotic combinations are frequently used and mostly as a cover for imprecise diagnosis. Every effort must be made towards accurate diagnosis and the administration of more than one antibiotic should be generally avoided. However, combinations are indicated in the following situations:

- mixed infection such as in peritonitis, when one drug is not effective against all pathogens
- a temporary measure during the investigation of an obscure illness.
- to prevent the development of resistance in long-term therapy as in tuberculosis.
- to achieve potentiation or synergism
- to permit dose reduction of potentially toxic drugs.

Most combinations result in indifference or summation; occasionally the result may be antagonism or

synergism. Few combinations act synergistically and none do invariably. No particular combination can be specified as generally synergistic but may be synergistic in relation to particular bacteria. Synergism occurs usually with bactericidal drugs.

Mixing of antibiotics with other drugs in the same syringe or container may result in **incompatibilities** due to physical and chemical interactions. The examples are too numerous to be remembered by the physician; it is better to avoid mixing drugs in the same syringe. Mixing antibiotics with intravenous solutions can also result in precipitation or instability of antibiotics due to chemical interactions or as a result of changes in the pH.

Resistance to antimicrobial agents

Pathogens develop resistance to antimicrobials through a process known as natural selection. When a microbial population is exposed to an antibiotic, more susceptible organisms will perish leaving behind only those resistant to the antimicrobial-mediated killing effect. These organisms can then either pass on their resistance genes to their new generation by replication, or to other related bacteria through a conjugation process whereby plasmids carrying the genes are transferred from one organism to

another. This process is a natural and unstoppable phenomenon which can be exacerbated by abuse, misuse and overuse of antimicrobials in the treatment of human illness and in animal and agricultural industries. It is the medical profession's great challenge to slow the rate at which resistance develops and spreads through the adoption of a rational selection and use of effective antimicrobials.

Patient related variables

The age of the patient is an important determinant of pharmacokinetic properties of antimicrobial agents. Mechanisms of elimination, especially renal excretion and hepatic metabolism are poorly developed in newborns, especially in premature infants. Failure to make adjustment for such differences can have serious consequences. Elderly patients also may have reduced rate of creatinine clearance and drug metabolism. Also, elderly patients are more susceptible to the ototoxic effects of aminoglycosides.

Renal function is a major factor in the choice of antimicrobials and the determination of the dose and its frequency. It is important that the renal function is assessed before and during the entire course of treatment, especially when nephrotoxic drugs are used. Drugs that are renally eliminated should

be given less frequently in the presence of renal impairment; serum creatinine level and drug concentration in the blood are used for such assessment.

Hepatic function is a major factor in the choice of antimicrobials that are eliminated by the bile or inactivated in the liver. For examples, the doses of erythromycin, chloramphenicol, metronidazole, doxycycline and rifampicin should be reduced in hepatic failure.

Certain **genetic factors** may determine the rate of biotransformation of some antibacterials. Rapid acetylators may need to have high doses of isoniazid to obtain therapeutic effects. However, patients with deficiency of G6PD may develop haemolytic anaemia with sulphonamides, chloramphenicol and nitrofurantoin.

Pregnancy imposes an additional risk of reaction to some antimicrobial agents both for mother and foetus. Penicillins, cephalosporins and erythromycins are probably safe during pregnancy; others are either contra-indicated or prescribed with caution.

The lactating mother can pass antimicrobials to her nursing child.

Sulphonamides and nalidixic acids taken by mothers have been associated with haemolytic anaemia in G6PD deficient infants

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Host defence mechanisms are a critical determinant of the therapeutic effectiveness of antimicrobial agents. Both humoral and cellular immunity are important. Inadequacy of type, quality and quantity of immunoglobulins, alteration in cellular immune system or a quantitative and qualitative defect in phagocytic cells may result in therapeutic failure despite the use of otherwise appropriate and effective drugs. If host defences are impaired, then bactericidal antimicrobials agents have to be applied for cure.

Superinfection. In general broad spectrum antibacterial drugs such as the cephalosporins, tetracycline, chloramphenicol or their combinations are more likely to be associated with adverse reactions related to the prevalence of resistant organisms causing for examples, fungal infections or antibiotic-associated pseudo-membranous colitis; other problems associated with superinfection include vaginitis and pruritus ani.

5 A: Antibacterials

5 A.1: Penicillins

The penicillins are bactericidal anti-bacterial drugs that interfere with bacterial cell wall synthesis. The various penicillin antibiotics share a common structure and mechanism of action. Their distribution in the body is extensive, but

in the cerebrospinal fluid it is poor except when the meninges are inflamed. They are mainly excreted in the urine.

These drugs are remarkably free of toxic effects, but in the presence of renal failure large doses may cause convulsion and coma. The most serious adverse effect of penicillins is hypersensitivity that results in anaphylactic shock; such reaction is sometimes fatal. Cross-sensitivity occurs with all penicillins and beta-lactam compounds (cephalosporins). Diarrhoea frequently occurs with oral penicillins and is more common with broad-spectrum drugs.

5 A.1.1: Benzylpenicillin and phenoxymethylpenicillin

Benzylpenicillin (Penicillin G) is active against many streptococcal, gonococcal and meningococcal infections, and also for anthrax, diphtheria, and gas gangrene. It is inactivated by beta-lactamase.

Procaine penicillin and benzathine benzylpenicillin are meant for intramuscular administration of penicillin with longer duration of actions.

Phenoxymethylpenicillin has a similar antibacterial activity to benzylpenicillin but is less effective and can be used orally.

Benzylpenicillin (Penicillin G) (Restricted)

Indications: pneumonia, otitis media, meningitis, septic arthritis, anthrax, gas gangrene;

Contra-indications: penicillin hypersensitivity.

Cautions: renal impairment necessitates dose reduction; history of sensitivity.

Side-effects: hypersensitivity reactions, including urticaria, rash, fever, joint pain, anaphylaxis, haemolytic anaemia and interstitial nephritis; cardiac disorders; blood disorders; CNS toxicity with very high dose.

Dose: by intramuscular (painful) or by slow intravenous injection or infusion, 300,000 units to 1.2 million units/day in divided doses every 3-4 hours, higher concentration can be administered up to 10-20million units/day in divided doses or by slow intravenous infusion as necessary.

Child, 300,000 – 1.2million units/day in divided doses every 3-4 hours, maximum 50,000units/kg/dose.

Preparations

Benzylpenicillin injection, powder for reconstitution, 500,000 units/vial

Procaine penicillin

Indications: infections with *Neisseria gonorrhoea*, *Treponema pallidum*, and other infections showing sensitivity to benzylpenicillin.

Contra-indications: sensitivity to penicillins.

Cautions: inadvertent intravascular injecting is dangerous; acute psychotic disorders.

Side-effects: hypersensitivity reactions *see* benzylpenicillin; seizure, psychotic reactions.

Dose: intramuscularly, 400,000–1,200,000 units daily in 2 divided doses.

Preparations

Benzylpenicillin + procaine penicillin injection, powder for reconstitution, 100,000 units + 300,000 units/vial

Benzathine benzylpenicillin

Indications: prophylaxis in rheumatic fever.

Contra-indications: *see* under benzylpenicillin.

Cautions: *see* under procaine penicillin.

Side-effects: *see* under benzylpenicillin.

Dose: intramuscularly, 1.2 million units once monthly.

Preparations

Benzathine benzylpenicillin injection, powder for reconstitution, 1.2 million unit/vial.

Phenoxymethylpenicillin

Indications: streptococcal infections, rheumatic fever prophylaxis.

Contra-indications: hypersensitivity to penicillin.

5. Infections

Cautions and side-effects: *see* under benzylpenicillin.

Dose: orally, adult 250-500 mg every 6 hours up to 1 g every 6 hours.

Child, less than 1 year 62.5 mg 6 hourly, 1-5 years 125 mg 6 hourly, 6-12 years 250 mg 6 hourly.

Preparations

Phenoxymethylpenicillin oral solution, 250 mg/5 mL solution; 100 mL/bottle

Phenoxymethylpenicillin tablets, 250 mg tab.

5 A.1.2: Penicillinase-resistant penicillins

Cloxacillin is resistant to the penicillinase enzyme produced by most staphylococci. It is acid stable and therefore can be used orally as well as by injection.

Clloxacillin (Restricted)

Indications: infections caused by penicillinase producing staphylococci; streptococcal pharyngitis, skin and soft tissue infections, osteomyelitis, lower respiratory tract infections and otitis media.

Contra-indications: hypersensitivity to penicillins.

Cautions: *see* under benzylpenicillin

Side-effects: *see* under benzylpenicillin; hepatitis and cholestatic jaundice reported.

Dose: oral and intramuscular injection, 250-500 mg every 6 hours

(oral: at least 30 minutes before meal). Child under 2 years, quarter adult dose, 2-10 years half adult dose.

Intravenous injection or slow intravenous infusion, 0.25-2 g every 6 hours. Child under 2 years quarter adult dose, 2-10 years half adult dose.

Preparations

Cloxacillin capsule, 250 mg cap.

Cloxacillin sodium injection, powder for reconstitution, 250 mg vial
Cloxacillin sodium injection, powder for reconstitution, 500 mg vial
Cloxacillin sodium, 125 mg/5 mL suspension, 100 mL/bottle

Flucloxacillin (Restricted)

Indications: infections due to beta-lactamase producing staphylococci including otitis externa; adjunct in pneumonia, impetigo, cellulitis, osteomyelitis and in staphylococcal endocarditis.

Cautions: *see* under benzylpenicillin; cholestatic jaundice may occur up to several weeks after treatment with flucloxacillin has stopped. Administration for more than 2 weeks and increasing age are risk factors.

Contra-indications: *see* under benzylpenicillin. Hypersensitivity to penicillins.

Side-effects: *see* under benzylpenicillin

Dose: by mouth 250-500 mg every 6 hours at least 30 minutes before food; Child under 2 years quarter adult dose; 2-10 years half adult

dose. By intramuscular injection, 250-500 mg every 6 hours; Child under 2 years quarter adult dose; 2-10 years half adult dose. By slow intravenous injection or by intravenous infusion, 250 mg – 2 g every 6 hours; Child under 2 quarter adult dose; 2-10 years half adult dose. *see above charts and tables.* May be substituted for cloxacillin.

Preparations

Flucloxacillin capsules, 250 mg cap.

Flucloxacillin suspension 125 mg/5 mL, 100 mL/bottle

Flucloxacillin injection, powder for reconstitution, 250 mg vial

Note: Either cloxacillin or flucloxacillin may be available for use

5A.1.3: Broad-spectrum penicillins

The broad-spectrum penicillins available are ampicillin, amoxicillin and the mixture of amoxicillin and clavulanic acid known as co-amoxiclav. Ampicillin and amoxicillin are not effective against penicillinase producing microorganisms. Ampicillin and amoxicillin are used alternatively; are orally effective as well as by injections, but amoxicillin is better absorbed from the gastrointestinal tract and is not

adsorbed to food particles. Amoxicillin produces diarrhoea less frequently than ampicillin.

The clavulanic acid is a beta-lactamase enzyme inhibitor with no significant antibacterial activity. The co-amoxiclav is more active against beta-lactamase-producing bacteria than amoxicillin alone.

Amoxicillin

Indications: broad spectrum antibacterial activity; otitis media, urinary tract infections, meningitis, various streptococcal infections and respiratory infections.

Contra-indications: penicillin hypersensitivity.

Cautions: renal impairment, history of allergy, skin rash, viral infections.

Side-effects: diarrhoea (discontinue treatment if severe), gastrointestinal discomfort.

Dose: orally, 250-500 mg every 8 hours. Child up to 10 years, 125-250 mg every 8 hours.

Preparations

Amoxicillin capsules, 250 mg cap.

Amoxicillin capsules, 500 mg cap.

Amoxicillin oral suspension, 125 mg/5 mL suspension; 100 mL/bottle

Ampicillin (Restricted)

Indications: *see under amoxicillin*

Contra-indications, cautions and side-effects: *see under amoxicillin*

Dose: by intramuscular or intravenous injection or infusion, 500 mg

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every 4-6 hours. Child, under 10 years half adult dose.

Preparations

Ampicillin sodium injection, powder for reconstitution, 250 mg vial
Ampicillin sodium injection, powder for reconstitution, 500 mg vial

Amoxicillin + clavulanic acid

Co-amoxiclav (Restricted)

Indications: infections caused by beta-lactamase producing strains where amoxicillin alone is not appropriate as in, respiratory tract infections, genitourinary and gastrointestinal infections, cellulitis, severe dental infection with spreading cellulitis; for antibacterial prophylaxis.

Contra-indications: penicillin hypersensitivity.

Cautions: see under amoxicillin, hepatic impairment.

Side-effects: see under amoxicillin; skin disorders, cholestatic jaundice, headache, dizziness, phlebitis at injection sites.

Dose: orally, 375 mg (amoxicillin 250 mg + clavulanic acid 125 mg) 3 times daily or double this dose twice daily. Severe infections and respiratory tract infection 750 mg 3 times daily. The frequency of administration should be reduced in presence of renal failure.

Paediatric dose is 20-45 mg/kg daily in three divided doses calculated as amoxicillin content.

By slow intravenous injection or infusion, adult, 1.2 g (amoxicillin 1 g and clavulanic acid 200 mg) every

8 hours; in severe infections every 6 hours.

For antibacterial prophylaxis, 1.2 g intravenously.

Preparations

Amoxicillin + clavulanic acid tablets, 250 mg + 125 mg tab.

Amoxicillin + clavulanic acid injection,

Powder for reconstitution, 500 mg + 100 mg vial

Amoxicillin + clavulanic acid injection,

Powder for reconstitution, 1 g + 200 mg vial

Amoxicillin + clavulanic acid suspension, 125 mg + 31 mg/5 mL suspension, 100 mL/bottle

5 A.1.4: Antipseudomonal penicillins

Piperacillin is the only antipseudomonal penicillin available. It has been used alone or in combination with the beta-lactamase inhibitor tazobactam. It is specifically active against *Pseudomonas aeruginosa* and has an activity against gram-negative and gram-positive microorganisms. The piperacillin and tazobactam combination broadens the antibacterial spectrum to include beta-lactamase producing microorganisms.

Piperacillin and aminoglycosides have synergistic effects when used simultaneously such use is highly recommended in pseudomonas septicemia.

Piperacillin + Tazobactam (Restricted)

Indications: infections with beta-lactamase-producing microorganisms resistant to piperacillin, gram-negative and gram-positive infections, anaerobic infections; effective in septicaemia, intra-abdominal infections, gynaecological infections, community-acquired pneumonia, cellulitis.

Contra-indications, cautions and side-effects: *see* under benzylpenicillin

Dose: should be determined according to creatinine clearance. Patients with creatinine clearance greater than 40 mL/minute the dose is, piperacillin 12 g + tazobactam 1.5 g daily divided in 4 doses.

Patients with creatinine clearance of 20-40 mL/minute, the dose is, piperacillin 8 g + tazobactam 1 g daily in 4 divided doses.

Patients with creatinine clearance of less than 20 mL/minute, the dose is, piperacillin 6 g + tazobactam 0.75 g daily in 3 divided doses.

Preparations

Piperacillin + Tazobactam injection, powder for reconstitution, 2 g + 250 mg vial

Piperacillin + Tazobactam injection, powder for reconstitution, 4 g + 500 mg vial

5 A.2: Cephalosporins and other beta-lactam antibiotics

Cephalosporins (CS) have a beta-lactam structure, which they share with penicillins as many other characteristics. They have broad-spectrum antibacterial activities although individual CS may possess differing activity against certain microorganisms. They are eliminated mainly by the renal system and few cephalosporins are partially metabolised. They poorly penetrate the CSF unless the meninges are inflamed.

As with penicillins, the major adverse effect of CS is hypersensitivity; cross sensitivity with penicillin is common.

Cephalosporins are classified into four classes or generations.

First generation CS include, cefradine and cefalexin, which are available in oral formulations; cefradine is also available as injection.

Cefuroxime is a **second generation** CS, which is less susceptible to beta-lactamase inactivation. Cefuroxime is therefore more active than other cephalosporins against *H. influenzae* and *N. gonorrhoea*. It is available in oral and injectable formulations.

The **third generation** CS are more effective against a wider range of microorganisms than second generation CS.

Ceftriaxone, cefotaxime and ceftazidime are 3rd generation CS available in Oman. They are used

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for serious infections in hospitalised patients; the possibility of superinfection with resistant bacteria and fungi is greater.

Ceftriaxone has a longer half-life and therefore is suitable for once daily administration in serious infections such as septicaemia, pneumonia and meningitis.

Cefepime is a **fourth generation** CS that is reserved for highly resistant infections.

5 A.2.1: First generation cephalosporins

Cefalexin (Cephalexin)

Indications: infections with gram positive and gram negative organisms in the respiratory tract, skin and soft tissues, otitis media and urinary tract.

Contra-indications: cephalosporins hypersensitivity, *see* notes above

Cautions: renal impairment, penicillin sensitivity.

Side-effects: diarrhoea, pseudomembranous colitis (on higher doses or prolonged use associated with diarrhoea) abdominal pain, nausea and vomiting, headache, allergic reactions.

Dose: oral, 250 mg every 6 hours increased to 500 mg every 8-12 hours. Higher doses may be applied in serious infections. Child under 1 year 125 mg twice daily, 1-5 years 125 mg 3 times daily, 6-12 years 250 mg 3 times daily.

Preparations

Cefalexin capsule, 250 mg cap.

Cefalexin suspension, 125 mg/5 mL susp.; 100 mL/bottle

Cefradine (Cephadrine)

Indications: antibacterial prophylaxis (); *see* under cefalexin above

Contra-indications, caution and side-effects: *see* cefalexin above

Dose: oral, 250-500 mg 4 times daily; in severe infections 1 g every 6 hours. Child 25-50 mg/kg daily in 2-4 divided doses.

Intramuscular, slow intravenous injection or intravenous infusion, 0.5-1 g 4 times daily. Child, 50-100 mg/kg daily in 4 divided doses.

Surgical prophylaxis, by deep intramuscular injection, or intravenous injection, 2 g at induction.

Preparations

Cefradine capsule, 250 mg cap..

Cefradine injection, powder for reconstitution, 500 mg vial (**Restricted**)

Cefradine syrup, 125 mg/5 mL susp.; 100 mL/bottle

Note: Ministry of health policy is that either of the cephalosporins, cefalexin or cefradine will be purchased and available for use depending on cost effectiveness

5 A.2.2: Second generation cephalosporins

Cefuroxime (Restricted)

Indications: infections with gram positive and gram negative organisms in the respiratory tract, skin and soft tissues, otitis media, urinary tract, pelvic inflammatory disease, bone and joint infections and septicaemia; surgical prophylaxis; *H. influenzae* and *N. gonorrhoea* infections.

Contra-indications cautions and side-effects: see cefalexin above

Dose: orally, (as cefuroxime axetil), 250 mg twice daily for most infections. In severe infections, double the dose. In UTI, 125 mg twice daily, double in pyelonephritis. Child, 125 mg twice daily, double the dose in severe infections. Gonorrhoea, 1 g single oral dose. By intramuscular injection or intravenous injection or infusion, 750 mg 3-4 times daily, increased to 1.5 g 3-4 times daily in severe infections. Child, 60 mg/kg daily (range 30-100 mg/kg daily) in 3-4 divided doses. Gonorrhoea, intramuscularly, 1.5 g single dose. Surgical prophylaxis, 1.5 g intravenously.

Preparations

Cefuroxime (as axetil) tablets, 250 mg tab.

Cefuroxime sodium injection, powder for reconstitution, 750 mg vial
Cefuroxime (as axetil) suspension, 125 mg/5 mL; 70-100 mL/bottle

5 A.2.3: Third generation cephalosporins**Cefotaxime (Restricted)**

Indications: infections with gram-negative organisms; surgical prophylaxis, gonorrhoea, meningitis, *Haemophilus epiglottitis*.

Contra-indications and cautions: see cefalexin above

Side-effects: see cefalexin above; rarely arrhythmias following rapid administration; pain and allergic reaction at site of injection.

Dose: by intramuscular or intravenous injection or intravenous infusion, uncomplicated infections, 1 g twice daily. In moderate to severe infections, 1-2 g 3 times daily. Reduce dose in patients with renal impairment.

In severe life threatening infections, up to 12 g daily in divided doses have been used.

Paediatric dose 50-100 mg/kg/day in divided doses.

Gonorrhoea, 500mg as a single intramuscular injection.

Preparations

Cefotaxime sodium injection, powder for reconstitution, 500 mg vial
Cefotaxime sodium injection, powder for reconstitution, 1 g vial

Ceftazidime (Restricted)

Indications: infections with multi-antibiotic resistant gram-negative

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organisms; infections due to *Pseudomonas aeruginosa*.

Contra-indications, cautions and side-effects: *see* cefalexin above

Dose: by intramuscular injection or intravenous injection or infusion, 1 g 2-3 times daily. In very severe life threatening infection and meningitis, 2 g 3 times daily. Child under 2 month, 25-60 mg/kg daily in 2 divided doses, over 2 months 30-100 mg/kg daily in 2-3 divided doses.

Preparations

Ceftazidime as pentahydrate with sodium carbonate injection, powder for reconstitution, 1 g vial

Ceftriaxone (*Restricted*)

Indications: infections with gram-negative multi-antibiotic resistant organisms; meningococcal meningitis.

Contra-indications, cautions and side-effects: *see* cefalexin above; pain, phlebitis and allergic reaction at site of injection.

Dose: by deep intramuscular injection or intravenous injection or infusion, 1-2 g once daily or in 2 divided doses.

In meningitis, 100 mg/kg/day (not to exceed 4 g).

Gonorrhoea, uncomplicated, 250 mg single intramuscular dose, disseminated infection, 1 g single intramuscular or intravenous.

Preparations

Ceftriaxone injection, powder for reconstitution, 250 mg vial

Ceftriaxone injection, powder for reconstitution, 500 mg vial

Ceftriaxone injection, powder for reconstitution, 1 g vial

5 A.2.4: Fourth generation cephalosporins

Cefepime (*Restricted*)

Indications: severe infections resistant to members of the third generation CS.

Contra-indications, cautions and side-effects: *see* cephalixin above

Dose: by deep intramuscular injection or slow intravenous injection or infusion, 0.5-2 g twice daily. Child, 50 mg/kg twice daily, maximum 2 g daily.

Preparations

Cefepime hydrochloride injection, powder for reconstitution, 1 g vial

5 A.2.5: Other beta-lactam antibiotics

Imipenem and meropenem are beta-lactam antibiotics of the carbapenem group. They possess a broader antibacterial spectrum and greater potency than other beta-lactam drugs.

Imipenem is metabolised by the kidney and is usually combined with cilastatin, a dehydropeptidase inhibitor, to block its renal metabolism. Adverse effects are similar to other beta-lactam compounds. High doses may cause neurotoxicity especially in the presence of renal failure.

Meropenem is similar to imipenem but more stable to the renal metabolism and therefore is used alone without cilastatin. Meropenem is less neurotoxic than imipenem and can be used to treat central nervous system infections.

Ertapenem is licensed for treating abdominal and gynaecological infections and for community acquired pneumonia, but it is not effective against atypical respiratory pathogens and it had limited activity against penicillin resistant pneumococci. Unlike the other carbapenems, ertapenem is not active against *Pseudomonas* or against *Acinetobacter* spp.

Ertapenem (Restricted)

Indications: Abdominal infections. Acute gynaecological infections. Community-acquired pneumonia. Diabetic foot infections of the skin and soft tissue. Surgical prophylaxis, colorectal surgery

Cautions: CNS disorders—risk of seizures; elderly

Side-effects: Diarrhoea; headache; injection-site reactions; nausea; pruritus; raised platelet count; rash (also reported with eosinophilia and systemic symptoms); vomiting; abdominal pain; anorexia; antibiotic-associated colitis; asthenia; bradycardia; chest pain; confusion; constipation; dizziness; dry mouth; dyspepsia; dyspnoea; hypotension; melaena; oedema; petechiae; pharyngeal discomfort; raised glucose;

seizures; sleep disturbances; taste disturbances.

Dose: Abdominal infections. Acute gynaecological infections. Community-acquired pneumonia 1 g once daily.

Diabetic foot infections of the skin and soft tissue 1 g once daily.

Surgical prophylaxis, colorectal surgery 1 g for 1 dose, dose to be completed within 1 hour before surgery.

Preparations

Ertapenem injection powder for reconstitution, 1 g vial

Imipenem + cilastatin (Restricted)

Indications: severe aerobic and anaerobic gram-negative and gram-positive infections and in multi-antibiotic resistant infections; alone or in combination with aminoglycosides in serious mixed infections including pulmonary, intra-abdominal, soft tissue and pseudomonas infections; surgical prophylaxis.

Contra-indications: hypersensitivity to beta-lactam compounds; breast-feeding.

Cautions: renal impairment; CNS disorders; pregnancy.

Side-effects: nausea, vomiting, diarrhoea, tooth and tongue discoloration, hearing loss; allergic reactions; CNS disturbances.

Dose: imipenem and cilastatin are mixed 1:1 and doses quoted hence after will refer to imipenem content.

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Intravenous injection or infusion, 500 mg 3-4 times daily. Half this dose is used in mild uncomplicated infections. In severe life threatening infections, 1 g 3-4 times daily. Daily doses should not exceed 50 mg/kg or a total of 4 g whichever is lower.

Child 60 mg/kg (up to 2g) daily in 4 divided doses (every 6 hours)

Preparations

Imipenem + cilastatin intravenous injection, powder for reconstitution, 500 mg + 500 mg vial

Meropenem (Restricted)

Indications: *see* under imipenem; febrile neutropenia, urinary tract infections and in meningitis caused by gram-negative bacilli.

Contra-indications: hypersensitivity to meropenem; and beta-lactam antibiotics.

Cautions: hepatic and renal impairment; pregnancy and breast-feeding.

Side-effects: headache, nausea, vomiting, abdominal pain, diarrhoea; liver function test abnormalities; hypersensitivity reactions.

Dose: by intravenous injection or infusion, 0.5-1 g 3 times daily. In meningitis, 2 g 3 times daily.

Child 20 mg/kg every 8 hours for intra-abdominal infections, and 40 mg/kg every 8 hours in meningitis.

Preparations

Meropenem trihydrate injection, powder for reconstitution, 500 mg vial

Meropenem trihydrate injection, powder for reconstitution, 1 g vial

5 A.3: Aminoglycosides

This group of antibacterial drugs include streptomycin, gentamicin, amikacin and netilmicin. Neomycin use has greatly declined though it is sometimes used in special procedures. This group is usually administered by injection since they are poorly absorbed from the gastrointestinal tract.

Aminoglycosides do not penetrate the cerebrospinal fluid and hence are not suitable in meningitis. They are mainly eliminated by the renal system without being metabolised by the liver. Renal function is an important factor in determining frequency of dosing and the degree of toxicity.

The most toxic effects of aminoglycosides are **ototoxicity** and to a lesser extent **nephrotoxicity**. Degree of toxicity is related to the dose (frequency of doses) and the status of renal function. There is a great risk of foetal ototoxicity when used during pregnancy.

Synergistic effects on ototoxicity may result from simultaneous use of other ototoxic drugs (furosemide, ethacrynic acid) with aminoglycosides. In high doses, aminoglycosides may induce a curare-

like effect on neuromuscular junction when used postoperatively. They may induce allergic reactions and superinfections.

Aminoglycosides are bactericidal drugs and active against some gram-positive and many gram-negative organisms. Amikacin and gentamicin are also active against *Pseudomonas aeruginosa*. Streptomycin is almost entirely reserved for the treatment of tuberculosis.

Gentamicin is indicated in the treatment of severe gram-negative infections including, complicated urinary tract infections, bacteraemia in burn patients, respiratory tract infections, endophthalmitis, osteomyelitis, and in endocarditis in combination with beta-lactam drugs. It is not effective against anaerobes and when used for the blind treatment of undiagnosed serious infections should be combined with metronidazole or penicillin or both.

Amikacin has a similar activity to gentamicin with an advantage that it is more stable to enzymatic degradation than gentamicin. It is mainly used in the treatment of infection with gentamicin-resistant gram-negative bacilli.

Netilmicin has similar activity to gentamicin but causes less ototoxicity; it is more suitable for long-term therapy. Netilmicin is active against a number of gentamicin-resistant gram-negative bacilli but is less active against *Pseudomonas aeruginosa*.

Gentamicin (Restricted)

Indications: severe gram-negative infections *see* notes above.

Contra-indications: myasthenia gravis.

Cautions: pregnancy; renal impairment, infants and elderly (adjust dose and frequency); avoid prolonged therapy.

Side-effects: ototoxic and nephrotoxic effects, neuromuscular blocking effect, allergic reactions.

Dose: in normal renal function, intramuscular, slow intravenous injection or intravenous infusion, 3-5 mg/kg daily in a single dose or 2-3 divided doses. A dose adjustment is required in renal impairment and the elderly.

Child, 2 weeks to 12 years, 2 mg/kg every 8 hours.

For other uses

Preparations

Gentamicin sulphate injection, 20 mg vial
Gentamicin sulphate injection, 80 mg vial

Amikacin (Restricted)

Indications: serious gram-negative infections resistant to gentamicin; others, *see* under gentamicin and notes above

Contra-indications, cautions and side-effects: *see* under gentamicin and notes above

Dose: dosing adjustment is required in renal impairment, in alcoholics, and in cirrhotic patients.

Intramuscular, or slow intravenous injection or by infusion, 15 mg/kg

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daily as a single dose or in 2-3 divided doses.

Neonates, loading intramuscular or intravenous dose of 10 mg/kg, with 7.5 mg/kg 2 times daily for maintenance.

Infants older than 7 days and child, 22.5 mg/kg daily in 3 divided doses.

Preparations

Amikacin sulphate injection, 250 mg/mL; 2 mL vial

Streptomycin (Restricted)

Indications: tuberculosis in combination with other antituberculous drugs; adjunct to doxycycline in brucellosis; plague, Ménière's disease, mycobacterial infections, tularemia.

Contra-indications and cautions: see gentamicin and notes above

Side-effects: see gentamicin and notes above; paraesthesia of mouth, hypersensitivity reactions, drug fever.

Dose: for tuberculosis, intramuscular injection of 15 mg/kg (maximum 1 g) daily. Dose is reduced in underweight patients and in those over 40 years or in the presence of renal impairment.

Preparations

Streptomycin sulphate injection, powder for reconstitution, 1 g vial

Tobramycin (Restricted)

Indications: see under gentamicin and notes above, the inhaled form is used to improve lung function and

reduce exacerbations in cystic fibrosis patients.

Contraindications: see under gentamicin and notes above

Cautions: see under gentamicin and notes above, other inhaled drugs should be administered before tobramycin; monitor for bronchospasm with initial dose, measure peak flow before and after nebulisation. If bronchospasm occurs, repeat test using bronchodilator; monitor renal function before treatment and then annually; severe haemoptysis.

Side-effects: see under gentamicin and notes above, *on inhalation*, mouth ulcers, voice alteration, cough, bronchospasm.

Dose: chronic pulmonary *Pseudomonas aeruginosa* infection in cystic fibrosis patients, by inhalation of nebulised solution, adult and child over 6 years, 300 mg every 12 hours for 28 days, courses repeated after 28-day interval.

Preparations

Tobramycin nebuliser solution, 60 mg/mL solution, 5 mL vial

5 A.4: Macrolides

Macrolides include erythromycin, azithromycin and clarithromycin, which are basically bacteriostatic antibacterial drugs. They have bactericidal activity against some microorganisms in high concentration.

Erythromycin has a similar *but not identical* antibacterial spectrum to penicillin. It has been used as an alternative to penicillin in hypersensitive patients. It is active against gram-positive bacteria, *Neisseria spp.*, *legionella spp.*, *chlamydia-ricicktsiae* and moderately active against anaerobes and mycoplasma. It is not active against most aerobic enteric gram-negative bacilli.

Azithromycin has been applied in the treatment of *chlamydia trachomatis* with an advantage over erythromycin of being long acting and once daily dose is recommended.

Clarithromycin is an erythromycin derivative with slightly greater activity than its parent compound. It is more potent against erythromycin-sensitive strains of streptococci and staphylococci. Effectively used in *H. pylori* eradication regimen.

Clarithromycin and azithromycin cause less gastrointestinal disturbances than erythromycin.

Erythromycin

Indications: as alternative to penicillin in allergic patients; campylobacter enteritis, acne vulgaris, pneumonia, legionnaires' disease, neonatal conjunctivitis, chlamydia infections, mycoplasma infections, pre-operative bowel preparation, syphilis and most infections with gram-positive organisms.

Contra-indications: hepatic disease; pregnancy.

Cautions: renal impairment; breast-feeding.

Side-effects: diarrhoea, nausea and vomiting, abdominal pain, allergic reactions, cholestatic jaundice.

Dose: orally, 250-500 mg 4 times daily

Child, up to 2 years 125 mg 4 times daily, 2-8 years 250 mg 4 times daily.

Doses are doubled in severe infections.

By intravenous infusion, severe infections, 50 mg/kg daily by continuous infusion, or in divided dose every 6 hours.

Preparations

Erythromycin stearate tablets, 250 mg tab .

Erythromycin as ethyl succinate oral suspension, 200 mg/5 mL; 100 mL/bottle

Erythromycin as lactobionate injection, powder for reconstitution, 1 g vial (**Restricted**)

Azithromycin (Restricted)

Indications: adjunct to Pyrimethamine in toxoplasmosis; chlamydia infections (specifically, *Chlamydia trachomatis*).

Contra-indications, cautions: see erythromycin above

Side-effects: see erythromycin above; anorexia, dyspepsia; headache, drowsiness; photosensitivity.

Dose: seek expert advice on the dose range and regimen.

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Preparations

Azithromycin capsule, 250 mg cap.

Azithromycin suspension, 200 mg/5 mL, 15 mL/bottle

Clarithromycin (Restricted)

Indications: adjunct to Pyrimethamine in toxoplasmosis; *H. pylori* eradication.

Contra-indications and cautions: see erythromycin above; reduce dose in renal impairment.

Side-effects: see erythromycin and azithromycin above; tooth and tongue discoloration, confusion, hypoglycaemia.

Dose: seek expert advice on the dose range and regimen.

Preparations

Clarithromycin tablets, 250 mg tab.

Clarithromycin suspension, 125 mg/5 mL.

Clarithromycin suspension, 250 mg/5 mL.

Clarithromycin injection powder for reconstitution, 500 mg vial

5 A.5: Other antibacterials

5 A.5.1: Sulphonamides and trimethoprim

More effective and less toxic antibiotics have superseded sulphonamide use. Sulphamethoxazole and trimethoprim (co-trimoxazole) has a synergistic antibacterial activity. However, the increasing bacterial resistance and the high incidence of

sulphonamide-related adverse effects have diminished the value of co-trimoxazole.

Trimethoprim + Sulphamethoxazole

(Co-trimoxazole) (Restricted)

Indications: chronic bronchitis, nocardiosis, brucellosis, prostatitis, urinary tract infections, granuloma inguinale, *Pneumocystis carinii* infection.

Contra-indications: porphyria; sensitivity to sulphonamides.

Cautions: hepatic and renal impairment; blood disorders; predisposition to folate deficiency; asthma; G6PD deficiency.

Side-effects: nausea, vomiting, skin reactions, blood disorders, hypoglycaemia, diarrhoea and antibiotic-associated colitis.

Dose: orally, 960 mg twice daily. Child 6 weeks-5months, 120 mg, 6 months-5years 240 mg, 6-12 years 480 mg twice daily for all age ranges.

Intravenous infusion, in *Pneumocystis carinii* pneumonia, 96-120 mg/kg/day divided in 3-4 equal doses.

Preparations

Trimethoprim + Sulphamethoxazole tablets, 160 mg + 800 mg tab.

Trimethoprim + Sulphamethoxazole oral suspension, 40 mg + 200 mg/5 mL, 50-60 mL/bottle

Trimethoprim + Sulphamethoxazole intravenous injection, 16 + 80 mg/mL, 5 mL ampoule (co-trimoxazole 480 mg total in one ampoule)

5 A.5.2: Metronidazole

Metronidazole is active against anaerobic bacteria and protozoal parasites. It is effective in the treatment of trichomonal vaginitis, bacterial vaginosis, *Entamoeba histolytica* and *Giardia lamblia* infections. It is also used in surgical and gynaecological sepsis and in antibiotic-associated colitis. It is available in oral, parenteral, topical and rectal formulations.

Metronidazole

Indications: alone or in combination with other antibacterials; trichomonal vaginitis, bacterial vaginosis, surgical and gynaecological sepsis, pseudomembranous colitis, gingivitis; giardiasis, amoebiasis; other uses,

Cautions: alcohol intolerance; hepatic impairment and hepatic encephalopathy, pregnancy and breast-feeding.

Side-effects: nausea and vomiting, unpleasant metallic taste, gastrointestinal disturbances, drowsiness and headache, darkening of urine, pruritus, urticaria.

Dose: in anaerobic infections, intravenous infusion, initially 15 mg/kg followed by 7.5 mg/kg every 6-8 hours. Orally, 800 mg initially followed by 400 mg OR 500 mg 3 times daily. Rectally, 1 g every 8 hours for 3 days and then 1 g every 12 hours. Treatment should be for 7-10 days.

Child, intravenously or orally, 7.5 mg/kg every 8 hours. Rectally, 3 times daily for 3 days then twice daily, up to 1 year 125 mg, 1-5 years 250 mg, 5-10 years 500 mg. Treatment for 7-10 days.

Oral gel, apply 1-2 times daily.

Preparations

Metronidazole injection, 5 mg/mL 100 mL vial (*Restricted*)

Metronidazole suppository, 500 mg supp.

Metronidazole suspension, 125-200 mg/ 5 mL; 100-120 mL/bottle
Metronidazole tablets, 200-250 mg tab.

Metronidazole oral gel, 2.5%

5 A.5.3: Quinolones

Nalidixic acid is the older member of this group, which has been used for urinary tract infections. Fluorinated quinolones such as ciprofloxacin, which has a broad antibacterial spectrum, is used for the treatment of a wide variety of infections. Few side-effects have been associated with the use of fluoroquinolones, and microbial resistance to their action does not develop rapidly. Ciprofloxacin is well absorbed after oral administration and mainly eliminated by the renal route. Renal impairment requires a dose adjustment of ciprofloxacin but not for nalidixic acid.

Ciprofloxacin (*Restricted*)

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Indications: gram-negative and gram-positive microorganisms; urinary tract infections, chronic prostatitis, gonorrhoea, pseudomonas lower respiratory tract infections; enteric fever; anthrax.

Cautions: renal impairment; patients with history of seizure or epilepsy, G6PD deficiency, pregnancy and breast-feeding, young children; patients should be advised to discontinue treatment at the first sign of pain or inflammation in the limbs and have some rest.

Side-effects: nausea and vomiting, gastrointestinal disturbances; headache, dizziness, sleep disturbances; hyperglycaemia; tremor; tendonitis (see cautions above)

Dose: orally, most infections, 250-750 mg twice daily.

Gonorrhoea, 500 mg single dose.

Chronic Prostatitis, 500 mg twice daily for 28 days.

By intravenous infusion, slow over 30-60 minutes, 200-400 mg twice daily.

Child under 5 years, not recommended, 5-17 years, up to 10 mg/kg 3 times daily, maximum 1.2 g daily.

Preparations

Ciprofloxacin tablets, 250 mg tab.

Ciprofloxacin infusion, 2 mg/mL; 100 mL bottle

Levofloxacin (Restricted)

Indications: community acquired pneumonia, complicated urinary tract infection, infection of skin and/or

subcutaneous tissue, chronic prostatitis, exacerbation of chronic bronchitis.

Cautions: see under ciprofloxacin. Predisposition to QT interval prolongation (including cardiac disease, congenital long QT syndrome, electrolyte disturbances, concomitant use with other drugs known to prolong QT interval).

Driving: may cause drowsiness and affect performance of skilled tasks.

Side-effects: see under ciprofloxacin, also flatulence, constipation, tachycardia, pneumonitis, peripheral neuropathy, rhabdomyolysis, potentially life-threatening hepatic failure; local reactions and transient hypotension.

Dose: orally and intravenously, the average dose is usually between 250-500 mg once or twice daily for 7-14 days depending on the type and severity of infection.

Preparations

Levofloxacin tablets, 500 mg tab.

Levofloxacin injection (intravenous infusion), 5 mg/mL, 100 mL bottle

Moxifloxacin (Restricted)

Indications: used as a second line when conventional therapy has failed or contraindicated in acute bacterial exacerbation of chronic bronchitis, sinusitis, community acquired pneumonia.

Contra-indications: history of QT-interval prolongation, bradycardia, symptomatic arrhythmias,

electrolytes disturbances, heart failure with reduced ejection fraction, severe hepatic impairment.

N.B: No dosage adjustment is required in renally impaired patients.

Cautions: conditions predisposing to arrhythmias.

Driving: may cause drowsiness and affect performance of skilled tasks.

Side-effects: stomatitis, glossitis, palpitations, blood pressure changes, constipation, dyspnoea, anxiety, peripheral oedema.

Dose: 400 mg once daily for 5-10 days.

Preparations

Moxifloxacin tablets, 400 mg tab.

Moxifloxacin injection (intravenous infusion), 400 mg/ 250 mL

Nalidixic acid (*Restricted*)

Indications: urinary tract infection; bacterial dysentery.

Cautions: *see* under ciprofloxacin. Liver disease; monitor blood count, liver and renal function if treatment exceeds 2 weeks.

Side-effects: *see* under ciprofloxacin; also, psychosis, intracranial hypertension, metabolic acidosis.

Dose: orally, for suppressive therapy 500mg 4 times daily. Child 33 mg/kg/day in divided doses.

For acute therapy, 4 g daily in 4 divided doses. Child, 55-60 mg/kg/day in 4 divided doses.

Preparations

Nalidixic acid tablets, 500 mg tab.

Nalidixic acid suspension, 125 mg/5 mL, 125 mL susp.

5 A.5.4: Tetracyclines and related compounds

The various tetracyclines share similar properties. Tetracycline is no longer available for use but doxycycline and minocycline are available in Oman. The use of tetracyclines has declined due to development of resistance specifically for gram-positive cocci. However, they remain effective against infections caused by *Chlamydia*, *Rickettsiae*, *Mycoplasma*, *Brucella* and *Vibrio cholera*.

They are well absorbed from the gut. However, absorption is reduced by alkalization with antacids or milk and milk products as insoluble products are formed with divalent and trivalent cations such as Ca, Mg, Fe and Al. Tetracyclines are deposited in growing bones and teeth. They should be avoided in children under 12 years and in breast-feeding mothers and during pregnancy

Tigecycline is a glycylcycline antibacterial structurally related to the tetracyclines. It is active against Gram-positive and Gram-negative bacteria, including tetracycline-resistant organisms, and some anaerobes. It is also active against met-cillin-resistant *Staphylococcus aureus* and vancomycin-resistant en-

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terococci, but *Pseudomonas aeruginosa* and many strains of *Proteus* spp are resistant to tigecycline.

Doxycycline

Indications: rosacea, mycoplasma infections, Chlamydia infections, brucellosis, cholera; brucellosis with aminoglycosides, pelvic inflammatory disease, syphilis, sinusitis; rickettsia; acne; lyme disease; anthrax; prophylaxis of malaria

Contra-indications: breast-feeding; children under 12 years.

Cautions: hepatic impairment; renal impairment; alcohol dependence.

Side effects: nausea and vomiting, gastrointestinal disturbances, allergic skin reactions; headache and visual disturbances may indicate intracranial hypertension; teeth discoloration, anorexia; tinnitus, dry mouth; anxiety; flushing; fungal superinfection.

Dose: orally, for general use, 100 mg twice daily for 1 day and then 100 mg once daily. In severe infections, 100 mg twice daily.

Preparations

Doxycycline capsules/tablets, 100 mg cap/tab.

Minocycline

Indications: rosacea, mycoplasma infections, Chlamydia infections, brucellosis, cholera; meningococcal carrier state, non-gonococcal urethritis; acne.

Contra-indications: see under doxycycline.

Cautions: hepatic impairment; alcohol dependence; systemic lupus erythematosus; renal impairment; monitor blood picture if used for more than 6 months period.

Side-effects: nausea and vomiting, gastrointestinal disturbances, allergic skin reactions; headache and visual disturbances may indicate intracranial hypertension; teeth discoloration; tinnitus, vertigo, anorexia and dizziness; discoloration of conjunctiva, tears and sweat.

Dose: 100 mg twice daily.

Preparations

Minocycline capsules, 100 mg cap.

Tigecycline (Restricted)

Indications: Treatment of complicated skin and soft-tissue infections and complicated abdominal infections caused by multiple-antibacterial resistant organisms when other antibacterials cannot be used

Cautions: Cholestasis; pregnancy; breastfeeding; hepatic impairment.

Side-effects: Abdominal pain; anorexia; bilirubinaemia; diarrhoea; dizziness; dyspepsia; headache; hypoglycaemia; injection-site reactions; nausea; prolonged activated partial thromboplastin time; prolonged prothrombin time; pruritus; rash; vomiting

Dose: Initially 100 mg, then 50 mg every 12 hours for 5–14 days, not recommended for the treatment of foot infections in patients with diabetes.

Maintenance dose should be reduced by one half in patients with

severe hepatic dysfunction. No dose adjustment is required in renally impaired or hemodialysis patients.

Preparations

Tigecycline injection, 50 mg

5 A.5.5: Chloramphenicol and other antibiotics

5 A.5.5.1: Chloramphenicol

Chloramphenicol is a potent bactericidal antibiotic, which should be reserved for life-threatening infections. Its use is associated with serious adverse effects and therefore should not be used for prolonged or repeated treatment courses. It is mainly reserved for enteric fever and typhoid (); it should not be used indiscriminately for minor infections. Chloramphenicol should be avoided in hepatic failure and during pregnancy or breast-feeding. Toxicity in neonates and infants has resulted in grey-baby syndrome with concentration exceeding 25 mg/kg daily.

Chloramphenicol (Restricted)

Indications: typhoid, enteric fever, meningitis.

Contra-indications: pregnancy, breast-feeding, porphyria.

Cautions: see notes above

Side-effects: blood disorders, peripheral neuritis, optic neuritis, nausea, vomiting, diarrhoea, stomatitis.

Dose: orally or by intravenous injection or infusion, 50 mg/kg daily in 4 divided doses, the dose can be doubled in severe infections but should be reduced as soon as clinical conditions improve.

Child, less than 2 weeks, 25 mg/kg/day in 4 divided doses, 2 weeks-1 year and older children, 50 mg/kg daily in 4 divided doses.

Preparations

Chloramphenicol capsules, 250 mg cap.

5 A.5.5: Other antibiotics

Fusidic acid is a narrow-spectrum antibiotic. It is effective against most gram-positive bacteria and gram-negative cocci. Its main use is in treatment of infections caused by penicillin resistant staphylococci especially in osteomyelitis, as it is highly concentrated in the bone. A second anti-staphylococcal antibiotic is preferably used with fusidic acid to prevent the emergence of resistance.

Fusidic acid is well absorbed from the gut and is metabolised in the liver to inactive metabolite.

Linezolid, an oxazolidinone antibacterial, is active against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), and glycopeptide-resistant enterococci. Resistance to linezolid can develop with prolonged treatment or if the dose is

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less than that recommended. Linezolid is not active against common Gram-negative organisms; it must be given in combination with other antibacterials for mixed infections that also involve Gram-negative organisms.

Fusidic acid and sodium fusidate (Restricted)

Indications: osteomyelitis, skin and soft tissue infection due to penicillin-resistant *Staphylococcus aureus*.

Cautions: hepatic impairment; pregnancy; breast-feeding.

Side-effects: nausea and vomiting, reversible jaundice after large doses or rapid infusion.

Dose: orally, (as sodium fusidate) 500 mg every 8 hours, doubled in severe infections. Child (as fusidic acid suspension) up to 1 year, 50 mg/ kg daily in 3 divided doses, 1-5 years, 250 mg every 8 hours, 6-12 years 500 mg every 8 hours.

Preparations

Fusidic acid suspension, 250 mg/5 mL susp, 90 mL/bottle

Sodium fusidate tablets, 250 mg tab.

Vancomycin and Teicoplanin

Vancomycin and teicoplanin are glycopeptide antibiotics with bactericidal activity against aerobic and anaerobic microorganisms.

Vancomycin is effective against gram-positive organisms but relatively ineffective against gram-negative organisms. It is specifically useful in treatment of methicillin-resistant *S. aureus* (MRSA) infections. It is also useful in endocarditis and pseudomembranous colitis caused by *Clostridium difficile*. It has a long duration of action that permits twice daily administration. Orally, its absorption is minimal and is used for its local effect as in pseudomembranous colitis; for serious infections, it is given by intravenous route.

Teicoplanin is an alternative to Vancomycin with a longer duration of action. It is administered by intravenous and intramuscular injection but not orally.

Vancomycin (Restricted)

Indications: see notes above, endocarditis prophylaxis and treatment, serious infection with staphylococci.

Cautions: avoid rapid infusion; renal impairment; avoid in elderly with a history of deafness; blood count.

Side-effects: nephrotoxicity, ototoxicity, blood disorders; anaphylaxis reactions; red-man syndrome (flushing of the upper body); nausea and vomiting.

Dose: orally in pseudomembranous colitis, 125 mg every 6 hours for 7-10 days. Child up to 5 years, 5 mg/kg every 6 hours; more than 5 years, half adult dose.

By intravenous infusion over 30-60 minutes, 500 mg every 6 hours or 1 g every 12 hours. Neonates, 15 mg/kg, then 10 mg/kg every 12 hours; Infants 1-4 weeks, initially 15 mg/kg and then 10 mg/kg every 8 hours; Child over 1 month, 10 mg/kg every 6 hours.

Preparations

Vancomycin hydrochloride injection, powder for reconstitution, 500 mg vial

Teicoplanin (Restricted)

Indications: see vancomycin

Cautions: vancomycin sensitivity, renal and liver function tests, monitor for ototoxicity.

Side-effects: nausea, vomiting, diarrhoea; blood disorders; tinnitus and temporary hearing loss; sensitivity reactions.

Dose: by intramuscular injection or intravenous injection or infusion, initially 400 mg and then 200 mg daily. In severe infections, initially 400 mg twice daily then 400 mg once daily.

Child over 2 months, initially 10 mg/kg every 12 hours then 6 mg/kg daily.

Preparations

Teicoplanin injection, powder for reconstitution, 200 mg vial

Clindamycin (Restricted)

Indications: staphylococcal joint and bone infections such as osteomyelitis, intra-abdominal sepsis, an

alternative to macrolides for erysipelas or cellulitis in penicillin allergic patients, infections associated with meticillin resistant *Staphylococcus aureus* (MRSA) in bronchiectasis, bone and joint infections, skin and soft tissue infections.

Contraindications: diarrhoeal states; avoid injections containing benzyl alcohol in neonates.

Cautions: bacterial overgrowth may occur; risk of *Clostridium difficile* induced diarrhoea and pseudomembranous colitis, concomitant use with erythromycin is not recommended, diarrhoea may occur two or more months after discontinuation of therapy, monitor liver and renal function on prolonged therapy and in neonates and infants, pregnancy, breast-feeding, avoid rapid intravenous administration, avoid in acute porphyria

Side-effects: diarrhoea (discontinue treatment), abdominal discomfort, oesophagitis, oesophageal ulcers, taste disturbances, nausea, vomiting, antibiotic-associated colitis; jaundice; leucopenia, eosinophilia, thrombocytopenia, rash, pruritus, urticaria, anaphylactoid reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative and vesiculobullous dermatitis, pain, induration, and abscess after intramuscular injection; thrombophlebitis after intravenous injection.

Dose: orally, 150-300 mg every six hours; up to 450 mg every 6 hours in severe infections; child, 3-6

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mg/kg every 6 hours. By deep intramuscular injection or by intravenous infusion, 0.6–2.7 g daily (in 2–4 divided doses); life-threatening infection, up to 4.8 g daily; single doses above 600 mg by intravenous infusion only; single doses by intravenous infusion not to exceed 1.2 g; child over 1 month, 15–40 mg/kg daily in 3–4 divided doses; severe infections, at least 300 mg daily regardless of weight.

Preparations

Clindamycin capsule, 150 mg cap.

Clindamycin suspension, 75 mg / 5 mL

Clindamycin injection, 150 mg/mL; 2 mL ampoule

Colistin (Restricted)

Indications: active against Gram-negative organisms including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* (should be reserved for Gram-negative infections resistant to other antibacterials).

Contraindications: myasthenia gravis, pregnancy, breast-feeding.

Cautions: renal impairment, acute porphyria, risk of bronchospasm on inhalation (may be prevented or treated with a selective β_2 agonist), plasma concentration monitoring required in neonates, renal impairment, and in cystic fibrosis; recommended peak plasma colistin concentration (approx. 30 minutes after intravenous injection or infusion) 10–15 mg/litre (125–200 units/mL).

Side-effects: neurotoxicity, nephrotoxicity, hypersensitivity reactions.

Dose: by slow intravenous injection into a totally implantable venous access device, or by intravenous infusion; adult and child body weight under 60 kg, 50,000–75,000 units/kg daily in three divided doses; body-weight over 60 kg, 1–2 million units every 8 hours. By mouth, bowel sterilisation, 1.5–3 million units every 8 hours. By inhalation of nebulised solution, adult and child over 2 years, 1–2 million units every 12 hours; child under 2 years, 0.5–1 million units every 12 hours.

Preparations

Colistin, injection, powder for reconstitution, 1 million unit vial

Linezolid (Restricted)

Indications: Pneumonia (when other antibacterials e.g. a glycopeptide, such as vancomycin, cannot be used) (initiated under specialist supervision)

Complicated skin and soft-tissue infections caused by Gram-positive bacteria, when other antibacterials cannot be used (initiated under specialist supervision)

Cautions: Pregnancy; breastfeeding; contaminant MAOIs; severe optic neuropathy may occur rarely, particularly if linezolid is used for longer than 28 days. Patients should be warned to report symptoms of visual impairment (including blurred vision, visual field defect,

changes in visual acuity and colour vision) immediately. Monitor full blood count (including platelet count weekly). Acute confusional states; bipolar depression; carcinoid tumour; elderly (increased risk of blood disorders); history of seizures; phaeochromocytoma; schizophrenia; thyrotoxicosis; uncontrolled hypertension. Unless close observation and blood pressure monitoring possible, linezolid should be avoided in uncontrolled hypertension, phaeochromocytoma, carcinoid tumour, thyrotoxicosis, bipolar depression, schizophrenia, or acute confusional states. **Side-effects:** Diarrhoea; eosinophilia; headache; nausea; taste disturbances; vomiting, anaemia; antibiotic-associated colitis; convulsions; hyponatraemia; lactic acidosis; optic neuropathy reported on prolonged therapy; pancytopenia; peripheral neuropathy reported on prolonged therapy; Stevens-Johnson syndrome; tooth discoloration; toxic epidermal necrolysis; myelosuppression.

Dose: 600 mg every 12 hours usually for 10–14 days (maximum duration of treatment 28 days).

Preparations

Linezolid tablets, 600 mg tab.

Linezolid suspension 100 mg / 5 mL.

Linezolid injection, 2 mg / mL injection.

5 A.6: Antituberculous and antileprotic drugs

5 A.6.1: Antituberculous drugs

For tuberculosis (TB) treatment protocols and procedures, refer to MOH TB treatment manual

Patients with TB are categorized into 4 categories and treatment is usually of 2 phases, initial phase and continuous phase.

Category I: new cases of smear-positive pulmonary TB and other newly diagnosed seriously ill patients with severe forms of TB.

Initial phase: INH, Rifampicin, Pyrazinamide and either Streptomycin or Ethambutol daily for 2 months

Continuous phase: INH and Rifampicin daily for 4 months

Category II: Relapse and treatment failure (smear-positive)

Initial phase: INH, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin daily for 2 months followed by INH, Rifampicin, Pyrazinamide and Ethambutol for 1 month.

Continuous phase: INH, Rifampicin and Ethambutol daily for 5 months.

Category III: Pulmonary smear-negative TB with limited parenchymal involvement and extra-pulmonary TB/ other than the forms in

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category I, TB in children and young people who develop primary TB usually appearing as pleural effusion or small parenchymal lesions in lungs.

Initial phase: INH, Rifampicin, Pyrazinamide, Ethambutol daily for 2 months

Continuous phase: INH, Rifampicin daily for 4 months.

Category IV: Chronic cases.

Patients of this category are managed at specialized centres as per individual case as most of these patients are resistant to conventional therapy.

Dosage, schedule and route of TB drugs

Drug strength	Route	Dose daily frequency	Adult daily dose	Child Daily dose
INH, 100 & 300 mg	Oral	1	5 mg/kg. Max.300 mg	10-15 mg/kg, max. 300 mg
Rifampicin. 150 & 300 mg	Oral	1 (to be taken early morning)	10 mg/kg if body weight <50 kgs (Max.450 mg) if body weight >50 kgs (Max.600 mg)	10-20 mg/kg, max. 600 mg
Ethambutol 400 mg	Oral	1	25 mg/kg for not more than 2 months. 15 mg/ kg if longer than 2 months	15-25 mg/kg, max. 2.5 g
Streptomycin 1 g	IM	1	15 mg/ kg	20-40 mg/kg, max. 1 g
Pyrazinamide 500 mg	Oral	1	25 mg/ kg	20-40 mg/kg, max.2 g

N.B. Antituberculous drugs are made available to Health Centres wherever TB cases are on treatment within their catchment area.

Ethambutol (Restricted)

Indications: TB treatment regimen.

Contra-indications: optic neuritis, poor vision.

Cautions: renal impairment, avoid in young and elderly, monitor for visual disturbances.

Side-effects: decreased visual acuity (reversible), optic neuritis, peripheral neuritis, gastrointestinal disturbances, confusion, hallucination.

Dose: see the table

Preparations

Ethambutol hydrochloride tablets, 400 mg tab.

Isoniazid***(Isonicotinic acid hydrazide, INH)***

Indications: TB treatment regimen.

Cautions: renal and hepatic function, diabetes, epilepsy, pregnancy and breast-feeding.

Side-effects: peripheral neuritis, optic neuritis, nausea and vomiting, impairment of memory, psychosis, allergic reactions, blood disorders.

Dose: see table above; consider concurrent pyridoxine administration in malnourished, diabetics, alcoholics, and slow acetylators to prevent peripheral neuritis.

Preparations

Isoniazid tablets, 100 mg tab.

Isoniazid elixir, 50 mg/5 mL, 500 mL/bottle

Pyrazinamide (Restricted)

Indications: TB treatment regimen.

Contra-indications: liver disease.

Cautions: pregnancy, hepatic impairment, gout, diabetes.

Side-effects: hepatotoxicity, urticaria, arthralgia, rash, nausea and vomiting.

Dose: see the table

Preparations

Pyrazinamide tablets, 500 mg tab.

Rifabutin (Restricted)

Indications: Prophylaxis of Mycobacterium avium complex infections in immunosuppressed patients with low CD4 count. Treatment of non-tuberculous mycobacterial disease, in combination with other drugs. Treatment of pulmonary tuberculosis, in combination with other drugs.

Cautions: Acute porphyrias; discolours soft contact lenses

Side-effects: Anaemia; blood disorders; leucopenia; myalgia; nausea; pyrexia; rash; thrombocytopenia, arthralgia; body secretions coloured orange-red; bronchospasm; corneal deposits; eosinophilia; hypersensitivity reactions; jaundice; raised liver enzymes; saliva coloured orange-red; skin coloured orange-red; urine coloured orange-red; uveitis (especially following high doses or concomitant use with drugs that increase plasma concentration); vomiting.

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Dose: Prophylaxis of *Mycobacterium avium* complex infections in immunosuppressed patients with low CD4 count, 300 mg once daily, also consult product literature. Treatment of non-tuberculous mycobacterial disease, in combination with other drugs 450–600 mg once daily for up to 6 months after cultures negative.

Treatment of pulmonary tuberculosis, in combination with other drugs, 150–450 mg once daily for at least 6 months.

Preparations

Rifabutin tablets, 150 mg tabs

Rifampicin (Restricted)

Indications: TB treatment regimen; brucellosis and legionnaire's disease in combination with other antibiotics; leprosy; prevention of meningococcal meningitis.

Contra-indications: sensitivity to rifampicin, jaundice.

Cautions: hepatic impairment; renal impairment; pregnancy and breast-feeding; porphyria; discolour soft contact lenses, brown-red colouration of faeces, urine and saliva; due to its ability to induce metabolic enzymes, contraceptive users should be advised to seek additional protection; enhances metabolism of warfarin, dapsone, oral hypoglycaemic drugs, and corticosteroids.

Side-effects: gastrointestinal disturbances, headache, drowsiness, dizziness, visual disturbances, con-

fusion, fatigue, menstrual irregularities, ataxia, pain in the extremities. Intermittent use of rifampicin may rarely induce flu-like syndrome, acute haemolytic anaemia, acute renal failure, hepatitis, skin reactions. Thrombocytopenia indicates the need to stop therapy and never to use rifampicin again in the same patient.

Dose: for TB, *see* tables above. Brucellosis, Legionnaires' disease and serious staphylococcal infections in combination with other antibiotics, 0.6–1.2 g daily in 2–4 divided doses.

Leprosy, *see* sec. 5A.6.2

Preparations

Rifampicin capsule, 150 mg cap.

Rifampicin capsule, 300 mg cap.

Rifampicin syrup, 100 mg/5 mL, 50–60 mL/bottle

Streptomycin (Restricted)

Indications: TB treatment regimen; *see* sec. 5A.3

Contra-indications, cautions and side-effects: *see* sec. 5A.3 and

Dose: *see* table

Preparations

Streptomycin sulphate injection, powder for reconstitution, 1 g vial

Complementary drugs for the treatment of TB include:

Capreomycin Sulphate (C.D.L)

Indications: adjunct to other TB treatment in TB cases resistant to conventional therapy.

Cautions: renal, hepatic or auditory impairment; pregnancy and breast-feeding.

Side-effects: hypersensitivity reactions; tinnitus, hearing loss; hepatotoxicity; nephrotoxicity.

Dose: by deep intramuscular injection, 1 g daily. Consult specialist for dose and duration of therapy.

Preparations

Capreomycin sulphate injection, powder for reconstitution, 1 g (1million unit) vial

D-cycloserine (C.D.L)

Indications: adjunct to other TB treatment in TB resistant to conventional therapy.

Contra-indications: severe renal impairment; psychotic and neuro-genic disorders.

Cautions: monitor renal, hepatic and haematological functions; pregnancy and breast-feeding.

Side-effects: headache, vertigo, sedation, psychosis.

Dose: 250 mg twice daily, increased if necessary to 1 g daily in divided doses. Consult specialist for dose and duration of therapy.

Preparations

D-cycloserine capsule, 250 mg cap.

Prothionamide (Prothionamide) (C.D.L)

Indications: adjunct to other TB treatment in TB resistant to conventional therapy.

Contra-indications: severe hepatic impairment; hypersensitivity.

Cautions: hepatic disease; depression and other psychotic illness; monitor blood glucose, thyroid function and visual disturbances.

Side-effects: gastrointestinal disturbances; mental disturbances; peripheral and optic neuritis; hypersensitivity reactions.

Dose: orally, 250 mg twice daily increase if necessary to 1 g daily in divided doses. Consult specialist for dose and duration of therapy.

Preparations

Prothionamide tablets, 250 mg tab.

Rifampicin and isoniazid are combined in one single oral formulation for the national TB control programme as follows:

Rifampicin 150 mg + isoniazid 75 mg tablets

Rifampicin 150 mg + isoniazid 100 mg tablets

Rifampicin 300 mg + isoniazid 150 mg tablets

Rifampicin 150 mg + isoniazid 75 mg + pyrazinamide 400 mg + ethambutol 275 mg tablets

5 A.6.2: Antileprotic drugs

For leprosy treatment protocols and procedures, refer to MOH leprosy treatment manual

The recommended treatment protocol involves a multi-drug therapy

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approach. The principal drugs in this protocol are, rifampicin, dapsone and clofazimine. Drugs such as minocycline, ofloxacin and clarithromycin, though not effective as rifampicin, are kept as second line therapy.

The recommended treatment protocol for multibacillary leprosy involves 3 drugs for a minimum period of 12 months as follows:

Rifampicin

300 mg once a month

Dapsone

100 mg daily (1-2 mg/kg daily)

Clofazimine

300 mg once a month + 100 mg on alternate days

The recommended treatment protocol for **paucibacillary leprosy** involves 2 drugs for a minimum period of **6 months** as follows:

Rifampicin

600 mg once a month (adult), 300 mg (child up to 6years)

450 mg (child 6-12 years)

Dapsone

100 mg daily (1-2 mg/kg daily)

If treatment is interrupted the regimen should be restarted where it was left off to complete the full course

Clofazimine (Restricted)

Indications: leprosy in combination with other drugs.

Cautions: Clofazimine should be reduced or discontinued if gastroin-

testinal symptoms such as abdominal pain or burning, nausea, vomiting, or diarrhoea appear.

Side-effects: gastrointestinal disturbances; brownish discoloration of lesions and exposed skin to light; coloration of faeces, urine and other body fluids; skin reactions.

Dose: see notes above

Preparations

Clofazimine capsule, 100 mg cap.

Dapsone (Restricted)

Indications: leprosy in combination with other drugs.

Cautions: cardiac and pulmonary disease, anaemia; G6PD deficiency; pregnancy and breast-feeding.

Side-effects: dose related haemolytic anaemia, methaemoglobinaemia, skin reactions, gastrointestinal disturbances, neuropathy; dapsone syndrome characterized by rash with fever and eosinophilia (leprotic reaction).

Dose: see notes above

Preparations

Dapsone tablets, 100 mg tab.

Rifampicin (Restricted)

For indications, contraindications, cautions and side-effects: see sec 5 A.6.1 under Rifampicin

Dose: in leprosy, see notes above.

5 A.7: Urinary tract antiseptics

Escherichia coli, is the most common cause of urinary tract infection. Other organism may be involved, and identification of the causative organism and its susceptibility are very important determinant of treatment. However, acute and disabling attack in women may call for prompt empirical therapy while awaiting the laboratory results. Most cases of uncomplicated urinary tract infections are efficiently treated with nalidixic acid, co-trimoxazole, nitrofurantoin, and ciprofloxacin. Complicated cases may require a combined therapy mostly of penicillins and aminoglycosides.

Prophylaxis of chronic urinary tract infections can be achieved with low doses of nitrofurantoin.

Certain measures can contribute to therapy and reduce the incidence of urinary tract infection. A dose of the drug given immediately before retiring to bed, after having emptied the bladder completely may control the regrowth of bacteria overnight. Large volume of fluid intake and frequent micturition help eliminate bacteria and reduces pain. Use of yoghurt, which is rich in non-pathogenic *Lactobacilli*, reduces the *E. coli* population in the bowel and hence mitigates urinary tract infection in women.

Drugs other than nitrofurantoin used in urinary tract infections

have been discussed under relevant sections above.

Nitrofurantoin

Indications: urinary tract infections.

Contra-indications: impaired renal function; infants less than 3 months of age, G6PD deficiency.

Cautions: anaemia, diabetes mellitus, pulmonary disease, hepatic impairment.

Side-effects: gastrointestinal disturbances; pulmonary reactions, peripheral neuropathy, blood disorders, skin reactions.

Dose: Acute uncomplicated urinary tract infection, 50-100 mg 4 times daily. Child, 3 mg/kg daily in 4 divided doses.

Prophylaxis, 100 mg single dose at night. Child 1 mg/kg single dose at night.

Preparations

Nitrofurantoin tablets 100 mg tab.

5 B: Antifungals

5 B.1: Polyene antifungals

Amphotericin and nystatin are not absorbed from gut and when applied orally they are effective only on the gastrointestinal tract. However, amphotericin is effective against systemic fungal infections when administered intravenously. It has a high toxicity and has been

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superseded by new generation of antifungals.

Various lipid formulations have been applied to reduce amphotericin toxicity.

Nystatin is effective against *Candida albicans* infections of the skin and mucous membrane, including oesophageal and intestinal candidiasis.

Amphotericin (Restricted) **(Amphotericin B)**

Indications: oropharyngeal fungal infections; systemic fungal infections.

Contra-indications: concurrent use of nephrotoxic drugs.

Cautions: (when given intravenously) monitor renal and hepatic function and blood count; corticoids; pregnancy and breast-feeding.

Side-effects: (when given intravenously) gastrointestinal disturbances, anaphylaxis; nephrotoxicity; headache, muscle and joint pain; blood disorders.

Dose: oropharyngeal fungal infections, *see* sec. 12C.2

Systemic fungal infections, intravenous infusion, initial test dose of 1 mg over 20-30 minutes, then 250 micrograms/kg daily. Increase gradually, maximum dose 1.5 mg/kg daily.

Preparations

Amphotericin sodium deoxycholate complex injection, powder for reconstitution, 50 mg vial

Amphotericin (liposome coated) injection, powder for reconstitution, 50 mg vial

Nystatin

Indications: candidiasis; (for vaginal and skin candidiasis *see* sec 7B and 13G.2.2)

Side-effects: nausea and vomiting, diarrhoea; oral burning sensation.

Dose: oral, 500,000 units 4 times daily. Child, 100,000 units 4 times daily.

Prophylaxis, 1 million units once daily.

Preparations

Nystatin oral suspension, 100,000 units/ mL; 24-30 mL/bottle

5 B.2: Triazole antifungals

Triazole derivatives such as fluconazole and itraconazole have similar activity to imidazole antifungals. They are orally effective, slowly metabolised and have less hepatotoxicity.

Fluconazole (Restricted)

Indications: vaginal candidiasis, candidal balanitis, mucosal candidiasis, invasive candidal infections, prophylaxis in fungal infection in immunosuppressed.

Cautions: renal impairment, pregnancy and breast-feeding; monitor hepatic function.

Side-effects: gastrointestinal disturbances; headache, dizziness; hepatic disorders; rash, anaphylaxis, blood disorders.

Dose: orally, for vaginal candidiasis, candidal balanitis, 150 mg single dose.

Mucosal candidiasis, orally 50 mg daily for 1-2 weeks.

Tinea infections and dermal candidiasis, orally 50 mg daily for 2-4 weeks.

Invasive candidal infections and cryptococcal meningitis, orally or by intravenous infusion, 400 mg initially, then 200 mg daily. Increase if necessary to 400 mg. Treatment assessment according to response. Child 6-12 mg/kg daily.

Prophylaxis in immunosuppressed, orally 50-400 mg daily adjusted according to severity of infection.

Preparations

Fluconazole capsule, 50 mg cap.

Fluconazole tablets, 150 mg tab.

Fluconazole intravenous infusion, 2 mg/mL; 100 mL vial

Itraconazole (Restricted)

Indications: onychomycosis.

Cautions: liver disease; renal impairment; pregnancy and breast-feeding.

Side-effects: gastrointestinal disturbances, liver disease, peripheral neuropathy.

Dose: orally, by pulse therapy regimen, 200 mg twice daily for 7 days, repeated 21 day intervals.

Preparations

Itraconazole tablets/capsule, 100 mg tab/cap.

Voriconazole (Restricted)

Indications: Invasive aspergillosis. Serious infections caused by *Scedosporium* spp., *Fusarium* spp., or invasive fluconazole-resistant *Candida* spp. (including *C. krusei*)

Contra-indications: Acute porphyrias.

Cautions: Avoid exposure to sunlight; bradycardia; cardiomyopathy; electrolyte disturbances; history of QT interval prolongation; patients at risk of pancreatitis; symptomatic arrhythmias. Monitor liver function before starting treatment, then at least weekly for 1 month, and then monthly during treatment. Monitor renal function.

Side-effects: Abdominal pain; acute renal failure; agitation; alopecia; altered perception; anaemia; anxiety; asthenia; blood disorders; blurred vision; cheilitis; chest pain; confusion; depression; diarrhoea; dizziness; haematuria; hallucinations; headache; hypoglycaemia; hypokalaemia; hypotension; influenza-like symptoms; jaundice; leucopenia; nausea; oedema; pancytopenia; paraesthesia; photophobia; photosensitivity; pruritus; rash; respiratory distress syndrome; sinusitis; thrombocytopenia; tremor; visual disturbances; vomiting; adrenocortical insufficiency; arrhythmias; arthritis; ataxia; blepharitis; cholecystitis; constipation; duodenitis;

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dyspepsia; flushing; fulminant hepatic failure; gingivitis; glossitis; hepatitis; hypersensitivity reactions; hypoaesthesia; hyponatraemia; nystagmus; optic neuritis; pancreatitis; psoriasis; QT interval prolongation; raised serum cholesterol; scleritis; Stevens-Johnson syndrome; syncope

Dose: Orally (body-weight up to 40 kg) 200 mg every 12 hours for 2 doses, then 100 mg every 12 hours, increased if necessary to 150 mg every 12 hours. Orally (body-weight 40 kg and above) 400 mg every 12 hours for 2 doses, then 200 mg every 12 hours, increased if necessary to 300 mg every 12 hours.

By intravenous infusion. Initially 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours for max. 6 months; reduced if not tolerated to 3 mg/kg every 12 hours.

Preparations

Voriconazol tablets, 200 mg tabs

Voriconazole powder for injection, 200 mg vial

5 B.3: Other antifungals

Anidulafungin (Restricted)

Indications: invasive candidiasis

Cautions: pregnancy, breast-feeding

Side effects: diarrhoea, nausea, vomiting, flushing, convulsion, headache, coagulopathy, hypokalaemia, raised serum creatinine, rash, abdominal pain, cholestasis,

hypertension, hyperglycaemia, urticaria, injection site pain, hypotension, dyspnoea, bronchospasm, hepatitis

Dose: by intravenous infusion, adult over 18 years, 200 mg on first day then 100 mg once daily

Preparations

Anidulafungin injection, powder for reconstitution, 100 mg vial

Caspofungin (Restricted)

Indications: invasive aspergillosis, invasive candidiasis, empirical treatment of systemic fungal infections in patients with neutropenia

Cautions: hepatic impairment, pregnancy, breast feeding

Side effects: nausea, diarrhoea, vomiting, dyspnoea, headache, hypokalaemia, arthralgia, rash, sweating, injection site reactions, abdominal pain, dyspepsia, dry mouth, dysphagia, taste disturbances, anorexia, constipation, flatulence, cholestasis, hepatic dysfunction, ascites, palpitation, arrhythmia, chest pain, heart failure, thrombophlebitis, flushing, hypotension, hypertension, bronchospasm, cough, dizziness, fatigue, paraesthesia, hypoaesthesia, sleep disturbances, tremor, anxiety, disorientation, hyperglycaemia, renal failure, hypomagnesaemia, hypocalcaemia, metabolic acidosis, anaemia, thrombocytopenia, leucopenia, myalgia, muscular weakness, blurred vision, anderythema multiforme, adult respiratory distress syndrome, anaphylaxis

Dose: by intravenous infusion, 70 mg on first day then 50 mg once daily (70 mg once daily if body weight over 80 kg)

Preparations

Caspofungin injection, powder for reconstitution, 50 mg vial

Griseofulvin (Restricted)

Indications: dermatophytes infections when topical treatment is ineffective.

Contra-indications: severe liver disease, pregnancy; avoid pregnancy during and 1 month after treatment. When a man is treated, contraceptive protection by spouse during and 6 months after treatment.

Cautions: breast-feeding.

Side-effects: headache, nausea, vomiting, dizziness; skin reactions, photosensitivity; blood disorders.

Dose: 500 mg daily once daily, or in divided doses. In severe cases, dose can be doubled. Child, 10-15 mg/kg daily as a single dose or in divided doses.

Preparations

Griseofulvin tablets, 125 mg tab.

Terbinafine (Restricted)

Indications: dermatophytes infections in adults when topical treatment is ineffective.

Cautions: hepatic and renal impairment; pregnancy and breast-feeding; psoriasis.

Side-effects: gastrointestinal disturbances; headache; skin reactions; taste disturbances.

Dose: orally, 250 mg daily for 2-6 weeks.

Preparations

Terbinafine tablets, 250 mg tab.

5 C: Antiviral drugs

5 C.1: Herpes simplex and Varicella-zoster

Aciclovir has replaced the old antiviral vidarabine. It has proved effective in treating systemic Varicella-zoster and systemic and topical herpes simplex infections of skin and the mucous membrane; it is also used topically on the eye. It is a life saving antiviral in immunocompromised patients with recurrent viral infections.

Other antivirals of similar activity to aciclovir include, famciclovir, which is a pro-drug of penciclovir, and valaciclovir, which is a pro-drug of aciclovir.

Antivirals are more effective in treating viral infections at the onset of episode and are of less value in recurrent infections.

Aciclovir (Acyclovir) (Restricted)

Indications: herpes simplex and Varicella-zoster infections.

Cautions: renal failure; maintain good hydration; pregnancy and breast-feeding.

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Side-effects: nausea and vomiting, abdominal pain, headache, fatigue, skin reactions; on intravenous infusion, severe local irritation, fever, tremor.

Dose: orally, herpes simplex, 200 mg (400 mg in immunocompromised) 5 times daily for 5Days. Child under 2 years, half adult dose; Child over 2 years, adult dose. Prevention of recurrence of herpes simplex infection, 200 mg 4 times daily, monitor dose according to response.

Prophylaxis of herpes simplex in the immunocompromised, 200-400 mg 4 times daily. Child under 2 years, half adult dose; Child over 2 years adult dose.

Varicella-zoster infections, 800 mg 5 times daily for a week; Child, Varicella, 20 mg/kg 4 times daily for 5Days.

By intravenous infusion, 5 mg/kg doubled in immunocompromised, simplex encephalitis, and severe initial genital herpes, over 1 hour, every 8 hours for 5-10 days. Child 3 months - 12 years, 250 mg/m² every 8 hours for 5-10 days.

Preparations

Aciclovir tablets, 200 mg tab.

Aciclovir injection, powder for reconstitution, 250 mg vial

Aciclovir oral Suspension, 200 mg/5 mL, 125 mL bottle

Famciclovir (Restricted)

Indications: herpes zoster, acute genital herpes simplex and suppression of recurrent genital herpes.

Cautions and side-effects: *see* Aciclovir above

Dose: herpes zoster, 250 mg 3 times daily or 750 mg once daily for 7 days, increase in immunocompromised.

Genital herpes, first episode, 250 mg 3 times daily for 5Days. Recurrent infection, 125 mg twice daily for 5Days, in immunocompromised, all episodes, 500mg twice daily for seven days.

Preparations

Famciclovir tablets, 250 mg tab.

Valaciclovir (Restricted)

Indications: treatment of initial and suppression of recurrent herpes simplex infection of the skin and mucous membranes including genital herpes.

Cautions and side-effects: *see* Aciclovir above

Dose: herpes simplex, initial episode and recurrent infection, 500 mg twice daily for 5Days.

Herpes simplex suppression, 500 mg daily in 1-2 divided doses. Increase in immunocompromised.

Preparations

Valaciclovir tablets, 500 mg tab.

5 C.2: Human Immunodeficiency Virus

No cure is yet available for human immunodeficiency virus (HIV), but a number of drugs slow and, if used very early, may halt the progression

of the disease. Extensive research is going on in this field. Monotherapy with zidovudine has been tried, though combined therapy is believed to be more efficient and helps to prevent the development of resistance. Treatment aims to prevent the mortality and morbidity associated with chronic HIV infection. Although treatment should be started prior to irreversible damage to the immune system, the need for early drug treatment should be balanced against the potential for toxicity. The choice and timing of treatment should take account of co-morbidities, clinical symptoms and the chances of cardiovascular events.

5 C.2.a: Nucleoside reverse transcriptase inhibitors (NRTI)

The initial treatment of HIV infection usually includes two NRTIs in a cocktail of medicines that attempts to address the infection and reduce the incidence of resistance. Zidovudine was the first anti-HIV drug to be used. The other NRTIs available in Oman include abacavir, didanosine, stavudine and tenofovir disoproxil. This class of agents should be used cautiously in obese women and those who abuse alcohol.

Abacavir (Restricted)

Indications: HIV infection in combination with other antiretroviral agents.

Contra-indications: breast feeding.

Cautions: hepatic impairment, hepatitis B or C, renal impairment, pregnancy.

Side-effects: gastrointestinal disturbances, liver damage, lactic acidosis, pancreatitis, insomnia, blood disorders, rash, osteonecrosis, lipodysphrophy syndrome, hypersensitivity reactions.

Dose: orally; 300 mg twice daily or 600 mg once daily

Preparations

Abacavir tablets, 300 mg tab.

Didanosine (Restricted)

Indications: HIV infection in combination with other antiretroviral agents.

Contra-indications: breast feeding.

Cautions: *see* under abacavir; also history of peripheral neuropathy, hyperuricaemia or pancreatitis.

Side-effects: *see* under abacavir; also peripheral neuropathy, diabetes mellitus, hypoglycaemia, acute renal failure, rhabdomyolysis, optic nerve and retinal changes, alopecia, parotid gland enlargement.

Dose: orally; if weight is ≥ 60 kg, 400 mg daily, if < 60 kg, 250 mg daily (1-2 divided doses).

N.B: to be taken on an empty stomach at least 2 hours before or 2 hours after food.

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Preparations

Didanosine tablets, 200 mg tab.

Stavudine (Restricted)

Indications: HIV infection in combination with other antiretroviral agents.

Contra-indications: breast feeding.

Cautions: *see* under abacavir; also, history of peripheral neuropathy or pancreatitis, concomitant use with didanosine (high risk of lactic acidosis).

Side-effects: *see* under abacavir, peripheral neuropathy, cognitive dysfunction, depression, pruritus.

Dose: orally; if weight is ≥ 60 kg, 40 mg twice daily. If < 60 kg, 30 mg twice daily.

Preparations

Stavudine capsules, 40 mg cap.

Tenofovir Disoproxil (Restricted)

Indications: HIV infection in combination with other antiretroviral agents.

Contra-indications: breast feeding.

Cautions: *see* under abacavir; also renal impairment, concurrent or recent use of a nephrotoxic drugs.

Side-effects: *see* under abacavir; also renal failure, hypophosphataemia, reduced bone density.

Dose: orally; 245 mg once daily.

Preparations

Tenofovir tablets, 245 mg tab.

Tenofovir with Efavirenz and Emtricitabine (Restricted)

Indications: HIV infection stabilised on antiretroviral therapy for more than 3 months

Contra-indications: See individual agents

Cautions: See individual agents

Side-effects: See individual agents

Dose: 1 tablet once daily

Preparations

Tenofovir disoproxil with Efavirenz and Emtricitabine tablets, 300/600/200 mg tabs

Zidovudine (Restricted)

Indications: HIV infection, alone or in combination with other drugs.

Contra-indications: blood disorders, liver disease, breast-feeding.

Cautions: monitor for haematological toxicity; renal and hepatic impairment; elderly; pregnancy.

Side-effects: anaemia, neutropoenia and leucopenia, nausea and vomiting and gastrointestinal disturbances, liver disorders, pancreatitis.

Dose: orally 500-600 mg daily in 2-3 divided doses. Seek specialist advice for other treatment regimens.

Preparations

Zidovudine capsule, 100 mg cap.

Zidovudine syrup, 10 mg / mL

With Lamivudine: for Contra-indications, Cautions and side-effects *see* under individual drugs

Dose: one tablet twice daily.

Preparations

Zidovudine/ Lamivudine tablets,
300 mg/150 mg tab.

5 C.2.b: Non-nucleoside reverse transcriptase inhibitors (NNRTI)

The non-nucleoside reverse transcriptase inhibitors efavirenz and nevirapine are used in the treatment of HIV-1 infection, but not against the subtype HIV-2. Nevirapine is associated with a high incidence of rash (including Stevens-Johnson syndrome) and occasionally fatal hepatitis. Rash is also associated with efavirenz but it is usually milder. Psychiatric or CNS disturbances are common with efavirenz; CNS disturbances are often self-limiting and can be reduced by taking the dose at bedtime (especially in the first 2–4 weeks of treatment). Efavirenz has also been associated with an increased plasma-cholesterol concentration.

Efavirenz (Restricted)

Indications: HIV infection in combination with other antiretroviral agents.

Contra-indications: pregnancy and breast feeding.

Cautions: renal impairment, hepatic impairment, hepatitis B or C, pregnancy, elderly, psychiatric disorders or seizures.

Side-effects: rash, gastrointestinal disturbances, depression, sleep disturbances, pruritus.

Dose: orally; 600 mg once daily (body weight > 40 kg).

Preparations

Efavirenz capsules, 50 mg cap.

Efavirenz capsules, 200 mg cap.

Efavirenz tablets, 600 mg tab.

Nevirapine (Restricted)

Indications: advanced HIV infection in combination with other antiretroviral agents.

Contra-indications: breast feeding, post exposure prophylaxis.

Cautions: hepatic impairment, chronic hepatitis B or C, pregnancy, high CD4 cell count (>250 cells/mm³

in women and >400 cells/mm³ in men).

Side-effects: rash, nausea, headache, hepatitis.

Dose: orally; 200 mg once daily for two weeks, if no rash increase the dose to 200 mg twice daily.

Preparations

Nevirapine tablets, 200 mg tab.

Nevirapine suspension, 10 mg/mL

5 C.2.c: protease inhibitors

Darunavir (Restricted)

Indications: HIV infection

Contra-indications: Acute porphyrias

Cautions: Diabetes; haemophilia (increased risk of bleeding)

Side-effects: Abdominal pain; anaemia; anaphylaxis; anorexia;

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blood disorders; diarrhoea; dizziness; fatigue; flatulence; gastro-intestinal disturbances; headache; hepatic dysfunction; hypersensitivity reactions; lipodystrophy; Lipodystrophy Syndrome; metabolic effects; myalgia; myositis; nausea; neutropenia; osteonecrosis; pancreatitis; paraesthesia; pruritus; rash; rhabdomyolysis; sleep disturbances; Stevens-Johnson syndrome; taste disturbances; thrombocytopenia; vomiting.

Dose: 600 mg twice daily, alternatively 800 mg once daily, once daily dose only to be used if no resistance to darunavir, if plasma HIV-RNA concentration less than 100 000 copies/mL, and if CD4 cell count greater than $100 \text{ cells} \times 10^6/\text{litre}$.

Preparations

Darunavir tablets, 300 mg tabs

Indinavir (Restricted)

Indications: HIV infection in combination with other antiretroviral agents.

Contra-indications: breast feeding.

Cautions: hepatic impairment, chronic hepatitis B or C, pregnancy, hyperglycaemia, haemophilia, ensure adequate hydration (risk of nephrolithiasis).

Side-effects: gastrointestinal disturbances, pancreatitis, liver damage, blood disorders, rash, osteonecrosis, lipodystrophy syndrome, hypersensitivity reactions, rhabdomyolysis, sleep disturbances, pruritus,

dry mouth and skin, hyperpigmentation, alopecia, paronychia, pyelonephritis.

Dose: orally; 800 mg thrice daily.

Preparations

Indinavir capsules, 400 mg cap.

Lopinavir with Ritonavir (Restricted)

Indications: HIV infection in combination with other antiretroviral agents.

Contra-indications: breast feeding.

Cautions: see under Indinavir; also, concomitant use with drugs that prolong QT interval.

Side-effects: see under Indinavir; also, electrolytes disturbances, weight changes, hypertension, myocardial infarction, depression, extrapyramidal effects, influenza like syndrome, Cushing syndrome, abnormal vision, tinnitus.

Dose: Tablets, 400/100 mg twice daily, alternatively 800/200 mg once daily in adults with a HIV strain that has less than 3 mutations to protease inhibitors

Oral solution, 400/100 mg twice daily with food.

Preparations

Lopinavir / Ritonavir capsules, 133.3 mg / 33.3 mg cap.

Lopinavir / Ritonavir capsules, 100 mg / 25 mg tab

Lopinavir / Ritonavir capsules, 200 mg / 50 mg tab

Lopinavir / Ritonavir syrup, 80 mg / 20 mg per mL.

Nelfinavir (Restricted)

Indications: HIV infection in combination with other antiretroviral agents.

Contra-indications: breast feeding.

Cautions: *see* under indinavir.

Side-effects: *see* under indinavir; also, fever.

Dose: orally; 1250 mg twice daily or 750 mg thrice daily.

Preparations

Nelfinavir tablets, 250 mg tab.

Ritonavir (Restricted)

Indications: HIV infection in combination with other antiretroviral agents.

Contra-indications: breast feeding.

Cautions: *see* under indinavir, avoid in porphyria.

Side-effects: *see* under indinavir; also, diarrhoea, vasodilatation, local throat irritation, paraesthesia, sweating, raised uric acid, decreased thyroxine level, renal failure.

Dose: orally; started at no less than 300 mg twice daily and increased at 2 to 3 day intervals by 100 mg twice daily. The recommended dosage of ritonavir is 600 mg twice daily.

Preparations

Ritonavir tablets, 100 mg tab.

5 C.3: Other Antivirals**Adefovir dipivoxil**

Indications: chronic hepatitis B infection with *either* compensated liver disease with evidence of viral replication, and histologically documented active liver inflammation and fibrosis *or* decompensated liver disease.

Contraindications: breast-feeding.

Cautions: monitor liver function tests every 3 months, and viral and serological markers for hepatitis B every 3–6 months; discontinue if deterioration in liver function, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis; recurrent hepatitis may occur on discontinuation; monitor renal function every 3 months, more frequently in renal impairment or in patients receiving nephrotoxic drugs; pregnancy; elderly; HIV.

Side-effects: nausea, vomiting, dyspepsia, abdominal pain, flatulence, diarrhoea; asthenia, headache; renal failure; hypophosphataemia; rash and pruritus; pancreatitis.

Dose: adult over 18 years, 10 mg once daily.

Preparations

Adefovir tablets, 10 mg tab.

Entecavir

Indications: chronic hepatitis B infection with compensated liver disease, evidence of viral replication,

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and histologically documented active liver inflammation or fibrosis.

Contraindications: breast-feeding.

Cautions: monitor liver function tests every 3 months, and viral and serological markers for hepatitis B every 3–6 months; discontinue if deterioration in liver function, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis; recurrent hepatitis may occur on discontinuation; renal impairment; pregnancy.

Side-effects: nausea, vomiting, dyspepsia, diarrhoea, raised serum amylase and lipase; headache, fatigue, dizziness, sleep disturbances; thrombocytopenia.

Dose: adult over 18 years, not previously treated with nucleoside analogues, 500 micrograms once daily.

Adult over 18 years with lamivudine-resistant chronic hepatitis B, 1 mg once daily

Counselling: To be taken at least 2 hours before or 2 hours after food

Preparations

Entecavir tablets, 500 micrograms tab.

Entecavir tablets, 1 mg tab.

Ganciclovir (C.D.L)

Indications: life-threatening or sight-threatening cytomegalovirus infections.

Contra-indications: pregnancy; avoid pregnancy during treatment; breast feeding; abnormally low neutrophil or platelet counts.

Cautions: monitor for haematological toxicity; renal impairment; ensure adequate hydration.

Side-effects: nausea, diarrhoea, abdominal pain, leucopenia, anaemia, asthenia.

Dose: by intravenous infusion, 5 mg/kg every 12 hours. Consult product literature for dosing schedules.

Preparations

Ganciclovir intravenous infusion, freeze-dried powder for reconstitution, 500 mg vial

Lamivudine (3TC) (Restricted)

Indications: chronic hepatitis B infection.

Contra-indications: breast-feeding.

Cautions: renal impairment; hepatic disease; pregnancy.

Side-effects: nausea and vomiting, diarrhoea; cough; headache; insomnia malaise and muscle disorders; alopecia.

Dose: orally, adult over 16 years, 100 mg daily.

Preparations

Lamivudine tablets, 100 mg tab.

Lamivudine tablets, 150 mg tab.

Lamivudine solution 10 mg / ml

Oseltamivir

Indications: treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days, for the

prophylaxis of influenza in patients 1 year and older.

Contraindications: known hypersensitivity to any of the components of the product.

Cautions: renal impairment, pregnancy, breast-feeding.

Side-effects: nausea, vomiting, abdominal pain, dyspepsia, diarrhoea; headache, fatigue, insomnia, dizziness, conjunctivitis, epistaxis, rash; hepatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, neuropsychiatric disorders.

Dose: Prevention of influenza, adult and adolescent over 13 years, 75 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic; child 1–13 years, body-weight under 15 kg, 30 mg once daily, body-weight 15–23 kg, 45 mg once daily, body-weight 23–40 kg, 60 mg once daily, body-weight over 40 kg, adult dose.

Treatment of influenza, adult and adolescent over 13 years, 75 mg every 12 hours for 5 days; child 1–13 years, body-weight under 15 kg, 30 mg every 12 hours, body-weight 15–23 kg, 45 mg every 12 hours, body-weight 23–40 kg, 60 mg every 12 hours, body-weight over 40 kg, adult dose.

Preparations

Oseltamivir tablets, 75 mg tab.

Ribavirin (Tribavirin) (Restricted)

Indications: chronic hepatitis C in combination with other drugs.

Contra-indications: pregnancy; severe cardiac disease.

Cautions: avoid pregnancy during treatment; monitor for cardiac disease.; haematological monitoring; gout; liver disease.

Side-effects: nausea, vomiting, dry mouth, anaemia, weight loss, cough, rhinitis, pharyngitis, sleep disturbance, asthenia.

Dose: orally, adult over 18 years, body weight under 65 kg, 400 mg twice daily. Body weight 65–85 kg, 400 mg in the morning and 600 mg in the evening. Body weight over 85 kg, 600 mg twice daily.

Preparations

Ribavirin capsule, 200 mg cap.

Valganciclovir

(Valganciclovir is a pro-drug of ganciclovir)

Indications: induction and maintenance treatment of cytomegalovirus retinitis in AIDS patients; prevention of cytomegalovirus disease following solid organ transplantation from a cytomegalovirus positive donor.

Cautions: *see* under ganciclovir

Side-effects: *see* under ganciclovir

Dose: CMV retinitis, induction, 900 mg twice daily for 21 days then 900 mg once daily; induction regimen may be repeated if retinitis progresses, prevention of cytomegalovirus disease following solid organ transplantation (starting within 10 days of transplantation), 900 mg

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once daily for 100 days, child under 18 years not recommended

Preparations

Valganciclovir tablets, 450 mg tab.

5 D: Antiprotozoal drugs

5 D.1: Antimalarials

The MOH manual for treatment of malaria and its complications should be consulted for treatment protocols. In this section of the formulary, antimalarials applied in malaria treatment protocols are discussed with as much information as possible about their characteristics. Investigative and intervention measures related to malaria treatment and control are best referred to in the MOH manual.

The recommended standard prophylaxis and treatment of malaria cases among all age groups involves the use of chloroquine. Chloroquine is usually given in a 3-day course for curative treatment of *P. malariae* and for the termination of an acute attack of *P. vivax* and *P. ovale* malaria. The treatment regimen consists of 10 mg/kg chloroquine base as a first dose, followed by 5 mg/kg 6-8 hours later and 5 mg/kg on each of the next two days. Taken in proper doses, chloroquine is an extraordinarily safe drug. However, chloroquine is no longer recommended for the treatment of

P. falciparum owing to widespread resistance. Acute chloroquine toxicity is most frequent when therapeutic or high doses are administered too rapidly by parenteral routes. Chloroquine has been considered safe during pregnancy, as risk of non-treatment is far more serious than drug induced adverse effects. It has been applied in the treatment of malaria in pregnant women starting at the 3-4 month of pregnancy.

Cerebral malaria is the most important and usually fatal complication of *P. falciparum* malaria. It is a medical emergency that calls for intensive care. Intravenous infusion of quinine should be commenced as soon as the diagnosis is confirmed.

Chemoprophylaxis in malaria is aimed at reducing morbidity and to prevent fatalities among persons at high risk from severe malaria. Basically this covers the non-immune travellers in areas of malaria transmission as well as pregnant women. Chloroquine with or without proguanil has been used for this purpose.

Malaria cases resistant to chloroquine have been reported. It is important to exclude other reasons for lack of response to chloroquine before starting other treatment protocols with drugs such as quinine, pyrimethamine and sulfadoxine or mefloquine.

Artesunate (Restricted)

Indications: Severe falciparum malaria

Cautions: The powder for injection is difficult to dissolve and care should be taken to ensure that it is completely dissolved before parenteral administration. It should always be used immediately following reconstitution. If the solution is cloudy or a precipitate is present, the parenteral preparation should be discarded.

Side-effects: Fever, gastrointestinal disturbances, pruritus; dizziness; headache; tinnitus, neutropenia; elevates liver enzyme levels; ECG abnormalities

Dose: A loading dose of 2 mg/kg should be followed by 1 mg/kg after 4 hours and 24 hours. Thereafter a dose of 1 mg/kg should be given daily until the patient is able to tolerate oral artesunate or for a maximum of 7 days.

Preparations

Artesunate injection 60 mg

Chloroquine

Indications: treatment and prophylaxis of malaria.

Contra-indications: epilepsy, hypersensitivity, psoriasis.

Cautions: renal and hepatic impairment; pregnancy; gastrointestinal disorders; neurological disorders.

Side-effects: gastrointestinal disturbances, headache, visual disturbances, skin reaction.

Dose: see notes above and MOH protocols.

Preparations

Chloroquine phosphate tablets, 250 mg tab. (150 mg chloroquine base)

Chloroquine sulphate syrup, 50 mg (base)/5 ml syrup, 60-100 mL/bottle

Chloroquine sulphate injection, 40 mg (base)/mL ampoule

Mefloquine

Indications: chloroquine resistant *P. falciparum* malaria.

Contra-indications: history of neuropsychiatric disorders, treatment with mefloquine in the previous 4 weeks, in those who are performing activities requiring fine coordination and spatial discrimination, risk of bradycardia with concomitant use of beta-blockers, calcium-channel blockers and digoxin.

Cautions: pregnancy, breast-feeding, cardiac conduction disorders; severe hepatic impairment; epilepsy.

Side-effects: mainly dose related: nausea, vomiting, abdominal pain, diarrhoea; headache, sleep disturbances, and loss of balance; neuropsychiatric disorders (such as depression, anxiety, panic attack, hallucination, psychosis, convulsion).

Dose: 15-25 mg/kg as single dose or in two divided doses 12 hours apart.

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Preparations

Mefloquine hydrochloride tablets, 250 mg tab.

Quinine

Indications: treatment of *P. falciparum* malaria; malaria of unknown origin.

Contra-indications: optic neuritis.

Cautions: cardiac conduction defects, heart block, G6PD deficiency, monitor glucose level during parenteral administration.

Side-effects: giddiness, tinnitus, blurred vision, tremor, abdominal pain, hot skin and flushes.

Dose: orally, 600 mg 3 times daily for 7-10 days; Child, 10 mg/kg every 8 hours for 7 days.

By intravenous infusion, in severe cases, initially 10 mg/kg diluted in 5% glucose, over a period of 4 hours. Maintenance dose, 5 mg/kg in 5% glucose over a period of 4-6 hours every 12 hours, to be repeated until patient is capable to swallow. Oral dose, 10 mg/kg every 8 hours to complete a 7-day course. Dose can be doubled in very severe cases.

Preparations

Quinine dihydrochloride injection, 300 mg/mL; 1-2 mL ampoule
Quinine dihydrochloride tablets, 300 mg tab.

Primaquine

Indications: anti-relapse treatment of *P. vivax* and *P. ovale* cases of malaria; as gametocytocide for *P. falciparum*.

Contra-indications: rheumatoid arthritis; lupus erythematosus.

Cautions: G6PD deficiency; pregnancy and breast-feeding.

Side-effects: nausea and vomiting, anorexia, haemolytic anaemia, methaemoglobinaemia.

Dose: orally, for anti-relapse therapy, 15 mg daily (as a base), for 14 days, or 21-28 days for cases from south East Asia or Oceania.

As a gametocytocide for *P. falciparum*, a single dose of 30-45 mg (as a base).

Preparations

Primaquine phosphate tablets, 7.5 mg tab..

Proguanil (Restricted)

Indications: prophylaxis of malaria in combination with chloroquine.

Cautions: renal impairment; folate supplementation during pregnancy (safe during pregnancy).

Side-effects: nausea and vomiting, mouth ulceration, anorexia.

Dose: orally, 200 mg as single dose with chloroquine. Child, 3-5 mg/kg single dose.

Preparations

Proguanil hydrochloride tablets, 100 mg tab.

Sulfadoxine + pyrimethamine (Restricted)

Indications: adjunct to quinine in *P. falciparum* resistant cases.

Cautions: haemolytic disorders; neurological disorders.

Side-effects: vomiting, anorexia, abdominal discomfort, tremor, seizure, megaloblastic anaemia due to folic acid deficiency.

Dose: orally, 3 tablets (each tablet of sulfadoxine 500 mg + pyrimethamine 25 mg). Child, 5-10 kg 0.5 tablet, 11-15 kg 1 tablet, 16-25 kg 1 and quarter of a tablet, 26-40 kg 1 and a half tablet, 41-50 kg 2 tablets.

Preparations

Sulfadoxine + pyrimethamine tablets, 500+25 mg tab.

Sulfadoxine + pyrimethamine injection, 500+25 mg/2.5 mL ampoule

Artemether/ lumefantrine (Restricted)

Indications: Treatment of acute uncomplicated falciparum malaria. Treatment of chloroquine-resistant non-falciparum malaria

Contra-indications: Family history of congenital QT interval prolongation; family history of sudden death; history of arrhythmias; history of clinically relevant bradycardia; history of congestive heart failure accompanied by reduced left ventricular ejection fraction

Cautions: Avoid in acute porphyrias; electrolyte disturbances

Side-effects: Abdominal pain; anorexia; arthralgia; asthenia; cough; diarrhoea; dizziness; headache; myalgia; nausea; palpitation; paraes-

thesia; prolonged QT interval; pruritus; rash; sleep disturbances; vomiting

Dose: Initially 4 tablets, followed by 4 tablets for 5 doses each given at 8, 24, 36, 48 and 60 hours (total 24 tablets over 60 hours)

Preparations

Artemether/ lumefantrine tablets, 20 mg Artemether/ 120 mg lumefantrine tab.

5 D.2: Leishmaniacides

Cutaneous, mucocutaneous and visceral types of leishmaniasis are treated with pentavalent antimonial drugs. Intramuscular or intravenous therapy with sodium stibogluconate has been found safe and effective in most cases. In visceral leishmaniasis, a 20-day treatment course with 20 mg/kg daily is commonly applied; 10-day treatment course for cutaneous infection.

Sodium stibogluconate (C.D.L)

Indications: leishmaniasis.

Contra-indications: severe renal impairment; breast-feeding.

Cautions: avoid rapid intravenous administration; heart disease, hepatic impairment.

Side-effects: pain at site of intramuscular injection, gastrointestinal disturbances, stiffness of joints, delayed muscle pain; ECG changes may precede arrhythmias.

Dose: see notes above.

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Preparations

Sodium stibogluconate injection,
100 mg/mL 100 mL bottle

5 D.3: Drugs for pneumocystis pneumonia

Pneumocystis pneumonia is more common among immunocompromised patients. It is mainly treated with co-trimoxazole (*see* sec 5A.5). Pentamidine is associated with high toxicity and should be used by specialists in cases resistant or intolerant to co-trimoxazole.

Pentamidine Isethionate (C.D.L)

Indications: pneumocystis pneumonia (*see* notes above)

Cautions: risk of hypotension; hepatic and renal impairment; blood disorders; pregnancy and breast-feeding (check with product literature).

Side-effects: severe reactions due to hypotension, hypoglycaemia, pancreatitis, and arrhythmias; blood disorders; acute renal failure.

Dose: intravenous infusion, 4 mg/kg daily for at least 14 days.

Inhalation: Adult 300 mg every four weeks or 150 mg every 2 weeks, using suitable equipment – consult the product literature.

Preparations

Pentamidine Isethionate injection,
powder for reconstitution, 300 mg vial

Pentamidine Isethionate solution
for inhalation, 300 mg vial

5 D.4: Anti-bilharziasis

Praziquantel (C.D.L)

Indications: schistosomiasis.

Contra-indications: hepatic impairment.

Cautions: monitor for ocular abnormalities; avoid tasks requiring mental alertness during therapy; reduce dose in liver disease.

Side-effects: abdominal disturbances, headache, dizziness, drowsiness.

Dose: orally, 40 mg/kg in 2 divided doses 4–6 hours apart on one day.

Preparations

Praziquantel tablets, 600 mg tab.

5 E: Anthelmintics

The availability of broad spectrum Anthelmintics has led to a better control of helminthic infections. Mebendazole is a widely used safe anthelmintic, which is highly effective against single or mixed infections with threadworms, hookworms and common roundworms. Albendazole, like mebendazole is safe and effective against the same range of helminthic infections. It has also been found useful in inoperable cases of hydatid cyst or in conjunction with surgery to prevent relapses.

Tapeworm infection is safely treated with niclosamide, an effective taenicide drug.

Filarial parasites infections are best treated with diethylcarbamazine.

Medical care is required in the early stages of treatment.

5 E.1: Drugs for round worms

Including, *Ascaris lumbricoides*, *Necator americanus*, *Ancylostoma duodenale*, *Trichuris trichiura*, *Strongyloides stercoralis*, *Enterobius vermicularis*.

Mebendazole

Indications: mixed or single infections with threadworm, roundworm, whipworm and hookworm (see notes above)

Cautions: pregnancy and breast-feeding, avoid in children under 2 years.

Side-effects: very rare due to low systemic bioavailability. Abdominal pain.

Dose: doses for adult and child over 2 years are the same.

Threadworms, 100 mg as single dose. Repeat if necessary 2-3 weeks later.

Whipworms, roundworms or hookworms, 100 mg twice daily for 3 days.

Preparations

Mebendazole suspension, 2% (20 mg/mL) susp. 20-30 mL/bottle

Albendazole

Indications: see under mebendazole; hydatid cyst (see notes above)

Contra-indications: hepatic cirrhosis; pregnancy and breast-feeding.

Cautions: children under 2 years; monitor liver function when used for protracted therapy.

Side-effects: on long-term use as for hydatid cysts, abdominal discomfort, headache, fatigue, fever, loss of hair.

Dose: for mixed or single intestinal helminths infection, 400 mg single dose. In heavy infections therapy may be needed for 2-3 days.

In hydatid cysts, 10 mg/kg daily in divided doses for 28 consecutive days. Treatment course may be repeated 2-3 times if necessary at 2-week intervals.

Preparations

Albendazole suspension, 100 mg/5 mL susp.; 20-30 mL/bottle

Albendazole tablets, 200 mg tab.

5 E.2: Taenicides (drugs for tapeworm infection)

Niclosamide

Indications: tapeworm infection.

Cautions: treat constipation before commencement of therapy.

Side-effects: very rare, abdominal pain.

Dose: orally, adult 2 g single dose. Child 11-40 kg, 1 g single dose; below 10kg, 0.5 g single dose. Treatment is better followed by a purge 2 hours after dose ingestion.

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Preparations

Niclosamide tablets, 500 mg tab.

Section 6: Endocrine system

- Diabetes and related disorders
- Thyroid and antithyroid hormones
- Corticosteroids
- Sex hormones
- Hypothalamic and pituitary hormones
- Drugs affecting bone metabolism
- Other endocrine drugs

6 A: Diabetes and related disorders

Diabetes mellitus results from relative or absolute deficiency of insulin. It has emerged as a major and growing health problem in the Sultanate of Oman. The National Health Survey of diabetes, which was conducted in 1991 showed that the prevalence rate was 9.75%, while the national health survey in the year 2000 showed that rate of prevalence had increased to 11.6% among adults over 20 years . In clinical practice, diabetes is presented as the commonest metabolic disorder. There are two principal types of diabetes;

-Type I also known as insulin dependent diabetes mellitus (IDDM), is characterized by subnormal or undetectable insulin secretion and requires daily insulin injection for treatment.

-Type II also known as non-insulin dependent diabetes mellitus

(NIDDM), is due to reduced secretion of insulin or to peripheral resistance to the effects of insulin. A good proportion of patients affected with this type are obese and may respond to diet control and weight reduction alone. However, many patients need to receive oral antidiabetic drugs to keep hyperglycaemia under control.

Treatment of diabetes mellitus is aimed at reducing symptoms and minimizing the risk of long-term complications by appropriate management protocols. Diabetes represents a high risk factor for cardiovascular disease. Other risk factors such as smoking, obesity, hyperlipidaemia and hypertension should also be considered.

Uncontrolled diabetes, will in the long run result in serious complications that involves the renal, nervous and microvascular systems.

In all types of diabetes, measures other than drugs are used to optimise treatment such as diet control and physical exercises.

Patient education is the cornerstone for long-lasting optimal glycaemic control. Without the patients understanding of the metabolic changes involved in diabetes, treatment and control become difficult. Preparations of insulin are used for the treatment of type I and under particular circumstances for type II diabetes mellitus. Oral antidiabetic drugs such as sulphonylurea and biguanides are exclusively available for the treatment of type II diabetes mellitus.

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6 A.1: Insulins

Physiologically, insulin is synthesized in the beta islet cells of the pancreas and released mainly in response to changes in blood glucose level. It plays a key role in the regulation of carbohydrate, fat and protein metabolism.

For therapeutic uses, insulin has been extracted from animal pancreas and most recently biosynthesised. The animal insulin slightly differs in the amino acid number and sequence from human insulin. Nowadays, most of the available preparations are recombinant human insulin with the strength of 100units/mL.

Insulin has a short half-life of 4-5 minutes due to hepatic and renal elimination. Gastrointestinal proteolytic enzymes degrade insulin, and therefore it is ineffective by mouth. An insulin preparation is an acidic solution of crystalline insulin with a variable amount of zinc and is normally administered by injection. The subcutaneous route is the common route for routine administration. However, it can also be administered by intramuscular route and for the soluble insulin by the intravenous route. To prolong its effect insulin is mixed with proteins such as protamine or globulin to form complexes that delay its absorption.

Animal insulin preparations are antigenic. The synthesis of human in-

sulin is thought to reduce this antigenicity, a claim which has not been substantiated in clinical practice.

Indications for insulin are;

- type I diabetes mellitus.
- uncontrolled hyperglycaemia in type II diabetes mellitus.
- when diet has failed during pregnancy.
- during stressful situation like infection, trauma, surgery and myocardial infarction.
- Ketoacidosis.

Insulin preparations: There are 3 types of insulin preparation;

- **Short acting** that has a relatively rapid onset such as regular or soluble insulin.
- **Intermediate acting** such as isophane and insulin zinc suspension.
- **Long acting**, with slower onset and prolonged duration such as glargine insulin suspension.

Variations in the duration and onset of action from one patient to another necessitate that patients are individually assessed.

Insulin dose regimens

- There are no rules of insulin dosage, but average requirements are often 0.5-1 unit/kg/day. The following are some regimens for insulin use;

The majority of patients will require more than one daily injection

if good glycaemic control is to be achieved. However, a one-daily injection of an intermediate acting preparation may be effectively used in some patients.

- Twice daily mixture of short and intermediate-acting insulin is a commonly used regimen.

- In some cases, a mixture of short and intermediate acting insulins may be given in the morning. Further doses of short acting insulin are given before lunch and evening meal and an evening dose of intermediate acting insulin is given at bed time. This may be used particularly when a strict glycaemic control is mandatory.

- The dose of insulin preparations is adjusted according to the blood glucose levels. Blood glucose monitoring should be intensified during intercurrent illness and other stressful conditions and insulin doses may have to be increased.

Side-effects: Hypoglycaemia is the most serious side effect of insulin and patients should carefully be directed to avoid it. It could result from an overdose of insulin, missed meal or an unusual physical activity. The early symptoms of hypoglycaemia are; fatigue, dizziness, cold, sweat, headache, hunger, weakness, nervousness, mental lapse and if not treated may lead to convulsion and coma.

Other side-effects include, local reaction and lipotrophy at the site of injection. It is advisable to frequently change the site of injection.

Routes of administration: the subcutaneous route is the most common route for all types of insulin. However, the soluble regular insulin can also be administered intramuscularly and intravenously. The abdominal wall is preferably used for faster absorption of short acting insulin. The thigh and the upper lateral gluteal region are preferred for slower absorption of intermediately acting insulins.

Insulin (Restricted)

Preparations

Recombinant regular human insulin injection, 100 unit/mL, 10 mL vial and 3 mL pen

Recombinant NPH (Neutral Protamine Hagedorn) human insulin injection (isophane suspension), 100 unit/mL, 10 mL vial and 3 mL pen

Recombinant regular human insulin 30% and NPH human insulin 70% (insulin mixture) injection, 100 unit/mL, 10 mL vial and 3 mL pen

Insulin Aspart injection, 100 units/mL, prefilled pen

Insulin Lispro injection, 100 units/mL, prefilled pen

(Note: Aspart & Lispro are short acting insulin analogues and approved as a group)

Biphasic insulin aspart (50%/ 50%) injection, prefilled pen

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Biphasic insulin lispro (50%/ 50%) injection, prefilled pen
(Note: Biphasic Aspart & Biphasic Lispro are intermediate acting insulin analogues and approved as a group)

Insulin Detemir injection, 100 units/ mL, prefilled pen

Insulin Glargine injection, 100 units/ mL, prefilled pen
(Note: Detemir & Glargine are long acting insulin analogues and approved as a group)

6 A.2: Oral antidiabetic drugs

Oral antidiabetic drugs are used for the treatment of type II diabetes mellitus. Drug treatment with oral antidiabetic drugs is only considered after regimen of dietary treatment combined with exercise has failed to achieve the therapeutic target.

The choice of oral antidiabetic drugs depends on the individual patient. Sulphonylureas are effective in reducing blood glucose level in patients uncontrolled by dietary restriction and exercises. Biguanides on the other hand, are more useful in obese patients when diet restriction is a problem. Biguanides interfere with carbohydrate metabolism, by increasing peripheral utilization of glucose and decreasing gluconeogenesis. They act in the presence of insulin and for this reason they are effective in diabetic

patients with residual functioning therapeutic beta cells. They do not, in normal doses, induce hypoglycaemia in normal people.

6 A.2.1: Sulphonylureas

The sulphonylureas stimulate the release of insulin from the beta cells of the pancreas and on long-term therapy improve sensitivity to insulin through extra-pancreatic mechanisms.

Hypoglycaemia may be induced with sulphonylureas as a side effect resulting from overdose or inadequate food intake.

The choice of sulphonylurea drug is determined by the potency, duration of action, cost, side-effects and potential interactions with other drugs. The patient's nutritional status, dietary habits and age associated medical conditions must be also considered.

Contra-indications:

- type I diabetes mellitus.
- severe renal and hepatic impairment.
- allergy to sulfa drugs.
- pregnancy and breast feeding.
- patients undergoing stressful conditions such as surgery, severe infection, trauma and myocardial infarction.
- ketoacidosis.

Side-effects: The main side-effects associated with the use of sulpho-

nylureas are, hypoglycaemia, gastrointestinal disturbances such as nausea, vomiting and constipation. Allergic skin reaction, renal, hepatic and blood disorders are more frequent side-effects with the older generation of long acting sulphonylureas.

The sulphonylureas available in Oman are:

Glibenclamide, a long acting drug, which should be avoided in the elderly because of the danger of hypoglycaemia. **Glimepride** is of intermediate duration of action.

Gliclazide is more useful in presence of renal impairment since it is mainly eliminated by liver metabolism.

Glibenclamide

Indications: type II diabetes mellitus.

Contra-indications, cautions and side-effects: *see* notes above

Dose: initially, 5 mg daily with or immediately after breakfast, adjust according to response. Reduce in elderly; *see* notes above. Maximum, 15 mg daily.

Preparations

Glibenclamide tablets, 5 mg tab.

Gliclazide (Restricted)

Indications: type II diabetes mellitus.

Contra-indications, cautions and side-effects: *see* notes above

Dose: initially, 40-80 mg daily with breakfast, adjust if necessary to 160 mg daily. Maximum daily dose 320 mg in divided doses.

Preparations

Gliclazide tablets, 80 mg tab.

Glimepride

Indications: type II diabetes mellitus.

Contra-indications: *see* notes above

Cautions: regular haematological and hepatic monitoring is recommended.

Side-effects: *see* notes above

Dose: initially, 1 mg daily shortly before or with breakfast. Increase if necessary in 1 mg steps every 1-2 week to a maximum of 4 mg daily.

Preparations

Glimepride tablets, 2 mg tab.

6 A.2.2: Biguanides

Biguanides differ from sulphonylureas in their mechanism of action. Metformin is the only biguanide available for use in Oman. It acts through decreasing gluconeogenesis and by increasing peripheral carbohydrate utilization. Metformin is only used in type II diabetes mellitus.

Diabetic obese patients benefit more with metformin. When sulphonylureas and diet restriction fail

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to bring glycaemic control, metformin is an alternative.

Hypoglycaemia is not a serious side effect with metformin and there is no weight gain.

Metformin may cause lactic acidosis, which is more often in patients with impaired renal function.

Metformin

Indications: type II diabetes mellitus.

Contra-indications: severe hepatic or renal impairment, ketoacidosis, heart failure, alcohol dependence, dehydration.

Side-effects: gastro-intestinal disturbances, such as anorexia, nausea, vomiting, diarrhoea, metallic taste, decreased vitamin B₁₂ absorption.

Dose: initially, 500 mg with breakfast for 1 week, then 500 mg with breakfast and dinner for 1 week, then 500 mg three times daily with meals. Maximum 3g daily in divided doses.

Preparations

Metformin hydrochloride tablets, 500 mg tab.

6 A.2.3: Dipeptidylpeptidase-4 inhibitors

Dipeptidylpeptidase-4 inhibitors (gliptins) impair the degradation of incretin hormones, which play a role in glucose homeostasis by increasing insulin synthesis and release, and reducing glucagon secretion. They are used in the management of type 2 diabetes mellitus.

Sitagliptin

Indications: type II diabetes mellitus.

Contra-indications: Ketoacidosis

Side-effects: Gastro-intestinal disturbances; nasopharyngitis; pain; peripheral oedema; upper respiratory tract infection; anorexia; dizziness; drowsiness; dry mouth; headache; hypoglycaemia; osteoarthritis; cutaneous vasculitis; pancreatitis; rash; Stevens-Johnson syndrome

Dose: 100 mg once daily.

Note: Discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain).

Preparations

Sitagliptin phosphate tablets, 100 mg tab.

Vildagliptin

Indications: type II diabetes mellitus.

Contra-indications: Ketoacidosis

Cautions: Manufacturer advises avoid in severe heart failure

Side-effects: Arthralgia; constipation; hypoglycaemia; hepatic dysfunction; nasopharyngitis; upper respiratory tract infection; bullous skin reactions; exfoliative skin reactions; pancreatitis

Dose: 50 mg twice daily, but if taken in combination with a sulphonylurea 50 mg once daily

Note: Monitor liver function before treatment and every 3 months for first year and periodically thereafter. Discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain).

Preparations

Vildagliptin tablets, 50 mg tab.

Ministry of Health policy is that only one of the above gliptins will be purchased and made available for use

6A.2.4: Glucagon-Like Peptide 1 Receptor Agonists

Glucagon-Like Peptide 1 Receptor Agonist binds to, and activates, the GLP-1 (Glucagon-Like Peptide 1) receptor to increase insulin secretion, suppresses glucagon secretion, and slows gastric emptying.

Exenatide

Indications: treatment of type 2 diabetes mellitus in combination with metformin or a sulphonylurea, or both, in patients who have not

achieved adequate glycaemic control with these drugs alone or in combination

Contra-indications: ketoacidosis, severe gastro-intestinal disease, pregnancy

Cautions: elderly, pancreatitis, may cause weight loss greater than 1.5 kg weekly, breastfeeding, renal impairment

Side effects: gastro-intestinal disturbances including nausea, vomiting, diarrhoea, dyspepsia, abdominal pain and distension, gastro-oesophageal reflux disease, decreased appetite, weight loss, headache, dizziness, agitation, asthenia, hypoglycaemia, increased sweating, injection site reactions, antibody formation, pancreatitis

Dose: By subcutaneous injection, adult over 18 years, initially 5 micrograms twice daily within 1 hour before 2 main meals (at least 6 hours apart), increased if necessary after at least 1 month to max. 10 micrograms twice daily

Counselling: If a dose is missed, continue with the next scheduled dose (do not administer after a meal). Some oral medications should be taken at least 1 hour before or 4 hours after exenatide injection (consult product literature for details)

Note: Dose of concomitant sulphonylurea may need to be reduced

Preparations

Exenatide Injection, 5 microgram/dose (60 doses) in pre-filled pen

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Liraglutide

Indications: treatment of type 2 diabetes mellitus in combination with metformin or a sulfonylurea, or both, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination

Contra-indications: ketoacidosis; inflammatory bowel disease; diabetic gastroparesis

Cautions: discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain), pregnancy, breastfeeding, hepatic impairment, renal impairment

Side effects: gastro-intestinal disturbances including nausea, vomiting, constipation, diarrhoea, dyspepsia, abdominal pain and distension, flatulence, gastritis, gastro-oesophageal reflux disease, decreased appetite; headache, dizziness, fatigue; fever, bronchitis, nasopharyngitis; hypoglycaemia; injection site reactions; acute pancreatitis, thyroid neoplasm, goitre, increased blood calcitonin, angioedema

Dose: By subcutaneous injection, adult over 18 years, initially 0.6mg once daily, increased after at least 1 week to 1.2mg once daily, further increased if necessary after an interval of at least 1 week to max. 1.8mg once daily

Note Dose of concomitant sulfonylurea may need to be reduced

Preparations

Liraglutide injection, 6 mg/mL, 3 mL prefilled pens

Ministry of Health policy is that only one of the GLP-1 receptor agonists above will be purchased and made available for use

6 A.2.5: Treatment of hypoglycaemia

Management of hypoglycaemia in a conscious patient could start with oral glucose in the form of sweetened drinks or as granulated sugar. In unconscious patients, intravenous glucose should be given; it is best to start with concentrated (50%) intravenous solution when available, otherwise, 5-10% glucose is an alternative although large volumes are required; and transfer the patients to higher level of health service.

When facilities for intravenous administration of glucose are not available, use 1 mg of glucagon intramuscularly, intravenously or subcutaneously and transfer the patients to a higher level of health service. See also sec 6 A.1 above.

Glucagon (Restricted)

Indications: acute insulin-induced hypoglycaemia.

Contra-indications: phaeochromocytoma.

Cautions: ineffective in chronic hypoglycaemia, starvation.

Side-effects: nausea, vomiting, diarrhoea, hypokalaemia.

Dose: by intramuscular, subcutaneous or intravenous injection, adult and child over 8 years, 1 mg; Child under 8 years or body weight less than 25 kg, 500 mg.

Preparations

Glucagon hydrochloride injection, powder for reconstitution, 1 mg vial

6 B: Thyroid hormones and anti-thyroid drugs

6 B.1: Thyroid hormones

The thyroid gland synthesises thyroxine or tetra-iodothyronine (T_4) and tri-iodothyronine (T_3), which are available commercially for treatment of hypothyroidism. T_3 is more potent and has a shorter half-life than T_4 , which has a longer duration and slower onset of action. Thyroxine is clinically used for maintenance therapy in hypothyroidism.

Levothyroxine sodium (Thyroxine sodium)

Indications: hypothyroidism.

Contra-indications: thyrotoxicosis.

Cautions: cardiovascular disease, elderly, diabetes mellitus and diabetes insipidus.

Side-effects: usually seen with excessive doses; tachycardia, arrhyth-

mias, anginal pain, tremor, excitability, diarrhoea, heat intolerance, sleep disturbances.

Dose: initially, do not exceed 100 micrograms daily. Adjust dose according to response, by a 25-50 micrograms increment not before a month use. Maintenance dose is 100-200 micrograms daily.

In children and infants doses of thyroxine have to be titrated according to clinical response.

Preparations

Levothyroxine sodium tablets, 25 micrograms tab.

Levothyroxine sodium tablets, 50 micrograms tab.

Levothyroxine sodium tablets, 100 micrograms tab.

Levothyroxine sodium, oral solution, 100 micrograms / 5 mL

6 B.2: Antithyroid drugs

Hyperthyroidism can be treated with antithyroid drugs, but other treatment options include surgically removing the gland or treating it with radioactive iodine.

The thyroid gland needs iodine in small quantity to function properly. Large quantities of iodine may reduce thyroid hormone production and the vascularity of the gland, which helps in safe surgical manipulation. Iodine is not used for routine treatment of hyperthyroidism. Carbimazole is a commonly used drug in hyperthyroidism, which slows down the gland's production

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of thyroid hormone. It is very effective and can control thyroid function in 6-8 weeks. Treatment may continue for 12-18 months with an adjustment of the dose according to response. Allergic reaction is the most common side effect that mandates shifting the patients to other types of therapy.

Propylthiouracil is an alternative in patients allergic to carbimazole. Antithyroid drugs are orally effective and once daily dose is needed because of their long duration of action.

Physical symptoms of hyperthyroidism such as tremor, palpitation, sweating and insomnia can be managed with propranolol at the initial stages of treatment with antithyroid drugs.

Carbimazole

Indications: hyperthyroidism.

Cautions: liver disorders, pregnancy, breast-feeding, monitor blood tests; warn patients to report immediately any sore throat, mouth ulcers, fever, or any non-specific illness.

Side-effects: allergic reactions, skin rash, pruritus; nausea, headache, bone marrow suppression.

Dose: adult, 15-40 mg daily for 4-8 weeks or when the patient becomes euthyroid. Reduce dose for maintenance, usually 5-15 mg daily. Child, initially 250 microgram/kg daily in divided doses, adjust according to response.

Preparations

Carbimazole tablets, 5 mg tab.

Carbimazole tablets, 20 mg tab.

Iodine and iodide

Indications: thyrotoxicosis (pre-operative).

Contra-indications: breast-feeding.

Cautions: pregnancy, young children, not for long course of therapy.

Side-effects: skin and mucous membrane irritation, headache, weakness, erythema.

Dose: 0.1-0.3 mL 3 times daily of aqueous iodine solution diluted with milk or water.

Preparations

Aqueous iodine oral solution (Lugol's solution), contains 5% iodine and 10% potassium iodide in water; 500 mL/bottle

Propylthiouracil (Restricted)

Indications: hyperthyroidism.

Cautions: renal impairment, *see* under carbimazole.

Side-effects: *see* under carbimazole, blood disorders.

Dose: adult, 200-400 mg daily until patient becomes euthyroid. Reduce dose gradually, for maintenance usually 50-150 mg daily.

Child, not recommended.

Preparations

Propylthiouracil tablets, 50 mg tab.

6 C: Corticosteroids

The adrenocorticotrophic hormone (ACTH) stimulates the adrenal cortex to secrete 3 groups of corticosteroids namely, glucocorticoids, mineralocorticoids and weak androgens that can be converted peripherally to more potent androgens.

Glucocorticoids (cortisone and hydrocortisone) exert a number of physiological actions on carbohydrate, protein, and fat metabolism; contribute to the maintenance of normal blood pressure, maintain normal balance of body fluids and electrolyte and suppress inflammation.

Mineralocorticoids such as aldosterone are mainly involved in water and electrolyte regulation.

In addition to the naturally occurring corticosteroids, a large number of synthetic derivatives have been introduced. Although their effectiveness is well recognised in some clinical conditions, they are generally used indiscriminately in clinical practice causing serious complications.

They are available in various formulations. Those orally administered are well absorbed from the gastrointestinal tract. Topical, rectal and inhalational preparations are well absorbed from the site of administration and may cause systemic effects. Absorbed, cortico-

steroids are bound to plasma protein, metabolised in the liver and kidney and excreted in the urine.

Therapeutic indications: With the exception of replacement therapy in deficiency states, the use of glucocorticoids is largely empirical, not curative but merely palliative. Small physiological doses are needed in replacement therapy, but larger doses are needed to suppress inflammatory and immune responses.

Based on extensive clinical experience with corticosteroids it has been proposed that due to the number and severity of potential side-effects, the decision to institute therapy with corticosteroids always requires a careful consideration of the relative risk and benefits in each patient. For any disease and in any patient the appropriate dose to achieve a therapeutic effect must be determined by trial and error and must be re-evaluated periodically as the underlying disease changes or the complications of therapy arise. If the use of corticosteroids can save life as in exfoliative dermatitis, pemphigus, leukaemia or acute transplant rejection, high doses may need to be given irrespective of the side-effects. However, when corticosteroids are used to relieve pain, as in rheumatoid arthritis, the initial dose should be small and increased gradually until pain has been reduced to a tolerable level.

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The mineralocorticoids effects of the selected corticosteroids should always be considered. The relative potencies of the various drugs are listed.

Relative potencies and doses of corticosteroids

Steroid	Glucocort effect	Mineralo effect	Equivalent dose
Hydrocortisone	1	1	20
Cortisone	0.8	0.8	25
Fludrocortisone	10	125	**
Prednisolone	4	0.8	5
Methylprednisolo	5	0.5	4
Dexamethasone	25	0.0	0.7

** not applied as a glucocorticoid

Replacement therapy

Cortisone has been used, but hydrocortisone (cortisol) is preferred in primary adrenal insufficiency (Addison's disease). The daily dose of hydrocortisone is 20-30 mg in divided doses. Two thirds of the daily dose is given in the morning and the rest is in the evening to simulate the normal diurnal rhythm. The maintenance dose is determined by the clinical response and the well being of the patient. To correct the mineralocorticoid effects, a small dose of fludrocortisone 100-200 micrograms orally, is given in addition, as single daily dose.

Acute adrenal insufficiency (Addisonian crisis) is a medical emergency which is treated by, fluid and electrolyte replacement, correction

of hypoglycaemia and the intravenous administration of hydrocortisone 100 mg initially and then at 6 hourly intervals. The precipitating cause should be identified and treated such as trauma, infection, haemorrhage.

Iatrogenic adrenal insufficiency is caused by suppression of the hypothalamic- pituitary-adrenal function due to prolonged use of high doses of corticosteroids. Sudden cessation of therapy or intercurrent disease will lead to cortical insufficiency. Abrupt withdrawal also leads to relapse of the disease that was being treated. In such situation, intravenous injection of 100 mg hydrocortisone is given followed by further injection until blood pressure is maintained at a safe level.

Indications in non-endocrine conditions: Corticosteroids are widely indicated for various clinical conditions as a result of their anti-inflammatory and immunosuppressive nature. Such clinical conditions include; allergic reactions, collagen diseases, bronchial asthma, some skin disease, some neoplastic diseases, cerebral oedema, some blood disorders, active chronic hepatitis, ulcerative colitis, and acute resistant gout.

Cautions: Whenever possible local treatment with creams, intra-articular injection, inhalational, eye drops or enemas should be used in preference to systemic treatment. Taking the corticosteroid in the morning

has less suppressive effects on endogenous hormones. To attempt reducing pituitary-adrenal suppression further, the total dose of two days can sometimes be taken as a single dose on alternate days; alternate-day administration has not been proven to be effective in asthma. Gradual withdrawal is recommended in those whose disease is unlikely to relapse and have;

- recently received repeated courses.
- received more than 40 mg daily prednisolone or equivalent.
- been given repeat doses in the evening.
- being on treatment for more than three weeks.

Caution should be considered when prescribing to children, adolescents, elderly, during breast-feeding and pregnancy. Frequent monitoring is required if there is a history of tuberculosis, hypertension, diabetes mellitus, cardiac disease, osteoporosis, peptic ulceration, glaucoma, affective disorders.

Side-effects: diabetes mellitus, osteoporosis, water and electrolyte retention, hypertension, mental disturbances with an increased risk of suicidal tendencies, muscle wasting, peptic ulceration, glaucoma, increased susceptibility for infections, skin atrophy, acne. Chronic use in children may lead to growth retardation.

High doses may cause Cushing's syndrome, which is usually reversible on gradual withdrawal of the drug.

6 C.1: Naturally occurring glucocorticoids

Hydrocortisone

Indications:

adrenal insufficiency; anaphylactic and angioedema; for other indications *see* notes above and relevant sections.

Contra-indications: systemic infections.

Cautions: *see* notes above

Side-effects: *see* notes above

Dose: orally, for replacement therapy, 20-30 mg daily in divided doses, *see* notes above.

By intramuscular injection or slow intravenous injection or infusion, 100-500 mg 3-4 times in 24 hours or as required.

Child, by slow intravenous injection up to 1-year 25 mg, 1-5 years 50 mg, 6-12 years 100 mg.

Preparations

Hydrocortisone sodium succinate injection, powder for reconstitution, 100 mg vial.

Hydrocortisone tablets, 10 mg tab.

6 C.2: Synthetic adrenocorticosteroids

Dexamethasone (Restricted)

Indications: suppression of inflammatory and allergic disorders;

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shock; cerebral oedema; nausea and vomiting with chemotherapy; rheumatic disease; asthma; congenital adrenal hyperplasia; diagnosis of Cushing's disease; *see* notes above

Contra-indications: systemic infections.

Cautions: *see* notes above

Side-effects: *see* notes above; perineal irritation may follow intravenous injection of phosphate esters.

Dose: oral, 0.5-2 mg daily in divided doses, maximum 15 mg in severe conditions.

Adrenal hyperplasia, orally 0.5-1.5 mg daily in divided doses.

By intramuscular, slow intravenous injection or infusion, initially 0.5-20 mg. Child, 200-500 micrograms/kg daily.

Cerebral oedema, by intravenous injection, 10 mg initially, then 4 mg by intramuscular injection every 6 hours as required.

Shock, by intravenous injection or infusion, 2-6 mg/kg, repeated if necessary after 2-6 hours.

Preparations

Dexamethasone tablets, 0.5 mg tab.

Dexamethasone tablets, 2 mg tab.

Dexamethasone sodium phosphate injection, 4-5 mg/mL, 1 mL ampoule

Dexamethasone sodium phosphate injection, 4-5 mg/mL, 2 mL ampoule

Methylprednisolone (Restricted)

Indications: inflammatory and allergic disorders.

Contra-indications: severe infections.

Cautions: *see* notes above; very large intravenous doses have been associated with cardiac collapse.

Side-effects: *see* notes above

Dose: by intramuscular injection, for depot preparation, 40-120 mg repeated if necessary after 2-3 weeks.

By intramuscular or intravenous injection or infusion, for soluble preparations, 10-500 mg as required. May be repeated if necessary.

Preparations

Methylprednisolone acetate depot injection, 40 mg/mL vial

Methylprednisolone sodium succinate injection, powder for reconstitution, 500 mg vial

Prednisolone (Restricted)

Indications: suppression of inflammatory and allergic disorders; *see* also notes above

Contra-indications: severe infections.

Cautions: *see* notes above

Side-effects: *see* notes above

Dose: varies widely according to condition and its severity, usual range 5-20 mg daily, in very severe condition up to 60 mg daily.

Preparations

Prednisolone tablets, 5 mg tab

Prednisolone tablets, 20 mg tab

Triamcinolone

Indications: for alleviating the joint pain, swelling and stiffness associated with rheumatoid arthritis and osteoarthritis; also for bursitis, epicondylitis, tenosynovitis, lichen simplex chronicus (neuro-dermatitis), granuloma annulare, lichen planus, keloids, alopecia areata and hypertrophic scars.

Contra-indications: see notes above; administration by intravenous, intrathecal or intraocular injection, hypersensitivity to any of the ingredients.

Cautions: see notes above; should not be injected into unstable joints. avoid given over a long period of time, recent intestinal anastomoses, diverticulitis, thrombophlebitis, existing or previous history of severe affective disorders (especially previous steroid psychosis), exanthematous disease, renal insufficiency, metastatic carcinoma, osteoporosis (post-menopausal females are particularly at risk); in patients with peptic ulcer, myasthenia gravis, latent or healed tuberculosis; in the presence of local or systemic viral infection, systemic fungal infections or in active infections not controlled by antibiotics, hypertension, congestive heart failure, glaucoma, previous steroid myopathy, epilepsy, liver failure.

Side-effects: see notes above

Dose: by deep intramuscular injection, 40 mg; maximum 100 mg as a single dose.

Preparations

Triamcinolone injection, 10 mg/mL

6 C.3: Naturally-occurring mineralocorticoids and related drugs

Fludrocortisone (Restricted)

Indications: mineralocorticoid replacement in adrenal insufficiency.

Cautions: to be used with hydrocortisone.

Dose: 50-300 micrograms daily; Child, 5 micrograms/kg daily.

Preparations

Fludrocortisone tablets, 100 micrograms tab.

6 D: Sex hormones

6 D.1: Female sex hormones

6 D.1.1: Oestrogens and hormonal replacement therapy HRT

Oestrogens are available in natural and synthetic forms. Synthetic oestrogens are more potent than natural preparations and therefore are not routinely recommended for women in menopause. Only small doses of natural oestrogens are needed to alleviate somatic symptoms and vaginal dryness of menopause and to prevent osteoporosis.

Oestrogens may be given in tablet form or skin gel and patches. Vaginal creams are applied when they

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are primarily used to prevent thinning of the vaginal lining, thereby prevent urinary tract infections and incontinence and also prevent painful intercourse. Oestrogen is well absorbed from skin, vaginal wall and gastrointestinal tract. Systemic side-effects may be experienced after local administration. Hormonal replacement therapy (HRT) in menopause may be initiated after careful assessment of the risks and benefit of oestrogens. Prolonged use of oestrogen is associated with some serious side-effects such as thromboembolic disorders, breast and endometrial cancers. However, side-effects such as, nausea, migraine-like headache, breast discomfort and mood changes are associated with small doses and short period of oestrogen use.

In menopausal women with intact uterus, the use of progestogen with oestrogen is recommended. Such combination significantly reduces the risk of developing endometrial cancer.

Long term HRT is almost certainly favourable in risk-benefit terms for menopausal women without a uterus, because they do not require additional progestogen therapy.

Conjugated oestrogen

Indications: hormonal replacement therapy in menopause.

Contra-indications: oestrogen dependent cancer, thromboembolic disorders; undiagnosed vaginal bleeding.

Cautions: to advise for breast awareness and regular mammograms; pre-existing endometriosis, hypertension, diabetes, affective disorders.

Side-effects: nausea and vomiting, headache, migraine, mood changes, lipid and carbohydrate metabolic changes, body weight changes; see notes above

Dose: orally, for menopausal symptoms and osteoporosis prophylaxis, 0.625-1.25 mg daily.

Preparations

Conjugated oestrogen tablets, 625 microgram tab.

Betaestradiol

Indications: hormonal replacement therapy in menopause.

Contra-indications, cautions and side-effects: see under oestrogens

Dose: topical gel applications, 1-2 mg spread over the dry clean skin of the shoulder, thigh or arms, allow to dry for 5 minutes before covering with clothing. Avoid application near the eyes, breast or vulval region. Do not wash for at least one hour after application.

Preparations

Betaestradiol gel, 60 mg/100g gel

Estradiol (Restricted)

Indications: improve the vaginal epithelium in menopausal atrophic vaginitis. Postmenopausal urogenital conditions (not suitable for vasomotor symptoms or osteoporosis prophylaxis).

Contra-indications: active arterial thromboembolic disease (e.g. angina or myocardial infarction); active thrombophlebitis; Dubin-Johnson syndrome (or monitor closely); history of breast cancer; history of recurrent venous thromboembolism (unless already on anticoagulant treatment); oestrogen-dependent cancer; recent arterial thromboembolic disease (e.g. angina or myocardial infarction); Rotor syndrome (or monitor closely); thrombophilic disorder; undiagnosed vaginal bleeding; untreated endometrial hyperplasia; venous thromboembolism

Cautions: interrupt treatment periodically to assess need for continued treatment; acute porphyrias; diabetes (increased risk of heart disease); history of breast nodules—closely monitor breast status (risk of breast cancer); history of endometrial hyperplasia; factors predisposing to thromboembolism; history of fibrocystic disease—closely monitor breast status (risk of breast cancer); hypophyseal tumours; increased risk of gall-bladder disease; migraine (or migraine-like headaches); presence of antiphospholipid antibodies (increased risk of thrombotic events); prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer; risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative); symptoms of endometriosis may be exacerbated; uterine fibroids may increase in size.

Side-effects: local irritation; Abdominal bloating; abdominal cramps; altered blood lipids (may lead to pancreatitis, rashes and chloasma); breast enlargement; breast tenderness; changes in libido; cholestatic jaundice; contact lenses may irritate; depression; dizziness; fluid retention; glucose intolerance; headache; headache (on vigorous exercise); leg cramps (rule out venous thrombosis); migraine; mood changes; nausea; premenstrual-like syndrome; sodium retention; vaginal candidiasis; vomiting; weight changes.

Dose: Improve the vaginal epithelium in menopausal atrophic vaginitis 1 tablet daily for 2 weeks, then reduced to 1 tablet twice weekly. Postmenopausal urogenital conditions (not suitable for vasomotor symptoms or osteoporosis prophylaxis). To be inserted into upper third of vagina and worn continuously; replace after 3 months; max. duration of continuous treatment 2 years

Preparations

Estradiol pessary, 10 microgram
Estradiol pump, 750 microgram pack

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6 D.1.2: Progestogens

Progestogens include the naturally occurring progesterone and a number of frequently used synthetic compounds with progestogenic activities. Progestogens are most often used in conjunction with oestrogens for hormone replacement therapy in postmenopausal women and either alone or combined with oestrogen for contraception (*see* sec 7C). Endometriosis, menstrual disorders and some malignancies may be treated with progestogens.

Progestogens are contra-indicated in presence of severe liver disease, progestogen-dependent genital or breast cancer or vaginal bleeding.

Progestogens may induce acne, gastrointestinal disturbances, oedema, changes in libido, breast tenderness, mood changes, irregular menstrual cycles. They should be used with caution in the presence of diabetes, hypertension, epilepsy and cardiac, hepatic or renal disease.

Medroxyprogesterone acetate

Indications: endometriosis; dysfunctional bleeding; contraception (*see* sec 7C); malignancies; progestogenic opposition of oestrogen HRT.

Contra-indications, cautions and side-effects: *see* notes above

Dose: endometriosis, mild to moderate cases, 10 mg 3 times daily for 90 consecutive days, beginning of day 1 of a cycle.

Dysfunctional uterine bleeding, 2.5-10 mg daily for 5-10 days beginning on day 16 to 21 of cycle, repeated for 2 cycles.

Progestogenic opposition of oestrogen HRT, 10 mg daily for the last 14 days of each 28-day oestrogen HRT cycle.

Malignancies, consult product literature.

Preparations

Medroxyprogesterone acetate tablets, 5 mg tab.

Medroxyprogesterone acetate tablets, 10 mg tab.

Medroxyprogesterone acetate injection, 150 mg vial

Megestrol acetate (Restricted)

Indications: breast cancer, endometrial cancer.

Contra-indications, cautions and side-effects: *see* notes above

Dose: breast cancer, 160 mg daily in single or divided doses.

Endometrial cancer, 40-320 mg daily in divided doses.

Preparations

Megestrol acetate tablets, 160 mg tab.

Norethisterone acetate

Indications: endometriosis, HRT, menstrual disorders

Contra-indications, cautions and side-effects: *see* notes above

Dose: endometriosis, 10-15 mg daily starting on day 5 of cycle; if spotting appears, increase dose to 20-25 mg daily and reduce when bleeding stops

Dysfunctional uterine bleeding, 5 mg 3 times daily for 10 days
Dysmenorrhoea, 5 mg 3 times daily from day 5 to 25 for 3-4 cycles
Postponement of menstruation, 5 mg 3 times daily starting 3 days before anticipated onset
Progestogenic opposition of oestrogen in oestrogen HRT, 0.32-1 mg daily starting on day 15-26 of each 28-day oestrogen HRT cycle.

Preparations

Norethisterone acetate tablets, 5 mg tab

6 D.1.3: Oestrogens-progestogens preparations

Estradiol valerate + norgestrel

Indications: HRT in postmenopausal and osteoporosis prophylaxis in women with uterus.

Contra-indications, cautions and side-effects: *see* notes under oestrogens and progestogens

Dose: each calendar pack contains, 11 tablets estradiol valerate 2 mg, and 10 tablets of estradiol valerate 2 mg + norgestrel 0.5 mg. One tablets daily starting at day 5 of cycle (or any day if cycle has ceased or infrequent), followed by 7-day interval.

Preparations

Estradiol valerate 2 mg tab (11 tablets), and estradiol valerate 2 mg + norgestrel 0.5 mg tablets (10 tablets)/packet

Conjugated oestrogen + norgestrel

Indications: HRT in postmenopausal and osteoporosis prophylaxis in women with uterus.

Contra-indications, cautions and side-effects: *see* notes under oestrogens and progestogens

Dose: each pack contains 28 tablets (maroon colour) of conjugated oestrogens 625 micrograms, and 12 tablets (brown colour) of norgestrel 150 micrograms.

One maroon tablets daily continuously starting on day 1 of cycle or at any time if cycle has ceased, and one brown tablets on days 17-28 of each 28-day treatment cycle, subsequent courses are repeated without interval.

Preparations

Conjugated oestrogens tablets, 625 micrograms (28 tablets), and norgestrel 150 micrograms tablets (12 tablets)

6 D.2: Male sex hormones and antagonists

6 D.2.1: Male sex hormones

Testosterone, or testosterone esters, replacement therapy is the standard treatment for primary hypogonadism due to testicular or pituitary disease. In the normal male, androgens inhibit pituitary gonadotrophin secretion and depress spermatogenesis.

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Androgens should not be used for the treatment of impotence unless evidence of hypogonadism is confirmed.

Other uses of androgens include metastatic carcinoma of the breast, osteoporosis and delayed puberty in children. In children, caution should be practiced to avoid early closure of epiphyses with the result of short stature.

Testosterone is often given as an intramuscular depot injection of the esters although subcutaneous implants and oral preparations are also employed. More recently, transdermal implants and topical gel have been developed.

Androgens are **contra-indicated** in men with prostatic or breast cancer, and during pregnancy and breastfeeding.

They should be used with **caution** in patients with cardiac, renal and hepatic impairment; hypertension, migraine, epilepsy, diabetes or thyroid diseases; elderly, pre-pubertal boys.

The main **side-effects** encountered with the use of androgens include sodium and water retention, increased skeletal growth, hypercalcaemia and hypercalciuria, prostate abnormalities and probably cancer, changes in libido. In women it may cause virilisation and suppression of ovulation.

Testosterone (Restricted)

Indications: androgen deficiency, *see* notes above

Contra-indications, cautions and side-effects: *see* notes above

Dose: orally, in androgenic deficiency, initially 120-160 mg daily of testosterone undecanoate; maintenance 40-120 mg daily.

By intramuscular injection, testosterone esters in depot preparation 250 mg every 2-4 weeks

Preparations

Testosterone depot injection, 250 mg/mL of various testosterone esters in oily solution, 1 mL ampoule
Testosterone undecanoate capsules, 40 mg cap.

Oxandrolone (C.D.L)

Indications: (specialist use only), for the treatment of constitutional delay of growth and puberty in boys and Turner's syndrome in girls.

Contra-indications, cautions and side-effects: *see* notes above; short course of treatment to avoid the risk of epiphyseal closure.

Dose: 1.25-2.5mg daily for 3 months, longer duration may be required.

Preparations

Oxandrolone tablets, 2.5 mg tab.

6 D.2.2: Anti-androgens

Anti-androgens are used to treat disorders associated with excessive androgen or when lower than normal androgens level is desirable.

Cyproterone is used in treatment of severe hypersexuality and sexual deviation in the male. It may also be used in the treatment of acne and hirsutism in women.

Finasteride interferes with testosterone metabolism by inhibiting the enzyme 5 α -reductase, which metabolises testosterone into the more potent androgen, dihydrotestosterone. Reducing the level of testosterone in the prostate results in reducing its size and an improvement of urinary flow rate and in obstructive symptoms.

Cyproterone (Restricted)

Indications: hypersexuality in the male; severe acne and hirsutism in women.

Contra-indications: hepatic disease; malignant or wasting disease; severe diabetes with vascular changes; youths under 18 years.

Cautions: sedation may impair psychomotor performances; chronic alcoholism; regularly monitor hepatic function, blood count, adrenocortical function.

Side-effects: fatigue and lassitude, weight changes, gynaecomastia; inhibition of spermatogenesis; osteoporosis.

Dose: orally in male hypersexuality, 50 mg twice daily.

Preparations

Cyproterone tablets, 50 mg tab.

Finasteride (Restricted)

Indications: benign prostatic hyperplasia.

Cautions: obstructive uropathy, prostate cancer; finasteride may cause feminisation of male foetus, it is recommended to use condom if sexual partner is pregnant (finasteride is excreted in semen).

Side-effects: impotence, decreased libido, ejaculation disorders, testicular pain, breast tenderness and enlargement, allergic reactions.

Dose: 5 mg daily for 6 months, reassess treatment then after. Longer therapy period may be needed.

Preparations

Finasteride tablets, 5 mg tab.

6 D.2.3: Somatostatin analogues

Somatostatin, a cyclic polypeptide, secreted from pancreas can regulate pituitary function, thereby acting as a true neurohormone. The therapeutic uses of Somatostatin are confined mainly to blocking hormone release in endocrine-secreting tumours, including insulinomas, VIPomas, glucagonomas, carcinoid tumours, somatotropinomas as in acromegaly. Because of its short half-life, somatostatin has been replaced by octreotide, a long-acting analogue. Octreotide successfully controls excess secretion of growth hormone and reduces the size of pituitary tumours. It has also been

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used for the prevention of complications following pancreatic surgery.

Lanreotide (Restricted)

Indications: Acromegaly and neuroendocrine (particularly carcinoid) tumours. Thyroid tumours.

Cautions: Cardiac disorders (including bradycardia); patients with carcinoid tumours—exclude the presence of an obstructive intestinal tumour before treatment. Diabetes mellitus (antidiabetic requirements may be reduced); insulinoma (increased depth and duration of hypoglycaemia may occur—observe patients and monitor blood glucose levels when initiating treatment and changing doses); may cause growth hormone-secreting pituitary tumour expansion during treatment (causing serious complications).

Side-effects: Alopecia; biliary dilatation; bradycardia; constipation; dizziness; dyspepsia; headache; lethargy; malaise; musculoskeletal pain; myalgia; raised bilirubin; Hot flushes; insomnia; hypothyroidism; Pancreatitis (shortly after administration); Abdominal pain; anorexia; bloating; diarrhoea; flatulence; gallstones (after long-term treatment); gastro-intestinal disturbances; hyperglycaemia (with chronic administration); hypoglycaemia; impaired postprandial glucose tolerance (with chronic administration); irritation at the injection site; nausea; pain at the injection site; steatorrhoea; vomiting

Dose: Acromegaly and neuroendocrine (particularly carcinoid) tumours. Initially 30 mg every 14 days, increased to 30 mg every 7–10 days, adjusted according to response.

Thyroid tumours. Initially 30 mg every 14 days, increased to 30 mg every 10 days, adjusted according to response.

Preparations

Lanreotide acetate injection, 30 mg vial

Octreotide (C.D.L)

Indications: *see* notes above

Cautions: do regular ultrasound examination of gallbladder; monitor glucose tolerance; check on growth hormone abnormal secretion.

Side-effects: sinus bradycardia, conduction abnormalities, arrhythmias; diarrhoea; hypo/hyperglycaemia; gallbladder abnormalities.

Dose: for doses in various therapeutic indications, consult product literature.

Preparations

Octreotide injection, 200 micrograms ampoule.

Octreotide acetate injection, powder and solvent for reconstitution, 20 mg vial

6 E: Hypothalamic and pituitary hormones

6 E.1: Anterior pituitary hormones and anti-oestrogens

6 E.1.1: Anti-oestrogens

The anti-oestrogens tamoxifen and clomifene are used primarily for the treatment of breast cancer and female infertility, respectively. These agents are therapeutically used for their anti-oestrogenic activity, but they are capable of producing anti-oestrogenic as well as oestrogenic effects. They block the oestrogen receptors in the hypothalamus leading to increased pituitary secretion of gonadotrophin.

Clomifene citrate (Clomiphene citrate)

Indications: anovulatory infertility.

Contra-indications: hepatic disease, ovarian cysts, abnormal uterine bleeding, endometrial carcinoma, pregnancy.

Cautions: use smallest dose possible in women with polycystic disease; patients should be warned of the possibility of multiple pregnancy; visual disturbances mandates discontinuation of therapy.

Side-effects: visual disturbances, hot flushes, gastrointestinal disturbances, liver impairment, ovarian enlargement and cyst formation, breast tenderness.

Dose: 50 mg daily for 5 days, starting within about 5 days of onset of cycle or at any time if there is amen-

orrhoea. If ovulation does not occur the dose may be doubled and treatment course repeated twice if necessary. Long-term cyclical therapy is not recommended.

Preparations

Clomifene citrate tablets, 50 mg tab.

Tamoxifen (Restricted)

Indications: oestrogen-receptor positive breast cancer in women.

Contra-indications: pregnancy.

Cautions: patients with leucopoenia or thrombocytopenia; occasional cystic ovarian swelling in premenopausal women, endometrial changes; breast-feeding.

Side-effects: hot flushes, nausea and vomiting, increased tumour pain, vaginal bleeding, endometriosis, blood disorders, masculinisation and hirsutism in females.

Dose: 20 mg daily.

Preparations

Tamoxifen tablets, 10 mg tab.

6 E.1.2: Anterior pituitary hormones

The peptide hormones of the anterior pituitary are essential for the regulation of growth, reproduction and intermediary metabolism. The synthesis and release of such hormones are controlled by hypothalamic hormones, by peripheral endocrine hormones, by disease, and by many drugs.

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Corticotropins (Corticotrophins)

The adrenocorticotrophic hormone (ACTH or corticotropin) stimulates the adrenal cortex to secrete glucocorticoids, mineralocorticoids, and androgens.

Tetracosactrin (tetracosactide) is a synthetic analogue of corticotropin that is of therapeutic and diagnostic uses. The use of ACTH and tetracosactide as alternative to corticosteroids is declining due to variable and unpredictable therapeutic response. Presently, they are mainly indicated for the diagnosis of adrenal insufficiency. Plasma cortisol concentration in normal adrenal function tends to rise after the administration of tetracosactrin or ACTH.

Tetracosactide acetate (Tetracosactrin acetate) (Restricted)

Indications: adrenocortical function test; *see* notes above

Contra-indications: as for corticosteroids; avoid using preparations containing benzyl alcohol in neonates.

Cautions and side-effects: as for corticosteroids *see* sec 6 C

Dose: diagnostic, intramuscularly 1 mg single dose.

Therapeutic indications, consult product literature.

Preparations

Tetracosactide acetate injection, 1 mg/mL aqueous suspension, 1 mL ampoule

Tetracosactide acetate injection, 250 micrograms/mL, 1 mL ampoule

Gonadotrophins

The pituitary hormones, luteinising hormone (LH), and follicle-stimulating hormone (FSH) as well as the related placental hormone, chorionic gonadotrophin (CG), are referred to as the gonadotropic hormones because of their actions on gonadal cells. These hormones are nowadays prepared from human urine and no more extracted from cadaverous pituitary glands. Menotrophin, which contains both FSH and LH is obtained from the urine of postmenopausal women and often referred to as human menopausal gonadotrophin. Human chorionic gonadotrophin (HCG) is obtained from the urine of pregnant women. Urofollitropin (urofollitrophin) is a menotrophin from which the LH has been removed and thus is primarily FSH.

The main therapeutic use of these hormones is in the treatment of female infertility resulting from hypopituitarism, or those not responded to clomiphene, or in superovulation treatment to assist conception. In the male, they are used for the treatment of hypogonadotrophin hypogonadism and associated oligospermia.

Human chorionic gonadotrophin (Restricted)

Indications: *see* notes above

Contra-indications: androgen-dependent tumours.

Cautions: cardiac or renal dysfunction, asthma, epilepsy, migraine.

Side-effects: headache, irritability, precocious puberty, gynaecomastia, injection site pain, multiple pregnancy.

Dose: by subcutaneous or intramuscular injection according to patient's response or need.

Preparations

Human chorionic gonadotrophin injection, powder for reconstitution 1500 units/ampoule.

Human chorionic gonadotrophin injection, powder for reconstitution 5000 units/ampoule.

Human menopausal gonadotrophin (Restricted)

Indications: *see* notes above

Contra-indications: undiagnosed abnormal vaginal bleeding, intracranial bleeding, adrenal and thyroid disorders, pre-existing ovarian cysts, primary ovarian or testicular failure, malignancies of breast, uterus, testes or prostate.

Cautions: tumour of the pituitary, rule out infertility caused by adrenal or thyroid disorders, hyperprolactinaemia.

Side-effects: allergic reactions; ovarian enlargement and rupture, increased risk of multiple pregnancies.

Dose: by subcutaneous or intramuscular injection, according to patient's response or need.

Preparations

Human menopausal gonadotrophin injection, powder for reconstitution, FSH 75 units + LH 75 units/ampoule

Urofollitropin (Urofollitropin) (Restricted)

Indications: *see* notes above

Contra-indications, cautions and side-effects: *see* under human menopausal gonadotrophin

Dose: by subcutaneous or intramuscular injection according to patient's response or need.

Preparations

Urofollitropin injection, powder for reconstitution, 75 units / ampoule

Growth hormone

Somatropin is an analogue of human growth hormone produced by using recombinant DNA technology. Its main therapeutic indication is in growth hormone-deficient children.

Human growth hormone HGH (Somatropin) (Restricted)

Indications: growth hormone deficiency.

Contra-indications: closed epiphyses, active tumours, hypersensitivity to m-cresol or glycerin (diluent).

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Cautions: diabetes mellitus, papilloedema, history of malignant disease, rotate site of injection to avoid lipatrophy.

Side-effects: development of antibodies, oedema.

Dose: by subcutaneous injection according to patient's response or need.

Preparations

Human growth hormone injection, powder for reconstitution, 4 units/ampoule (1.33 mg / ampoule)
Growth Hormone 15 Units pen.

Thyroid stimulating hormone

Thyrotropin alfa is a recombinant form of thyrotrophin (thyroid stimulating hormone)

Thyrotropin alfa (recombinant thyroid stimulating hormone) (Restricted)

Indications: Detection of thyroid remnants and thyroid cancer in post-thyroidectomy patients, together with serum thyroglobulin testing (with or without radioiodine imaging). To increase radio-iodine uptake for the ablation of thyroid remnant tissue in suitable post-thyroidectomy patients

Cautions: Presence of thyroglobulin autoantibodies may give false negative results

Side-effects: Dizziness; fatigue; headache; nausea; vomiting

Dose: 900 micrograms every 24 hours for 2 doses, dose to be administered into the gluteal muscle, consult product literature for further information on indications and dose.

Preparations

Thyrotropin Alfa injection, powder for reconstitution, 900 microgram vial.

6 E.1.3: Hypothalamic hormones

The hypothalamic hormone gonadorelin, which causes the release of LH and FSH, is mainly used for diagnostic purposes. However, gonadorelin analogues such as goserelin and triptorelin are indicated for the treatment of prostate cancer and endometriosis (*see sec 8C*).

Protirelin is a hypothalamic-releasing hormone that stimulates the release of thyrotrophin from the pituitary. It is indicated for the diagnosis of mild hyperthyroidism or hypothyroidism.

Gonadorelin (Restricted)

Indications: assessment of pituitary function in adults.

Cautions: pituitary adenoma.

Side-effects: irritation at injection site; hypersensitivity reactions on repeated administration.

Dose: subcutaneous or intravenous injection, 100 micrograms.

Preparations

Gonadorelin injection, powder for reconstitution, 100 micrograms vial

Protirelin (C.D.L)

Indications: assessment of thyroid function.

Cautions: severe hypopituitarism, asthma, ischemic heart disease, pregnancy and breast-feeding.

Side-effects: hypertension, hypotension, nausea and vomiting, urinary urgency, warmth.

Dose: by intravenous injection, adult 200 micrograms. Child 1 microgram/kg.

Preparations

Protirelin injection, 200 micrograms / 2 mL ampoule

Protirelin injection, 250 micrograms / ampoule

Goserelin (C.D.L)

See under Goserelin sec.8C

Triptorelin (C.D.L)

Indications: Advanced prostate cancer, endometriosis.

Contra-indications and cautions: see under goserelin

Side-effects: see under goserelin; dry mouth, excessive salivation.

Dose: consult product literature

Preparations

Triptorelin injection, powder for reconstitution, 3.75 mg vial

Triptorelin injection, powder for reconstitution, 11.25 mg vial

6 E.2: Posterior pituitary hormones and antagonists

Antidiuretic hormone (vasopressin) promotes water conservation by the kidney. In large therapeutic doses, it can also cause peripheral vasoconstriction and stimulates the smooth muscles of the intestine, gall bladder and urinary bladder. Lack of this hormone leads to diabetes insipidus with characteristic excessive excretion of diluted urine.

Desmopressin is an analogue of vasopressin with longer duration of action and no vasoconstrictor effects. It is indicated in the treatment and diagnosis of hypothalamic (cranial) diabetes insipidus. Nephrogenic diabetes insipidus is better treated with thiazide diuretics. Desmopressin is also used to boost the effect of factor VIII in haemophilic patients, in the treatment of bleeding oesophageal varices because it decreases hepatic blood flow and portal venous pressure.

Desmopressin (Restricted)

Indications: diagnosis and treatment of hypothalamic diabetes insipidus; boosting Factor VIII in haemophilia.

Contra-indications: cardiac insufficiency and disorders treated with diuretics.

Cautions: migraine, epilepsy, heart failure, asthma; pregnancy; avoid fluid overload.

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Side-effects: fluid retention when fluid intake is not restricted, gastric pain, headache, convulsions due to hyponatraemia, nausea and vomiting.

Dose: Treatment of hypothalamic (cranial) diabetes insipidus, intranasally, adult 10-40 micrograms daily in 1-2 divided doses. Child 5-20 micrograms daily. By injection, adult 1-4 micrograms daily. Child 400 nanograms daily. Orally, adult and child, 300 micrograms daily in divided doses; maintenance, 300-600 micrograms.

Diagnosis of diabetes insipidus, intranasally, adult and child 20 micrograms. By injection, adult and child 2 micrograms. Restrict fluid intake 1 hour before and 8 hours after administration.

In mild to moderate haemophilia, by subcutaneous or intramuscular injection, consult literature.

Preparations

Desmopressin acetate injection, 4 micrograms/mL, 1 mL ampoule

Desmopressin tablets, 100 microgram tab.

Desmopressin tablets, 200 microgram tab. .

Terlipressin (Restricted)

Indications: bleeding from oesophageal varices.

Contra-indications and cautions: *see* under desmopressin

Side-effects: *see* under desmopressin, but effects milder

Dose: by intravenous injection, 2 mg followed by 1 mg or 2 mg every 4-6 hours until bleeding is controlled, for up to 72 hours.

Preparations

Terlipressin acetate injection, powder for reconstitution, 1 mg vial with diluent

6 F: Drugs affecting bone metabolism

6 F.1: Calcitonin

Calcitonin is a polypeptide hormone that lowers calcium and phosphate plasma levels. It is secreted by the thyroid gland and causes an increase in mineral stores in bone and increase renal excretion of calcium. Therapeutically, salmon calcitonin is used for the treatment of severe hypercalcaemia and in disorders of increased skeletal remodelling such as Paget's disease, and in some patients with osteoporosis.

Calcitonin (Salmon) (Salcatonin) (Restricted)

Indications: hypercalcaemia; Paget's disease; osteoporosis.

Contra-indications: hypersensitivity to synthetic calcitonin.

Cautions: administration may lead to hypocalcaemic tetany; monitor for possible allergic reactions to

calcitonin since it is an exogenous protein; resistance to salmon calcitonin may develop due to antibody formation.

Side-effects: gastrointestinal disturbances; skin rash; nasal spray may cause local irritation and ulceration, rhinitis sinusitis, epistaxis.

Dose: hypercalcaemia, by subcutaneous or intramuscular injection, 5–10 units/kg daily in 1–2 divided doses, adjust according to clinical and biochemical response.

Paget's disease of bone, intramuscular or subcutaneous injection, a dose range of 50 units 3 times weekly to 100 units daily are used as single or divided doses.

Postmenopausal osteoporosis, intramuscular or subcutaneous injection, 100 units daily. Intranasally, 200 units daily. Supplement of dietary calcium and vitamin D is recommended.

Preparations

Calcitonin injection, 50 micrograms/mL, 1 mL ampoule

Calcitonin metered nasal spray, 200 units/metered spray

treatment of established osteoporosis, and in conditions characterized by increased bone remodelling as in Paget's disease or hypercalcaemia in malignancies. These drugs should be avoided in the presence of upper gastrointestinal disease, hypocalcaemia and in renal impairment.

Alendronate (Restricted)

Indications: treatment and prevention of postmenopausal osteoporosis, Paget's disease.

Contra-indications: hypocalcaemia; pregnancy and breast-feeding; upper gastrointestinal disorders.

Cautions: upper gastrointestinal disorders, renal impairment, routine check for calcium and other minerals.

Side-effects: oesophageal reactions, gastrointestinal disturbances, musculoskeletal pain, headache, rash and photosensitivity.

Dose: treatment of postmenopausal osteoporosis, 70 mg once weekly.

Note: to be taken on an empty stomach at least 30 minutes before breakfast and patient should stand or sit upright for at least 30 minutes after taking tablet.

Preparations

Alendronate tablets, 70 mg tab.

6 F.2: Bisphosphonates

Bisphosphonates increase bone mass by reducing the activity of individual osteoclasts and increasing osteoclast apoptosis. They are indicated for, the prevention of bone loss in early menopausal women,

6: Endocrine system

Clodronate (Restricted)

Indications: hypercalcaemia in malignancies, Paget's disease, osteolytic lesions and bone pain associated with malignancies.

Contra-indications: renal impairment, pregnancy and breast-feeding.

Cautions: renal and hepatic disease, elderly; regularly monitor water and electrolytes; concomitant use of NSAIDs may be associated with renal dysfunction.

Side-effects: nausea, diarrhoea.

Dose: by mouth, 1.6 g daily in single or 2 divided doses, increase if necessary to 3.2 g.

Preparations

Clodronate sodium capsules, 400 mg cap.

Disodium pamidronate (Restricted)

Indications: hypercalcaemia in malignancies, Paget's disease, osteolytic lesions and bone associated with malignancies.

Contra-indications: see notes above; pregnancy and breast-feeding.

Cautions: renal disease, elderly; thyroid dysfunction; regularly monitor water and electrolytes.

Side-effects: hypophosphataemia, fever and flu-like symptoms, nausea and vomiting, gastrointestinal discomfort.

Dose: by slow intravenous infusion;

in hypercalcaemia of malignancy, 15-60 mg in single infusion or in divided doses over 2-4 days according to level of serum calcium.

In Paget's disease, 30 mg once a week for 6 weeks or 30 mg first week and the 60 mg every other week with a total of 210 mg. Maximum total 360 mg.

In osteolytic lesions and bone pain in bone metastases associated with breast cancer or multiple myeloma, 90 mg every 3-4 weeks.

Preparations

Disodium pamidronate injection, powder for reconstitution, 15 mg vial

Zoledronic acid

Indications: hypercalcaemia of malignancy, osteoporosis, Paget's disease, multiple myeloma and patients with documented bone metastases from solid tumours, in conjunction with standard antineoplastic therapy.

Contra-indications: pregnancy and breast-feeding.

Cautions: patient must be adequately rehydrated prior to administration, serum levels of calcium, phosphate, and magnesium, as well as serum creatinine, should be carefully monitored following initiation of therapy, if hypocalcaemia, hypophosphataemia, or hypomagnesaemia occur, short-term supplemental therapy may be necessary.

Side-effects: hypophosphataemia, anaemia, influenza like syndrome

including bone pain, gastrointestinal disturbances, headache, renal impairment.

Dose: in hypercalcaemia of malignancy, by intravenous infusion, 4 mg as a single dose infused over no less than 15 minutes. In osteoporosis, by intravenous infusion, 5 mg infused over no less than 15 min every 12 months.

Note: daily calcium and vitamin D supplements should also be taken.

Preparations

Zoledronic acid injection, 4 mg vial
Zoledronic acid injection, 50 micrograms/ mL, 100 mL bottle

Denosumab (Restricted)

Indications: Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. Prevention of skeletal related events in patients with bone metastases from solid tumours. Treatment of giant cell tumour of the bone.

Contra-indications: Hypocalcaemia, unhealed lesions from dental or oral surgery.

Cautions: Atypical femoral fractures; hypocalcaemia; osteonecrosis of the jaw—consider temporary interruption of treatment if occurs.

Side-effects: Abdominal discomfort; cataracts; constipation; diarrhoea; dyspnoea; eczema; hypocalcaemia (fatal cases reported);

hypophosphataemia; musculoskeletal pain; osteonecrosis of the jaw; pain in extremity; rash; sciatica; sweating; upper respiratory tract infection; urinary tract infection.

Dose: Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures and the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, by subcutaneous injection: 60 mg every 6 months, supplement with calcium and vitamin D. Prevention of skeletal related events in patients with bone metastases from solid tumours, by subcutaneous injection: 120 mg every 4 weeks, supplementation of at least Calcium 500 mg and vitamin D 400 units daily should also be taken unless hypercalcaemia is present.

Treatment of giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity in adults and skeletally mature adolescent, by subcutaneous injection: 120 mg every 4 weeks, give additional dose on days 8 and 15 of the first month of treatment only, supplementation of at least Calcium 500 mg and vitamin D 400 units daily should also be taken unless hypercalcaemia is present.

Preparations

Denosumab injection, 60 mg / 1 ml
Denosumab injection 70 mg / 1 ml

6: Endocrine system

6 G: Other endocrine drugs

6 G.1: Bromocriptine

Bromocriptine is a dopaminergic agonist that inhibits the pituitary release of prolactin. It is useful in galactorrhoea and in the treatment of infertility due to hyperprolactinaemia. It may be used to reduce the level of growth hormone in patients with acromegaly. When ordinary measures fail, bromocriptine may be used to suppress lactation. It is also used in treatment of benign breast disorders and prolactinoma.

Bromocriptine (Restricted)

Indications: *see* notes above

Contra-indications: sensitivity to bromocriptine; toxæmia of pregnancy and hypertension in postpartum women or in puerperium.

Cautions: peptic ulcer; mental disorders; cardiovascular disease.

Side-effects: nausea, vomiting, constipation; dyskinesia, fatigue; hypotension.

Dose: prevention of lactation, orally 2.5 mg on day 1 and then 2.5 mg twice daily for 14 days.

Suppression of lactation, 2.5 mg daily for 2-3 days and then 2.5 mg twice daily for 14 days. Hypogonadism, galactorrhoea, infertility, initial dose of 1-1.25 mg at bed time to minimize the hypotensive effect, increase gradually to 7.5 mg daily in divided doses.

Cyclical benign breast disease, 1-1.25 mg at bedtime, increase gradually to 2.5 mg twice daily.

Acromegaly, initially 1-1.25 mg, increase gradually to 5 mg every 6 hours.

Preparations

Bromocriptine tablets, 2.5 mg tab.

Cabergoline (Restricted)

Indications: Prevention of lactation. Suppression of established lactation. Hyperprolactinaemic disorders. Parkinson's disease.

Contra-indications: Avoid in pre-eclampsia; cardiac valvulopathy (exclude before treatment); history of pericardial fibrotic disorders; history of puerperal psychosis; history of pulmonary fibrotic disorders; history of retroperitoneal fibrotic disorders

Cautions: Acute porphyrias; cardiovascular disease; history of peptic ulcer (particularly in acromegalic patients); history of serious mental disorders (especially psychotic disorders); Raynaud's syndrome. In hyperprolactinaemic patients, the source of the hyperprolactinaemia should be established (i.e. exclude pituitary tumour before treatment).

Side-effects: Abdominal pain; angina; breast pain; confusion; constipation; depression; dyspepsia; epigastric pain; gastritis; hallucinations; headache; nausea; syncope

Dose: Prevention of lactation 1 mg, to be taken as a single dose on the first day postpartum.

Suppression of established lactation 250 micrograms every 12 hours for 2 days.

Hyperprolactinaemic disorders Initially 500 micrograms once weekly, dose may be taken as a single dose or as 2 divided doses on separate days, then increased in steps of 500 micrograms every 1 month until optimal therapeutic response reached, increase dose following monthly monitoring of serum prolactin levels; usual dose 0.25–2 mg once weekly, usually 1 mg weekly; reduce initial dose and increase more gradually if patient intolerant, doses over 1 mg weekly to be given as divided dose; maximum 4.5 mg per week.

Parkinson's disease Initially 1 mg daily, then increased in steps of 0.5–1 mg every 7–14 days, concurrent dose of levodopa may be decreased gradually while dose of cabergoline is increased; maximum 3 mg per day.

Preparations

Cabergoline tablets, 500 microgram tab.

6 G.2: Trilostane

Danazol is a synthetic androgen with strong antigonadotrophic effects that leads to secondary endometrial atrophy. It is used for the treatment of endometriosis. Danazol possesses an antagonistic effect and hence is used in precocious puberty, gynaecomastia, and

menorrhagia. It may be of value in the long-term therapy of hereditary angioedema.

Danazol (*Restricted*)

Indications: see notes above

Contra-indications: pregnancy; severe renal, hepatic and cardiac disease; thromboembolic disorders; hormone-dependent tumours.

Cautions: epilepsy, diabetes mellitus, migraine, elderly, polycythaemia, hypertension, non-hormonal contraceptive to be used if appropriate.

Side-effects: dizziness, flushes, muscle spasm, hair loss, acne, oedema, mild hirsutism, mood changes, changes in libido, vaginal dryness and irritation, menstrual disturbances, reduction in breast size.

Dose: endometriosis, initially 200–400 mg daily in 2–4 divided doses for 6 months, adjust according to response.

Precocious puberty, 100–400 mg daily in 2–4 divided doses, adjust according to age and response.

Menorrhagia. 100–400 mg in 2–4 divided doses, starting on the first day of cycle, adjust dose according to response, reassess after 3 months.

Gynaecomastia, 400 mg daily in divided doses, for six months. Smaller dose may be used in adolescents.

Preparations

Danazol capsules, 200 mg cap.

7: Obstetrics, gynaecology and urinary tract disorders

Section 7: Obstetrics, gynaecology and urinary tract disorders

- Drugs acting on smooth muscles
- Drugs used in vaginal and vulval conditions
- Contraceptives
- Urinary disorders
- Irrigation fluids and dialysis

7 A: Drugs acting on smooth muscles

7 A.1: Prostaglandins and oxytocics

Drugs such as prostaglandins and oxytocics (oxytocin and ergometrine) are used to induce or augment labour. They are also used to induce abortion or to stop postpartum haemorrhage. The uterine contractions induced vary in strength and duration and the pain caused is contraction dependent.

Dinoprostone (prostaglandin PGE₂) is available in various formulations. Vaginal applications in the form of gel and pessaries are mostly preferred because of low incidence of side-effects. It is used for induction and augmentation of labour at term. Carboprost (prostaglandin PGF_{2α}) is administered by injection for the treatment of postpartum haemorrhage that is uncontrolled by oxytocin and ergometrine.

Oxytocin alone or in combination with ergometrine is usually administered by injection. Oxytocin is used to induce or augment labour. Uterine motility must be monitored during oxytocin infusion and hyper-stimulation must be avoided. Ergometrine in combination with oxytocin is applied for the treatment of postpartum haemorrhage or to reduce bleeding during surgical uterine evacuation. Misoprostol is a synthetic prostaglandin analogue that has antisecretory and protective properties, promoting healing of gastric and duodenal ulcers. It also acts as a potent uterine stimulant.

Dinoprostone (Restricted)

Indications: induction and augmentation of labour at term; medical induction of therapeutic abortion.

Contra-indications: cardiac, pulmonary, renal, hepatic disease; foetal distress; untreated pelvic infection; placenta praevia or unexplained vaginal bleeding; history of difficult cephalopelvic disproportion or traumatic delivery; foetal malpresentation, grand multipara, multiple pregnancy; history of caesarean section or major uterine surgery.

Cautions: asthma, glaucoma, cardiac, hepatic or renal impairment; hypertension; epilepsy; closely monitor uterine contractility when oxytocin is used in sequence.

Side-effects: nausea, diarrhoea; dizziness; bronchospasm, fever,

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backache; severe uterine contraction; pulmonary or amniotic fluid embolism; abruptio placentae, foetal distress, uterine rupture.

Dose: vaginal gel, for induction of labour 1 mg inserted high into posterior fornix, followed after 6 hours by 1-2 mg, maximum 3 mg gel.

Vaginal tablets, for induction of labour, 3 mg tablets inserted high into posterior fornix, followed after 6-8 hours by another 3 mg tablet, maximum 6 mg as vaginal tablets.

Injections, consult manufacturer's literature.

Preparations

Dinoprostone vaginal gel, 400 micro-grams/mL, 2.5 mL gel application (total 1 mg per application)

Dinoprostone vaginal gel, 800 micro-grams/mL, 2.5 mL gel application (total 2 mg per application)

Dinoprostone vaginal tablets, 3 mg pessary

Carboprost (CDL)

Indications: postpartum haemorrhage due to uterine atony unresponsive to ergometrine and oxytocin.

Contra-indications: renal, cardiac, pulmonary or hepatic disease; untreated pelvic infection.

Cautions: glaucoma, hypertension, hypotension, epilepsy, uterine scar.

Side-effects: see dinoprostone above

Dose: by deep intramuscular injection, 250 micrograms repeated if necessary every 60-90 minutes, total dose should not exceed 2 mg.

Preparations

Carboprost (as trometamol or tromethamine salt) injection, 250 microgram/mL, 1 mL ampoule

Ergometrine maleate + oxytocin

Indications: postpartum haemorrhage; to reduce bleeding during surgical uterine evacuation.

Contra-indications: induction of labour; second and third stages of labour; circulatory disease; impaired pulmonary, renal or hepatic functions; sepsis; severe hypertension, eclampsia.

Cautions: multiple pregnancy, toxæmia, sepsis.

Side-effects: nausea and vomiting, abdominal pain, dizziness, tinnitus, palpitation, transient hypertension.

Dose: intramuscular injection, single 1 mL ampoule (see preparation).

Preparations

Ergometrine maleate + oxytocin injection, 500 micrograms + 5 units/mL, 1 mL ampoule

Misoprostol (Restricted)

Indications: to induce medical abortion, cervical ripening procedure, management of post partum haemorrhage, prophylaxis for NSAID-induced gastric ulcer.

Contraindication: pregnancy, severe asthma requiring corticosteroids, hepatic failure, adrenal failure, bleeding disorders of concurrent anticoagulation therapy, allergy to misoprostol, suspected ectopic

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pregnancy, IUCD in situ, inherited porphyria

Cautions: Conditions where hypotension might precipitate severe complications (e.g. cerebrovascular disease, cardiovascular disease); inflammatory bowel disease, renal failure, previous cesarean birth

Side-effects: abdominal pain, diarrhoea, indigestion, nausea, cardiac dysrhythmia, anaemia, vaginal bleeding, chills and fever.

Dose: Benign gastric ulceration

Benign duodenal ulceration

NSAID-associated ulceration: 800 micrograms daily in 2–4 divided doses continued for at least 4 weeks or may be continued for up to 8 weeks if required, dose to be taken with breakfast (or main meals) and at bedtime.

Prophylaxis of NSAID-induced gastric ulcer. Prophylaxis of duodenal ulcer: 200 micrograms 4 times a day, reduced if not tolerated to 200 micrograms 2–3 times a day/day, use lower dose is less

Termination of pregnancy following mifepristone (gestation up to 49 days) 400 micrograms for 1 dose, dose to be given 24–48 hours after mifepristone.

Termination of pregnancy following mifepristone (gestation 50 to 63 days). Initially by vagina, or by buccal administration, or by sublingual administration 800 micrograms for 1 dose, dose to be given 24–48 hours after mifepristone, if abortion has not occurred 4 hours after first misoprostol dose a further dose may be given, (by

mouth or by vagina) 400 micrograms for 1 dose.

Termination of pregnancy following mifepristone (gestation of 9 to 13 weeks.) Initially by vagina 800 micrograms for 1 dose, dose to be given 36–48 hours after mifepristone, followed by (by vagina or by mouth) 400 micrograms every 3 hours if required for a maximum of 4 doses.

Termination of pregnancy following mifepristone (gestation of 13 to 24 weeks). Initially by vagina 800 micrograms for 1 dose, dose to be given 36–48 hours after mifepristone, followed by (by vagina or by mouth) 400 micrograms every 3 hours if required for a maximum of 4 doses, if abortion has not occurred 3 hours after the last dose of misoprostol, a further dose of mifepristone may be given, and misoprostol may be recommenced 12 hours later.

Induction of abortion (0–12 weeks): 800 micrograms vaginally every 12 hours (total: 3 doses). Missed abortion (0–12 weeks): 800 micrograms vaginally every 12 hours (total: 3 doses). Incomplete abortion (0–12 weeks): 600 micrograms orally stat and to be repeated every 12 hours (total: 3 doses). Also, patients will need antibiotic cover. Induction of abortion (13–22 weeks): 400 micrograms vaginally to be given every 3 hours (5 doses). Intrauterine fetal death (13–17 weeks): 400 micrograms vaginally every 6–12 hours for 4 doses. Intrauterine fetal

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death (18-26 weeks): 100 micrograms vaginally every 6-12 hours for 4 doses. Intrauterine fetal death beyond 26 weeks: 25-50 micrograms vaginally every 4 hours up to 6 doses. Post partum haemorrhage: 800 micrograms stat dose rectally

Preparations

Misoprostol tablets, 200 micrograms tab.

Oxytocin

Indications: induction and augmentation of labour; postpartum haemorrhage; missed or incomplete abortion.

Contra-indications: mechanical obstruction to delivery, hypertonic uterine; when vaginal delivery is contra-indicated; foetal distress.

Cautions: previous caesarean section, multiple pregnancy, multipara, hypertension, concomitant use of prostaglandins, borderline cephalopelvic disproportion.

Side-effects: uterine hyper-stimulation, uterine spasm; nausea and vomiting, water intoxication when infused with large volume of electrolyte-free fluids; amniotic fluid embolism; placenta abruption.

Dose: for induction or augmentation of labour, by slow intravenous infusion, 0.001-0.002 unit/minute; maximum is 5 units per day. Closely monitor foetal heart rate and uterine motility.

For prevention or treatment of postpartum haemorrhage, 5-10 units by

slow intravenous injection; in severe cases 5-30 units in 500 mL infusion fluid by slow intravenous infusion.

For missed or incomplete abortion, by slow intravenous injection, 5 units followed if necessary by 0.02-0.04 units/minute or faster.

Preparations

Oxytocin injection, 10 units/mL, 1 mL ampoule

Hydroxyprogesterone hexanoate (Restricted)

Indications: Preterm birth risk reduction

Contra-indications: Current thrombosis or thromboembolic disorders or history of these conditions, known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions, undiagnosed abnormal vaginal bleeding unrelated to pregnancy, cholestatic jaundice of pregnancy, liver tumors, uncontrolled hypertension, herpes.

Cautions: Thromboembolic disorder, sensitivity reactions, allergic reactions, decreased glucose tolerance, fluid retention, depression, jaundice, hypertension

Side-effects: Diarrhea; mild bruising, itching, or pain at the injection site; nausea

Dose: 250 mg once weekly (every 7 days) by slow IM injection. Treatment should begin between 16 weeks 0 days and 20 weeks 6 days of gestation, and continue once weekly until week 37 (through 36

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weeks, 6 days) of gestation or delivery, whichever occurs first.

Hydroxyprogesterone hexanoate injection, 250 mg / injection

7 A.2: Ductus arteriosus

Ductus arteriosus patency is physiologically maintained by prostaglandins. In neonates with congenital heart defects, alprostadil (prostaglandin E_1) is used to maintain and increase pulmonary blood flow and oxygenation of blood.

Alprostadil (CDL)

Indications: congenital heart defect in neonates prepared for corrective surgery.

Cautions: intensive care facility should be available; monitor arterial pressure.

Side-effects: neonatal apnoea, blood pressure changes, disseminated intravascular coagulation, flushing, fever.

Dose: by intravenous infusion, 50–100 nanograms/kg/minute, then decrease to lowest effective dose.

Preparations

Alprostadil injection, 500 micrograms / mL, 1 mL ampoule

7 A.3: Myometrial relaxants

The uterine muscle is rich during pregnancy with β_2 -receptors. Stimulation of such receptors with β_2 -agonists leads to uterine muscle relaxation. Salbutamol is commonly used to inhibit uncomplicated premature labour between 24 and 33 weeks of gestation and it may delay delivery at least 48 hours. Prolonged use should be avoided since risk to mother increases after 48 hours of use and there is a lack of evidence of any benefit from further treatment. Oral treatment after initial parenteral therapy is therefore not recommended. The oxytocin receptor antagonist, Atosiban, is licensed for the inhibition of uncomplicated premature labour between 24 and 33 weeks of gestation. Atosiban may be preferable to β_2 -agonists because it has fewer side-effects.

Atosiban

Indications: uncomplicated premature labour.

Contra indications: cardiac disease, eclampsia and severe pre-eclampsia, intra-uterine infection, intra-uterine fetal death, antepartum haemorrhage, placenta praevia, cord compression, premature rupture of membranes after 30 weeks' gestation.

Caution: hepatic impairment, renal impairment, intrauterine growth retardation.

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Side-effects: nausea, vomiting, flushing, sweating, tremor, tachycardia.

Dose: by intravenous injection, initially 6.75 mg over 1 minute, then by intravenous infusion 18 mg/hour for 3 hours, then 6 mg/hour for up to 45 hours; max. duration of treatment 48 hours.

Preparations

Atosiban injection, 7.5 mg/mL, 5 mL vial

Salbutamol

See notes in sec 3 A.1.1.

7 B: Drugs used in vaginal and vulval conditions

Vaginal infections: Symptoms of vulvo-vaginitis are likely to be primarily presented as vulvitis but infection almost invariably involves the vagina also. External application of drugs to the vulva alone may give symptomatic relief, without curing the infection.

Creams, vaginal ovules and pessaries are applied but not ointments. The natural secretion and evaporation should not be impeded in the vagina during treatment. Systemic treatment is also recommended especially in infections, which are sexually transmitted. Fungal, bacterial and rarely viral infections are treated with specific drugs. Identification of the causative microorganism should be done before selecting a preparation for treatment.

Treatment with creams should involve both the vulva and the vagina. Pessaries or ovules must be inserted high into the vagina.

Fungal infections

Recurrence is common in fungal infections if treatment is not adequate or there are predisposing factors such as antibacterial therapy, diabetes mellitus or the use of contraceptive pills. The use of nystatin vaginal tablets, imidazole derivative cream or vaginal tablets are recommended.

Bacterial infections

Bacterial vaginosis is commonly due to gram-negative organisms. It can be treated with systemic metronidazole or amoxicillin. Vaginal antibacterial creams such as Clindamycin or metronidazole are used for bacterial vaginosis and cervicitis. Sexually transmitted bacterial infections are treated systemically.

Trichomonal infections

They commonly involve the lower urinary tract as well as the genital system and needs systemic treatment with metronidazole.

Preparations

Nystatin vaginal tablets, 100,000 IU / vaginal tab.

Dose: one pessary at night for 14-28 days.

Clindamycin vaginal cream, 2%

Dose: one application (5 g) at night for 3-7 Days

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Clotrimazole vaginal tablets, 500 mg vaginal tab.

Dose: one pessary single application

Imidazole derivatives vaginal cream (e.g. clotrimazole, econazole, miconazole, ketoconazole)

Dose: vulval-vaginal applications once or twice daily for at least 7 Days.

7 C: Contraceptives

7 C.1: Combined oral monophasic contraceptives

These contain oestrogen and progestogen together in one pill and they are the most effective, reliable and reversible method of contraception available. In addition to contraception, these preparations have the following advantages;

- lighter, shorter, regular period with decreased menstrual cramp
- reduced risk of ovarian and endometrial cancers
- decreased benign breast disease
- reduced risk of pelvic inflammatory disease
- decrease the risk of developing functional ovarian tumour
- decrease the risk of ectopic pregnancy
- decreased peri-menopausal bone loss
- improve anaemia.

A fixed concentration of oestrogen and progestogen are contained in each pill; such preparation is also called monophasic. The concentration of oestrogens may vary among different preparations from 25-50 micrograms. There are low, standard and high oestrogen types of pills. Standard type of combined contraceptive pills contains 30-35 micrograms of oestrogens; the approved preparations in Oman are of this type.

There are major and minor adverse effects associated with the use of combined contraceptives. The incidence of complications in women under 30 years of age who do not have risk factors for cardiovascular disease appears to be small. An assessment of the risk benefit ratio for each patient is essential prerequisite for use.

The risks associated with the pill use are directly related to the oestrogen contents, and are low with the low oestrogen type and increase, as oestrogen content gets higher.

There is an increased risk of venous thromboembolism in users of oral contraceptives though this risk remains smaller than any risk associated with pregnancy. The risk of venous thromboembolism increases with age and in presence of other risk factor such as smoking and obesity.

Combined oral contraceptives

Indications: contraception; menstrual symptoms.

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Contra-indications: pregnancy; previous history of venous or arterial thromboembolic disorders; cerebral vascular disease; breast cancer, oestrogen-dependent tumours, benign or malignant liver tumour; active liver disease; migraine; ophthalmic vascular disease; sickle cell anaemia; undiagnosed vaginal bleeding; breast feeding; cholestatic jaundice.

Cautions: in women with hypertension, psychic depression, epilepsy, asthma, renal or hepatic dysfunction, cardiac disease, diabetes mellitus, multiple sclerosis, varicose veins; cigarette smoking increases the risk of serious C-V side-effects.

Caution if severe diarrhoea or vomiting occurs during the use of oral contraception, as absorption of content may be incomplete. Travellers on long journeys may take precaution not to stay immobile for more than 5 hours; risk of venous thrombus in the lower extremities is increased. Undergoing surgery necessitates the discontinuation of contraceptive pills and arrangement for other contraceptive methods is sought.

Missing a pill

- *if one active pill is missed, take it as soon as you remember and take the next active pill at the regular time*
- *If two active pills or more are missed, start taking active pills as soon as you remember, and continue on regular*

schedule. For additional protection from pregnancy use condoms or refrain from sex until you have taken one active pill each day for 7 Days in a row.

- *If two or more active pills are missed and bleeding has started, stop taking pills and restart a new pack 7 Days later.*
- *If one or more of the inactive (coloured pills in every day pill pack) are missed, throw away the missed pills and continue to take the remaining pills each day until the end of the pack.*

Side-effects: nausea, vomiting, headache, breast tenderness, weight changes, thrombosis, changes in libido, depression, chorea, skin reaction, chloasma, hypertension, liver function impairment, spotting in early cycle.

Dose: A pill is taken at approximately the same time each day; delay of longer than 12 hours may lead to loss of contraceptive protection.

For 21-combined monophasic contraceptives, 1 pill daily for 21 days, subsequent courses repeated after 7 Days interval; first course usually starts at day 1 of the cycle, if delayed further additional precautionary measures are needed for the following seven days.

For every day (28 pill pack) combined monophasic contraceptives, one active pill daily as above; then one coloured (inert) pill is used

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daily for the seven days following the full use of the active 21 pills.

Note: Only one of the following preparations will be available at any time depending on cost effectiveness.

Preparations

Ethinylestradiol + desogestrel tablets, 30 micrograms + 150 micrograms pill

Ethinylestradiol + levonorgestrel tablets, 30 micrograms + 150 micrograms pill
Ethinylestradiol + Norgestrel tablets, 30 micrograms + 300 micrograms pill (birth spacing programme)

Ethinylestradiol + gestodine tablets, 30 micrograms + 75 micrograms pill

7 C.2: Progestogen-only contraceptives

7 C.2.1: Oral progestogen-only contraceptives

Oral progestogen only contraceptives are suitable alternatives when oestrogens are contraindicated (*see notes above*). There is a higher failure rate than with combined contraceptives. They are suitable for older women, for heavy smokers, and those with hypertension, valvular heart disease, diabetes and migraine.

Daily use on a continuous basis characterizes this group of oral contraceptives. Starting at the first day of the cycle and continuing uninterrupted, the pill is taken at the same time every day. A delay of longer than three hours may lead to loss of contraceptive protection. In such cases, the woman takes the pill any time she remembers it and additional protection technique is advisable for the next 7 Days. Counseling is an important element due to the shortcomings of interrupted use and the higher rate of failure. For patients selection and counselling, consult MOH guidelines on Birth Spacing.

Oral progestogen-only contraceptives

Indications: contraception, *see notes above*

Contra-indications: pregnancy, undiagnosed vaginal bleeding, arterial disease.

Cautions: heart disease, sex-steroid dependent cancer, past ectopic pregnancy, functional ovarian cyst, active liver disease, concurrent use of enzyme inducing drugs, history of jaundice in pregnancy.

Side-effects: menstrual irregularities, nausea, vomiting, headache, body weight changes, depression, change in libido.

Dose: one tablet daily at the same time each day starting on day 1 of a cycle then continuously. *See notes above.*

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Note: Only one of the following preparations will be available at any time depending on cost effectiveness.

Preparations

Norethisterone tablets, 350 micrograms tab.

Norgestrel tablets, 75 micrograms tab. (birth spacing programme)

Levonorgestrel tablets, 30 micrograms tab.

Lynestrenol tablets, 500 micrograms tab.

7 C.2.2: Parenteral progestogen only contraceptives

Long-acting progestogen only preparations are as effective as combined oral contraceptives. Patient's education is an important element as the long term effects may result in menstrual disturbances and a potential for a delay in return to normal fertility.

Medroxyprogesterone acetate, 150 mg depot preparation is a long acting progestogen only injectable contraceptive that is available at MOH; it provides 12-week contraception. For users' selection see MOH guidelines on Birth Spacing.

Etonogestrel (Restricted)

Indications: Contraception

Contra-indications: Acute porphyria; history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal

contraceptive methods unacceptable; severe arterial disease; undiagnosed vaginal bleeding

Cautions: Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice; arterial disease; disturbances of lipid metabolism; history during pregnancy of deterioration of otosclerosis; history during pregnancy of pruritus; history of jaundice in pregnancy; malabsorption syndromes; possible risk of breast cancer; sex-steroid dependent cancer; systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies.

Side-effects: Breast discomfort; changes in libido; depression; disturbance of appetite; dizziness; headache; injection-site reactions; menstrual irregularities; nausea; vomiting

Dose: Contraception (no hormonal contraceptive use in previous month). By subdermal implantation 1 implant inserted during first 5 days of cycle, implant should be removed within 3 years of insertion.

Contraception (postpartum)

By subdermal implantation 1 implant to be inserted 21–28 days after delivery, 1 implant to be inserted after 28 days postpartum in breastfeeding mothers, implant should be removed within 3 years of insertion.

Contraception following abortion or miscarriage in the second trimester 1 implant to be inserted 21–

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28 days after abortion or miscarriage, implant should be removed within 3 years of insertion.

Contraception following abortion or miscarriage in the first trimester 1 implant to be inserted within 5 days, implant should be removed within 3 years of insertion.

Contraception (changing from other hormonal contraceptive). Implant should be removed within 3 years of insertion (consult product literature).

Preparations

Etonogestrel 68 mg intradermal implant

Medroxyprogesterone acetate depot preparation

Indications: contraception.

Contra-indications, cautions and side-effects: see sec Oral preparations above

Dose: by deep intramuscular injection, 150 mg within the first 5 days of cycle or within the first 5 days after parturition. It could be delayed to 6 weeks in breast-feeding mothers. Repeat every 12 weeks.

Preparations

Medroxyprogesterone acetate depot injection, 150 mg in aqueous suspension (birth spacing programme)

7 D: Urinary disorders

7 D.1: Drugs for urinary retention

Urinary retention may be acute or chronic. Acute urinary retention is best managed by catheterisation. Chronic retention can be managed with drugs such as bethanechol, a parasympathomimetic, that increases detrusor muscle tone. Urinary retention caused by benign prostatic hyperplasia is well treated by alpha-blockers that relax smooth muscles and increase urinary flow rate resulting in an improvement in obstructive symptoms.

Bethanechol chloride

Indications: urinary retention.

Contra-indications: intestinal and urinary obstruction; gastrointestinal ulceration, asthma, hypotension, epilepsy, pregnancy and breast feeding.

Cautions: hyperthyroidism, cardiac disorders.

Side-effects: nausea, vomiting, intestinal cramp, sweating, bradycardia.

Dose: 10-25 mg 3-4 times daily before meal.

Preparations

Bethanechol chloride tablets, 25 mg tab.

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7 D.2 Drugs for urinary incontinence

Urinary incontinence is treated with various drugs possessing antimuscarinic effects that relax detrusor muscle and increases bladder capacity.

Solifenacin (Restricted)

Indications: Urinary frequency. Urinary urgency. Urinary incontinence

Contra-indications: Gastro-intestinal obstruction; intestinal atony; myasthenia gravis (but some antimuscarinics may be used to decrease muscarinic side-effects of anticholinesterases); paralytic ileus; prostatic enlargement; pyloric stenosis; severe ulcerative colitis; significant bladder outflow obstruction; toxic megacolon; urinary retention; narrow-angle glaucoma

Cautions: Acute myocardial infarction; arrhythmias (may be worsened); autonomic neuropathy; cardiac insufficiency (due to association with tachycardia); cardiac surgery (due to association with tachycardia); conditions characterised by tachycardia; congestive heart failure (may be worsened); coronary artery disease (may be worsened); diarrhoea; elderly (especially if frail); gastro-oesophageal reflux disease; hiatus hernia with reflux oesophagitis; hypertension; hyperthyroidism (due to association with tachycardia); individuals susceptible to angle-closure

glaucoma; prostatic hyperplasia; pyrexia; ulcerative colitis; neurogenic bladder disorder; susceptibility to QT-interval prolongation

Side-effects: Constipation; dilation of pupils with loss of accommodation; dry mouth; photophobia; reduced bronchial secretions; skin dryness; skin flushing; transient bradycardia (followed by tachycardia, palpitation and arrhythmias); urinary retention; urinary urgency, confusion (particularly in the elderly); giddiness; nausea; vomiting.

Dose: 5 mg once daily, increased if necessary to 10 mg once daily (Max. 5 mg daily with concomitant potent inhibitors of cytochrome P450 enzyme CYP3A4 such as itraconazole, ketoconazole, or ritonavir).

Preparations

Solifenacin succinate tablets 5 mg tab

Tolterodine tartrate

Indications: urinary frequency, urgency and incontinence.

Contraindications: pregnancy and breast-feeding.

Cautions: history of QT-interval prolongation; concomitant use with other drugs known to prolong QT interval.

Side-effects: chest pain, peripheral oedema; sinusitis, bronchitis; paraesthesia, fatigue, vertigo, weight gain, flushing.

Dose: adult over 18 years, 2 mg twice daily; reduce to 1 mg twice

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daily if necessary to minimise side-effects.

Preparations

Tolterodine tartrate tablets, 1 mg tab.

Tolterodine tartrate tablets, 2 mg tab.

7 D.3: Drugs used in urological pain

Ureteric colic can be relieved by an injection of narcotic analgesic or diclofenac sodium. However, alkalinising the urine may promote the relief of pain in cystitis.

The following preparation is used to render the pH of urine more alkaline.

Urinary alkaliniser in effervescent granules or syrup form

7 D.4: Drugs used for impotence

Recent development in the treatment of erectile dysfunction has lead to the introduction of many drugs that are orally effective with high efficacy and wider margin of safety. Such drugs have rendered the old generation of drugs that are given by intracavernosal injection obsolete. However, papaverine is still approved and available in Oman for use as an intracavernosal injection for the treatment of erectile dysfunction under strict medical supervision by a specialist.

Papaverine (Restricted)

Indications: erectile dysfunction.

Contra-indications: predisposal for prolonged erection.

Cautions: persistent erection for longer than 4 hours calls for an emergency interference.

Side-effects: priapism, penile pain, haematoma, local irritation.

Dose: by intracavernosal injection, 25-90 mg.

Preparations

Papaverine hydrochloride injection, 30 mg /mL, 2 mL ampoule

Sildenafil (CDL)

Indications: erectile dysfunction, pulmonary hypertension.

Contra-indications: in patients receiving nitrates, hypotension (systolic BP < 90 mmHg), recent stroke, myocardial infarction or unstable angina.

Cautions: cardiovascular disease, anatomical deformation of the penis, in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), concomitant use of sildenafil with other treatments for erectile dysfunction.

Side-effects: dyspepsia, vomiting, headache, flushing, nasal congestion, abnormal vision (non-arteritic anterior ischemic optic neuropathy).

Dose: 50 mg taken, as a single dose per day, approximately 1 hour before sexual activity, the dose may

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be increased to a maximum dose of 100 mg or decreased to 25 mg.

Preparations

Sildenafil tablets, 25 mg tab.

Sildenafil tablets, 50 mg tab.

Cl⁻ 107 + Lactate 35 mmol/litre; 2 litre/bag

Peritoneal dialysis solution 2

Contents: Dextrose 4.25% + Na⁺ 135 + Ca⁺⁺ 2 + Cl⁻ 104.5 + Lactate 35 mmol/litre; 2 or 5 litre/bag

7 D.5: Irrigation fluids and dialysis concentrates

For the following preparations consult manufacturer's literature for information about contents, strengths, and method of preparations and dilutions.

7 D.5.3: Irrigation fluids and perfusion solutions

Kidney perfusion solution, 20 mg / mL

Sodium Chloride 0.9% irrigation solution

Sterile water for irrigation

Amino acetic acid 1.5% irrigation solution

Glycine 1.5% urological irrigation solution

7.D.5.1:Haemodialysis preparations

Concentrated haemodialysis solution

Contents: Na⁺ 135 + K⁺ 2 + mg⁺⁺ 1 + Ca⁺⁺ 1.75 + Cl⁻ 107.5 + Acetate 35 mmol/litre; 5 litre /jar.

Dilution ratio 1:34

Sodium bicarbonate powder

Gambro D204 special acid solution for BICART dialysis

7 D.5.2: Peritoneal dialysis preparations

Peritoneal dialysis solution 1

Contents: Dextrose 1.5% + Na⁺ 134 + K⁺ 2.5 + mg⁺⁺ 0.75 + Ca⁺⁺ 1.75 +

8: Malignant disease and immunosuppression

Section 8: Malignant disease and immunosuppression

- Cytotoxic drugs.
- Drugs affecting the immune response.
- Sex hormone and hormone antagonists in malignant disease.

All drugs included in this section are **restricted** and intended for use by specialists.

Treatment of tumours with chemotherapy has shown that some are highly responsive but most are not. Due to the high toxicity of cytotoxic drugs, their inappropriate use may lead to increased morbidity and mortality.

Cytotoxic drugs do not differentiate between normal and malignant cells. Highly proliferating cells are more seriously affected than non-proliferating cells. Serious side-effects should always be balanced against benefit in determining the regimen for treatment.

Chemotherapy is applied with an intention to cure, with the aim to prolong life, or to palliate symptoms. Single agent chemotherapy has been found effective in treatment of only few tumours; combined multiple drug therapy is more often applied for the majority of tumours. Drug combination is more toxic than a single drug but may have the advantage of reducing tu-

mour resistance, enhancing responsiveness and increasing rate of remission.

General **side-effects** encountered with the use of cytotoxic drugs are discussed hence after. Characteristic side-effects of a single drug will be specified in the relevant section.

Nausea and vomiting are very common distressing side-effects in patients receiving chemotherapy. It could be acute in onset or delayed. Acute nausea and vomiting is easy to treat with conventional antiemetic agents (*see* sec 4 G.2). Drugs such as dexamethasone, lorazepam and 5-HT₃ antagonists are used with or without conventional antiemetics in the treatment of severe delayed nausea and vomiting.

Bone marrow depression is caused by all cytotoxic agents except vincristine and bleomycin. Differential blood counts should be performed to determine the degree of neutropoenia. Antibacterial therapy may be needed in high-risk patients.

Hyperuricaemia. Tumour cell destruction by cytotoxic drugs will result in high protein catabolism and a rise in uric acid production. Urinary dysfunction may be caused by uric acid crystal deposition in the renal system. To mitigate such complications, allopurinol is administered with chemotherapy; in addition, patients should be kept

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well hydrated. The dose of mercaptopurine and azathioprine must be reduced if allopurinol needs to be given concomitantly.

Alopecia is a reversible side effect with cytotoxic drugs with variable severity among drugs and individual patients. Pharmacological methods for preventing this side effect are not available.

Reproductive functions. Cytotoxic drugs affect male and female reproductive systems causing an often-permanent amenorrhoea in premenopausal women and an irreversible azoospermia in men. They are teratogenic and should not be administered during pregnancy.

Well-trained staff should carefully carry out intravenous administration of cytotoxic drugs. Extravasation of intravenous cytotoxic solution will cause severe local tissue necrosis.

8 A: Cytotoxic drugs

8 A.1: Alkylating drugs

8 A.1.1: Nitrogen mustards

Chlorambucil

Indications: chronic lymphocytic leukaemia, indolent non-Hodgkin's lymphomas, Hodgkin's disease, ovarian cancer.

Cautions and side-effects: bone marrow depression; skin rash. If

skin rash develops, better stop therapy and replace with other cytotoxic drug.

Dose: used alone, 100-200 micrograms / kg daily for 4-8 weeks.

Preparations

Chlorambucil tablets, 2 mg tab.

Cyclophosphamide

Indications: chronic lymphocytic leukaemia, solid tumours, lymphomas.

Cautions and side-effects: see notes above; hepatic and renal impairment; haemorrhagic cystitis.

Preparations

Cyclophosphamide tablets, 50 mg tab.

Cyclophosphamide injection, powder for reconstitution, 500 mg/vial

Ifosfamide

Indications: see cyclophosphamide

Contra-indications: hepatic impairment.

Cautions and side-effects: mesna is routinely given to reduce urothelial toxicity.

Preparations

Ifosfamide injection, powder for reconstitution, 500 mg/vial

Melphalan

Indications: myeloma; solid tumours and lymphomas.

Cautions and side-effects: see notes above, bone marrow toxicity is delayed.

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Dose: orally, for multiple myeloma, 150 micrograms / kg daily in divided doses for 4 days, repeated at intervals of 6 weeks.

Preparations

Melphalan tablets, 2 mg tab.

Melphalan injection, powder for reconstitution, 50 mg vial

Bendamustine

Indications: Treatment of chronic lymphocytic leukaemia. Treatment of non-Hodgkin's lymphoma. Treatment of multiple myeloma.

Contra-indications: Jaundice; low leucocyte count; low platelet count; major surgery less than 30 days before start of treatment; severe bone marrow suppression.

Cautions: Avoid in acute porphyrias; cardiac disorders—monitor serum potassium and ECG.

Side-effects: Amenorrhoea; angina; anorexia; arrhythmias; chills; constipation; dehydration; diarrhoea; electrolyte disturbances; haemorrhage; hypertension; hypokalaemia; hypotension; infection; insomnia; malaise; pain; palpitation; pyrexia; respiratory dysfunction.

Dose: Consult local protocol.

Preparations

Bendamustine injection, powder for reconstitution, 25 mg / vial

Bendamustine injection, powder for reconstitution, 100 mg / vial

8 A.1.2: Nitrosoureas

Lomustine

Indications: Hodgkin's disease, solid tumours.

Cautions: bone marrow depression may be permanent with prolonged use.

Side-effects: *see* notes above

Dose: used alone, 120-130 mg / m² body surface, every 6-8 weeks.

Preparations

Lomustine tablets, 10 mg tab.

Lomustine tablets, 40 mg tab.

8 A.2: Natural products

8 A.2.1: Vinca alkaloids

Vinblastine sulphate

Indications: acute leukaemias, lymphomas, solid tumours.

Contra-indications: not to be administered by **intrathecal** injection.

Cautions and side-effects: *see* notes above; dose reduction when neurological toxicity is manifested. Myelosuppression is a dose-limiting side effect.

Preparations

Vinblastine sulphate injection, 1 mg/mL, 10 mL vial

Vincristine sulphate

Indications: acute leukaemias, lymphomas, solid tumours.

8: Malignant disease and immunosuppression

Contra-indications: *see* under vinblastine **Cautions and side-effects:** *see* notes above; hepatic impairment, dose reduction when neurological toxicity is manifested.

Preparations

Vincristine sulphate injection, 1 mg/mL, 1 mL vial

8 A.2.2: Epipodophyllotoxins

Etoposide

Indications: small cell carcinoma, lymphomas, testicular cancer.

Cautions and side-effects: *see* notes above; treatment should not be repeated before an interval of 21 days.

Dose: orally, 120-240 mg /m² daily for 3-5 days.

Intravenously, double the oral dose.

Preparations

Etoposide capsules, 50 mg cap.

Etoposide injection, powder for reconstitution, 100 mg vial

8 A.2.3: Enzymes

Crisantaspase (L-asparaginase)

Indications: acute lymphoblastic leukaemia.

Cautions: monitor for hyperglycaemia.

Side-effects: liver function and blood lipid changes; CNS depression, anaphylactic reaction.

Preparations

Crisantaspase (Erwina brand) injection, powder for reconstitution, 10,000 units vial

8 A.2.4: Taxanes

Docetaxel

Indications: is indicated for the treatment of patients with advanced or metastatic breast cancer and lung cancer.

Contra-indications: *see* notes above; in patients with neutrophil counts of < 1500 cells/mm³, severe hypersensitivity.

Cautions: *see* notes above; hepatic impairment.

Side-effects: *see* notes above; myelosuppression, hypersensitivity reactions, fluid retention.

Preparations

Docetaxel injection, 40 mg/mL, 0.5 mL vial

Docetaxel injection, 40 mg/mL, 2 mL vial

Paclitaxel

Indications: primary ovarian cancer with cisplatin; metastatic ovarian cancer resistant to platinum compound therapy.

Cautions: pre-treatment with corticosteroid, antihistamine and H₂-receptor antagonists are recommended to prevent hypersensitivity reactions.

Side-effects: *see* notes above; bradycardia, hypotension, peripheral neuropathy.

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Preparations

Paclitaxel intravenous infusion, 6 mg/mL 5 mL vial

Paclitaxel intravenous infusion, 100 mg/ 16.7 mL vial

Paclitaxel intravenous infusion 150 mg/25 mL vial

8 A.3: Antimetabolites

Antimetabolites have similarity in their structures to molecules essential for protein synthesis. They combine irreversibly with vital cellular enzymes, preventing normal cellular multiplication. Folic acid, pyrimidine and purine analogues are effective cytotoxic drugs.

8 A.3.1: Folic acid analogues

Methotrexate is the main drug in this group. It acts by inhibiting the enzyme dihydrofolate reductase, which is essential for the synthesis of purine and pyrimidine. It can be orally and parenterally administered.

Methotrexate

Indications: maintenance therapy of childhood lymphoblastic leukaemia; choriocarcinoma, non-Hodgkin's lymphoma, solid tumours. Intrathecal methotrexate is used in meningeal cancer or lymphoma.

Contra-indications: severe renal impairment, severe hepatic impairment.

Cautions: avoid in pleural effusion or ascites. Administer folic acid to prevent methotrexate induced mucositis or myelosuppression.

Side-effects: see notes above; myelosuppression which may be prolonged in presence of renal dysfunction.

Preparations

Methotrexate tablets, 2.5 mg tab.

Methotrexate suspension

Methotrexate sodium injection, 50 mg vial

Methotrexate sodium injection, 1 g vial

Methotrexate sodium injection, 10 mg in pre-filled syringe

Methotrexate sodium injection, 20 mg in pre-filled syringe

Pemetrexed

Indications: as a single agent for the treatment of locally advanced or metastatic non-small cell lung cancer, in combination with cisplatin for the treatment of malignant pleural mesothelioma which is unresectable.

Contra-indications: see notes above

Cautions: see notes above; prophylactic folic acid and vitamin B12 supplementation required.

Side-effects: see notes above; myelosuppression, gastro-intestinal toxicity and skin disorders are the commonest adverse effects.

Preparations

Pemetrexed injection; 500 mg vial

8: Malignant disease and immunosuppression

8 A.3.2: Pyrimidine analogues

This group encompasses many drugs with diverse activities; they have the capacity to inhibit the synthesis of pyrimidine nucleotides or mimic these natural metabolites to the extent that they interfere with vital cellular functions.

Capecitabine

Indications: colorectal carcinoma, breast carcinoma and gastric carcinoma.

Contra-indications: see notes above; hypersensitivity, severe renal and hepatic impairment.

Cautions: see notes above; cardiovascular diseases, diabetes mellitus.

Side-effects: see notes above; diarrhoea, hand-foot syndrome.

Preparations

Capecitabine tablets, 150 mg tab.

Capecitabine tablets, 500 mg tab.

Cytarabine

Indications: acute leukaemia.

Cautions and side-effects: see notes above; careful haematological monitoring because of potentially severe myelosuppression.

Preparations

Cytarabine injection, 100 mg, 5 mL vial

Cytarabine injection, 500 mg, 25 mL vial

5-Fluorouracil

Indications: gastro-intestinal tract cancers, breast cancer, with folinic acid in colorectal cancer.

Cautions and side-effects: see notes above; irritant to tissues-careful handling.

Preparations

5-Fluorouracil sodium injection, 50 mg/mL, 5 mL vial

Gemcitabine

Indications: used in a wide variety of malignancies, both as a single-agent and in combination with other cytotoxic drugs e.g. pancreatic cancer, ovarian cancer, breast cancer, non-small cell lung cancer and bladder cancer.

Contra-indications: see notes above; hypersensitivity to the drug.

Cautions: see notes above; renal and hepatic impairment, prolongation of the infusion time beyond 60 minutes and more frequent than weekly dosing has been shown to increase toxicity. Side-effects: see notes above; gastrointestinal disturbances, myelosuppression, haemolytic uraemic syndrome.

Preparations

Gemcitabine injection, 1 g vial

8 A.3.3: Purine analogues

Mercaptopurine and thioguanine are important purine analogues with wide therapeutic applications. They are cell cycle specific and interfere with DNA synthesis. They

8: Malignant disease and immunosuppression

possesses some immunosuppressive effects and some of their derivatives are effectively used for this purpose.

Fludarabine

Indications: B-cell chronic lymphocytic leukaemia unresponsive to treatment with alkylating agents.

Cautions and side-effects: *see* notes above; severe myelosuppression.

Preparations

Fludarabine injection, powder for reconstitution, 50 mg vial

Fludarabine tablets, 10 mg tab.

Mercaptopurine

Indications: maintenance therapy for acute leukaemias.

Cautions and side-effects: *see* note above; reduce dose when used with allopurinol; avoid in renal impairment.

Dose: initially, 2.5 mg/kg daily.

Preparations

Mercaptopurine tablets, 50 mg tab.

Tioguanine (Thioguanine)

Indications: acute leukaemias.

Cautions and side-effects: *see* notes above; avoid in renal impairment.

Dose: initially, 2-2.5 mg/kg daily.

Preparations

Tioguanine tablets, 40 mg tab.

8 A.4: Antineoplastic antibiotics

8 A.4.1: Dactinomycin group

Dactinomycin

Indications: paediatric cancers.

Cautions and side-effects: *see* notes above; elevated bilirubin concentration is an indication for dose reduction; caution in handling.

Preparations

Dactinomycin injection, powder for reconstitution, 500 microgram vial

8 A.4.2: Anthracyclines

Doxorubicin

Indications: acute leukaemias, lymphomas and solid tumours, bladder cancer by bladder instillation. **Cautions:** cardiac disease; elevated bilirubin concentration is an indication for dose reduction; Cumulative dose limit should not exceed 450 mg/m² body surface area because fatal heart failure is more frequent beyond this concentration.

Side-effects: *see* notes above; mucositis.

Preparations

Doxorubicin hydrochloride injection, 10 mg vial

Doxorubicin hydrochloride injection, 50 mg vial

Pegylated Doxorubicin hydrochloride injection (encapsulated in liposomes), 2 mg/ml, 10 mL and 25 mL vials (for AIDS-related Kaposi's

8: Malignant disease and immunosuppression

sarcoma, advanced breast and ovarian cancer)

Epirubicin

Indications: breast cancer, superficial bladder cancer by bladder instillation.

Cautions and side-effects: *see* notes above and doxorubicin; hepatic impairment.

Preparations

Epirubicin hydrochloride injection, powder for reconstitution, 10 mg vial

Idarubicin

Indications: breast cancer as a second line therapy; acute leukaemias.

Cautions: *see* notes above and doxorubicin; hepatic and renal impairment; caution in handling.

Side-effects: *see* notes above.

Preparations

Idarubicin tablets, 5 and 10 mg tabs.
Idarubicin injection, powder for reconstitution, 5 and 10 mg vials

8 A.4.3: Bleomycin group

Bleomycin

Indications: squamous cell carcinoma, solid tumour.

Cautions: *see* notes above; renal impairment, caution in handling.

Side-effects: *see* notes above; dermatological toxicity; mucositis; hypersensitivity reactions; dose related pulmonary fibrosis, more common with elderly.

Preparations

Bleomycin injection, powder for reconstitution, 15 mg vial

8 A.4.4: Mitomycin group

Mitomycin

Indications: upper gastro-intestinal cancer; breast cancer; by bladder instillation in superficial bladder cancer.

Cautions: *see* notes above; prolonged use may cause permanent bone marrow depression. Hepatic and renal impairment; caution in handling.

Side-effects: *see* notes above; lung fibrosis, renal damage.

Preparations

Mitomycin injection, powder for reconstitution, 10 mg vial

8 A.4.5: Antimetabolites

Azacitidine

Indications: Treatment of intermediate-2 and high-risk myelodysplastic syndromes, chronic myelomonocytic leukaemia, and acute myeloid leukaemia.

Contra-indications: Advanced malignant hepatic tumour.

Cautions: History of severe congestive heart failure; unstable cardiac disease (consider cardiopulmonary assessment before and during treatment); unstable pulmonary disease (consider cardiopulmonary

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assessment before and during treatment).

Side-effects: Abdominal pain; anorexia; anxiety; arthralgia; cerebral haemorrhage; constipation; diarrhoea; dizziness; drowsiness; dyspepsia; dyspnoea; gastro-intestinal disturbances; haematoma; haematuria; haemorrhage; headache; hypertension; hypokalaemia; hypotension; injection-site reactions; insomnia; myalgia; pneumonia; rash.

Dose: Consult local protocol.

Preparations

Azacitidine injection, powder for reconstitution, 100 mg/ vial

Clofarabine

Indications: Relapsed or refractory acute lymphoblastic leukaemia.

Cautions: Cardiac disease.

Side-effects: Abdominal pain; agitation; alopecia; anxiety; arthralgia; bone-marrow suppression; cough; diarrhoea; dizziness; drowsiness; dyspnoea; extravasation; flushing; haematoma; haematuria; hand-foot (desquamative) syndrome; headache; hyperuricaemia; hypotension; jaundice; myalgia; nausea; oedema; oral mucositis; pancreatitis; paraesthesia; pericardial effusion; peripheral neuropathy; pruritus; rash; restlessness; sweating; tachycardia; thromboembolism; tumour lysis syndrome; vomiting.

Dose: Consult local protocol.

Preparations

Clofarabine injection, 1 mg/ ml, 20 mg vial

8 A.4.6: Others

Mitoxantrone (Mitozantrone)

Indications: breast cancer.

Cautions: *see* notes above; intrathecal administration not recommended; cardiac disease.

Side-effects: *see* notes above; cardiac toxicity.

Preparations

Mitoxantrone hydrochloride injection, 2 mg/mL 10 mL, 12.5 mL and 15 mL vials

8 A.5: Miscellaneous cytotoxics

8 A.5.1: Platinum compounds

Carboplatin

Indications: advanced ovarian and lung cancers.

Cautions: *see* notes above; dose to be determined according to renal function; keep patients well hydrated.

Side-effects: *see* notes above; less severe nephrotoxicity, neurotoxicity, ototoxicity and hypomagnesaemia than with cisplatin; severe myelosuppression.

Preparations

Carboplatin injection, 10 mg/mL, 5 mL vial

Cisplatin

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Indications: metastatic germ cell cancers; bladder, lung and upper gastro-intestinal cancers.

Cautions: *see* notes above; keep patients well hydrated.

Side-effects: *see* notes above; nephrotoxicity, neurotoxicity, ototoxicity and hypomagnesaemia; severe nausea and vomiting.

Preparations

Cisplatin injection, 1 mg/mL, 10 mL vial

Cisplatin injection, 1 mg/mL, 50 mL vial

Oxaliplatin

Indications: used in combination with 5-Fluorouracil and Folinic acid in advanced colorectal cancer.

Contra-indications: *see* notes above; peripheral neuropathy.

Cautions: *see* notes above; renal impairment.

Side-effects: *see* notes above; neurotoxic side-effects, gastro-intestinal disturbances, ototoxicity and myelosuppression.

Preparations

Oxaliplatin injection, 50 mg vial

Oxaliplatin injection, 100 mg vial

Cautions: leg ulcers (review treatment if cutaneous vasculitic ulcerations develop). Monitor renal and hepatic function before and during treatment, monitor full blood count and monitor for secondary malignancies. Patients should be advised to protect skin from sun exposure

Side-effects: headache; myelosuppression; skin reactions, Alopecia; bleeding (in sickle-cell disease); bone-marrow suppression; dizziness; hyperuricaemia; hypomagnesaemia (in sickle-cell disease); nausea; oral mucositis; rash; reduced sperm count and activity; skin cancers (particularly in elderly patients); thromboembolism; tumour lysis syndrome; vomiting.

Dose : for chronic myeloid leukaemia; cancer of the cervix; polycythaemia: 20–30 mg/kg daily, alternatively 80 mg/kg every 3 days. For Sickle Cell Disease: Initially 15 mg/ kg daily, increased in steps of 2.5-5 mg/kg daily every 12 weeks according to response; usual dose 15-30 mg/ kg daily; maximum 35 mg/ kg per day

Preparations

Hydroxycarbamide capsules, 500 mg cap.

8 A.5.2: Substituted urea

Hydroxycarbamide (Hydroxyurea)

Indications: chronic myeloid leukaemia; cancer of the cervix; polycythaemia; sickle cell disease

8 A.5.3: Methyl hydrazine derivatives

Dacarbazine

Indications: metastatic melanoma; in combination therapy of soft tissue sarcomas.

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Side-effects: *see* notes above; nausea and vomiting are very severe, irritation to skin and tissues.

Preparations

Dacarbazine injection, powder for reconstitution, 100 mg vial

Procarbazine

Indications: Hodgkin's disease.

Caution and side-effects: *see* Dacarbazine above

Dose: alone, initially 50 mg daily, increased by 50 mg daily to 250-300 mg daily in divided doses; maintenance (on remission) 50-150 mg daily to cumulative total of at least 6 g.

Preparations

Procarbazine hydrochloride capsules, 50 mg cap.

Temozolomide

Indications: is indicated for the treatment of adult patients with brain cancer, sometimes concomitantly with radiotherapy.

Contra-indications: *see* notes above; hypersensitivity reaction to the drug.

Cautions: *see* notes above; severe hepatic or renal impairment.

Side-effects: *see* notes above; rarely, erythema multiforme, opportunistic infections including Pneumocystis carinii pneumonia (PCP).

Preparations

Temozolomide capsules, 100 mg cap.

Temozolomide capsules, 250 mg cap.

8 A.5.4: Protein kinase inhibitors

Dasatinib

Indications: chronic myeloid leukaemia or acute lymphoblastic leukaemia in those who have resistance to or intolerance of previous therapy.

Contraindications: *see* notes above; breast-feeding.

Cautions: *see* notes above; susceptibility to QT-interval prolongation; hypokalaemia; hypomagnesaemia; hepatic impairment, pregnancy

Side-effects: *see* notes above; diarrhoea, anorexia, weight gain, abdominal pain, taste disturbance, constipation, dyspepsia, colitis, gastritis; arrhythmias, congestive cardiac failure, chest pain, flushing, haemorrhage (including gastro-intestinal and CNS haemorrhage), palpitation; dyspnoea, cough, oedema (including pleural effusion); depression, dizziness, headache, insomnia, neuropathy; influenza-like symptoms; musculoskeletal pain; visual disturbances; acne, dry skin, sweating, pruritus, urticaria.

Dose: chronic phase chronic myeloid leukaemia, adult over 18 years 100 mg once daily, increased if necessary to max. 140 mg once daily. Accelerated and blast phase chronic myeloid leukaemia, adult over 18 years 70 mg twice daily, increased if necessary to max.

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100 mg twice daily. Acute lymphoblastic leukaemia, adult over 18 years 70 mg twice daily increased if necessary to max. 100 mg twice daily.

Preparations

Dasatinib tablets, 50 mg tab.

Dasatinib tablets, 70 mg tab.

Erlotinib

Indications: for the treatment of patients with locally advanced non-small cell lung cancer after failure of at least one chemotherapy regimen, in combination with gemcitabine for metastatic pancreatic cancer.

Contra-indications: *see* notes above

Cautions: *see* notes above; hepatic and renal impairment, concomitant use with hepatotoxic drugs.

Side-effects: *see* notes above; diarrhoea, anorexia, depression, fatigue, rigor, conjunctivitis, dry skin.

Preparations

Erlotinib tablets, 150 mg tab.

Everolimus

Indications: Renal cell carcinoma, unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin, hormone-receptor-positive, human epidermal growth factor-2 (HER-2) negative advanced breast cancer. Subependymal giant cell astrocytoma associated with tuberous sclerosis complex. Renal angiomyolipoma associated with tuberous sclerosis complex.

Cautions: History of bleeding disorders.

Side-effects: Abdominal pain; anorexia; arthralgia; asthenia; chest pain; convulsions; dehydration; diarrhoea; dry mouth; dysphagia; electrolyte disturbance; epistaxis; eyelid oedema; fatigue; hand-foot syndrome; headache; hypercholesterolaemia; hyperglycaemia; hyperlipidaemia; hypertension; hypoglycaemia; increased susceptibility to aspergillosis; increased susceptibility to candidiasis; increased susceptibility to infections; increased susceptibility to pneumonia; insomnia; interstitial lung disease; irritability; nail disorders; peripheral oedema; pneumonitis; renal failure; skin disorders; taste disturbance.

Dose: Renal cell carcinoma, unresectable or metastatic neuroendocrine tumours of pancreatic origin, hormone-receptor-positive, human epidermal growth factor-2 (HER-2) negative advanced breast cancer, 10 mg once daily.

Subependymal giant cell astrocytoma associated with tuberous sclerosis complex and renal angiomyolipoma associated with tuberous sclerosis complex, consult product literature.

Preparations

Everolimus tablets, 0.75 mg tab.

Everolimus tablets, 5 mg tab.

Everolimus tablets, 10 mg tab.

Gefitinib

Indications: Treatment of locally advanced or metastatic non-small

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cell lung cancer with activating mutations of epidermal growth factor receptor.

Cautions: Keratitis and ulcerative keratitis have been reported following treatment with epidermal growth factor receptor (EGFR) inhibitors for cancer. Treatment should be interrupted or discontinued if ulcerative keratitis is diagnosed during therapy. Monitor for worsening of dyspnoea, cough and fever. Monitor liver function

Side-effects: Acne; anorexia; asthenia; blepharitis; conjunctivitis; diarrhoea; dry eye; dry mouth; dry skin; epistaxis; haematuria; interstitial lung disease—discontinue if confirmed; nail disorder; proteinuria; pruritus; pyrexia; rash; skin reactions.

Dose: 250 mg once daily.

Preparations

Gefitinib tablets, 250 mg tab.

Imatinib

Indications: chronic myeloid leukaemia, acute lymphoblastic leukaemia, myelodysplastic/myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene rearrangement, hypereosinophilic syndrome and/or chronic eosinophilic leukaemia, dermatofibrosarcoma, gastrointestinal stromal tumours.

Contra-indications: pregnancy and breastfeeding.

Cautions: see notes above; renal and hepatic impairment, cardiac disease.

Side-effects: see notes above; gastrointestinal disorders, oedema and fluid retention, influenza like syndrome, visual disturbances, epistaxis, pruritus.

Preparations

Imatinib mesilate tablets, 100 mg tab.

Imatinib mesilate tablets, 400 mg tab.

Lapatinib

Indications: Treatment of advanced or metastatic breast cancer in patients with tumours that over-express human epidermal growth factor receptor-2 (HER2) with hormone-receptor-negative disease.

Cautions: Diarrhoea—withhold treatment if severe (consult product literature); low gastric pH (reduced absorption); susceptibility to QT-interval prolongation (including electrolyte disturbances).

Side-effects: Anorexia; cardiac failure (fatal cases reported); decreased left ventricular ejection fraction; diarrhoea (treat promptly); hepatotoxicity (discontinue permanently if severe); hyperbilirubinaemia; malaise; nail disorders; rash.

Dose: Hormone receptor negative disease with previous treatment with trastuzumab 1 g once daily.

Previous treatment with anthracycline, a taxane and trastuzumab (in combination with capecitabine) 1.25 g once daily

Hormone receptor positive disease combination with an aromatase inhibitor 1.5 g once daily.

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Consult product literature for more details

Preparations

Lapatinib tablets, 250 mg tab.

Sorafenib

Indications: Advanced renal cell carcinoma. Treatment of progressive, locally advanced, or metastatic, differentiated thyroid carcinoma that is refractory to radioactive iodine. Treatment of hepatocellular carcinoma.

Cautions: Cardiac ischaemia; major surgical procedures; potential risk of bleeding—treat tracheal, bronchial, or oesophageal infiltration with localised therapy before initiating sorafenib in patients with differentiated thyroid carcinoma (DTC) and consider permanent withdrawal of sorafenib in any patient that requires medical intervention for bleeding; susceptibility to QT-interval prolongation.

Consider periodic monitoring of ECG and electrolytes in patients susceptible to QT-interval prolongation. Monitor blood pressure regularly and consider permanent discontinuation of sorafenib if resistant to antihypertensive therapy. Monitor plasma-calcium concentration (increased risk of hypocalcaemia if history of hypoparathyroid). Monitor thyroid stimulating hormone in patients with differentiated thyroid carcinoma.

Side-effects: Acne; anorexia; arthralgia; asthenia; congestive heart failure; constipation; depression;

dermatitis; desquamation; diarrhoea; dry skin; dysgeusia; dyspepsia; dysphagia; dysphonia; electrolyte disturbances; erectile dysfunction; erythema; fatigue; fever; flushing; gastro-oesophageal reflux disease; haemorrhage; hand-foot skin reaction; hoarseness; hyperkeratosis; hypertension; hypophosphataemia; hypophosphataemia; keratoacanthoma; malaise; muscle spasms; myalgia; myocardial infarction; myocardial ischaemia; peripheral neuropathy; proteinuria; pruritus; rash; renal failure; rhinorrhoea; thyroid dysfunction; tinnitus.

Dose: 400 mg twice daily, for dose adjustments due to side-effects, consult product literature.

Preparations

Sorafenib tablets, 200 mg tab.

Sunitinib

Indications: Treatment of unresectable or metastatic malignant gastro-intestinal stromal tumours, after failure of imatinib

Treatment of advanced or metastatic renal cell carcinoma. Treatment of unresectable or metastatic pancreatic neuroendocrine tumours

Cautions: Cardiovascular disease—discontinue if congestive heart failure develops; hypertension; increased risk of bleeding; susceptibility to QT-interval prolongation. Treatment with sunitinib may be a risk factor for the development of osteonecrosis of the jaw.

Side-effects: Abdominal pain; alopecia; anorexia; arthralgia; bone-

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marrow suppression; constipation; cough; dehydration; diarrhoea; dizziness; dry skin; dyspnoea; epistaxis; fatigue; fistula formation (interrupt treatment if occurs); gastro-intestinal perforation; hair discoloration; hand-foot syndrome; headache; hepatic failure; hypertension; hyperuricaemia; hypothyroidism; increased lacrimation; insomnia; myalgia; nausea; oedema; oral mucositis; osteonecrosis of the jaw; pancreatitis; paraesthesia; peripheral neuropathy; proteinuria; rash; seizures; skin discoloration; taste disturbance; thromboembolism; tumour lysis syndrome; urine discoloration; vomiting.

Dose: Unresectable or metastatic malignant gastro-intestinal stromal tumours and advanced or metastatic renal cell carcinoma 50 mg once daily for 4 weeks, followed by a 2-week treatment-free period to complete 6-week cycle, adjusted in steps of 12.5 mg, doses adjusted according to tolerability; usual dose 25–75 mg daily.

Unresectable or metastatic pancreatic neuroendocrine tumours 37.5 mg once daily without treatment-free period; adjusted in steps of 12.5 mg, doses adjusted according to tolerability; maximum 50 mg per day.

Preparations

Sunitinib capsules, 12.5 mg cap

Sunitinib capsules, 50 mg cap

8 A.5.5: Topoisomerase I inhibitors

Irinotecan hydrochloride

Indications: for colorectal carcinoma in combination with other antineoplastic drugs.

Contra-indications: see notes above; hypersensitivity to the drug, chronic inflammatory bowel disease, bowel obstruction.

Cautions: see notes above; raised plasma bilirubin concentration.

Side-effects: see notes above; acute cholinergic syndrome.

Preparations

Irinotecan hydrochloride injection, 20 mg/mL, 5 mL vial

Topotecan

Indications: as second line treatment for small cell lung cancer or ovarian cancer.

Contra-indications: see notes above; in patients with severe bone marrow depression.

Cautions: see notes above; hepatic and renal impairment.

Side-effects: see notes above; diarrhoea, febrile neutropoenia, abdominal pain, stomatitis, hypersensitivity, hyperbilirubinemia, malaise.

Preparations

Topotecan injection, powder for reconstitution, 1 mg vial

Topotecan injection, powder for reconstitution, 4 mg vial

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8.A.5.6: Monoclonal antibodies

Bevacizumab

Indications: used along with chemotherapy to treat patients with metastatic colorectal and breast cancer.

Contra-indications: *see* notes above; untreated CNS metastases.

Cautions: *see* notes above; history of hypertension, cardiovascular diseases, intra-abdominal inflammation (risk of gastro-intestinal perforation), withhold prior and after elective operations.

Side-effects: *see* notes above; gastro-intestinal perforation, impaired wound healing, mucocutaneous bleeding, arterial thromboembolism, congestive heart failure, proteinuria, tracheoesophageal fistula formation.

Preparations

Bevacizumab injection, 100 mg vial

Bevacizumab injection, 400 mg vial

Cetuximab

Indications: used along with chemotherapy to treat patients with metastatic colorectal, in combination with radiotherapy for the treatment of locally advanced squamous cell cancer of the head and neck.

Contra-indications: *see* notes above

Cautions: *see* notes above; cardio-pulmonary disease, interstitial lung disease.

Side-effects: *see* notes above; vomiting, headache, chills, fever, hypersensitivity reactions (patient must receive an antihistamine before infusion and resuscitation facilities should be available), acne, pruritus, nail disorders, conjunctivitis, hypomagnesaemia.

Preparations

Cetuximab injection, 100 mg vial

Panitumumab

Indications: Treatment of non-mutated RAS metastatic colorectal cancer.

Contra-indications: Interstitial pulmonary disease; the combination of panitumumab with oxaliplatin-containing chemotherapy is contra-indicated in patients with mutant RAS metastatic colorectal cancer or for whom RAS status is unknown.

Cautions: History of keratitis; history of severe dry eye; history of ulcerative keratitis; pulmonary disease—discontinue if interstitial lung disease develops; risk factors for keratitis; risk factors for severe dry eye; risk factors for ulcerative keratitis (including contact lens use).

Side-effects: Anorexia; anxiety; back pain; biochemical disturbances; cellulitis; cheilitis; chills; cough; deep vein thrombosis; dyspepsia; dyspnoea; electrolyte disturbances; epistaxis; eyelash

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growth; flushing; folliculitis; gastro-oesophageal reflux disease; hyperhidrosis; insomnia; malaise; pain in extremities; peripheral oedema; pulmonary embolism; pyrexia; rectal haemorrhage; severe hypersensitivity reactions (possibly delayed); urinary tract infection; weight loss.

Dose: (consult product literature).

Preparations

Panitumumab injection, 100 mg vial

Rituximab

Indications: monoclonal antibody indicated in non-Hodgkin's lymphoma.

Contra-indications: see notes above; allergy to Rituximab.

Cautions: see notes above; cardiovascular diseases, antihypertensives (may need to be withheld for 12 hours before infusion), hepatitis B carriers (risk of reactivation of hepatitis), large tumour burden (increased risk of severe tumour lysis syndrome).

Side-effects: see notes above; infusion-related symptoms like chills, nausea, vomiting (consider pre-medication with corticosteroids).

Preparations

Rituximab injection, 10 mg/mL, 10 mL vial

Rituximab injection, 10 mg/mL, 50 mL vial

Trastuzumab

Indications: as a single or adjuvant treatment of early breast cancer which over-expresses human epidermal growth factor receptor-2 (HER2).

Contra-indications: see notes above; severe dyspnoea at rest, breast-feeding.

Cautions: see notes above; hypertension, heart failure, uncontrolled arrhythmias, concomitant use with anthracyclines is associated with cardiotoxicity, pregnancy.

Side-effects: see notes above; fever, infusion reactions, cardiotoxicity, increased cough, headache, fatigue, shortness of breath, rash, low white and red blood cells, muscle pain.

Preparations

Trastuzumab injection, 440 mg vial

8.A.5.7: Anti-androgens

Bicalutamide

Indications: Prostate Cancer

Cautions: Risk of photosensitivity—avoid excessive exposure to UV light and sunlight.

Side-effects: Abdominal pain; alopecia; anaemia; asthenia; breast tenderness; chest pain; cholestasis; constipation; decreased appetite; decreased libido; depression; dizziness; dry skin; dyspepsia; flatulence; gynaecomastia; haematuria; hepatotoxicity; hirsutism; hot flushes; impotence; jaundice; nausea; oedema; pruritus; rash; somnolence; weight gain.

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Dose: 150 mg once daily.

Preparations

Bicalutamide tablets, 150 mg tab.

8 A.6: Others

Amsacrine

Indications: acute myeloid leukaemia.

Cautions: electrolytes to be monitored to avoid hypokalaemia.

Side-effects: see note above; mucositis

Preparations

Amsacrine concentrate for intravenous infusion, 75 mg/1.5 mL, when reconstituted with 13.5 mL of diluent, a 5 mg/mL solution is obtained

Bortezomib

Bortezomib is a proteasome inhibitor

Indications: monotherapy for the treatment of multiple myeloma which has progressed despite the use of at least one therapy, and where the patient has already had bone-marrow transplantation or cannot have it. **Contraindications:** see notes above; acute diffuse infiltrative pulmonary disease; pericardial disease; pregnancy; breast-feeding.

Cautions: see notes above; cardiovascular disease; pulmonary disease; history of seizures; amyloidosis; risk of neuropathy; monitor

blood-glucose concentration in patients on oral antidiabetics; hepatic impairment; renal impairment.

Side-effects: see notes above; gastro-intestinal disturbances including constipation, taste disturbance, dry mouth, decreased appetite; postural hypotension, hypertension, haematoma, phlebitis, chest pain, oedema; dyspnoea, cough; confusion, depression, insomnia, anxiety, peripheral neuropathy, paraesthesia, headache, dizziness, tremor, asthenia, fatigue; influenza-like symptoms; renal impairment, dysuria; dehydration, hypokalaemia, hyperglycaemia; muscle cramps, arthralgia, bone pain; blurred vision, eye pain; epistaxis; urticaria, pruritus, erythema, dry skin, eczema, rash, increased sweating.

Preparations

Bortezomib injection, powder for reconstitution, 3.5 mg vial

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8 A.7: Agents used to treat cytotoxic adverse reactions

8 A.7.1: Chelating agents

MESNA

Indications: haemorrhagic cystitis caused by cyclophosphamide and ifosfamide.

Contra-indications: hypersensitivity to thiol-containing drugs.

Side-effects: nausea and vomiting, abdominal cramp, diarrhoea, fatigue, tachycardia and hypotension, irritability.

Dose: by intravenous injection, with treatment with cytotoxic drugs repeated 4 and 8 hours after treatment. For dose calculation, consult product literature.

Preparations

MESNA injection, 100 mg/mL, 4 mL ampoule

8 A.7.2: Vitamins

Folinic acid

(as calcium folinate)

Indications: Folate rescue therapy, for counteracting folate-antagonist action of methotrexate to speed up recovery from mucositis and myelosuppression.

Cautions: avoid simultaneous administration of methotrexate.

Side-effects: hypersensitivity reactions.

Dose: as antidote to methotrexate, usually given 24 hours after methotrexate treatment. Intravenous or intramuscular injection, 120 mg in divided doses over 12-24 hours. Followed by 12-15 mg intramuscularly or 15 mg orally every 6 hours for the next 48-72 hours.

Preparations

Folinic acid (as calcium folinate) injection, 100 mg/10 mL, 10 mL ampoules

Folinic acid (as calcium folinate) tablets, 15 mg tab.

8 B: Drugs affecting the immune response

Drugs in this group are used to suppress rejection in organ transplants and in patients with chronic inflammatory and autoimmune diseases. Drugs such as corticosteroids, ciclosporin or azathioprine are used in solid organ transplant patients. The use of such drugs may cause a rapid spread of infections due to a suppressed immune system.

8 B.1: Cytotoxic immunosuppressants

Azathioprine is similar in structure, and is metabolised in the body to mercaptopurine. It is widely used for chronic management of transplant recipients and in treatment of a number of autoimmune conditions. Myelosuppression is the main adverse effect and blood test

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and monitoring should be carried out regularly.

Mycophenolate mofetil has more selective mode of action than azathioprine. It is used in acute rejection of renal transplantation. When used in combination with ciclosporin and corticosteroids, the risk of rejection is reduced; the risk of opportunistic viral infections and blood disorders may be higher.

Azathioprine

Indications: transplant rejection; autoimmune diseases.

Contra-indications: hypersensitivity to azathioprine or mercaptopurine.

Cautions: monitor blood count regularly; hepatic impairment; renal impairment; reduce dose in elderly.

Side-effects: hypersensitivity reactions; dose related bone marrow depression; alopecia; increase incidence of infections; nausea.

Dose: oral or by intravenous injection or infusion, for treatment of autoimmune diseases, 1-3 mg/kg daily adjusted according to response.

Suppression of transplant rejection, initially up to 5 mg/kg then 1-4 mg/kg daily according to response.

Preparations

Azathioprine tablets, 50 mg tab.

Mycophenolate mofetil

Indications: prophylaxis of acute rejection in renal transplantation.

Contra-indications: pregnancy, breast feeding.

Cautions: regularly monitor blood count; elderly; children.

Side-effects: nausea, diarrhoea, constipation, dyspepsia; hypertension, oedema; dyspnoea, cough; insomnia, headache; blood disorders; infections.

Dose: Mycophenolate mofetil renal transplantation, orally 1 g twice daily starting with 72 hours of transplantation.

Mycophenolic acid (as Mycophenolate sodium/(CDL)) 720 mg twice daily, to be started within 72 hours of transplantation.

Preparations

Mycophenolate mofetil capsules, 250 mg cap.

Mycophenolate mofetil capsules, 500 mg cap.

Mycophenolate mofetil suspension, 1 g/5 mL when reconstituted with water, 175 mL bottle

Mycophenolic acid tablets, 360 mg tab. {gastro-resistant tablets}.

8 B.2: Corticosteroids and other immunosuppressants

8 B.2.1: Corticosteroids

See section 6 C.2.

Prednisolone

Indications and side-effects: see section 6 C.2.

Preparations

Prednisolone tablets, 5 mg tab.

Prednisolone tablets, 20 mg tab.

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8 B.2.2: Others

Antilymphocyte immunoglobulins

These are antibodies, raised in animals, which act against lymphocytes to produce suppression of cell mediated immunity. They may be used alone or added to other immunosuppressants to treat acute rejection episodes in patients who have undergone organ or tissue transplantation or they can be used routinely in multiple immunosuppressants therapy.

Indications: *see* notes above

Side-effects: hypersensitivity reactions.

Dose: by slow intravenous infusion, 10-30 mg/kg daily. The dose is diluted with normal saline solution.

Preparations

Antilymphocyte immunoglobulin injection, 50 mg/mL, 10 mL vial

Ciclosporin (Cyclosporin)

Indications: prevention of graft rejection following tissue or organ transplantation; treatment and prophylaxis of graft-versus-host disease.

Contra-indications: uncontrolled hypertension; uncontrolled infections; malignancies.

Cautions: patients may be more prone to infection while being treated with ciclosporin; patients with nephrotic syndromes, impaired renal and hepatic functions;

avoid concomitant use of other potent nephrotoxic drugs such as aminoglycosides.

Side-effects: dose-dependent increase in serum creatinine and urea during early stages of treatment; hypertension; tremor; gastro-intestinal disturbances; burning sensation in hands and feet; gingival hypertrophy.

Dose: Organ transplantation, adult and child over 3 months, alone 10-15 mg/kg by mouth 4-12 hours before transplantation followed by 10-15 mg/kg daily 1-2 weeks post-operatively then reduced gradually to 2-6 mg/kg daily for maintenance. Dose is reduced if used concomitantly with other immunosuppressants.

Bone marrow transplantation, prevention of graft-versus-host disease, adult and child over 3 months, 3-5 mg/kg daily by intravenous infusion over 3-6 hours from day before transplantation to 2 weeks postoperatively (or by mouth 12.5-15 mg/kg daily) then 12.5 mg/kg daily by mouth for 3-6 months then tailed off, may take over a year after transplantation.

Preparations

Ciclosporin capsules, 25 mg cap.

Ciclosporin capsules, 50 mg cap.

Ciclosporin capsules, 100 mg cap.

Ciclosporin oral solution, 100 mg/mL; 50 mL /bottle

Ciclosporin injection, 50 mg/mL, 1 and 5 mL ampoule

Daclizumab

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Indications: prophylaxis of acute rejection in allogenic renal transplantation with regimen including ciclosporin and corticosteroids.

Contra-indications: pregnancy and breast-feeding.

Side-effects: gastro-intestinal disturbances, hypersensitivity reactions.

Dose: by intravenous infusion, adult and child, 1 mg/kg within the 24-hour period before transplantation, then 1 mg/kg every 14 days for a total of 5 doses.

Preparations

Daclizumab injection, 5 mg/mL, 5 mL vial

Sirolimus

Indications: prophylaxis of organ rejection in kidney allograft recipients.

Contra-indications: pregnancy, breast-feeding.

Cautions: monitor kidney function when given with ciclosporin; Afro-Caribbean patients may require higher doses; hepatic impairment.

Side-effects: abdominal pain, diarrhoea, stomatitis; oedema, tachycardia, hypercholesterolaemia, hypertriglyceridaemia, venous thrombo-embolism; pneumonitis; pyrexia, increased susceptibility to infection, proteinuria, haemolytic uraemic syndrome; anaemia, thrombocytopenia, thrombotic thrombo-cytopenic purpura, leucopenia, neutropenia, hypokalaemia, hypophosphataemia, hyperglycae-

mia, lymphocele; arthralgia, osteonecrosis; epistaxis; acne, rash, impaired healing, pancreatitis, pulmonary embolism, pulmonary haemorrhage, pericardial effusion, nephrotic syndrome, increased susceptibility to lymphoma and other malignancies particularly of the skin, and pancytopenia, interstitial lung disease, hepatic necrosis, lymphoedema, and hypersensitivity reactions including anaphylactic reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis.

Dose: Initially 6 mg, after surgery, then 2 mg once daily (dose adjusted according to blood - sirolimus concentration) in combination with ciclosporin and corticosteroid for 2–3 months (sirolimus given 4 hours after ciclosporin); ciclosporin should then be withdrawn over 4–8 weeks (if not possible, should be discontinued and an alternate immunosuppressive regimen used).

Preparations

Sirolimus tablets, 1 mg tab.

Tacrolimus

Indications: the prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants. Also, in patients resistant to conventional immunosuppressive regimens.

Contraindication: hypersensitivity to tacrolimus.

Cautions: see under ciclosporin; also, monitor ECG (cases of cardiomyopathy have been reported),

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should not be taken with ciclosporin (risk of nephrotoxicity).

Side-effects: gastro-intestinal disturbances, infections, nephrotoxicity, neurotoxicity, hyperglycaemia, hypertension, tremor.

Dose: In liver allograft recipient: by mouth 100-200 micrograms/kg/day in two divided doses or by intravenous infusion over 24 hours, 10-50 micrograms/kg daily for up to max.7 days. (Then transfer to oral therapy). Paediatric dose: orally: 300 micrograms/kg daily in two divided doses or by intravenous infusion over 24 hours, 50 micrograms/kg daily for up to max.7 days. (Then transfer to oral therapy). In kidney allograft recipient: by mouth 200-300 micrograms/kg/day in two divided doses or by intravenous infusion over 24 hours, 50-100 micrograms/kg daily for up to max.7 days. (Then transfer to oral therapy). Paediatric dose: orally: 300 micrograms/kg daily in two divided doses or by intravenous infusion over 24 hours, 75-100 micrograms/kg daily for up to max.7 days. (Then transfer to oral therapy).

Preparations:

Tacrolimus capsules, 500 micrograms cap.

Tacrolimus capsules, 1 mg cap.

Tacrolimus capsules, 5 mg cap.

Tacrolimus sachets, 200 micrograms per sachet

Tacrolimus sachets, 1 mg per sachet.

Tacrolimus intravenous injection, 5 mg/mL ampoule

Thalidomide

Indications: multiple myeloma

Cautions: High tumour burden—risk of tumour lysis syndrome. Thromboembolism. Second primary malignancy. Peripheral neuropathy

Side-effects: Anaemia; asthenia; bradycardia; cardiac failure; confusion; constipation; deep vein thrombosis; depression; dizziness; drowsiness; dry mouth; dysaesthesia; dyspepsia; dyspnoea; interstitial lung disease; leucopenia; lymphopenia; neutropenia; paraesthesia; peripheral neuropathy; peripheral oedema; pneumonia; pulmonary embolism; pyrexia; skin reactions; Stevens-Johnson syndrome; syncope; thrombocytopenia; tremor; vomiting

Dose: 200 mg once daily for 6-week cycle for a maximum of 12 cycles, dose to be taken at bedtime.

Preparations

Thalidomide tablets, 100 mg tab.

Thalidomide tablets, 200 mg tab.

Lenalidomide

Indications: Multiple myeloma. Treatment of transfusion-dependent anaemia

Cautions: High tumour burden—risk of tumour lysis syndrome; patients with risk factors for myocardial infarction. Risk factors for thromboembolism (such as smoking, hypertension, hyperlipidaemia)

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should be minimised and thromboprophylaxis should be considered in patients with multiple risk factors. Patients should be carefully evaluated before and during treatment with lenalidomide using routine cancer screening for occurrence of second primary malignancy and treatment should be instituted as indicated.

Side-effects: Abdominal pain; anaemia; arrhythmias; arthralgia; ataxia; atrial fibrillation; bacterial infections; bradycardia; cardiac failure; cataract; cerebrovascular events; chest pain; cholestasis; constipation; decreased appetite; deep vein thrombosis; dehydration; depression; diarrhoea; dizziness; dry mouth; dyspepsia; dysphagia; dyspnoea; electrolyte disturbances; falls; flu-like illness; fungal infections; haematoma; haematuria; haemorrhagic disorders; headache; hearing disturbances; hyperglycaemia; hyperhidrosis; hypertension; hypotension; hypothyroidism; insomnia; iron-overload; lethargy; leucopenia; malaise; mood changes; musculoskeletal disorders; myalgia; myocardial infarction; nausea; oedema; peripheral neuropathy; pneumonia; pruritus; pulmonary embolism; pyrexia; rash; renal failure; respiratory distress; respiratory tract infections; sepsis; severe neutropenia; sexual dysfunction; sinusitis; skin disorders; stomatitis; syncope; tachycardia; taste disturbance; thrombocytopenia; tremor; urinary incontinence; urinary retention; vasculitis;

viral infections; visual disturbances; vomiting.

Dose: When given in combination with dexamethasone until disease progression 25 mg once daily for 21 consecutive days of repeated 28-day cycles

With melphalan and prednisone, 10 mg once daily for 21 consecutive days of repeated 28-day cycles for up to 9 cycles. For doses of melphalan and prednisone and cycle timings consult the product literature. Treatment of transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with an isolated deletion 5q cytogenetic abnormality when other treatment options are insufficient or inadequate, 10 mg once daily for 21 consecutive days of repeated 28-day cycles. Consult the product literature for more details

Preparations

Lenalidomide capsules, 10 mg cap.

Lenalidomide capsules, 25 mg cap.

8 B.3: Interferons

Human recombinant interferon alfa has shown to have several effects that result in immunostimulation, including activation of macrophages, T-lymphocytes and natural killer cells. Clinical benefits have been obtained with interferon alfa in some malignancies including hairy cell leukaemia, chronic myeloid leukaemia, solid tumors and

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lymphomas. Viral infections have also been treated with interferon alfa such as hepatitis.

Interferon alfa

Indications: *see* notes above

Contra-indications: avoid benzyl alcohol containing injection in neonates.

Side-effects: are dose related, including anorexia, nausea, flu like symptoms and lethargy.

Preparations

Interferon alfa injection, 6,000,000 units/ mL, 0.5 mL ampoule (3,000,000 units /ampoule) Interferon alfa injection, 15,000,000 units/mL, 1.2 mL ampoule (18,000,000 units/ampoule)

Peginterferon alfa

It is a covalent conjugate of recombinant alfa-2a interferon with a single branched monomethoxy polyethylene glycol (PEG) chain. This pegylation increases the persistence of the interferon in the blood.

Indications, contraindications and side-effects: *see* under interferon alfa

Preparations:

Peginterferon alfa-2a injection: 180 microgram in 0.5 mL prefilled syringe.

Interferon beta

Indications: treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations.

Contra-indications: pregnancy and breast feeding, severe depression, decompensated liver disease.

Cautions: renal and hepatic impairment, cardiac disorders, depressive disorders, seizures, myelosuppression.

Side-effects: flu-like symptoms, injection site pain and inflammation, hypersensitivity reactions, alopecia, blood disorders, menstrual disorders, mood changes, hepatitis.

Preparations

Interferon beta-1a injection, powder for reconstitution, 30 microgram (6 million unit) vial

Interferon beta-1b injection, powder for reconstitution, 300 microgram (9.6 million unit) vial

8 B.4: Immunomodulating drugs

Fingolimod is an immunomodulating drug. It is known to cause transient bradycardias and heart block after the first dose. Fingolimod is not recommended in the following patient groups who are at high risk of cardiovascular events unless the anticipated benefits outweigh the potential risks, and advice from a

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cardiologist is sought before initiation:

Patients with the following medical conditions:

- 2nd degree Mobitz Type II or higher degree atrioventricular block, sick sinus syndrome, or sino-atrial heart block
- Significant QT prolongation (QT-interval greater than 470 milliseconds in women, or greater than 450 milliseconds in men)
- History of symptomatic bradycardia or recurrent syncope, known ischaemic heart disease, cerebrovascular disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension, or severe sleep apnoea.

Patients receiving the following antiarrhythmic or heart-rate lowering drugs:

- class Ia or class III antiarrhythmics
- beta blockers
- heart rate-lowering calcium channel blockers
- other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic drugs or pilocarpine).

All patients receiving fingolimod should be monitored at treatment initiation, (first dose monitoring), and after treatment interruption (see note below); monitoring should include:

Pre-treatment - a 12-lead ECG and blood pressure measurement before starting

During the first 6 hours of treatment - continuous ECG monitoring for 6 hours blood pressure and heart rate measurement every hour

After 6 hours of treatment - a further 12-lead ECG and blood pressure measurement

If heart rate at the end of the 6 hour period is at its lowest since fingolimod was first administered, monitoring should be extended by at least 2 hours and until heart rate increases.

Extended monitoring, (at least overnight), should be performed in patients with evidence of clinically important cardiac effects during first dose monitoring. Monitoring in patients requiring pharmacological intervention for bradyarrhythmia-related symptoms during first dose monitoring should be extended at least overnight, and first dose monitoring should be repeated after the second dose.

8: Malignant disease and immunosuppression

Note

First dose monitoring as above should be repeated in all patients whose treatment is interrupted for:

- 1 day or more during the first 2 weeks of treatment
- more than 7 days during weeks 3 and 4 of treatment
- more than 2 weeks after one month of treatment

If the treatment interruption is of shorter duration than the above, repeated monitoring is not required and treatment should be continued with the next dose as planned.

Fingolimod

Indications: Multiple sclerosis

Contra-indications: Active infection; active malignancies (except cutaneous basal cell carcinoma); immunosuppression

Cautions: Check varicella zoster virus status—consult product literature for further information; chronic obstructive pulmonary disease; pulmonary fibrosis; risk of macular oedema; severe respiratory disease; susceptibility to QT-interval prolongation (including electrolyte disturbances. Effective contraception is needed two months after stopping treatment.

Side-effects: Alopecia; AV block; back pain; blurred vision; bradycardia; bronchitis; cough; depression; diarrhoea; dizziness; dyspnoea; eczema; gastroenteritis; headache;

herpes; hypertension; influenza; leucopenia; lymphopenia; malaise; migraine; paraesthesia; pruritus; sinusitis; tinea versicolor; macular oedema; neutropenia; pneumonia; haemophagocytic syndrome; lymphoma; posterior reversible encephalopathy syndrome; progressive multifocal leukoencephalopathy

Dose: 500 micrograms daily.

Preparations

Fingolimod hydrochloride capsules, 500 microgram caps.

8 C: Sex hormones and hormone antagonists in malignant diseases.

8 C.1: Aromatase inhibitors

Anastrozole

Indications: adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer either as a sole therapy or following two to three years of tamoxifen, for the treatment of advanced breast cancer in postmenopausal women in whom disease has progressed following tamoxifen therapy.

Contra-indications: see notes above; severe renal and hepatic impairment, not indicated for premenopausal women.

8: Malignant disease and immunosuppression

Cautions: see notes above; assess bone mineral density (BMD) before and after treatment (risk of osteoporosis).

Side-effects: see notes above; hot flushes, vaginal bleeding and dryness, bone fractures, drowsiness, increased cholesterol levels, rash.

Dose: 1 mg daily.

Preparations

Anastrozole tablets, 1 mg tab.

Exemestane

Indications: adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen, for the treatment of advanced breast cancer in postmenopausal women in whom disease has progressed following tamoxifen therapy.

Contra-indications: see notes above; not indicated for premenopausal women.

Cautions: see notes above; hepatic and renal impairment.

Side-effects: see notes above; fatigue, depression, insomnia, hot flushes, sweating.

Dose: 25 mg daily.

Preparations

Exemestane tablets; 25 mg tab.

Letrozole

Indications: adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer, for the treatment of ad-

vanced breast cancer in postmenopausal women in whom disease has progressed following tamoxifen therapy.

Contra-indications: see notes above; severe hepatic impairment, not indicated for premenopausal women.

Cautions: see notes above; severe renal impairment.

Side-effects: see notes above; hot flushes, depression, bone fractures, drowsiness, increased appetite, rash.

Dose: 2.5 mg daily.

Preparations

Letrozole tablets, 2.5 mg tab.

Fulvestrant

Indications: Treatment of oestrogen-receptor-positive metastatic or locally advanced breast cancer in postmenopausal women in whom disease progresses or relapses while on, or after, other anti-oestrogen therapy.

Side-effects: Anorexia; asthenia; back pain; diarrhoea; headache; hot flushes; hypersensitivity reactions; injection-site reactions; nausea; rash; urinary-tract infections; venous thromboembolism; vomiting.

Dose: by deep intramuscular injection, 500 mg every 2 weeks for the first 3 doses, then 500 mg every 1 month, to be administered into the buttock.

Preparations

Fulvestrant injection, 250 mg/5 mL in prefilled syringe

8: Malignant disease and immunosuppression

8 C.2: Gonadorelin analogues

Standard treatment of metastatic prostate cancer includes bilateral subcapsular orchidectomy or the use of gonadorelin analogues such as goserelin. They cause initial stimulation and then depression of luteinising hormone release by the pituitary. The initial effect (flare) will cause an increase in testosterone production and a progression of prostate cancer. Concomitant use of an anti-androgen such as flutamide may suppress this effect. In females, goserelin may be used in the treatment of breast cancer, endometriosis and infertility.

Goserelin (CDL)

Indications: prostate cancer; advanced breast cancer; *see* notes above.

Contra-indications: pregnancy; undiagnosed vaginal bleeding.

Cautions: caution is required in patients with metabolic bone disease; men at risk of 'flare' effects should be monitored closely; avoid pregnancy during treatment.

Side-effects: goserelin causes side-effects similar to menopause in women and orchidectomy in men; transient change in blood pressure, paraesthesia.

Preparations

Goserelin implant, 10.8 mg in syringe applicator

Goserelin implant, 10.8 mg in syringe applicator

Flutamide

Indications: advanced prostate cancer; adjunct to goserelin (*see* above notes)

Cautions: cardiac disease; hepatic impairment.

Side-effects: gynaecomastia; nausea and vomiting, diarrhoea, increased appetite, insomnia.

Dose: 250 mg 3 times daily.

Preparations

Flutamide tablets, 250 mg tab.

8 C.3: Progestogens

Megestrol acetate

Indications: as appetite-enhancing agent in cachexia associated with AIDS or cystic fibrosis, palliative treatment of advanced breast cancer or endometrial carcinoma.

Cautions: diabetes, history of thromboembolic disease, not intended for prophylactic use to avoid weight loss, possibility of adrenal insufficiency in patients receiving or being withdrawn from chronic megestrol acetate therapy, use of megestrol in other types of neoplastic disease is not recommended.

Side-effects: sweating, hot flashes, weight gain, diarrhoea, dyspepsia, flatulence, nausea, vomiting, insomnia, mood swings, impotence, anaemia, deep venous thrombosis, thrombophlebitis, pulmonary embolism.

8: Malignant disease and immunosuppression

Preparations

Megestrol acetate suspension, 40
mg/mL

9: Nutrition and blood

Section 9: Nutrition and blood

- Anaemias and some other blood disorders
- Electrolyte and water replacement
- Intravenous nutrition
- Oral nutrition
- Minerals
- Vitamins

9 A: Anaemias and some other blood disorders

The underlying cause should be determined before initiating therapy for anaemia. The use of iron in anaemias other than those due to iron deficiency may lead to a serious iron overload with harmful consequences.

9 A.1: Iron

9 A.1.1: Iron deficiency anaemias

The body recycles iron from the dead blood cells. The loss of iron is only seen when red blood cells are lost through bleeding. Iron deficiency is one of the most common causes of anaemia, and blood loss is virtually the only cause of anaemias in adult. A diet low in iron may lead to iron deficiency in infants and growing children.

Normal dietary intake of iron is not sufficient to replace iron lost by

chronic bleeding. Consequently an iron supplement must be given. Because a developing foetus uses iron, pregnant women also need iron supplements.

Orally administered iron salts are recommended for supplement therapy unless a good reason indicates the use of other routes. Ferrous salts are recommended for their good absorption in the gut. The oral dose of elemental iron for deficiency should be 100-200 mg daily. Different iron salts contain elemental iron as follows:

Iron salt	Dose	Elemental iron
Ferrous fumarate	200 mg	65 mg
Ferrous succinate	100 mg	35 mg
Ferrous sulphate	300 mg	60 mg
Ferrous sulphate, dried	200 mg	65 mg

Though rarely used, iron injections are reserved for patients who can not tolerate oral iron or those who continue to lose large amount of haemoglobin from ongoing bleeding.

Iron salts may cause gastro-intestinal irritation, nausea and epigastric pain which are dose related. Constipation or diarrhoea, however are also common. In the elderly, the constipating effect may be very severe with oral iron preparations. Iron salts almost always turn stools

to black; a normal and harmless side effect.

Iron Preparations

Indications: iron deficiency anaemia.

Cautions: other forms of anaemias; irritable bowel syndrome.

Side-effects: *see* notes above

Dose: *see* under preparation.

Iron preparations purchased and supplied by Ministry of Health will either be ferrous sulphate or ferrous fumarate depending on cost effectiveness

Preparations

Dried ferrous sulphate tablets, 200 mg tab. (65 mg iron)

Dose: adult, prophylactic, 200 mg once daily; treatment, 200 mg 2-3 times daily.

Ferrous sulphate 150-200 mg/5 mL syrup (25 – 45) mg iron ; 100-150 mL/bottle

Dose: adult, prophylactic, 10 mL once daily; treatment, 10 mL 2-3 times daily.

Child, prophylactic, 1-6 years, 1.25 mL daily, 6-12 years 2.5 mL once daily.

Child, treatment, 1-6 years, 2.5 mL twice daily, 6-12 years, 5 mL 2-3 times daily.

Ferrous sulphate drops, 75 mg/0.6 mL (15 mg iron), 30 mL/bottle

Dose: infants and child under 1 year, prophylaxis, 0.6 mL once daily; treatment, 0.6 mL 2-3 times daily.

Ferrous sulphate and Folic acid

Indications: iron deficiency prophylaxis during pregnancy.

Caution and side-effects: *see* notes above

Preparations

Dried ferrous sulphate 150 mg (47 mg iron) + folic acid 500 micrograms spansule/tablets

Dose : one spansule/tablet daily.

Iron injection

Indications: iron deficiency anaemia in renal dialysis patient.

Contra-indications: pregnancy; allergic disorders; liver disease; infection.

Cautions: oral iron should not be given before five days of the last injection.

Side-effects: taste disturbances, nausea, vomiting, headache, hypotension.

Dose: by intravenous injection or infusion calculated according to patients need (consult manufacturer instruction).

Preparations

Iron (as iron sucrose) injection, 20 mg/mL, 5 mL ampoule

9 A.1.2: Treatment of iron overload

Iron overload may result from repeated blood transfusions in aplastic or refractory anaemias. Excessive iron absorption in the gut and

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inappropriate iron therapy in thalassaemia major aggravate iron overload problems.

Deferoxamine mesilate is a chelating agent that is useful in the treatment of iron overload resulting from the above-mentioned conditions or in iron poisoning (*see also sec 17B*).

Deferiprone is an oral iron chelator that is used for patients when deferoxamine is contra-indicated or not tolerated.

Deferoxamine mesilate (Desferrioxamine mesilate)

Indications: iron overload; emergency iron poisoning (*see sec 17B*)

Cautions: renal impairment; routine eye and ear examination during treatment; pregnancy, breast-feeding.

Side-effects: anaphylactic reaction and hypotension, more frequent with rapid intravenous infusion.

Dose: iron overload; consult product literature.

Preparations

Deferoxamine mesilate injection, 500 mg vial

Deferiprone

Indications: iron overload for patient intolerant to deferoxamine.

Contra-indications: pregnancy and breast feeding.

Cautions: neutropoenia; renal and hepatic impairment, use with great caution in children 3-10 years of age.

Side-effects: agranulocytosis, neutropoenia; gastro-intestinal disturbances; red colouration of urine.

Dose: adult and child over 6 years, 25 mg/kg 3 times daily; maximum 100 mg/kg daily.

Preparations

Deferiprone tablets, 500 mg tab.

Deferasirox (Restricted)

Indications: Chronic iron overload. Transfusion-related chronic iron overload.

Cautions: Elderly (increased risk of side-effects); history of liver cirrhosis; not recommended in conditions which may reduce life expectancy (e.g. high-risk myelodysplastic syndromes); platelet count less than $50 \times 10^9/\text{litre}$; risk of gastro-intestinal ulceration and haemorrhage; renal impairment; hepatic impairment; eye and ear examination before and during treatment; unexplained cytopenia—consider treatment interruption.

Side-effects: Fatal gastro-intestinal haemorrhage; gastro-intestinal disturbances; gastro-intestinal ulceration; headache; proteinuria; pruritus; rash; elevated transaminases; earache; disturbances of hearing and vision

Dose: Treatment of chronic iron overload: initially 10 mg/kg once daily; adjusted in steps of 5–10 mg/kg every 3–6 months, dose adjusted for maintenance according to serum-ferritin concentration and liver-iron concentration (consult

product literature); maximum 20 mg/kg per day.

Transfusion-related chronic iron overload: initially 10–30 mg/kg once daily, dose adjusted according to serum-ferritin concentration and amount of transfused blood—consult product literature; adjusted in steps of 5–10 mg/kg every 3–6 months, dose adjusted for maintenance according to serum-ferritin concentration; usual dose up to 30 mg/kg daily, increased if necessary up to 40 mg/kg daily and reduced in steps of 5–10 mg/kg, dose to be reduced once control achieved.

Preparations

Deferasirox dispersible tablet 125 mg tab.

Deferasirox dispersible tablet 250 mg tab.

Deferasirox dispersible tablet 500 mg tab.

9 A.2 Platelet Disorders

Romiplostim (Restricted)

Indications: Chronic idiopathic thrombocytopenic purpura.

Cautions: renal impairment; hepatic impairment; monitor full blood count and peripheral blood smears for morphological abnormalities before and during treatment. Monitor platelet count weekly until platelet count reaches 50×10^9 / litre or more for at least 4 weeks without dose adjustment, then monthly thereafter. Dizziness may

affect performance of skilled tasks (driving)

Side-effects: Arthralgia; asthenia; bone pain; dizziness; ecchymosis; fatigue; flushing; gastro-intestinal disturbances; increased bone marrow reticulin; influenza-like symptoms; injection site reactions; insomnia; migraine; muscle spasm; myalgia; oedema; paraesthesia; rash.

Dose: by subcutaneous injection: initially 1 microgram/kg once weekly, adjusted in steps of 1 microgram/kg once weekly (max. per dose 10 micrograms/kg once weekly) until a stable platelet count of 50×10^9 / litre or more is reached, discontinue treatment if inadequate response after 4 weeks at maximum dose, consult product literature for dose adjustments.

Preparations

Romiplostim injection, powder for reconstitution, 250 micrograms vial

9 A.3 Megaloblastic anaemias

Vitamin B₁₂ and folic acid in addition to iron are needed by bone marrow to produce red blood cells. If any of these vitamins is lacking, megaloblastic anaemia will develop.

Although megaloblastic anaemia results from lack of vitamin B₁₂ or folic acid in diet or inability to absorb them, it is some times caused

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by drugs used for treatment of neoplastic diseases or antiepileptics.

Folic acid deficiency results from either low dietary supply or due to decreased absorption caused by drugs such as antiepileptics or contraceptive pills. Less commonly, pregnant and lactating women and people undergoing haemodialysis develop this deficiency due to their increased need for folic acid.

In infants, folic acid deficiency may cause neurological abnormalities.

In pregnant women, deficiency of folic acid can cause spinal cord defects and other malformation in the foetus.

In folic acid deficiency anaemia, oral folic acid 5 mg daily for 4 months is administered to bring about a haematological remission and replenish body stores. Maintenance dose may be given once weekly depending on underlying disease.

For prophylaxis in pregnancy the dose of folic acid is 200-500 microgram daily before conception and during the first 12 weeks of pregnancy. However, if there is a history of neural tube defect in a previous child, a higher dose of 5 mg daily is needed.

Folic acid

Indications: treatment and prophylaxis of folic acid deficiency anaemia.

Cautions: should not be given alone in pernicious anaemia or other vitamin B₁₂ deficiencies.

Dose: see notes above

Preparations

Folic acid tablets, 5 mg tab.

Vitamin B₁₂ deficiency causes pernicious anaemia, which is a megaloblastic anaemia. Vitamin B₁₂, which is available in meat, is readily absorbed in the ileum. However, to be absorbed it must combine with gastric intrinsic factor. Without the intrinsic factor, vitamin B₁₂ remains unabsorbed in the gut and excreted in the stool.

Hydroxocobalamin and cyanocobalamin are the two forms of vitamin B₁₂ for therapeutic use. Hydroxocobalamin is retained in the body longer than cyanocobalamin. Treatment is generally initiated with frequent administration of intramuscular injections to replenish the depleted body stores. Thereafter, maintenance therapy, which is for life, can be instituted.

Oral doses of vitamin B₁₂ are not recommended for treatment of megaloblastic anaemia. It could be added to supplementary vitamin preparations just to compensate for low dietary intake in otherwise normal people.

Although vitamin B₁₂ has been used in several other conditions like neuropathies, psychiatric illnesses, and as a general tonic in various chronic conditions, such use has not been shown to have any beneficial effects and lacks scientific validity.

Cyanocobalamin

Indications: vitamin B₁₂ deficiency anaemia.

Cautions: should not be used unless diagnosis is fully established.

Side-effects: itching, fever, flushes, dizziness, exanthema.

Dose: intramuscularly, 1 mg repeated 10 times at intervals of 2-3 days. Maintenance, 1 mg monthly.

Preparations

Cyanocobalamin injection, 1 mg ampoule

9 A.4: Hypoblastic, haemolytic and renal anaemias

Recombinant human erythropoietin (epoetin) is used for anaemias associated with erythropoietin deficiency in chronic renal failure, to increase the yield of autologous blood in normal individuals and to shorten the period of anaemia in patients undergoing chemotherapy with platinum compounds.

The use of erythropoietin reduces the requirement for blood transfusion. Other factors which contribute to anaemias such as iron or folate deficiency should be corrected before and during therapy.

Recombinant human erythropoietin (Restricted)

Indications: anaemias associated with chronic renal failure in patients on haemodialysis or perito-

neal dialysis; anaemia in adult patients receiving platinum-containing chemotherapy.

Contra-indications: uncontrolled hypertension.

Cautions: uncontrolled blood pressure; exclude other causes of anaemia; chronic liver failure; malignancies; pregnancy and breast feeding.

Side-effects: dose dependent increase of blood pressure; dose dependent increase in platelet count; flu-like symptoms.

Dose: initially, subcutaneous or slow intravenous injection, 50-100unit/kg 3 times weekly adjusted according to patient need. Maintenance dose would be determined according to haemoglobin level and patient response.

Preparations

Human recombinant erythropoietin injection, 1,000 units vial

Human recombinant erythropoietin injection, 2,000 units vial

Human recombinant erythropoietin injection, 4,000 units vial

Human recombinant erythropoietin injection, 10,000 units vial

Darbepoetin Alfa (Restricted)

Indications: Symptomatic anaemia

Contra-indications: Patients unable to receive thromboprophylaxis; pure red cell aplasia following erythropoietin therapy; uncontrolled hypertension.

Cautions: Aluminium toxicity (can impair the response to erythropoi-

9: Nutrition and blood

etin); concurrent infection (can impair the response to erythropoietin); correct factors that contribute to the anaemia of chronic renal failure, such as iron or folate deficiency, before treatment.; during dialysis (increase in unfractionated or low molecular weight heparin dose may be needed); epilepsy; inadequately treated or poorly controlled blood pressure—interrupt treatment if blood pressure uncontrolled; ischaemic vascular disease; malignant disease; other inflammatory disease (can impair the response to erythropoietin); risk of thrombosis may be increased when used for anaemia before orthopaedic surgery—avoid in cardiovascular disease including recent myocardial infarction or cerebrovascular accident; risk of thrombosis may be increased when used for anaemia in adults receiving cancer chemotherapy; sickle-cell disease (lower target haemoglobin concentration may be appropriate); sudden stabbing migraine-like pain (warning of a hypertensive crisis); thrombocytosis (monitor platelet count for first 8 weeks).

Side-effects: Aggravation of hypertension (dose-dependent); cardiovascular events; diarrhoea; dose-dependent increase in platelet count regressing during treatment (but thrombocytosis rare); headache; hypertensive crisis (in isolated patients with normal or low blood pressure); increase in blood pressure (dose-dependent); influenza-like symptoms (may be reduced if

intravenous injection given over 5 minutes); nausea; shunt thrombosis especially if tendency to hypotension or arteriovenous shunt complications; vomiting.

Dose: Symptomatic anaemia associated with chronic renal failure in patients on dialysis, by subcutaneous injection: initially 450 nanograms/kg once weekly, dose to be adjusted according to response by approximately 25% at intervals of at least 4 weeks, maintenance dose to be given once weekly or once every 2 weeks, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose, when changing route give same dose then adjust according to weekly or fortnightly haemoglobin measurements, adjust doses not more frequently than every 2 weeks during maintenance treatment.

Symptomatic anaemia associated with chronic renal failure in patients not on dialysis, by subcutaneous injection: initially 450 nanograms/kg once weekly, alternatively initially 750 nanograms/kg every 2 weeks, dose to be adjusted according to response by approximately 25% at intervals of at least 4 weeks, maintenance dose can be

given once weekly, every 2 weeks, or once a month, subcutaneous route preferred in patients not on haemodialysis, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose, when changing route give same dose then adjust according to weekly or fortnightly haemoglobin measurements, adjust doses not more frequently than every 2 weeks during maintenance treatment.

By intravenous injection: initially 450 nanograms/kg once weekly, dose to be adjusted according to response by approximately 25% at intervals of at least 4 weeks, maintenance dose given once weekly, subcutaneous route preferred in patients not on haemodialysis, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose, when changing route give same dose then

adjust according to weekly or fortnightly haemoglobin measurements, adjust doses not more frequently than every 2 weeks during maintenance treatment.

Symptomatic anaemia in adults with non-myeloid malignancies receiving chemotherapy, by subcutaneous injection: initially 6.75 micrograms/kg every 3 weeks, alternatively initially 2.25 micrograms/kg once weekly, if response inadequate after 9 weeks further treatment may not be effective; if adequate response obtained then reduce dose by 25–50%, reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and restart at a dose approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy.

Preparations

Darbepoetin Alfa , 10 micrograms prefilled syringes

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9 A.5: Drugs used in neutropoenia

Recombinant human granulocyte-colony stimulating factor stimulates the production of neutrophils and may reduce the duration of chemotherapy induced neutropoenia and thereby reduce the incidence of associated sepsis. **Cautions:** should be used with caution in patients with pre-malignant or malignant myeloid conditions, patients with a history of pulmonary infiltrates or pneumonia and patients with sickle cell disease. (Full blood count and spleen size should be monitored). Recombinant human granulocyte-colony stimulating factors are not recommended in pregnancy or breast feeding. **Side-effects:** gastro-intestinal disturbances, musculoskeletal pain, alopecia, hypersensitivity reactions, pulmonary side-effects and splenic rupture.

Filgrastim (Restricted)

(Recombinant human granulocyte-colony stimulating factor)

Indications: (special use) severe neutropoenia following autologous bone marrow transplantation and high dose chemotherapy; severe congenital neutropoenia; cyclic neutropoenia.

Contra-indications: sensitivity to the drug.

Cautions: *see* notes above; also leukaemic or preleukaemic conditions, patients with psoriasis and

pre-existing cardiac conditions; monitor blood counts regularly.

Side-effects: *see* notes above; also musculoskeletal pain, disturbances in serum uric acid, urinary abnormalities, allergic reactions.

Dose: consult product literature.

Preparations

Filgrastim injection, 300 micrograms/mL (30 million units/mL), 1 mL vial

Pegfilgrastim (Restricted)

Is a covalent conjugate of recombinant methionyl human G-CSF (Filgrastim) and monomethoxypolyethylene glycol. This conjugation/Pegylation increases the duration of filgrastim activity.

Indications: is indicated for decreasing the risk of infection (as manifested by febrile neutropoenia) associated with myelosuppressive treatment of non-myeloid malignancies

Cautions: *see* notes above

Contraindications: sensitivity to the drug.

Side-effects: *see* notes above

Dose: for adult, by subcutaneous injection of 6 mg (0.6 mL) administered once per chemotherapy. *(The 6 mg fixed-dose formulation should not be used in infants, children, and smaller adolescents weighing less than 45 kg)*

Preparations

Pegfilgrastim Injection, 10 mg/mL, available as 6 mg (0.6 mL) prefilled syringes

Plerixafor (Restricted)

Indications: Mobilise haematopoietic stem cells to peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma or multiple myeloma (specialist use only).

Cautions: monitor platelets and white blood cell count, pregnancy, renal impairment

Side-effects: Arthralgia; dizziness; dry mouth; erythema; fatigue; gastro-intestinal disturbances; headache; injection-site reactions; insomnia; musculoskeletal pain; oral hypoaesthesia; sweating

Dose: By subcutaneous injection: 240 micrograms/kg daily usually for 2–4 days (max 7 days), to be administered 6–11 hours before initiation of apheresis, dose to be given following 4 days treatment with a granulocyte-colony stimulating factor.

Preparations

Plerixafor injection, 24 mg in 1.2 mL vial

Molgramostim (Restricted)

(Recombinant human granulocyte macrophage – colony stimulating factor)

Indications: (special use) severe neutropoenia following autologous bone marrow transplantation and high dose chemotherapy; severe congenital neutropoenia; cyclic neutropoenia.

Contra-indications: myeloid malignancies.

Cautions: monitor serum albumin, full blood counts, platelet and haemoglobin; not recommended for patients under 18 years.

Side-effects: nausea, diarrhoea, vomiting, anorexia; dyspnoea; asthenia, fatigue fever, rash musculoskeletal pain; local reaction after subcutaneous injection.

Dose: consult product literature.

Preparations

Molgramostim injection, 3.33 million unit (300 microgram) vial

Ministry of Health policy is that only one of the above colony stimulating factors will be purchased and made available for use depending on cost effectiveness

9 B: Electrolyte and water replacement

9 B.1: Orally administered electrolytes

9 B.1.1: Potassium supplement

Potassium is a vital ion for the cell metabolism and the normal function of nerve and muscle cells. Most of the potassium body reserves are located intracellularly. The concentration of potassium in the blood is very critical and must be maintained within a narrow margin. Variation in plasma potassium level could have serious consequences on the heart. Intracellular

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potassium helps maintaining the level in plasma. The plasma content of sodium is balanced between the intakes from dietary sources with the amount lost in the urine. A daily intake of 60-100 mmol is required. A balanced diet usually provides the body with its requirement of potassium.

Potassium supplement is needed in hypokalaemia associated with, chronic diarrhoea, intestinal malabsorption or laxative overuse. In patients using cardiac glycosides or antiarrhythmic agents, maintaining normal potassium level is mandatory.

Oral potassium supplement are better given in the liquid form to minimize irritation. Slow release preparations are also available to provide better prolonged absorption with anticipated less irritation.

Potassium chloride

Indications: potassium depletion.

Contra-indications: severe renal impairment.

Cautions: elderly, mild to moderate renal impairment, history of peptic ulceration, hiatus hernia; avoid with drugs that raise plasma potassium level such as potassium sparing diuretics or ACE inhibitors

Side-effects: nausea and vomiting, oesophageal or small bowel ulceration.

Dose: 1 sustained release tablets once or twice daily with plenty of water during meals while sitting or standing.

Preparations

Potassium chloride sustained release tablets, 600 mg tab.

Potassium Chloride syrup, 500 mL/bottle

9 B.1.2: Sodium bicarbonate supplement

Sodium bicarbonate (Restricted)

Indications: metabolic acidosis.

Preparations

Sodium bicarbonate tablets, 500 mg tab.

9 B.1. 3: Drugs for potassium removal

Calcium polystyrene sulphonate

Indications: hyperkalaemia associated with renal impairment.

Contra-indications: obstructive bowel disease, malignancies, hyper-parathyroidism.

Cautions: children; monitor for electrolyte disturbances; pregnancy and breast feeding.

Side-effects: gastric irritation, anorexia, nausea and vomiting; constipation or diarrhoea.

Dose: by mouth, 15 g 3-4 times daily in water. Child, 0.5-1g/kg daily in divided doses.

Preparations

Calcium polystyrene sulphonate powder; 300 g/pack

9 B.2: Intravenous administration

Body water is distributed between intracellular and extracellular compartments; the distribution is solute dependent. Sodium is the main osmotically important ion in the extracellular compartment.

Loss of water results in depletion of both extracellular and intracellular compartments, while loss of sodium leads to more severe depletion in the extracellular compartment.

Electrolytes and water depletion can occur singly and in combination with or without disturbing the acid-base balance. In an individual patient the nature and severity of the electrolyte imbalance must be assessed from the history and clinical and biochemical examination.

9 B.2.1: Electrolyte preparations

Sodium chloride

Indications: electrolyte imbalance; sodium depletion.

Cautions: restrict intake in patients with renal failure, hypertension, cardiac failure, oedema, toxæmia of pregnancy.

Side-effects: large dose may cause sodium accumulation and oedema.

Preparations

Sodium chloride intravenous infusion, 0.9% solution, 500 mL pack
Sodium chloride intravenous infusion, 0.45% solution, 500 mL pack

Sodium chloride intravenous infusion, 2.7-3% solution, 500 mL pack
Sodium chloride injection, 0.9% solution, 5 mL vial/ampoule
Sodium chloride injection, 0.9% solution, 100 mL bottle
Sodium chloride injection, 14.6% solution, 40 mL vial (CDL)
Sodium chloride injection, 7% sterile (Hypertonic saline) (Restricted)

Potassium chloride solution (strong)

Indications: electrolyte imbalance.

Cautions: rapid infusion is toxic to the heart; specialist advice and ECG monitoring.

Dose: by slow intravenous infusion, the concentration should not usually exceed 3.2 g (43 mmol) / litre.

Preparations

Potassium chloride injection, 15% solution, 10 mL ampoule

Compound sodium lactate (Hartmann's solution)

Indications: as a substitute to sodium chloride in surgery or in the initial management of the injured or wounded.

Cautions and side-effects: see sodium chloride

Preparations

Intravenous infusion containing, sodium chloride 0.6%, sodium lactate 0.25%, potassium chloride 0.04%, calcium chloride 0.027% is available as :

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Compound sodium lactate solution (Hartmann's solution) full strength, 500 mL bag

Compound sodium lactate solution (Hartmann's solution) half strength, 500 mL pack

Ringer's solution (CDL)

Indications: electrolyte imbalance.

Cautions and side-effects: *see* sodium chloride

Preparations

Intravenous infusion containing, calcium chloride 0.032%, potassium chloride 0.03% and sodium chloride 0.86% available as :
Ringer's solution for intravenous infusion, 500 mL pack

Sodium bicarbonate

Indications: metabolic acidosis.

Dose: by intravenous injection, a strong solution (up to 8.4%), or by intravenous infusion of a weaker solution, in an amount appropriate to body's need for a base.

Preparations

Sodium bicarbonate injection, 8.4% solution, 50 mL vial

Sodium bicarbonate injection, 8.4% solution, 250 mL bottle

Sodium bicarbonate injection, 8.4% solution, 10 mL preloaded syringe

Sodium bicarbonate injection, 8.4% solution, 50 mL preloaded syringe

9 B.2.2: Electrolyte with dextrose preparations

Combined sodium chloride and glucose solutions are indicated when there is water and sodium depletion. Various strengths are available and the selection among them is usually determined by the degree of sodium depletion.

Dextrose + sodium chloride

Preparations

Dextrose 5% + sodium chloride 0.9% intravenous infusion, 500 mL pack

Dextrose 5% + sodium chloride 0.45% intravenous infusion, 500 mL pack

Dextrose 10% + sodium chloride 0.18% intravenous infusion, 500 mL pack

Dextrose 4.3% + sodium chloride 0.18% intravenous infusion, 500 mL pack

9 B.2.3: Dextrose preparations

Glucose solution is used to provide energy and to help replenish water deficit. It should be given alone when there is no significant loss of electrolytes. Treatment of severe hypoglycaemia may require high concentration glucose solution.

Dehydration may result from an imbalance between water intake and water loss through the skin, lung and urinary excretion. Excessive loss of water without loss of electrolyte is uncommon, occurring in

fevers, hyperthyroidism and in uncommon water-losing renal states such as diabetes insipidus or hypercalcaemia.

The volume of glucose solution needed to correct the deficit varies with the severity of the disorder, but usually lies within the range of 2-6 litres of 5% concentration. As a source of energy, glucose is given in higher concentrations.

Dextrose

Indications: *see above*

Contra-indications: diabetes mellitus.

Caution and side-effects: hypertonic glucose injection may cause venous irritation and thrombophlebitis.

Dose: water replacement, 2-6 litres of 5% glucose. Energy source, 1-3 litres of 20-50% glucose solution.

Preparations

Dextrose 5% intravenous infusion, 500 mL pack

Dextrose 10% intravenous infusion, 500 mL pack

Dextrose 50% intravenous infusion, 500 mL pack

Dextrose 50% injection, 20-50 mL ampoule

9 B.2.4: Water for injection

Preparations

Water for injection, 5 mL ampoule

Water for injection, 100 mL bottle

9 B.3: Plasma and plasma substitutes

Concentrated Human Albumin

A solution containing protein derived from plasma, serum or normal placenta. The concentrated solution contains 20-25% protein; mainly albumin. It can be given without regard to the recipient's blood group.

Indications: severe hypovolaemia; plasma exchange.

Contra-indications: cardiac disease, severe anaemia.

Cautions: correct dehydration, avoid or administer very cautiously in patients with cardiac disease.

Side-effects: hypersensitivity reactions.

Dose: consult product literature.

Preparations

Human albumin concentrated solution 20%; 50 mL vial

Human plasma protein fraction

Indications: hypovolaemia due to burns, severe infections, and as protein replacement in hypoproteinaemia.

Contra-indications: hypersensitivity to albumin; severe anaemia, cardiac or circulatory disease.

Cautions: avoid rapid infusion; renal insufficiency.

Side-effects: hypersensitivity reactions.

9: Nutrition and blood

Dose: consult product literature.

Preparations

Human plasma protein fraction solution 5%, 50 mL vial

Human plasma protein fraction solution 5%, 250 mL vial

Gelatin (succinylated gelatin or polygeline)

Indications: low blood volume.

Cautions: used as immediate short-term measure to treat haemorrhage until blood is available. Rarely needed when hypovolaemia is due to water and sodium depletion. Avoid in cardiac disease.

Side-effects: hypersensitivity reactions.

Dose: consult product literature.

Preparations

Plasma volume replacement gelatin intravenous solution (succinylated gelatin) 3.5-4%, 500 mL bag

Hetastarch in sodium chloride solution

Indications: low blood volume.

Contra-indications: *see* gelatin above

Cautions: *see* gelatin above; children.

Side-effects: hypersensitivity reactions.

Dose: consult product literature.

Preparations

Hetastarch (average mol. weight 200,000) intravenous infusion, 6% in sodium chloride 0.9% solution, 500 mL bottle

9 C: Intravenous nutrition

Parenteral nutrition is indicated in malnourished patients who are unable to eat or absorb food, in comatose patients when tube feeding is not possible and other conditions when oral food intake is either impossible or hazardous. This may be in addition to oral or tube feeding and hence is called **supplementary parenteral nutrition** or may be the sole source of nutrition and then it is **total parenteral nutrition (TPN)**. The nutrients solution should include amino acids for protein synthesis, glucose and lipids for energy supply as well as vitamins, trace elements and electrolytes.

The nutrient preparation is made according to the individual's amino acid and energy requirements and should be freshly prepared by well trained personnel using aseptic techniques. The contents of the nutrient solution may vary in various clinical conditions such as diabetes, renal and hepatic failure, and electrolyte imbalance.

9 C.1: Electrolyte containing preparations

Amino acids + electrolytes

Amino acids + electrolyte + carbohydrate

10 mL ampoule containing vitamin A, D, E and K

Electrolyte + trace elements

Consult manufacturer's notes for contents and dose calculation.

Vitamin B complex + vitamin C (Restricted)

Consult manufacturers notes for contents and dose calculation.

9 C.2: Amino acid preparations

Essential amino acids plain

Essential amino acids + carbohydrate

Glutamine

Consult manufacturer's notes for contents and dose calculation.

Preparations

Glutamine injection, 200 mg inj.

9 C.3: Fat preparations

Fractionated soya oil 100 g + glycerol 22g to give energy of 4600 kJ/litre

Fractionated soya oil 300 g + glycerol 16.7 g to give energy of 12600 kJ/litre

Consult manufacturer's notes for contents and dose calculation.

9 C.4: Miscellaneous preparations

Fat-soluble vitamins in soya oil emulsion for infants

9 D: Oral nutrition

A special diet may be needed in certain clinical conditions. Foods are prepared for special diet to help eliminate or add certain common constituents of the complete food elements.

Enteral nutrition may, however, be needed in special cases where extra calories, protein, other nutrients and vitamins are given to supplement normal diet. There are many formulations of nutritionally complete foods available; selecting a preparation is determined by the patient's need and the contents of the preparation.

9 D.1: Carbohydrate

Glucose powder

Used mainly for performance of the Oral Glucose Tolerance Test (OGTT).

This usually involves giving 75g of anhydrous glucose by mouth to the fasting patient and measuring the blood glucose concentration at appropriate intervals. The glucose

9: Nutrition and blood

should be given with at least 300 mL fluid.

Note:

Anhydrous glucose powder 75g is equivalent to glucose monohydrate 82.5g

Glucose polymer powder

Indicated for malnutrition and malabsorption states or other conditions requiring fortification with a high or readily available carbohydrate supplement.

Preparation

Glucose polymer powder; 350 g/can (providing 380 kcalori/100 g of powder)

9 D.2: Miscellaneous

Medium chain triglycerides oil (CDL)

Sodium benzoate tablets, 500 mg

9 D.3: Special feeding

Protein + carbohydrate + fat + vitamins + minerals (energy 1674kJ)

Indicated as a sole source of nutrition or as nutritional supplement for patients with short-bowel syndrome, intractable malabsorption, following total gastrectomy. Available in liquid and powder forms.

9 E: Minerals

9 E.1: Calcium and magnesium

9 E.1.1: Calcium supplement

The requirement for calcium varies and is relatively greater in childhood, pregnancy, and lactation, due to increased demands, and in old age due to decreased absorption. In osteoporosis an increase in calcium daily intake would reduce the rate of bone loss. Calcium supplement are usually orally given.

In hypocalcaemic tetany parenteral calcium is required. Calcium injections may also be needed in treatment of hyperkalaemia and cardiac resuscitation.

Calcium salts

Indications: calcium deficiency.

Contra-indications: hypercalcaemia; hypercalciuria.

Cautions: renal impairment.

Side-effects: mild gastro-intestinal disturbances; bradycardia, arrhythmias.

Dose: orally, a daily supplement of as much as 40mmol in divided doses.

By slow intravenous injection, acute hypocalcaemia, calcium gluconate 1-2g (2.25-4.5mmol of Ca²⁺).

Preparations

Calcium chloride injection, 10% solution, 10 mL ampoule (27.3 mg calcium or 680 micromol Ca^{2+} /mL)
 Calcium gluconate injection, 10% solution, 10 mL ampoule (8.9 mg calcium or 220 micromol Ca^{2+} /mL)
 Calcium carbonate tablets, 500 mg tab.
 Calcium carbonate + glycine tablets, 420 mg + 180 mg tab. (4.2 mmol Ca^{2+})
 Calcium syrup, 100 mg / 5 ml

9 E.1.2: Calcium removal

Treatment of hypercalcaemia should be directed to correct the prime cause if possible, in addition to rehydration and reduction in dietary intake of calcium. Plasma calcium can be lowered by various drugs; phosphates effectively lower plasma calcium level by enhancing calcium urinary excretion. Disodium or trisodium edetate chelates calcium ions and lowers plasma calcium level.
 Slow administration rate of phosphates is important to avoid rapid lowering of calcium level and the development of hypocalcaemia.

Potassium phosphate

Indications: hypercalcaemia.

Cautions: hyperkalaemia, renal impairment.

Side-effects: diarrhoea; magnesium deficiency.

Preparation

Potassium phosphate injection, 5-10 mL vial

Cinacalcet (Restricted)

Indications: Secondary hyperparathyroidism in patients with end-stage renal disease on dialysis. Treatment of hypercalcaemia in parathyroid carcinoma. Primary hyperparathyroidism in patients where parathyroidectomy is inappropriate.

Cautions: Treatment should not be initiated in patients with hypocalcaemia.

Side-effects: Anorexia; asthenia; dizziness; myalgia; nausea; paraesthesia; rash; reduced testosterone concentrations; vomiting.

Dose: Secondary hyperparathyroidism initially 30 mg once daily, dose to be adjusted every 2-4 weeks; maximum 180 mg per day.

Hypercalcaemia and primary hyperparathyroidism. Initially 30 mg twice daily (max. per dose 90 mg 4 times a day), dose to be adjusted every 2-4 weeks according to response.

Preparations

Cinacalcet tablets, 30 mg tab.

9 E.1.3: Magnesium

Magnesium sulphate

Indications: hypomagnesaemia; prevention of seizure in severe pre-eclampsia or eclampsia.

Cautions: renal impairment; initial administration should be slow.

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Side-effects: generally associated with hypermagnesaemia, nausea, vomiting, thirst, flushing of skin, loss of tendon reflexes, arrhythmias, hypotension.

Dose: prevention of recurrent seizure, initially by intravenous injection 4g over 5-10 minutes, followed by intravenous infusion at a rate of 1 g every hour for 24 hours after the last seizure. Recurrent seizure may require intravenous bolus of additional 2 g.

Preparations

Magnesium sulphate tablets, 100 mg tab. (CDL)

Magnesium sulphate injection, 50% (500 mg/mL), 5 mL ampoule

9 E.2. Phosphorus

9 E.2.1 Phosphate supplements

Supplement of phosphate is required in a minority of patients with hypophosphataemic, vitamin D resistant rickets. Diarrhoea is a common side effect that reflects overdosing and indicates a reduction in dosage.

Sodium acid phosphate (CDL)

Preparations

Phosphate effervescent tablets containing, anhydrous sodium acid phosphate 1.936 g equivalent to 500 mg phosphorus

9 E.2.2 Phosphate binding agents

Sevelamer

Indications: hyperphosphataemia in patients on haemodialysis or peritoneal dialysis.

Contraindications: bowel obstruction.

Cautions: pregnancy, breast-feeding, gastro-intestinal disorders.

Side-effects: gastro-intestinal disturbances; hypotension, hypertension; headache; pruritus and rash; intestinal obstruction.

Dose: adult over 18 years, initially 2.4–4.8 g daily in 3 divided doses with meals, then adjusted according to plasma-phosphate concentration (usual dose range 2.4–12 g daily in 3 divided doses).

Preparations

Sevelamer tablets, 800 mg, tab.

Sevelamer powder, 800 mg per sachet

9 E.3. Zinc

Zinc (Restricted)

Indications: Zinc deficiency

Side-effects: gastrointestinal pain, nausea, vomiting and diarrhoea.

Dose: The dose beyond the RDA is not established. Dietary supplements contain 5–25 mg (elemental zinc) per daily dose.

Preparations

Zinc syrup, 20 mg/ 5 ml

9 F: Vitamins

Vitamins and minerals are an essential part of a healthy diet. If a person is eating a variety of foods, the likelihood of developing a deficiency of these nutrients is very small.

Vitamins should only be used to treat or prevent a specific deficiency or to supplement otherwise inadequate diet.

People who follow strict diet may not get enough of certain vitamins or minerals. For example, strict vegetarian may develop vitamin B₁₂ deficiency as this vitamin is only found in animal products. On the other hand consuming large doses of vitamin and mineral supplements, without medical supervision, may lead to toxic effects. Vitamins are in general classified into water-soluble vitamins (B group and vitamin C) and fat-soluble vitamins (A, D, E and K).

9 F.1: Water soluble vitamins

9 F.1.1: Vitamin B group

The vitamin B group or sometimes called B complex includes vitamins that are essential for certain biological reaction in the body. Important members of this group are: thiamine (B₁), riboflavin (B₂), pyridoxine (B₆), and nicotinamide (B₇). Folic acids and cyanocobalamin are

mentioned in sec 9 A.2. Others like biotin, choline, aminobenzoic acid, inositol, pantothenic acid do not seem to have any major importance.

Thiamine (B₁) deficiency is manifested as anorexia, muscle cramp and in severe cases (beriberi) by neuropathy and cardiac failure. Alcoholics, due to deficient diet and the increased requirement for alcohol metabolism, manifest severe deficiency of thiamine and the development of neuropathy and beriberi. Treatment is initiated with parenteral administration of thiamine followed by oral administration over a long period.

Thiamine hydrochloride

Indications: deficiency of vitamin (B₁).

Cautions: anaphylaxis may follow injection.

Dose: for mild to moderate deficiency, orally 10-25 mg daily. Severe deficiency 200-300 mg daily.

Preparations

Thiamine hydrochloride tablets/capsules, 50 mg tab/cap.

Thiamine hydrochloride tablets, 100 mg tab.

Thiamine hydrochloride injection, 100 mg ampoule

Pyridoxine (B₆) isolated deficiency is rare. It could occur during therapy with isoniazid and is characterized by peripheral neuritis. It has been applied in the treatment of

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some metabolic disorders such as homocystinuria.

Pyridoxine has been widely applied, though with a doubtful benefit, in the management of nausea and vomiting occurring during pregnancy.

Pyridoxine Hydrochloride

Indications: vitamin B6 deficiency; nausea and vomiting in pregnancy (*see* notes above), premenstrual syndrome, with isoniazid to prevent peripheral neuritis.

Cautions: penicillamine antagonises pyridoxine effects and may precipitate clinical deficiency state.

Dose: deficiency states, 20-50 mg up to 3 times daily.

Isoniazid neuropathy, prophylaxis 10-20 mg daily; therapeutics 50 mg 3 times daily.

Nausea and vomiting during pregnancy (*see* notes above), 50 mg at bed time.

Preparations

Pyridoxine hydrochloride tablets, 50 mg tab.

Pyridoxine hydrochloride injection, 100 mg ampoule (**Restricted**)

Biotin (vitamin B7/ vitamin H)

daily requirement is estimated to be 100-200 micrograms. Balanced diet provides 200-300 micrograms daily. However, part of the biotin synthesized by intestinal flora is available for absorption. Large dose of biotin (5-10 mg daily) are administered to babies with infantile seborrhoea and to individuals

with genetic alteration of biotin-dependent enzymes. In adults it may be used as an adjuvant therapy in some cases of alopecia.

Biotin

Indications and dose: *see* notes above

Preparations

Biotin tablets, 5 mg tab.

Vitamin B complex is a combination of all vitamins of the B group. Oral as well as parenteral preparations are available with various strengths of each individual vitamin.

Vitamin B complex and vitamin C injection (Restricted)

Preparations

Vitamin B complex and vitamin C injection containing, biotin 60 microgram, B₁₂ 5 microgram, B₁ 3.2 mg, B₆ 4 mg, vitamin C 100 mg, nicotinamide 40 mg, folic acid 0.4 mg, pantothenic acid 15 mg/ampoule

9 F.1.2: Vitamin C

Vitamin C is essential in the synthesis of connective tissues. Severe deficiency will lead to scurvy, which is rarely seen these days. The daily requirement for vitamin C is about 30-60 mg. Balanced diet usually provides the body with its need of the vitamin.

People, elderly in particular, who have been kept on very poor or restricted diet for a long time, may develop scurvy. Infants fed on formula that lacks vitamin C should be supplemented with vitamin C. Treatment of scurvy is achieved with oral or parenteral vitamin C doses of 500 mg daily in adults and 50-100 mg daily in infants and children, plus a balanced diet. Vitamin C has been indicated for a variety of clinical conditions with controversial benefits.

Ascorbic acid (vitamin C)

Indications and dose: *see* notes above

Preparations

Ascorbic acid tablets, 50 mg tab.

Ascorbic acid tablets, 100 mg tab.

50,000 units daily for two weeks and the 10,000 –20,000 units daily for 2-3 months.

Overdosage resulting from chronic un-recommended use may lead to hypervitaminosis A which is manifested clinically by dryness of the skin, brittle nails, hair loss, cheilosis, hyperostosis and bone pains, weight loss, hepatosplenomegaly, and benign intracranial hypertension.

Vitamin A should be avoided during pregnancy unless otherwise indicated and should be strictly supervised.

Vitamin A

Indications and side-effects and cautions: *see* notes above

Preparations

Vitamin A capsules, 50,000 units cap.

Vitamin A capsules, 100,000 units cap.

Vitamin A capsules, 200,000 units cap.

9 F.2: Fat soluble vitamins

9 F.2.1: Vitamin A

Requirement for vitamin A is mainly derived from dietary sources. Vitamin A is essential for retinal function and epithelial cell structure and function. Deficiency results in development of night blindness as an early sign, dry skin and hyperkeratosis progressing to xerophthalmia and keratomalacia. Mild deficiency can be treated with 30,000 to 50,000 units daily, while severe cases need higher doses up to 100,000 units for 3 days and then

9 F.2.2: Vitamin D

Vitamin D is the term used to describe a range of compounds used for the prevention or curing of rickets. Alfalcidol and calcitriol are new derivatives that are of a short duration of action. This makes them safer over chronic use since the resulting hypercalcaemia is short lived and easily treated.

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Vitamin D requires hydroxylation in the kidney, therefore the new hydroxylated derivatives alfacalcidol and calcitriol can be safely used in patients with renal impairment.

Alfacalcidol

Indications: vitamin D deficiency.

Contra-indications: hypercalcaemia, metastatic calcification.

Cautions: accurate dosing must be observed in infants; monitor calcium level in high doses of Vitamin D in adults and in renal impairment.

Side-effects: in overdose: anorexia, lassitude, nausea and vomiting, diarrhoea, weight loss.

Dose: orally or intravenously, adults and child over 20 kg, initially 1 microgram daily which should be reduced in elderly. Maintenance usually 0.25-1 microgram daily. Neonates, premature infants and child under 20 kg, 50-100 nanograms/kg daily.

Preparations

Alfacalcidol oral drops, 2 micrograms/mL drops, 20 mL/bottle

Alfacalcidol capsules, 0.25 microgram cap.

Alfacalcidol capsules, 1 microgram cap.

Alfacalcidol injection, 2 micrograms/mL, 1 mL ampoule

Calcitriol

Indication, cautions and side-effects: *see* alfacalcidol above

Dose: initially 250 nanograms (0.25 micrograms) daily increased if necessary to 0.5-1 microgram daily.

Preparations

Calcitriol tablets, 250 nanograms (0.25 microgram) tab.

Colecalciferol (Restricted)

Indications: Prevention and treatment of vitamin D deficiency

Contra-indications: Hypercalcaemia; metastatic calcification

Cautions: Take care to ensure correct dose in infants

Side-effects: Symptoms of overdose include anorexia, lassitude, nausea and vomiting, diarrhoea, constipation, weight loss, polyuria, sweating, headache, thirst, vertigo, and raised concentrations of calcium and phosphate in plasma and urine.

Dose: Prevention of vitamin D deficiency 400 units daily.

Treatment of vitamin D deficiency 800 units daily, higher doses may be necessary for severe deficiency.

Preparations

Colecalciferol capsule, 50,000 IU cap.

Colecalciferol drops 400 IU / mL

Colecalciferol drops 10,000 IU / mL

Ministry of Health policy is that only one of the above vitamin D preparations will be purchased and made available for use depending on cost

Calcium with vitamin D

Preparations

Calcium lactate or carbonate + vitamin D tablets

Preparations

Alpha tocopheryl acetate suspension, 500 mg/5 mL, 100 mL bottle

9 F.2.3 Vitamin E

The daily requirement of vitamin E has not been well defined but is probably about 3 to 15 mg daily. There is little evidence that oral supplements of vitamin E are essential in adults, even where there is fat malabsorption secondary to cholestasis. In young children with congenital cholestasis, abnormally low vitamin E concentrations may be found in association with neuromuscular abnormalities, which usually respond only to the parenteral administration of vitamin E. Vitamin E has been tried for various other conditions but there is little scientific evidence of its value.

Alpha tocopheryl acetate (Restricted)

Indications: see notes above; vitamin E deficiency, malabsorption in cystic fibrosis.

Cautions: predisposition to thrombosis; increased risk of necrotising enterocolitis in preterm neonates, pregnancy, breast-feeding.

Side-effects: diarrhoea and abdominal pain in high doses.

Dose: Malabsorption in cystic fibrosis, 100–200 mg daily; child 1 month–1 year 50 mg daily; 1–12 years, 100 mg daily.

9 F.3: Multivitamin preparations

It has been publicly promoted that the regular use of multivitamin preparations is beneficial to health, provides energy and protects against disease. This belief has no scientific validity, and of no therapeutic benefit in well fed people. Vitamins should only be prescribed to treat a specific vitamin deficiency or for prophylaxis in certain clinical states.

The overuse of multivitamin preparations may damage health and cause serious adverse consequences in particular with those preparations containing high concentration of vitamin A and D.

Multivitamin preparations

Preparations

Multivitamin syrup; 90 - 120 mL/bottle

High potency Multivitamins tablet and suspension (Restricted)

9 G: Drugs used for metabolic disease

Breakdown of protein produces nitrogen compound such as ammonia. Hyperammonaemia may be the result of overloading with protein in total parenteral nutrition.

Carnitine (CDL)

(carnitine is biosynthesized primarily in the liver and kidneys from the aminoacids and plays an important role in fatty acids metabolism)

Indications: carnitine deficiency due to inborn errors of metabolism or of secondary deficiency in haemodialysis patients.

Cautions: diabetes mellitus, renal impairment, pregnancy, breast feeding, monitoring of free and acyl carnitine in blood and urine recommended.

Side-effects: gastrointestinal disturbances, fishy body odour.

Dose: in primary deficiency, intravenously over 2-3 minutes, up to 100 mg/kg daily in 3-4 divided doses. In secondary deficiency, intravenously over 2-3 minutes, 20 mg/kg after each session of dialysis.

Preparations

Carnitine injection, 1 g vial

Sodium benzoate and sodium phenylacetate (Controlled)

are used orally or parenterally to treat hyperammonaemia (see sec 9 D.3)

Preparations

Sodium benzoate injection, 1 g/5 mL ampoule

sodium phenylacetate injection, 10% ampoule

Sodium phenylacetate and sodium benzoate injection, 100 mg/mL of each in vials for injection.

Sodium Phenylbutyrate (CDL)

Indications: used singly or in combination with sodium benzoate in the management of urea cycle disorders e.g. hyperammonaemia.

Contra-indications: pregnancy, breast feeding.

Cautions: hepatic and renal failure, congestive heart failure or any clinical conditions involving sodium retention with oedema.

Side-effects: menstrual cycle irregularities, body odour, decreased appetite, gastrointestinal and taste disturbances.

Dose: in acute hyperammonaemia, by intravenous infusion 250 mg/kg over 90 minutes followed by 20 mg/kg/hour adjusted according to response.

Preparations

Sodium Phenylbutyrate injection, 1g ampoule

Sodium phenylbutyrate tablets, 500 mg tab.

Nitisinone (Restricted)

Indications: Hereditary tyrosinaemia type I (in combination with dietary restriction of tyrosine and phenylalanine) (specialist use only)

Side-effects: Conjunctivitis; corneal opacity; eye pain; granulocytopenia; keratitis; leucopenia; photophobia; thrombocytopenia; blepharitis; erythematous rash; exfoliative dermatitis; leucocytosis; pruritus

Dose: Initially 500 micrograms/kg twice daily, adjusted according to

response; maximum 2 mg/kg per day.

Preparations

Nitisinone capsules 2 mg cap.

10: Musculoskeletal and joint diseases

Section 10: Musculoskeletal and joint diseases

- Drugs used in rheumatic diseases and gout
- Drugs used in neuromuscular disorders

10 A: Drugs used in rheumatic diseases and gout

10 A.1: Non-steroidal anti-inflammatory drugs (NSAIDs)

All NSAIDs are antipyretic, analgesic and anti-inflammatory, but there are important differences in their activities. When employed as **analgesics** these drugs are effective only against pain of low to moderate intensity. Chronic postoperative pain or pain arising from inflammation is particularly well controlled by NSAIDs, whereas pain arising from hollow viscera is not relieved.

As **antipyretics**, NSAIDs reduce body temperature in febrile states. However, some NSAIDs are not suitable for either routine or prolonged use.

NSAIDs find their main clinical application as **anti-inflammatory agents** in the treatment of musculoskeletal disorders such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. They only provide symptomatic relief of pain and inflammation associated with the disease without actively inter-

fering in the progression of the tissue damage associated with severe episodes of the disease.

NSAIDs have also been successfully used in the closure of the ductus arteriosus in neonates when it has remained patent. Dysmenorrhoea, which might be caused by excessive release of prostaglandins by the endometrium, can be relieved by NSAIDs.

The **choice** among NSAIDs for an antipyretic or analgesic agent is seldom a problem. The choice of a NSAID for arthritides is largely empirical as there are individual patient variations in tolerance and response. The majority of patients respond to any NSAID, those who do not respond to one may well respond to another.

The main differences between NSAIDs are in the incidence and type of side-effects. Prescribers are advised always to weigh the efficacy of NSAIDs therapy against possible side-effects.

NSAIDs vary in their selectivity to inhibit the different types of cyclooxygenase enzymes (COX); the nonselective inhibition of the enzymes is thought to be the reason for the high incidences of GI adverse effects. Selective cyclooxygenase 2 (COX-2) enzyme inhibitors are claimed to be free from GI side-effects, a claim which needs to be further ratified.

In principle, one week is needed to show a maximal analgesic effect; while anti-inflammatory effect might not be seen before 3 weeks or

10: Musculoskeletal and joint diseases

more. If appropriate responses are not obtained within these times another NSAID should be tried.

The **side-effects** of NSAIDs vary in severity and frequency. GI disturbances, nausea, vomiting, occasional bleeding and ulceration; dyspepsia can be minimized by taking the drug with food and or milk. Other side-effects include hypersensitivity reactions (particularly angioedema, rashes and bronchospasm), headache, dizziness, vertigo, hearing disturbances such as tinnitus

Cautions and contra-indications for the use of NSAIDs include:

- *do not use more than one NSAID at a time*
- *NSAIDs with lower risk of GI toxicity (e.g. Ibuprofen) should be tried first in the lowest recommended dose.*
- *contraindicated in patients with peptic ulcer.*
- *should be used with caution in patients with infection since symptoms such as fever and inflammation may be masked.*
- *should be used with great caution in patients with asthma and allergic disorders. They are contraindicated in patients with a history of hypersensitivity reaction to such drugs.*
- *should be cautiously administered to patients with haemor-*

rhagic disorders, hypertension, impaired renal, hepatic and cardiac functions.

- *elderly patients may require dose reduction.*
- *regular use of NSAIDs during the third trimester of pregnancy may result in early closure of foetal ductus arteriosus in utero, and possibly in persistent pulmonary hypertension of the new born.*
- *There are concerns about the cardiovascular safety of selective COX-2 inhibitors (all are now withdrawn from use in Oman)*

Ibuprofen

Indications: pain and inflammation in rheumatic disease and other musculoskeletal disorders (anti-inflammatory effects are weaker); mild to moderate pain including dysmenorrhoea; post-operative analgesia, fever and pain in children.

Contra-indications: *see notes above*; not recommended for children under 7 kg.

Cautions: *see notes above*. Avoid concurrent use in patients on regular low dose aspirin.

Side-effects: fewer side-effects than other NSAIDs. *See notes above.*

Dose: 1.2-1.6 g daily dose in 3-4 divided doses preferably after food with adequate quantity of water. Maintenance, 0.8-1.2 g daily in divided doses (maximum 2.4 g daily).

10: Musculoskeletal and joint diseases

Child 20 mg/kg daily in divided doses. (Increase in juvenile arthritis up to 40 mg/kg daily).

Preparations

Ibuprofen tablets, 400 mg tab.

Ibuprofen syrup, 100 mg/5 mL

syrup; 100 mL/bottle (*Restricted*)

Ibuprofen injection, 10 mg/mL (*Restricted*)

Celecoxib (Restricted)

Indications: Pain and inflammation in osteoarthritis. Pain and inflammation in rheumatoid arthritis. Ankylosing spondylitis

Contra-indications: Active gastrointestinal bleeding; active gastrointestinal ulceration; cerebrovascular disease; inflammatory bowel disease; ischaemic heart disease; mild to severe heart failure; peripheral arterial disease

Cautions: Allergic disorders; cardiac impairment (NSAIDs may impair renal function); coagulation defects; connective-tissue disorders; Crohn's disease (may be exacerbated); elderly (risk of serious side-effects and fatalities); history of cardiac failure; hypertension; left ventricular dysfunction; oedema; risk factors for cardiovascular events; ulcerative colitis (may be exacerbated).

Side-effects: Dyspnoea; influenza-like symptoms; cerebral infarction; fatigue; muscle cramps; palpitation; paraesthesia; stomatitis; alopecia; alveolitis; aseptic meningitis (patients with connective-tissue

disorders such as systemic lupus erythematosus may be especially susceptible); hepatic damage; interstitial fibrosis associated with NSAIDs can lead to renal failure; pancreatitis; papillary necrosis associated with NSAIDs can lead to renal failure; pulmonary eosinophilia; Stevens-Johnson syndrome; taste disturbance; toxic epidermal necrolysis; visual disturbances

Dose: Pain and inflammation in osteoarthritis 200 mg daily in 1–2 divided doses, then increased if necessary up to 200 mg twice daily, discontinue if no improvement after 2 weeks on maximum dose.

Pain and inflammation in rheumatoid arthritis 100 mg twice daily, then increased if necessary to 200 mg twice daily, discontinue if no improvement after 2 weeks on maximum dose.

Ankylosing spondylitis 200 mg daily in 1–2 divided doses, then increased if necessary up to 400 mg daily in 1–2 divided doses, discontinue if no improvement after 2 weeks on maximum dose

Preparations

Celecoxib tablets, 200 mg tab.

Diclofenac

Indications: pain and inflammation in rheumatic disease, other musculoskeletal disorders; post-operative pain; acute gout.

Contra-indications: *see* notes above; intravenous administration in patients on other NSAIDs or anticoagulants; history of confirmed

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or suspected cerebrovascular bleeding; history of asthma.

Cautions: *see* notes above; porphyria.

Side-effects: *see* notes above; rectal irritation is common with suppositories.

Dose: Maximum daily dose by any route 150 mg.

Orally, 75-150 mg daily in divided doses after meal with adequate quantity of water.

By deep intramuscular injection, for acute conditions, ureteric colic and post-operative pain, 75 mg once daily (maximum twice daily in severe case) for two days.

By intravenous infusion, in hospital settings only, 75 mg may be repeated after 4-6 hour, maximum 2 days.

Preparations

Diclofenac sodium tablets, 50 mg tab.

Diclofenac sodium retard tablets, 100 mg tab. (*Restricted*)

Diclofenac sodium injection, 25 mg/mL, 3 mL ampoule (*Restricted*)

Diclofenac sodium suppositories, 25 mg tab. (*Restricted*)

Diclofenac sodium suppositories, 100 mg tab. (*Restricted*)

Etoricoxib (*Restricted*)

Indications: Pain and inflammation in osteoarthritis. Pain and inflammation in rheumatoid arthritis. Ankylosing spondylitis. Acute gout

Contra-indications: Active gastrointestinal bleeding; active gastro-

intestinal ulceration; cerebrovascular disease; inflammatory bowel disease; ischaemic heart disease; mild to severe heart failure; peripheral arterial disease; uncontrolled hypertension (persistently above 140/90 mmHg).

Cautions: Allergic disorders; cardiac impairment (NSAIDs may impair renal function); coagulation defects; connective-tissue disorders; Crohn's disease (may be exacerbated); dehydration; history of cardiac failure; hypertension; left ventricular dysfunction; oedema; risk factors for cardiovascular events; ulcerative colitis (may be exacerbated), elderly (risk of serious side-effects and fatalities).

Side-effects: Ecchymosis; fatigue; influenza-like symptoms; palpitation.

Dose: Pain and inflammation in osteoarthritis. 30 mg once daily, then increased if necessary to 60 mg once daily.

Pain and inflammation in rheumatoid arthritis/ Ankylosing spondylitis 90 mg once daily.

Acute gout 120 mg once daily for maximum 8 days.

Preparations

Etoricoxib tablets, 90 mg tab.

Etoricoxib tablets 120 mg tab.

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Indometacin (Indomethacin) (Restricted)

Indications: indications are limited because of high incidences of adverse effects; prevention of heterotopic (ectopic) ossification in hip replacement.

Contra-indications: *see* notes above.

Cautions: *see* notes above; epilepsy, Parkinsonism, psychiatric disturbances; regularly examine the eye on chronic use, avoid during infection as it might mask the symptoms.

Side-effects: *see* notes above; more severe GI disturbances, morning headache, dizziness.

Dose: 75-150 mg daily after meal in 1-2 doses.

Preparations

Indometacin capsule, 75 mg cap.

Mefenamic acid

Indications: mild to moderate pain; rheumatoid arthritis, osteoarthritis; dysmenorrhoea and menorrhagia.

Contra-indications: *see* notes above; inflammatory bowel disease.

Cautions: *see* notes above; stop treatment if diarrhoea or rash develops; use for short course therapy (not exceeding 7 days).

Side-effects: *see* notes above; diarrhoea and rash; haemolytic anaemia; thrombocytopenia; convulsions in overdose.

Dose: 500 mg 3 times daily after food with adequate quantity of water.

Child, for a short course therapy, 25 mg /kg daily. Not recommended under 6 months.

Preparations

Mefenamic acid capsules/tablets, 500 mg cap/tab.

Naproxen (Restricted)

Indications: Pain and inflammation in rheumatic disease. Pain and inflammation in musculoskeletal disorders. Dysmenorrhoea. Acute gout

Contra-indications: Active gastrointestinal bleeding; active gastrointestinal ulceration; history of gastrointestinal bleeding related to previous NSAID therapy; history of gastrointestinal perforation related to previous NSAID therapy; history of recurrent gastrointestinal haemorrhage (two or more distinct episodes); history of recurrent gastrointestinal ulceration (two or more distinct episodes); severe heart failure.

Cautions: Allergic disorders; cardiac impairment (NSAIDs may impair renal function); cerebrovascular disease; coagulation defects; connective-tissue disorders; Crohn's disease (may be exacerbated); elderly (risk of serious side-effects and fatalities); heart failure; ischaemic heart disease; peripheral arterial disease; risk factors for cardiovascular events; ulcerative colitis (may be exacerbated); uncontrolled hypertension.

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Side-effects: Alveolitis; aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible); hepatic damage; interstitial fibrosis associated with NSAIDs can lead to renal failure; pancreatitis; papillary necrosis associated with NSAIDs can lead to renal failure; pulmonary eosinophilia; Stevens-Johnson syndrome; toxic epidermal necrolysis; visual disturbances.

Dose: Pain and inflammation in rheumatic disease 0.5–1 g daily in 1–2 divided doses.

Pain and inflammation in musculoskeletal disorders/ Dysmenorrhoea initially 500 mg, then 250 mg every 6–8 hours as required, maximum dose after the first day 1.25 g daily. Acute gout Initially 750 mg, then 250 mg every 8 hours until attack has passed.

Preparations

Naproxen tablets, 250 mg tab.

Tenoxicam (Restricted)

Indications: pain and inflammation in rheumatoid arthritis and other musculoskeletal disorders.

Contra-indications: see notes above

Cautions: see notes above

Side-effects: see notes above

Dose: 20 mg daily in rheumatic disease. In acute conditions, 20 mg daily for 7 days (maximum 14 days).

Child, not recommended.

Preparations

Tenoxicam tablets, 20 mg tab.

10 A.2: Drugs which suppress the rheumatic disease process

A group of drugs including, penicillamine, gold, antimalarials, cytokine modulators and sulphasalazine may suppress the disease process in rheumatoid arthritis. They are known as disease modifying antirheumatic drugs (DMARDs). Unlike NSAIDs, these drugs need a longer time to show a therapeutic effect; 4–6 months may elapse before a full response is achieved.

Penicillamine is a chelating agent that has a similar action to gold in severe rheumatoid arthritis but is better tolerated. Treatment should be discontinued if there is no benefit within one year. Improvement is not expected before 6–12 weeks of treatment. If remission has been sustained for 6 months, reduction of dose by 125–250 mg every 12 weeks may be initiated.

Penicillamine has other therapeutic uses in Wilson's disease, treatment of copper and lead poisoning and in cystinuria.

Sulfasalazine is beneficial in suppressing the inflammatory process of rheumatoid arthritis. Side-effects such as gastrointestinal disturbances are frequent. Blood count should be closely monitored.

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Adalimumab

Indications: moderately to severely active rheumatoid arthritis, active psoriatic arthritis and ankylosing spondylitis in combination with methotrexate in patients who have had an inadequate response to one or more diseases modifying

Contra-indications: active infection, pregnancy and breast-feeding.

Cautions: congestive heart failure, history of active or chronic infections (tuberculosis should be excluded), demyelinating CNS disorders, renal and hepatic impairment.

Side-effects: diarrhoea, dyspnoea, chest pain, hypertension, mouth ulceration, taste disturbances, drowsiness, menorrhagia, haematuria, proteinuria.

Dose: by subcutaneous injection, 40 mg on alternate weeks; if necessary increased to 40 mg weekly in patients receiving adalimumab alone, discontinue if no response after 12 weeks.

Preparations

Adalimumab injection, 40 mg in prefilled syringe

Etanercept

Indications: moderately to severely active rheumatoid arthritis, active psoriatic arthritis and ankylosing spondylitis in combination with methotrexate or used alone in patients who have had an inadequate response to one or more dis-

eases modifying antirheumatic arthritis, poly articular-course juvenile idiopathic arthritis, also in psoriasis.

Contra-indications: active infection, pregnancy and breast-feeding, avoid injections containing benzyl alcohol in neonates

Cautions: congestive heart failure, patients with a significant exposure to varicella virus, history of active or chronic infections (tuberculosis should be excluded), demyelinating CNS disorders, blood disorders.

Side-effects: infections including tuberculosis and reactivation of hepatitis B, nausea, worsening of heart failure, hypersensitivity reactions, blood disorders, depression, diabetes, ulcerative colitis, malignancy, injection site reactions.

Dose: by subcutaneous injection, 25 mg twice weekly or 50 mg once weekly, child (4-17 years) with poly articular-course juvenile idiopathic arthritis, 400 micrograms/kg; maximum 25 mg twice weekly

Preparations

Etanercept injection, powder for reconstitution, 25 mg vial

Etanercept injection, 50 mg in prefilled syringe

Hydroxychloroquine

Indications: rheumatoid arthritis, discoid and systemic lupus erythematosus, malaria.

Contra-indications: long-term therapy in children and pregnant mothers, hypersensitivity to the drug.

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Cautions: ophthalmologic examinations are recommended (irreversible retinal damage has been observed in some patients who had received long-term or high-dosage), hepatic and renal impairment, G6PD, pregnancy, breast-feeding, elderly, dangerous in overdose (doses above 8 g are usually fatal).

Side-effects: gastrointestinal complaints, headache, retinopathy, nystagmus, bleaching of hair, alopecia, pruritus, tinnitus, nystagmus, nerve deafness.

Dose: orally, initially 400 mg daily in divided doses, maintenance 200-400 mg daily; maximum 6.5 mg/kg daily (but not exceeding 400 mg daily).

Preparations

Hydroxychloroquine tablets, 200 mg tab.

Infliximab

Indications: moderately to severely active rheumatoid arthritis, active psoriatic arthritis and ankylosing spondylitis in combination with methotrexate or used alone in patients who have had an inadequate response to one or more diseases modifying antirheumatic arthritis, inflammatory bowel disease, also in psoriasis.

Contra-indications: active infection, pregnancy and breast-feeding.

Cautions: congestive heart failure, history of active or chronic infections (tuberculosis should be excluded), demyelinating CNS disorders, history of malignancy, history

of prolonged immunosuppressant or PUVA treatment in patient with psoriasis.

Side-effects: hypersensitivity reactions, diarrhoea, dyspnoea, dry skin, chest pain, cholecystitis, hypertension, oedema.

Dose: by intravenous infusion, in active rheumatoid arthritis, 3 mg/kg, repeated 2 weeks and six weeks after initial infusion, then every 8 weeks (discontinue if no response by 12 weeks), in active psoriatic arthritis and ankylosing spondylitis, increase the dose to 5 mg/kg with the same frequencies of infliximab in active rheumatoid arthritis.

Preparations

Infliximab injection, 100 mg vial

Leflunomide (Restricted)

Indications: Moderate to severe active rheumatoid arthritis. Active psoriatic arthritis.

Contra-indications: Serious infection; severe hypoproteinaemia; severe immunodeficiency.

Cautions: Anaemia (avoid if significant and due to causes other than rheumatoid arthritis); history of tuberculosis; impaired bone-marrow function (avoid if significant and due to causes other than rheumatoid arthritis); leucopenia (avoid if significant and due to causes other than rheumatoid arthritis); thrombocytopenia (avoid if significant and due to causes other than rheumatoid arthritis).

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Side-effects: Abdominal pain; alopecia; anorexia; asthenia; diarrhoea; dizziness; dry skin; headache; increased blood pressure; leucopenia; nausea; oral mucosal disorders; paraesthesia; pruritus; rash; tenosynovitis; vomiting

Dose: Moderate to severe active rheumatoid arthritis. Initially 100 mg once daily for 3 days, then reduced to 10–20 mg once daily.

Active psoriatic arthritis. Initially 100 mg once daily for 3 days, then reduced to 20 mg once daily.

Preparations

Leflunomide tablets, 20 mg tab.

Penicillamine (*Restricted*)

Indications: severe active rheumatoid arthritis; Wilson's disease; cystinuria; copper and lead poisoning.

Contra-indications: sensitivity to penicillamine, lupus erythematosus.

Cautions: *see* notes above; pregnancy and breast feeding; avoid concurrent use of other disease modifying antirheumatic drugs; watch carefully for the development of unusual side-effects during treatment.

Side-effects: nausea, vomiting, anorexia, taste disorders, myelosuppression, proteinuria, blood disorders.

Dose: severe active rheumatoid arthritis under strict specialist supervision. Adult, initially 125–250 mg daily before food for 1 month, in-

creased gradually at one month intervals by 125–250 mg. The dose should not exceed 1.5 g daily. Elderly, initially less than 125 mg daily increase gradually to a maximum maintenance dose of 1 g daily. Child, maintenance dose 15–20 mg / kg daily.

Preparations

Penicillamine tablets, 250 mg tab.

Sulfasalazine (*Sulphasalazine*)

Indications: active rheumatoid arthritis; ulcerative colitis, *see* sec 1D.3

Contra-indications, cautions and side-effects: *see* sec 1D.3

Dose: orally as enteric coated tablets, initially 500 mg daily increased by 500 mg at intervals of 1 week to a maximum of 2–3 g daily in divided doses.

Preparations

Sulfasalazine tablets, 500 mg tab.

Tocilizumab (*Restricted*)

Indications: Moderate to severe active rheumatoid arthritis (in combination with methotrexate or alone if methotrexate inappropriate).

Contra-indications: Do not initiate if absolute neutrophil count less than 2×10^9 /litre; severe active infection

Cautions: History of diverticulitis; history of intestinal ulceration; history of recurrent or chronic infection (interrupt treatment if serious infection occurs); low absolute neutrophil count; low platelet count;

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predisposition to infection (interrupt treatment if serious infection occurs)

Side-effects: Abdominal pain; antibody formation; dizziness; gastritis; headache; hypercholesterolaemia; hypersensitivity; hypertension; infection; leucopenia; mouth ulceration; neutropenia; peripheral oedema; pruritus; raised hepatic transaminases; rash; upper respiratory-tract infection

Dose: 8 mg/kg every 4 weeks (max. per dose 800 mg), for dose adjustments in patients with liver enzyme abnormalities, or low absolute neutrophil or platelet count, consult product literature.

Preparations

Tocilizumab injection 20 mg / ml, 10 ml vial

10 A. 3: Drugs used in the treatment of gout and hyperuricemia

Gout is an articular manifestation of hyperuricaemia. The acute attack is caused by deposition of urate crystals in the synovial fluids of the affected joint. This deposition will initiate inflammatory processes with phagocytosis of the urate crystals; these actively phagocytic leucocytes will produce lactic acid and this will promote further urate crystallization in the joint tissues.

Acute gout is best treated with high doses of NSAIDs. Colchicine is used as alternative especially in patients with heart disease since it does not cause fluid retention.

The normal serum uric acid levels range from 1-7 mg / dL. It is important to note that hyperuricaemia and gout are not synonymous. It has been reported that 90% of hyperuricaemic patients with plasma uric acid above 9 mg / dL eventually develop gout. Hyperuricaemia must be corrected with drugs only when there is an acute attack of gout, soft tissue deposition, renal urate calculi or the serum uric acid level is markedly elevated.

Long term prophylactic treatment of gout can be effectively achieved with allopurinol. Allopurinol, a xanthine oxidase inhibitor, reduces the formation of uric acid. It shows less adverse effects than uricosuric agents especially in patients with renal impairment or urate stones. Treatment with allopurinol should only be initiated after complete remission of an acute attack.

Allopurinol

Indications: prophylactic long term management of gout, renal urate stone, hyperuricemia associated with cancer therapy.

Contra-indications: Not a treatment for acute gout; sensitivity to the drug.

Cautions: ensure adequate water intake; pregnancy and breast feeding; start treatment with allopurinol

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before commencement of anti-neoplastic agents.

Side-effects: rashes, pruritus, nausea and vomiting, blood disorders.

Dose: initially, 100-300 mg daily as single dose, then adjusted according to plasma urate level. Maximum in severe conditions 900 mg daily.

Preparations

Allopurinol tablets, 100 mg tab.

Allopurinol tablets, 300 mg tab.

Colchicine (*Restricted*)

Indications: acute attack of gout; prophylaxis in initial therapy with allopurinol.

Contra-indications: pregnancy and breast feeding.

Cautions: elderly, GI disease, cardiac, renal and hepatic impairment.

Side-effects: nausea and vomiting, diarrhoea and abdominal pain. Large doses may cause rashes, GI bleeding and renal and hepatic damage.

Dose: treatment of gout; initially 1 mg, then 500 microgram every 2-3 hours until relief is obtained or vomiting or diarrhoea occurs or until a total of 6 mg has been reached. Do not repeat the course of therapy before three days.

Prophylaxis therapy with allopurinol, 500 micrograms 2-3 times daily.

Preparations

Colchicine tablets, 500 microgram tab.

Rasburicase (*Restricted*)

Indications: Prophylaxis and treatment of acute hyperuricaemia, before and during initiation of chemotherapy, in patients with haematological malignancy and high tumour burden at risk of rapid lysis.

Contra-indications: G6PD deficiency.

Cautions: Atopic allergies.

Side-effects: Fever; anaphylaxis; bronchospasm; diarrhoea; haemolytic anaemia; headache; hypersensitivity reactions; methaemoglobinemia; nausea; rash; vomiting.

Dose: 200 micrograms/kg once daily for up to 7 days according to plasma-uric acid concentration.

Preparations

Rasburicase injection, powder for reconstitution, 1.5 mg / vial

Rasburicase injection, powder for reconstitution, 7.5 mg / vial

10 A.4: Topical NSAIDs and counter irritants

Pain whether superficial or deep seated may be relieved by any method that produces local inflammation associated with a feeling of warmth and comfort. Drugs which evoke such effects are termed counter-irritants. Preparations containing NSAIDs are also applied for the

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relief of pain in musculoskeletal conditions.

Such preparations should be applied gently to the skin away from the eyes, mucous membranes, and broken or inflamed skin. Do not use with occlusive dressings.

Preparations

Analgesic balm cream tube

10 B: Drugs used in neuromuscular disorders

10 B.1: Drugs which enhance neuromuscular transmission

Anticholinesterase drugs prevent the degradation of acetylcholine and enhance transmission at the neuromuscular junctions. Excessive dosage of these drugs may impair neuromuscular transmission and cause depolarizing block.

They are useful in myasthenia gravis, and as antagonists to the excessive effect of non-depolarizing neuromuscular blockers.

Edrophonium, neostigmine and pyridostigmine are anticholinesterase drugs which are used in the diagnosis and treatment of myasthenia gravis. Edrophonium is a short acting drug and is therefore more useful for diagnosis. Neostigmine is a potent anticholinesterase drug which may act for up to 4 hours. Its pronounced muscarinic action is a disadvantage.

Pyridostigmine is less powerful and slower in action than neostigmine.

It is preferred for its smoother and longer action and less frequent GI side-effects.

Neostigmine

Indications: myasthenia gravis; for other indications *see sec 15*

Contra-indications: intestinal or urinary obstruction.

Cautions: asthma, bradycardia, hypotension, epilepsy, peptic ulceration, pregnancy and breast feeding.

Side-effects: muscarinic effects such as excessive salivation, gastrointestinal discomfort, bronchial secretion, miosis.

Dose: orally for myasthenia gravis, neostigmine bromide 15-30 mg at suitable intervals, total daily dose 75-300 mg in divided doses. Child, 1-6 years initially 7.5 mg, 6-12 years initially 15 mg, maximum daily dose 15-90 mg.

Intramuscular or subcutaneous injection, neostigmine methylsulphate, 1-2.5 mg at suitable intervals, total daily dose 5-20 mg; Child, 200-500 microgram as required.

Preparations

Neostigmine methylsulphate injection, 500 microgram/mL injection, 1 mL ampoule.

Neostigmine methylsulphate injection, 2.5 mg/mL injection, 5 mL ampoule

Neostigmine methylsulphate injection, 2.5 mg/mL, 1 mL ampoule

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Edrophonium chloride (C.D.L)

Indications: diagnosis of myasthenia gravis.

Contra-indications, cautions and side-effects: *see* under neostigmine

Dose: for diagnosis of myasthenia gravis, by intravenous injection, 2 mg followed after 30 seconds by 8 mg. Intramuscular injection, 10 mg.

Preparations

Edrophonium chloride injection, 10 mg/mL, 1 mL ampoule

Pyridostigmine bromide

Indications: myasthenia gravis.

Contra-indications, cautions and side-effects: *see* under neostigmine.

Dose: orally, 30-120 mg at suitable intervals, total daily dose 0.3-1.2 g. Child, up to 6 years, 30 mg, 6-12 years 60 mg, total daily dose 30-360 mg.

Preparations

Pyridostigmine bromide tablets, 60 mg tab.

Baclofen

Indications: is useful for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis or in patients with spinal cord injuries.

Contra-indications: peptic ulceration.

Cautions: abrupt drug withdrawal, impaired renal function, stroke, epilepsy, Parkinson's disease, diabetes mellitus, pregnancy.

Side-effects: drowsiness, hypotension, coordination disorder, tremor, rigidity, dystonia, ataxia, blurred vision, nystagmus, urinary frequency, urinary retention, dysuria, sexual dysfunction, haematuria, nausea, constipation.

Dose: orally, 5 mg thrice daily, can be increased gradually up to 100 mg daily.

Preparations

Baclofen tablet, 10 mg tab.

Baclofen tablet, 25 mg tab.

Baclofen oral solution, 5 mg/5 mL, 300 mL bottle

10 B. 2: Skeletal muscle relaxants

Skeletal muscle relaxants in general produce their effects centrally except for dantrolene which acts peripherally with very few central side-effects. These drugs are used for chronic muscle spasm; they are not indicated for muscle spasm associated with minor injury.

Dantrolene sodium (Restricted)

Indications: voluntary muscle spasticity, malignant hyperthermia.

Contra-indications: hepatic impairment, acute muscle spasm.

Cautions: history of liver disease or dysfunction, impaired pulmonary function or chronic obstructive pulmonary disease, impaired cardiac function secondary to myocardial disease, women over 30 years of age (greater likelihood of drug

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induced, potentially fatal, hepatocellular disease).

Side-effects: drowsiness, dizziness, photosensitivity, nausea and vomiting, abdominal cramps, hepatitis, malaise, fatigue, anorexia.

Dose: orally for muscle spasm, initially 25 mg daily may be increased at weekly intervals to a maximum 100 mg 4 times daily.

Preparations

Dantrolene capsules, 25 mg cap.

Dantrolene injection, 20 mg vial

11. Eye

Section 11: Eye

- Mydriatics and cycloplegics
- Treatment of glaucoma
- Anti-infective preparations
- Corticosteroid, anti-allergy and anti-inflammatory preparations
- Miscellaneous preparations

Administration of eye drops to the eye will allow drugs to penetrate to the globe probably through the cornea. Systemic effects may result from eye drops, mostly through absorption from conjunctival blood vessels or from the nasal mucosa during drainage across the tear ducts. The extent of systemic absorption following ocular administration is highly variable.

One drop, in most cases, is enough to produce the desired effect. Instillation should be properly done into the conjunctival sack that is formed by a gentle pulling outwards of the lower eyelid; the eye should be closed after application for as long as 1-2 minutes. In cases of more than one eye drops administration, an interval of 5 minutes should be kept between applications. Eye ointments are applied similarly; the ointment melts rapidly and blinking helps to spread it.

A high degree of sterility should be maintained when eye drops are

used. It is wise to use single-application containers during surgical procedures

Patients should be counselled to dispose of any unused eye drops after one month from opening.

11 A: Mydriatics and cycloplegics

11 A.1: Antimuscarinics

Antimuscarinics dilate the pupil and paralyze the ciliary muscle. They are either short acting such as tropicamide, or long acting such as atropine.

Atropine sulphate

Indications: refraction procedures in children, anterior uveitis.

Contra-indications: glaucoma.

Cautions: systemic effects may follow topical application especially in children; patients should be advised not to drive immediately after instillation.

Side-effects: local irritation, increased intra-ocular pressure, systemic side-effects (*see sec 1B*).

Preparations

Atropine sulphate eye drops, 1%; 5-10 mL/bottle

Atropine sulphate eye ointment, 1%; 3-5 g/tube

Cyclopentolate (Restricted)

Indications: Cycloplegia. Uveitis. Anterior uveitis.

Cautions: Darkly pigmented iris is more resistant to pupillary dilatation and caution should be exercised to avoid overdosage; mydriasis can precipitate acute angle-closure glaucoma (usually in those aged over 60 years and hypermetropic (long-sighted), who are predisposed to the condition because of a shallow anterior chamber)

Side-effects: Conjunctivitis (on prolonged administration); contact dermatitis; eye oedema (on prolonged administration); hyperaemia (on prolonged administration); local irritation (on prolonged administration); raised intraocular pressure; transient stinging.

Dose: Cycloplegia. Child 3 months–11 years apply 1 drop, 30–60 minutes before examination, using 1% eye drops. Child 12–17 years apply 1 drop, 30–60 minutes before examination, using 0.5% eye drops.

Uveitis child 3 months–17 years apply 1 drop 2–4 times a day, using 0.5% eye drops (1% for deeply pigmented eyes).

Anterior uveitis. Consult product literature.

Preparations

Cyclopentolate eye drops 0.5%, 5 mL bottle

Cyclopentolate eye drops 1.0%, 5 mL bottle

Homatropine hydrobromide

Indications: *see* under atropine (shorter duration than atropine).

Contra-indications, cautions and side-effects: *see* under atropine.

Preparations

Homatropine hydrobromide eye drops, 2% ; 10-15 mL/bottle

Tropicamide (Restricted)

Indications: *see* under atropine (shorter duration than atropine).

Contra-indications, cautions and side-effects: *see* under atropine.

Preparations

Tropicamide eye drops, 1%, 15 mL/bottle

Tropicamide minims, 0.1% single use eye drops/0.5 mL

Tropicamide minims, 0.5% single use eye drops/0.5 mL

Tropicamide minims, 1% single use eye drops/0.5 mL

11 A.2: Sympathomimetics

Phenylephrine hydrochloride (Restricted)

Indications: mydriasis.

Contra-indications: angle-closure glaucoma.

Cautions: use low strength in children and elderly; caution in presence of cardiovascular disease.

Side-effects: eye pain and stinging; blurred vision, photophobia.

Preparations

Phenylephrine HCl eye drops, 10%; 10 mL/bottle

11. Eye

Phenylephrine HCl minims, 1%
single use eye drops/0.5 mL

Phenylephrine HCl minims, 10%
single use eye drops/0.5 mL

11 B: Treatment of glaucoma

Glaucoma is a disorder in which the pressure in the eyeball increases, damaging the optic nerve and causing a loss of vision. Treatment of glaucoma is aimed at reducing the intra-ocular pressure which is more likely to be successful if started early; when vision is impaired, treatment may prevent further deterioration but it can not restore vision completely.

Medications that will increase the outflow from the anterior chamber are effective in reducing IOP in glaucoma. Topical therapy with beta blockers, pilocarpine can usually control glaucoma. Carbonic anhydrase inhibitors such as acetazolamide are orally effective. New approaches have been introduced in the management of glaucoma, such as topical prostaglandin analogues and carbonic anhydrase inhibitors.

11 B.1: Miotics

Pilocarpine

Indications: glaucoma.

Contra-indications: acute iritis, uveitis, acute inflammatory disease of the anterior segment.

Cautions: asthma, hypertension and other cardiac disease, peptic ulceration; darkly pigmented iris may

require higher concentration or more frequent administration to achieve therapeutic effects, avoid overdosage.

Side-effects: headache and brow-ache, local irritation, blurred vision, conjunctival vascular congestion.

Dose: apply eye drops up to 4 times daily.

Preparations

Pilocarpine eye drops, 2%; 10 mL/bottle

11 B.2: Sympathomimetics

Brimonidine tartrate (Restricted)

Indications: ocular hypertension, open-angle glaucoma.

Contraindication: concomitant MAOI therapy.

Cautions: severe cardiovascular disease; cerebral or coronary insufficiency, Raynaud's syndrome, postural hypotension, depression, hepatic or renal impairment; pregnancy, breast-feeding.

Driving: May cause drowsiness and affect performance of skilled tasks.

Side-effects: ocular reactions including conjunctival hyperaemia, stinging, pruritus, allergy, and conjunctival folliculosis, visual disturbances, blepharitis, epiphora, corneal erosion, superficial punctuate keratitis, eye pain, discharge, dryness, and irritation, eyelid inflammation, oedema, pruritus con-

junctivitis, photophobia; also, hypertension, headache, depression, dry mouth, fatigue, drowsiness.

Dose: Apply twice daily

Preparations

Brimonidine tartrate eye drops, 0.2%, 5 mL/bottle

11 B.3: Beta- adrenoceptor blockers

Betaxolol (C.D.L)

Indications: glaucoma.

Cautions: in asthmatic or patients with cardiovascular disorders.

Contraindications: bradycardia, overt heart failure.

Side-effects: local irritation, pain, dry eyes, erythema.

Dose: apply eye drops twice daily.

Preparations

Betaxolol eye drops, 0.5%; 5 mL/bottle

Timolol maleate

Indications: glaucoma.

Contra-indications: asthma.

Cautions: cardiac disease, angle-closure glaucoma.

Side-effects: local irritation, pain, dry eyes, erythema.

Dose: apply eye drops twice daily.

Preparations

Timolol maleate eye drops, 0.5%; 5 mL/bottle

11 B.4: Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors reduce the production of aqueous humor and hence reduce intra-ocular pressure. Orally (such as acetazolamide; *see* sec 2B.5) and topically applied preparations such as dorzolamide are available. Dorzolamide eye drops are used in patients resistant to or who can not use beta-blockers.

Dorzolamide (Restricted)

Indications: glaucoma uncontrolled with β -blockers.

Contra-indications: hyperchloraemic acidosis; pregnancy and breast-feeding.

Cautions: hepatic impairment; systemic absorption follows topical administration; chronic corneal defects.

Side-effects: local ocular irritation, eyelid inflammation and crusting, corneal oedema, bitter taste, epistaxis, paraesthesia.

Dose: apply 3 times daily if used alone or twice daily if used with beta-blockers.

Preparations

Dorzolamide hydrochloride eye drops, 2%, 5 mL/bottle

11 B.5: Prostaglandin analogue

Prostaglandin analogues are capable of increasing uveoscleral outflow hence reduce intra-ocular pressure. They are used in open-an-

11. Eye

gle glaucoma and ocular hypertension in patients unresponsive to beta-blockers or when beta-blockers are contra-indicated. Darkening of eye coloration is a notable side effect with prostaglandin analogues. It is due to an increased brown pigmentation of the iris.

Latanoprost (Restricted)

Indications: glaucoma in patients unresponsive or intolerant to other drugs.

Cautions: monitor for changes in eye coloration; brittle or severe asthma; pregnancy and breast-feeding.

Side-effects: darkening of eye coloration, ocular irritation, exacerbation of asthma.

Dose: apply once daily preferably in the evening.

Preparations

Latanoprost eye drops, 0.005% (50 micrograms / mL) 2.5 mL/bottle

Latanoprost with Timolol (Restricted)

Indications: Raised intra-ocular pressure in patients with open-angle glaucoma and ocular hypertension when a beta-blocker or prostaglandin analogue alone not adequate

Cautions: see under individual drugs

Side-effects: see under individual drugs

Dose: apply once daily

Preparations

Latanoprost with Timolol eye drops, 50 microgram latanoprost and 5 mg timolol per mL

11 B.6: Alpha2 adrenoceptor agonists

Apraclonidine (Restricted)

Indications: Control or prevention of postoperative elevation of intra-ocular pressure after anterior segment laser surgery. Short-term adjunctive treatment of chronic glaucoma in patients not adequately controlled by another drug.

Contra-indications: History of severe or unstable and uncontrolled cardiovascular disease.

Cautions: Cerebrovascular disease; depression; heart failure; history of angina; hypertension; loss of effect may occur over time; Parkinson's syndrome; Raynaud's syndrome; recent myocardial infarction; reduction in vision in end-stage glaucoma (suspend treatment); severe coronary insufficiency; thromboangiitis obliterans; vasovagal attack.

Side-effects: Conjunctivitis; dry eye; ocular intolerance; rhinitis; taste disturbance.

Dose: Control or prevention of postoperative elevation of intra-ocular pressure after anterior segment laser surgery. Apply 1 drop, 1 hour before laser procedure, then 1 drop, immediately after completion of procedure, 1% eye drops to be administered.

Short-term adjunctive treatment of chronic glaucoma in patients not adequately controlled by another drug. Apply 1 drop 3 times a day usually for maximum 1 month, 0.5% eye drops to be administered, may not provide additional benefit if the patient is already using two drugs that suppress the production of aqueous humour.

Preparations

Apraclonidine eye drops, 0.5%

Apraclonidine eye drops, 1.0%

11 C: Anti-infective preparations

Acute infection of the eye should be promptly and intensively treated. Most acute infections respond to topically applied anti-infective agents. Blepharitis and conjunctivitis are often caused by staphylococci, while keratitis and endophthalmitis may be bacterial, viral or fungal. In severe infections systemic therapy may accompany topical applications as in gonococcal conjunctivitis in neonates. Subconjunctival injection may be required, as in keratitis and corneal ulcer, to increase the intraocular concentration of an appropriate anti-infective drug.

Systemic treatment may occasionally be required and is usually undertaken after culturing organism from lid margin and determining their antibiotic sensitivity.

11 C.1: Antibacterials

11 C. 1.1: Tetracycline and chloramphenicol

Chloramphenicol has a broad spectrum of activity and is the drug of choice for superficial infections. Tetracycline is used to treat *Chlamydial* infections including *trachoma*.

Chloramphenicol

Indications: superficial eye infections.

Side-effects: transient stinging.

Dose: apply one drop to the eye every 2- 3 hours then reduce frequency when infection controlled; continue for 48 hours after healing.

Preparations

Chloramphenicol eye drops, 0.5%; 10 mL/bottle

Tetracycline hydrochloride

Indications: local treatment of infection including trachoma.

Contra-indications: sensitivity to tetracycline.

Dose: apply small quantity to the eye twice daily.

Preparations

Tetracycline HCl eye ointment, 1%; 3-5 g/tube

11. Eye

11 C.1.2: Aminoglycosides

Gentamicin is a broad spectrum antibiotic which is effective against *Pseudomonas aeruginosa*.

Gentamicin sulphate

Indications: ophthalmic infections, specifically with *P. aeruginosa*.

Contra-indications: sensitivity to gentamicin.

Side-effects: local irritation.

Dose: apply 3-6 times daily.

Preparations

Gentamicin sulphate eye/ear drops, 0.3%; 5-10 mL/bottle

Gentamicin eye ointment, 0.3%; 3-5 g/tube

11 C.1. 3: Miscellaneous

Erythromycin

Indications: blepharitis; conjunctivitis.

Dose: apply small quantity to the eye twice daily.

Preparations

Erythromycin eye ointment, 0.5%; 3.5 g/tube

Fusidic acid

Indications: ophthalmic infections, specifically staphylococcal infections.

Dose: apply every 3-6 hours.

Preparations

Fusidic acid eye drops, 1%; 5 g/tube

Ofloxacin

Indications: conjunctivitis.

Cautions: pregnancy; not to be used for more than 10 days.

Side-effects: local irritation, photophobia

Dose: apply one drop to the eye every 2- 3 hours then reduce frequency when infection controlled; continue for 48 hours after healing.

Preparations:

Ofloxacin eye drops, 0.3%; 5-10 mL/bottle

Moxifloxacin (Restricted)

Indications: Local treatment of infections (MOH: only to be used in children under 1 year old)

Cautions: Not recommended for neonates

Side-effects: hyperaemia; ocular discomfort; ocular dryness; ocular irritation; ocular pain; taste disturbances.

Dose: Child. Apply 3 times a day continue treatment for 2-3 days after infection improves; review if no improvement within 5 days.

Preparations

Moxifloxacin eye drops, 0.5%

11 C. 2: Antivirals

Aciclovir has been found very effective in treating herpes simplex infections such as dendritic corneal ulcer.

Aciclovir

Indications: viral infections of the eye.

Side-effects: mild stinging and local inflammation.

Dose: apply 5 times daily and continue for 3 days after complete healing.

Preparations

Aciclovir eye ointment, 3%; 4.5 g/tube

11 C.3: Antifungal preparations

Most of the ophthalmic fungal infections are caused by agricultural injuries. Specialists in specialized centres where antifungal preparations are made available invariably treat such infections.

Miconazole eye drops are made available in limited quantities at Al-Nahdha Ophthalmology Department

Miconazole

Indications: fungal keratitis, endophthalmitis.

Dose: consult product literature.

Preparations

Miconazole eye drop, 1%

11 D: Corticosteroids, anti-allergy and anti-inflammatory preparations**11 D.1: Corticosteroids**

It should be strongly emphasized that untreated bacterial or viral eye infections may be aggravated by topical application of corticosteroids. The use of steroids should be supervised by a specialist. Therapy with corticosteroids in bacterial infection should be accompanied by effective antibacterial drugs. Prolonged topical use of corticosteroids especially dexamethasone and prednisolone, may precipitate glaucoma in predisposed patients. Long term oral use of corticosteroids may cause lens opacity.

Dexamethasone

Indications: short term treatment of local inflammation.

Contra-indications: undiagnosed red-eye.

Cautions: glaucoma, acute untreated infection, cataract.

Side-effects: thinning of the cornea and sclera.

Dose: apply 4-6 times daily. More frequent administration in severe inflammation.

Preparations

Dexamethasone eye drops, 0.1%; 5-10 mL/bottle

Dexamethasone eye ointment, 1%

11. Eye

Fluorometholone

Indications: short term treatment of local inflammation.

Contra-indications, cautions and side-effects: *see* under dexamethasone.

Dose: apply 2-4 times daily. Frequency may be increased in severe inflammation.

Preparations

Fluorometholone eye drops, 0.1%; 5 mL/bottle

Prednisolone

Indications: short term treatment of local inflammation.

Contra-indications, cautions and side-effects: *see* under dexamethasone.

Dose: apply every 1-2 hours until inflammation is controlled then reduce frequency.

Preparations

Prednisolone eye drops, 1 %; 5 mL/bottle (**Restricted**)
Prednisolone minims, 0.5% single use eye drops/0.5 mL

11 D.2: Anti-inflammatory and anti-allergy preparations

Lodoxamide 0.1% eye drops (Restricted)

Indication: vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis.

Contraindication: Hypersensitivity to the drug.

Side-effects: burning, tingling, dizziness.

Dose: from 4 years and onwards, 1-2 drops 4 times daily for up to 3 months.

Preparations

Lodoxamide eye drops 0.1%, 10 mL/bottle.

Sodium cromoglicate (Sodium cromoglycate)

Indications: allergic conjunctivitis, vernal keratoconjunctivitis.

Side-effects: transient stinging and burning.

Dose: apply 4 times daily.

Preparations

Sodium cromoglicate eye drops, 2%; 10 mL/bottle

Antihistamine and astringent eye drops

Non-infective allergic conjunctivitis can be treated with topical application of antihistamine and decongestant eye drops such as antazoline, naphthazoline, zinc sulphate, phenylephrine etc.

Preparations

Antihistamine eye drops; 10 mL/bottle

11 D.3: Non-steroidal anti-inflammatory drugs

Diclofenac or flurbiprofen

They are used to inhibit intra-operative miosis during cataract surgery, or in postoperative inflammation in cataract surgery. They are also applied to relieve pain in trauma or in corneal epithelial defects.

Preparations

Diclofenac eye drops, 0.1%; 5 mL/bottle

Flurbiprofen eye drops, 0.03%; 5 mL/bottle

11 E: Miscellaneous preparations

11 E.1: Tear deficiency preparations

Methyl cellulose and hypromellose are viscous preparations that are used to lubricate the eye. They are used as tear replacement to prevent the damage to the cornea in keratitis sicca or keratitis, and to lubricate artificial eyes.

The choice is determined by the severity of the condition and patient preference.

Hypromellose

Indications: tear deficiency.

Dose: apply frequently to avoid dryness of the eye.

Hypromellose eye drops, 0.5%; 10 mL/bottle

Hypromellose (preservative free) eye drops, 0.5%; 10 mL/bottle

Methyl cellulose

Indication: tear deficiency

Dose: apply frequently to avoid dryness of the eye

Preparations

Methyl cellulose eye drops, 2%; 10-15 mL/bottle

11 E. 2: Diagnostic ophthalmic preparations

Fluorescein sodium is an indicator dyes used topically for the diagnosis of corneal and conjunctival abnormalities, and intravenously (fluorescein angiography) to evaluate retinal function and other ocular structures or conditions.

Fluorescein sodium

Indications: detection of lesions and foreign bodies; angiographies in ocular disorders.

Side-effects: nausea and vomiting, GI distress, bronchospasm, anaphylaxis, abnormal taste, hypotension.

11. Eye

Preparations

Fluorescein strips, individual sterile impregnated with fluorescein sodium; 1 mg/strip

Fluorescein injection, 20% solution, 5 mL ampoule (**Restricted**).

Fluorescein minims, 2% single application eye drops/0.3 mL (**CDL**)

11 E.3: Other ophthalmic preparations

Acetylcholine chloride + Mannitol (**Restricted**)

Indications: cataract surgery, penetrating keratoplasty, anterior segment surgery requiring complete rapid miosis.

Preparations

Acetylcholine chloride + Mannitol solution, 1% + 3% (upon reconstitution) sterile solution; 2 mL/ampoule

Balanced salt solution (**Restricted**)

Indications: ocular irrigation.

Preparations

Balanced salt solution, sodium chloride 0.64%, sodium acetate 0.39%, sodium citrate 0.17%, calcium chloride 0.048%, magnesium chloride 0.03%, potassium chloride 0.075%, sterile solution
BSS, 15 mL bottle.

Oxybuprocaine hydrochloride (**Restricted**)

Indications: local anaesthetic.

Contra-indications: should not be used on infected area.

Cautions: frequent use may lead to tolerance.

Side-effects: corneal swelling, burning sensation.

Dose: apply 1-2 drops every 30-90 seconds.

Preparations

Oxybuprocaine HCL eye drops, 0.4% eye drops; 10-15 mL/bottle

Oxybuprocaine HCL minims, 0.4% single application eye drops/0.5 mL

Silicone oil (**Restricted**)

Indications: severe cases of retinal detachment e.g. severe detachment in massive proliferative vitreoretinopathy, traumatic detachments, which can not be treated with other forms of therapy.

Contra-indications: intraocular lenses made from silicon.

Side-effects: cataract, glaucoma.

Dose: Consult manufacturer literature

Preparations

Silicone oil, 10 mL/bottle

Sodium hyaluronate (**C.D.L**)

Indications: surgical aid in anterior segment procedures.

Cautions: overfilling the eye chambers, warm the refrigerated solution before use.

Side-effects: postoperative increase in intra-ocular pressure.

Dose: as needed for the procedures.

Preparations

Sodium hyaluronate injection, 1% (10 mg/mL) 0.4-0.5 mL/ampoule

Sodium hyaluronate and sodium chondroitin sulphate injection, 3% (30 mg / mL) and 4% (40 mg / mL) respectively, 0.5 mL disposable syringe

Ranibizumab (Restricted)

Indications: Neovascular (wet) age-related macular degeneration (specialist use only). Diabetic macular oedema. Macular oedema secondary to retinal vein occlusion (specialist use only). Choroidal neovascularisation secondary to pathologic myopia (specialist use only). Concomitant treatment of diabetic macular oedema, or macular oedema secondary to branch retinal vein occlusion, with laser photocoagulation (specialist use only)

Contra-indications: Ocular or periocular infection; severe intra-ocular inflammation; signs of irreversible ischaemic visual function loss in patients with retinal vein occlusion.

Cautions: Active systemic infection; diabetic macular oedema due to type 1 diabetes (limited information available); diabetic patients with HbA1c over 12%; history of stroke; history of transient ischaemic attack; patients at risk of retinal pigment epithelial tear; previous intravitreal injections; proliferative diabetic retinopathy; retinal detachment or macular hole (discontinue treatment if rhegmatogenous retinal detachment or stage 3

or 4 macular holes develop); uncontrolled hypertension. Ranibizumab is given by intravitreal injection by specialists. There is a potential risk of arterial thromboembolic events and non-ocular haemorrhage following the intravitreal injection of vascular endothelial growth factor inhibitors. Endophthalmitis can occur after intravitreal injections—patients should be advised to report any signs of infection immediately. Pregnancy

Side-effects: Allergic skin reactions; anaemia; anterior chamber flare; anxiety; arthralgia; blepharitis; cataract; conjunctival disorders; conjunctivitis; cough; eye haemorrhage; eyelid oedema; headache; iridocyclitis; iritis; nasopharyngitis; nausea; ocular discomfort; photophobia; photopsia; posterior capsule opacification; punctate keratitis; raised intra-ocular pressure; retinal disorders; urinary tract infection; uveitis; visual disturbance; vitreous disorders.

Dose: Neovascular (wet) age-related macular degeneration (specialist use only). By intravitreal injection 500 micrograms once a month, to be administered into the affected eye, monitor visual acuity monthly, continue treatment until visual acuity is stable for 3 consecutive months, thereafter monitor visual acuity monthly, if necessary subsequent doses may be given at least 1 month apart.

Diabetic macular oedema. Macular oedema secondary to retinal vein occlusion (specialist use only)

11. Eye

By intravitreal injection. Initially 500 micrograms once a month, to be administered into the affected eye, monitor visual acuity monthly, continue treatment until visual acuity is stable for 3 consecutive months (discontinue treatment if no improvement in visual acuity after initial 3 injections), thereafter monitor visual acuity monthly, if necessary subsequent doses may be given at least 1 month apart.

Choroidal neovascularisation secondary to pathologic myopia (specialist use only)

By intravitreal injection initially 500 micrograms, to be administered as a single injection into the affected eye, monitor for disease activity monthly for first 2 months, then at least every 3 months thereafter during the first year, then as required, if necessary subsequent doses may be given at least 1 month apart.

Concomitant treatment of diabetic macular oedema, or macular oedema secondary to branch retinal vein occlusion, with laser photocoagulation (specialist use only)

By intravitreal injection 500 micrograms, to be administered at least 30 minutes after laser photocoagulation

Preparations

Ranibizumab injection, 10 mg/ 1 mL in prefilled syringe

Section 12: Ear, nose and oropharynx

- Drugs acting on the ear
- Drugs acting on the nose
- Drugs acting on the oropharynx

12 A: Drugs acting on the ear**12 A.1: Drugs for otitis externa**

Therapy of otitis externa involves thorough cleansing of the meatal skin and restoration of acidic surface pH, reduction of swelling, eradication of infection and avoidance of scratching.

Before initiating therapy, an underlying chronic otitis media should be excluded.

Eczematous otitis externa is initially treated by dry mopping or careful cleansing by suction. If these measures fail, a cotton gauze wick soaked with corticosteroid is gently inserted into the meatus. Topical antibiotics are only applied when infection is present. Systemic antimicrobial is used in acute infection.

Acute oedematous otitis externa is treated as above for infected eczematous otitis externa.

Otomycosis is treated with topical application of clotrimazole solution in addition to careful cleansing.

Acute furunculosis is caused by localized inflammation of the hair follicle in the cartilaginous part of

the ear canal. It may follow abrasion or maceration in the ear canal. After cleansing, a cotton wick is saturated with a topical antibacterial ointment and inserted in the ear canal. An oral antimicrobial, which is effective against staphylococcus organism such as cloxacillin, is given in addition to analgesics. If furuncle bursts, aural cleansing and drainage are necessary.

Malignant otitis externa may occur in diabetics and in anaemic and malnourished children. It should be treated with systemic antimicrobial and local cleansing. Control of diabetes, if present, is essential.

Acetic acid 2% solution

Indications: topical antibacterial and antifungal; acidifying agent.

Contra-indications: perforated tympanic membrane.

Side-effects: stinging or burning sensation

Dose: 3-4 drops applied to the ear canal 4-5 times daily.

Preparations

Acetic acid solution, 2% ear drops;
15 mL /bottle

Clotrimazole

Indications: fungal infection in otitis externa.

Cautions: causes staining of skin and clothing.

Side-effects: local sensitivity.

Dose: apply 2-3 times daily continuing for at least 14 days after disappearance of infection.

12: Ear, nose and oropharynx

Preparations

Clotrimazole solution, 1% ear drops; 15 mL/bottle

Dexamethasone + framycetin sulphate + gramicidin

Indications: eczematous inflammation in otitis externa with infection.

Contra-indications: acute infection.

Side-effects: local sensitivity.

Dose: 2-3 drops 3-4 times daily.

Preparations

Dexamethasone + framycetin sulphate + gramicidin ear drops, 0.05% + 0.5% + 0.005% ear drops; 8 mL/bottle

Prednisolone

Indications: eczematous inflammation in otitis externa.

Contra-indications: untreated infection.

Cautions: avoid prolonged use.

Side-effects: local sensitivity.

Dose: 2-3 drops every 3-4 hours, reduce frequency when relief is obtained.

Preparations

Prednisolone sodium phosphate eye/ear drops, 0.5% eye/ear drops/bottle

Gentamicin

Indications: bacterial infection in otitis externa.

Contra-indications: perforated tympanic membrane.

Cautions: avoid prolonged use.

Side-effects: local sensitivity.

Dose: 2-3 drops 3-4 times daily, reduce frequency upon relief.

Preparations

Gentamicin eye/ear drops, 0.3%; 5-10 mL/bottle

12 A.2: Drugs for otitis media

Acute otitis media is a bacterial or viral infection of the middle ear. Although this disorder can develop in people of all ages, it is more common in children between 3 months and 3 years of age. Usually this disorder develops as a complication of upper respiratory tract infection of viral origin but could also be secondary to the introduction of water through a perforation in eardrum.

Otitis media with effusion (glue ear) is present in about 10% of the child population; it is a major cause of deafness in children with consequent delay in speech and language development.

Mild viral infections characterized by pinkness or infections of the eardrum often resolve spontaneously and require only analgesics and nasal decongestants. A bulging and inflamed eardrum indicates bacterial otitis media, which requires antimicrobial therapy. If discharge is present it should be examined to determine the causative organism. Local treatment in acute otitis media should be avoided, as it is ineffective.

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Chronic otitis media may follow untreated or resistant acute otitis media. It is a longstanding infection characterized by perforated eardrum. Careful and adequate cleansing of the external canal and middle ear by the use of suction or mopping may control infection for long periods. Prolonged local antibacterial therapy with frequent cleansing usually dries up most chronic infections. Acute exacerbation of chronic otitis media should be treated with systemic antibiotics after identifying the causative organism.

Acediasulfonum + cinchocaine + N,N-dihydroxymethyl carbamidum + glycerin

Indications: chronic otitis media.

Contra-indications: acute otitis media.

Side-effects: local sensitivity.

Dose: 2-3 drops 2-3 times daily.

Preparations

Acediasulfonum + cinchocaine + N,N-dihydroxymethyl carbamidum + glycerin ear drops, 0.84 g + 0.96 g + 0.42 g; 12 g/bottle

12 A.3: Agents for removal of wax

Wax is a normal bodily secretion with a protective role, which needs only be removed if it impairs hearing or interferes with eardrum examination. Syringing with warm water may be sufficient; soaking

the ear with glycerol ear drops or almond oil ear drops could precede this procedure.

Glycerol ear drop

Indications: ear wax removal.

Dose: 2-3 drops 4-6 times daily for 2 days to soften hard wax and prepare the patient for syringing. If the wax is not very hard sufficient amount is applied on the same day of syringing.

Preparations

Glycerol ear drops; 10-15 mL/bottle

12 B: Drugs acting on the nose

12 B.1: Topical nasal decongestants

Nasal congestion associated with common cold, vasomotor rhinitis or nasal polyps may be symptomatically relieved by topical decongestants. Topical decongestants provide temporary relief, which might be followed by rebound congestion; their prolonged use may damage the nasal cilia and cause nasal obstruction. Normal saline nasal drops may relieve congestion associated with common cold by liquefying the mucous secretion. Inhalations of moist warm air are useful in the treatment of symptoms of acute infective conditions, and the use of volatile compounds such as menthol or eucalyptus oil may encourage their use. There is no evidence

12: Ear, nose and oropharynx

that nasal preparations containing antihistamines and anti-infective agents have any therapeutic effect.

Oxymetazoline hydrochloride

Indications: nasal congestion.

Cautions: avoid excessive use.

Side-effects: local irritation, headache; tolerance with prolonged use; rebound congestion.

Dose: 1-2 sprays twice daily.

Preparations

Oxymetazoline HCl nasal spray, 0.05%; 20 mL/spray

Sodium Chloride 0.9% Nasal Drops (Normal Saline Nasal Drops)

Indications: nasal congestion by helping to liquefy mucous secretions.

Dose: 1-2 drops installed in each nostril 3-4 times daily when required.

Preparations

Sodium Chloride 0.9% Nasal Drops (Normal Saline Nasal Drops); 15 mL /bottle

12 B.2: Anti-infective agents

Chlorhexidine HCl 0.1% and Neomycin 0.5% cream

For elimination of staphylococci from the nasal vestibule but re-colonisation frequently occurs. For eradication, apply to nostril 4 times

daily for 10 days, for preventing nasal carriage of staphylococci apply to nostril twice daily.

Preparations

Chlorhexidine HCl 0.1% and Neomycin 0.5% cream, 15 g/tube

Mupirocin (Restricted)

A nasal ointment containing mupirocin is reserved for resistant cases of *Staphylococcal* infection of the nasal vestibules. The ointment should be applied 3 times daily for 5 days and a sample taken 2 days after treatment to confirm eradication. To avoid the development of resistance, the treatment course should not exceed 7 days and should only be repeated for one occasion.

Preparations

Mupirocin nasal ointment, 2% nasal ointment; 3 g/tube

12 B.3: Drugs used in nasal allergy

Mild nasal allergies can effectively be treated with oral antihistamines and decongestants. Antihistamines offer much relief from rhinorrhoea and sneezing but are less effective for the relief of nasal congestion. Severe allergies can be effectively controlled with topical application of corticosteroids or cromoglycate. In seasonal allergic rhinitis, treatment starts 2-3 weeks before the

season commences and may have to be continued for several months.

Beclometasone dipropionate (Beclomethasone dipropionate)

Indications: prophylaxis and treatment of allergic and vasomotor rhinitis.

Cautions: should be avoided in the presence of infections, and also after nasal surgery until healing has occurred; systemic absorption make take place after excessive and prolonged use leading to systemic effects (*see sec 6C.*).

Side-effects: dryness, irritation of the nose and throat, epistaxis.

Dose: adult and child over 6 years, apply 100 microgram (2 sprays) into each nostril twice daily, or 50 microgram (one spray) 3-4 times daily. Maximum 400 micrograms (8 sprays) daily.

Preparations

Beclometasone dipropionate aqueous nasal spray, 50 microgram/metered spray, 200 doses/metered spray

Budesonide Nasal Spray (Restricted)

Indications: Prophylaxis and treatment of allergic and vasomotor rhinitis. Nasal polyps

Cautions: Avoid after nasal surgery (until healing has occurred); avoid in pulmonary tuberculosis; avoid in the presence of untreated nasal infections; patients transferred from

systemic corticosteroids may experience exacerbation of some symptoms.

Side-effects: Glaucoma; raised intra-ocular pressure; Nasal septal perforation (usually following nasal surgery); Aggression (particularly in children); anxiety (particularly in children); bronchospasm; depression (particularly in children); dryness; epistaxis; headache; hyperactivity (particularly in children); hypersensitivity reactions; nasal irritation; nasal ulceration; sleep disturbances (particularly in children); smell disturbances; taste disturbances; throat irritation.

Dose: 128 micrograms once daily, dose to be administered into each nostril in the morning, alternatively 64 micrograms twice daily; reduced to 64 micrograms once daily when control achieved. Use for maximum 3 months, doses to be administered into each nostril.

Nasal polyps 64 micrograms twice daily for up to 3 months, dose to be administered into each nostril.

Preparations

Budesonide nasal spray, 64 micrograms / spray

12 C: Drugs acting on the oropharynx

12 C.1: Drugs for oral ulceration and inflammation

12: Ear, nose and oropharynx

Ulceration of the oral mucosa may be caused by trauma, recurrent aphthae, infections, gastrointestinal disease, carcinoma, drug therapy, blood disorders and nutritional deficiencies. The cause for ulceration of oral mucosa should be identified before commencement of treatment. In general, treatment is local and is aimed at protecting the ulcerated area, or to relieve pain or reduce inflammation.

Lidocaine (Lignocaine)

Indications: relief of pain in oral lesion.

Cautions: avoid prolonged use; care must be taken not to produce anaesthesia in the pharynx before a meal as this might lead to choking.

Dose: apply on need to the affected area in the oral cavity.

Preparations

Lidocaine topical solution, 4% solution; 30 mL/bottle

Triamcinolone acetonide

Indications: oral and perioral lesions.

Contra-indications: untreated oral infection.

Side-effects: occasional exacerbation of local infection.

Dose: apply a thin layer 2-4 times daily, do not rub; use to be limited to 5 days for children and elderly.

Preparations

Triamcinolone acetonide in orabase, 0.1% oral paste; 10 g/tube

12 C.2: Oropharyngeal anti-infective drugs

Viral infection is a common cause of sore throat where anti-infective drugs are ineffective. Bacterial sore throats require systemic antibiotic therapy.

Antifungal drugs such as amphotericin and miconazole are effective in the treatment of *candida albicans* and other fungal infections.

Amphotericin is not absorbed from the GI tract and is applied locally in the mouth. Miconazole, though applied locally, is absorbed and therefore is more prone to cause adverse effects and interacts with other drugs.

Amphotericin

Amphotericin B

Indications: oral and perioral fungal infections

Side-effects: gastrointestinal disturbances

Dose: allow one lozenge to dissolve slowly in the mouth 4 times daily for 10-15 days. Increase up to 8 lozenges daily in severe infections.

Preparations

Amphotericin lozenges, 10 mg lozenge

Miconazole

Indications: prevention and treatment of oral fungal infections.

Contra-indications: hepatic impairment.

Cautions: pregnancy and breast feeding.

Side-effects: nausea and vomiting, diarrhoea.

Dose: for generalized oral fungal infection, place 5-10 mL in the mouth after meal and retain near lesions 4 times daily.

For localized lesions, smear a small quantity of gel on affected area with clean finger 4 times daily.

Preparations

Miconazole oral gel, 20 mg/mL oral gel; 40 g/tube

12 C.3: Mouth washes, gargles and dentifrices

Mouth washes are used for the improvement of oral hygiene. Their cleansing effect is principally mechanical. Chlorhexidine is used as a mouth wash in oral infections and when tooth brushing is not possible. Mouth Gargles are of doubtful benefit

Chlorhexidine Gluconate

Indications: oral hygiene.

Side-effects: localized irritation, reversible brown staining of teeth.

Dose: rinse mouth with about 10 mL twice daily.

Preparations

Chlorhexidine Gluconate mouth wash, 0.2% mouth wash solution, 150–250 mL /bottle

13: Skin preparations

Section 13: Skin preparations

- Emollients and barrier preparations
- Local anaesthetics and antipruritics
- Topical corticosteroids
- Psoriasis and eczema preparations
- Preparations for acne
- Preparations for warts
- Anti-infective skin preparations
- Skin disinfectants
- Antiperspirants
- Depigmenting agents
- Pigmenting agents

Topical preparations

The active ingredients (virtually the medications) in a topical preparation are mixed with a vehicle, which is an inert carrier of the medications. Thus the formulation and consistency vary among topical preparations. The vehicle determines the consistency of the product and whether the active ingredients remain on the surface or penetrate the skin; whether the preparation is thick and greasy or light and watery. Depending on the vehicle used the preparation will be an ointment, cream, lotion, solution, powder or gel etc.

Applications are usually viscous solutions, emulsions, or suspensions for application to the skin

Collodions are painted on the skin and allowed to dry to leave a flexible film over the site of application. Creams are emulsion of oil in water, they are easy to apply and vanish when rubbed into the skin.

Lotions have more water content than creams. They are suitable for a cooling effect and for application on a hairy area. They may contain fine dispersed powder in a base of water or oil and water

Ointments contain a lot of oil and very little water, feel greasy and are difficult to wash off. Ointments are more appropriate when the skin is scaly and dry. Some ointments have hydrophilic and lipophilic properties; they may have occlusive properties on the skin surface, enhance hydration, and be miscible with water.

Gels consist of active ingredients in suitable hydrophilic or hydrophobic bases; generally they have a high water content with very little absorption through the intact skin.

Pastes are stiff preparations containing a high proportion of finely powdered solids such as zinc oxide and starch suspended in ointment.

Solutions are liquids in which drugs are dissolved. They tend to dry rather than moisturize the skin.

13 A: Emollients and barrier preparations

Emollients are used to soothe and hydrate the skin. Barrier preparations are used to protect the skin against hydration and irritation.

Moisturizing cream

A moisturizing cream with liquid paraffin or dimeticone base is available.

Indications: for dry skin conditions.

Preparations

Moisturel® cream; 500 g/jar

Zinc oxide cream

A barrier preparation with zinc oxide.

Indications: napkin rash and eczema.

Preparations

Zinc oxide + castor oil cream; 15-40%, 57 g/tube

Lubricating jelly for gynaecological and surgical use

A sterile water-soluble lubricating jelly.

Preparations

K-Y® jelly; 82 g/tube

13 B: Topical local anaesthetics and antipruritics

Pruritus (itching) may be caused by systemic (jaundice, kidney failure,

malignant disease and endocrine disorders) as well as skin disease (scabies, pediculosis, allergic and contact dermatitis). The underlying cause should be eliminated; treatment could be initiated with simple moisturising preparations. Systemic antihistamine may help but they tend to cause drowsiness. Calamine and crotamiton are used locally in pruritus and insect stings. Topical antihistamines and local anaesthetics should be avoided since they are of little value and may cause skin sensitisation.

13 B.1: Local anaesthetics***Lidocaine (Lignocaine Hydrochloride)***

Indications: relief of local pain, (see sec 15.).

Cautions: occasional hypersensitivity, excessive absorption may occur specially from mucous surface, avoid in children.

Preparations

Lidocaine HCl ointment, 5%; 15-35 g/tube

Lidocaine HCl jelly, 2% ; 20-30 g/tube

Lidocaine + Prilocaine (Emla®)

Indications: local anaesthesia.

Contraindications: infants under 1 year.

Cautions: not for wound, mucous membrane, or atopic dermatitis; avoid use near eyes or middle ear.

13: Skin preparations

Side-effects: transient paleness, redness and oedema.

Preparations

Lidocaine + Prilocaine cream, 2.5% + 2.5% cream; 5 g/tube

13 B.2: Antipruritics

Calamine

Indications: pruritus.

Preparations

Calamine lotion containing: Calamine 15% + zinc oxide 5% + glycerol 5% + bentonite 3% + sodium citrate 0.5% + liquefied phenol 0.5% in freshly boiled and cooled purified water, 100 mL/bottle

Crotamiton (Restricted)

Indications: pruritus including pruritus after scabies.

Contraindications: acute exudative dermatoses.

Cautions: avoid use on broken skin and near eyes; avoid use in children under 3 year.

Application: apply 2-3 times daily.

Preparations

Crotamiton cream, 10% cream, 20 g/tube

13 C: Topical Corticosteroids

13 C.1: Topical corticosteroids plain

Many skin inflammatory disorders respond to topical corticosteroids. Choice of a preparation depends on the severity of skin disease, the site of involvement and potency of the chosen steroid. Corticosteroids vary in their potency (*see* table). In severe skin disorders, a potent steroid preparation may be initially used followed by a less potent one. Twice a day application is mostly sufficient; more frequent application does not improve response. Steroids offer temporary relief and rebound inflammation may occur on withdrawal.

The extent of absorption through the skin varies with different steroids and formulations. It is greater when large areas are treated, duration of therapy is prolonged, large amount used, the surface of the skin is soft, and when occlusive dressing is applied. Extensive absorption leads to systemic toxicity, including suppression of hypothalamic-pituitary-adrenal axis and growth retardation, particularly in young children.

Prolonged application may cause local adverse effects especially when occlusive therapy is employed. These include, skin atrophy, striae, telangiectasias, purpura, acneiform eruptions, perioral dermatitis, overgrowth of fungus and bacteria, hypopigmentation and rosacea. Potent steroids should be avoided in children; mild preparations such as hydrocortisone are preferable.

Potency of selected topical steroids:

Mild: Hydrocortisone 1%
Moderate: Clobetasone butyrate 0.05%; Fluocinolone acetonide 0.01%
Potent: Betamethasone valerate 1%; Triamcinolone 0.1%
Very Potent: Clobetasol propionate 0.05%

Betamethasone Valerate

Indications: severe inflammatory skin disorders.

Contraindications: untreated bacterial, fungal or viral skin infections, acne vulgaris, rosacea.

Cautions: avoid prolonged use especially in children and infants; avoid prolonged use on the face.

Side-effects: *see* notes above

Application: apply topically 1-2 times daily.

Preparations

Betamethasone valerate cream, 0.1% cream, 15 g/tube

Betamethasone valerate ointment, 0.1% ointment, 15 g/tube

Betamethasone valerate scalp application, 0.1% solution, 30 mL/bottle

Clobetasol propionate (Restricted)

Indications: short term therapy of severe resistant inflammatory skin disorders.

Contraindications: *see* under betamethasone.

Cautions: *see* notes above; not more than 50g of 0.05% should be applied per week.

Side-effects: *see* notes above.

Application: apply thinly to the skin 1-2 times daily for not more than 4 weeks.

Preparations

Clobetasol propionate cream, 0.05% cream, 25 g/tube

Clobetasol propionate ointment, 0.05% ointment, 25 – 30 g/tube

Clobetasone butyrate (Restricted)

Indications: eczema and dermatitis of all types; being moderate in potency it is applied between courses of potent steroids.

Contraindications, cautions and side-effects: *see* notes above.

Application: apply thinly 1-2 times daily.

Preparations

Clobetasone butyrate cream, 0.05% cream; 25-30 g/tube

Clobetasone butyrate ointment, 0.05% ointment; 25-30 g/tube

Hydrocortisone

Indications: mild inflammatory skin disorders.

Contraindications, cautions and side-effects: *see* notes above.

Application: apply thinly 1-2 times daily.

Preparations

Hydrocortisone cream, 1% cream, 15 g/tube

Hydrocortisone ointment, 1% ointment; 15 g/tube

13: Skin preparations

13 C.2: Topical corticosteroids with antimicrobials

Antifungal + corticosteroids

Preparations containing antifungal agents such as nystatin or econazole in combination with hydrocortisone are recommended for use in inflammation with fungal skin infections. Application to skin is 1-2 times daily.

Preparations

Antifungal + steroid cream; 15 g/tube

13 C.3: Topical corticosteroids with keratolytics

Betamethasone dipropionate + salicylic acid (Restricted)

Indications: psoriasis and seborrhoea.

Application: apply thinly 1-2 times daily.

Preparations

Betamethasone dipropionate + salicylic acid lotion, 0.05% + 2% lotion; 30 mL/bottle

Betamethasone dipropionate + salicylic acid ointment, 0.05% + 3%; 30 g/tube

Dexamethasone acetate + salicylic acid (Restricted)

Indications: psoriasis and seborrhoea.

Application: apply thinly 1-2 times daily.

Preparations

Dexamethasone acetate + salicylic acid skin ointment, 0.12% + 3% ointment; 30 g/tube

13 D: Psoriasis and eczema preparations

13 D.1: Creams and ointments for psoriasis

Calcipotriol with betamethasone (Restricted)

Indications: Psoriasis

Dose: Scalp psoriasis: Apply 1–4 g once daily usual duration of therapy 4 weeks; if necessary, treatment may be continued beyond 4 weeks or repeated, on the advice of a specialist, shampoo off after leaving on scalp overnight or during day, when different preparations containing calcipotriol used together, maximum total calcipotriol 5 mg in any one week.

Mild to moderate plaque psoriasis: Apply once daily for 8 weeks; if necessary, treatment may be continued beyond 8 weeks or repeated, on the advice of a specialist, apply to maximum 30% of body surface, when different preparations containing calcipotriol used together, max. total calcipotriol 5 mg in any one week; maximum 15 g per day. Stable plaque psoriasis: Apply once daily for 4 weeks; if necessary, treatment may be continued beyond 4 weeks or repeated, on the advice of a specialist, apply to a maximum

30% of body surface, when different preparations containing calcipotriol used together, max. total calcipotriol 5 mg in any one week; maximum 15 g per day.

Preparations

Calcipotriol with betamethasone cream containing betamethasone 500 microgram per 1 gram, calcipotriol 50 microgram per 1 gram
Calcipotriol with betamethasone gel containing betamethasone 500 microgram per 1 gram, calcipotriol 50 microgram per 1 gram

13 D.3: Oral preparation for psoriasis

Acitretin (Restricted)

Indications: severe extensive psoriasis, severe ichthyosis, palmoplantar pustular psoriasis.

Contraindications: hepatic and renal impairment; pregnancy and breast feeding.

Cautions: serious precautions must be taken to avoid pregnancy during therapy and at least 2 years after treatment; avoid high doses of vitamin A; regularly monitor hepatic and renal functions; not recommended for children except in very serious cases; avoid excessive exposure to sunlight.

Side-effects: dryness of mucous membranes, of skin and of conjunctiva; palmoplantar exfoliation, epidermal fragility, paronychia, reversible hair thinning and alopecia,

myalgia and arthralgia, nausea, malaise, headache, drowsiness and sweating; photosensitivity, mood changes and blood disorders.

Dose: a specialist should strictly supervise administration and use. Initially, adult 25-30 mg daily for 2-4 weeks then adjust dose according to response, usually 25-50 mg daily.

Preparations

Acitretin capsules, 10 mg cap.
Acitretin capsules, 25 mg cap.

13 E: Preparations for acne

Acne results from excessive sebaceous gland secretion and colonization of glands by bacteria. The skin pores become clogged leading to pimples and inflamed, infected abscesses. Treatment of acne should be centred on early prevention of excessive scarring. Treatment choice depends on whether the acne is predominantly inflammatory or comedonal and its severity.

Topical treatment is useful in most mild to moderate acne. Systemic treatment with antibiotics is kept for moderate to severe cases or when topical treatment is not effective. Severe acne may be treated with oral retinoids under the supervision of specialist dermatologist. Comedonal and inflamed acne respond well to topical application of benzoyl peroxide. Alternatively, topical antibiotic preparations such as clindamycin may be effective.

13: Skin preparations

Benzoyl peroxide

Indications: acne vulgaris.

Cautions: avoid contact with eyes, mouth and mucous membrane; has a bleaching property.

Side-effects: initial skin irritation.

Application: initiate treatment with lower strength, apply 1-2 times daily; increase strength gradually.

Preparations

Benzoyl peroxide in clay base, 2.5% , 20 g/tube

Clindamycin phosphate (Restricted)

Indications: acne vulgaris.

Cautions: should be immediately discontinued if severe skin reaction occurs.

Side-effects: rash and urticaria.

Application: apply twice daily.

Preparations

Clindamycin phosphate topical solution. 1% solution; 30-50 mL/bottle

Erythromycin

Indications: acne vulgaris.

Side-effects: irritation.

Dose: apply twice daily.

Preparations

Erythromycin topical solution, 2% solution, 50 mL/bottle

Isotretinoin (Restricted)

Indications: severe acne, which has not responded to other, forms of treatment; severe recalcitrant cystic and conglobate acne.

Contraindications: pregnancy and breast feeding; renal and hepatic impairment, hyperlipidaemia.

Cautions: pregnancy should be excluded before initiating therapy, and to be avoided during and one month after treatment. Hepatic function and plasma lipid are to be monitored before and during treatment.

Side-effects: see under Acitretin (sec.13 D.3).

Dose: initially 500 microgram/kg daily in 1-2 divided doses for 4 weeks; when good response is achieved, continue for 8-12 weeks; if response is not good, increase dose to 1 mg/kg daily.

Preparations

Isotretinoin capsules, 5 mg cap.

Isotretinoin capsules, 10 mg cap.

Isotretinoin capsules, 20 mg cap.

Tretinoin

Indications: mild to moderate acne.

Contra-indications: pregnancy, cutaneous epithelioma.

Cautions: severe acne, exposure to UV, contact with mucous membranes, eczematous, broken or sunburned skin should be avoided.

Side-effects: redness, skin peeling, pruritus.

Dose: apply 1-2 times daily.

Preparations

Tretinoin cream, 0.025%, 60 g/tube

Tretinoin cream, 0.05%

13 F: Preparations for warts

Warts are small skin growths caused by any of the human papilloma virus types. Warts can develop at any age and are more common at childhood and least common in the elderly. Although warts on the skin are easily spread from one area on the body to another, they are rarely contagious from one person to another. Genital warts however are contagious. The least destructive measures should be applied to remove warts, as they tend to be self-limiting and eventually disappear spontaneously. Strong salicylic acid, lactic acid or trichloro-acetic acids preparations are applied for the removal of warts. They tend to cause considerable irritation of the treated skin. Preparations containing silver nitrate are also applied for the removal of warts.

Salicylic acid + lactic acid (Restricted)

Indications: warts.

Contraindications: diabetes.

Cautions: avoid application on broken skin, ano-genital region, large surface areas or the face.

Application: apply daily.

Preparations

Salicylic acid + lactic acid in flexible collodion paint, 16.7% + 16.7% solution; 15 mL/bottle

Silver nitrate sticks

Indications: warts.

Cautions: avoid application to intact skin, open wound or the face. Not suitable for ano-genital region or large areas.

Side-effects: staining of skin and cloths.

Application: apply daily to affected skin for a maximum of 3 applications.

Preparations

Silver nitrate caustic pencil; 75% Silver Nitrate + 25% Potassium Nitrate/pencil

13 G: Anti-infective skin preparations

The skin can be infected by various aerobic and anaerobic bacteria, herpes viruses, dermatophytes, monilia and protozoa. Superficial and mild skin infections require only local cleansing with disinfectants. In severe widespread life threatening skin infections, it is prudent to initiate treatment promptly with suitable systemic anti-infective agents.

13 G. 1: Antibacterial agents

Staphylococcus and streptococcus microorganisms mostly cause bacterial skin infections. Infections from less common bacteria may develop in hospitals or while gardening or swimming in a lake, ocean or a pond. Some people are at special

13: Skin preparations

risk of developing skin infections such as diabetics and the immuno-compromised.

Topical application of antibacterials may cause systemic toxicity if a large area of the skin is being treated. To minimize the emergence of resistance, it is preferable to use topically only those antibacterials that are not given systemically. The infecting microorganism and its sensitivity should be identified prior to treatment especially in patients residing in hospitals where resistant organisms are common.

Deeply sited infections as in *erysipelas* and *cellulites* are treated with systemic antibacterials.

Fusidic acid

Indications: staphylococcal skin infections.

Cautions: avoid contact with eyes.

Application: apply 3-4 times daily.

Preparations

Fusidic acid skin cream, 2% cream; 15 g/ tube

Sodium fusidate skin ointment, 2% ointment; 15 g/tube

Mupirocin (Restricted)

Indications: bacterial skin infections.

Cautions: avoid over use to prevent the emergence of bacterial resistance.

Application: apply 3 times daily for not more than 10 days.

Preparations

Mupirocin skin ointment, 2% ointment, 15 g/tube

Silver Sulfadiazine (Silver Sulphadiazine)

Indications: prophylaxis and treatment of infection in burn.

Contraindications: sensitivity to sulphonamides; pregnancy and breast feedings.

Cautions: renal and hepatic impairment; G6PD deficiency.

Side-effects: blood disorders on prolonged use; allergic reactions, argyria (skin discolouration).

Application: apply daily until satisfactory healing of the burn is achieved.

Preparations

Silver Sulfadiazine cream, 1% ; 50 g/tube

Silver Sulphadiazine cream, 1% ;500 g/jar

Tetracycline

Indications: sensitive bacterial skin infections including acne vulgaris, prophylaxis of treatment of infections following skin abrasions, minor cuts, wounds or burns.

Caution: Avoid contact with skin around eyes; may stain clothing.

Application: apply 2 or 3 times a day.

Preparation

Tetracycline skin ointment 3%; 20 g/tube

13 G.2: Antifungal agents

Correct diagnosis should be established before treatment with topical antifungal preparations begins. Most ringworm infections, including *tinea pedis*, can be treated with topical imidazole derivatives such as clotrimazole, econazole and miconazole, which are very effective. Widespread fungal skin infections should be treated systemically with fluconazole, itraconazole or ketoconazole (*see* sec 5 B.2)

Other preparations such as nystatin and compound benzoic acid (Whitfield's ointment) are broad-spectrum antifungals.

Lotions and sprays are generally preferred when large or hairy areas are involved. Ointment is better avoided on moist surfaces because of its occlusive properties.

13 G.2.1: Imidazole derivatives

Clotrimazole

Indications: fungal skin infections.

Side-effects: skin irritation and some times sensitivity.

Application: apply 2-3 times daily. Continue treatment for further 2 weeks after lesions have healed.

Preparations

Clotrimazole cream, 1% cream; 15-20 g/tube

Clotrimazole solution, 1% solution; 30 mL/ bottle

Econazole nitrate

Indications: fungal skin infections.

Side-effects: skin irritation and some times sensitivity.

Application: apply 2-3 times daily. Continue treatment for further 2 weeks after lesions have healed.

Preparations

Econazole nitrate cream, 1% cream; 15-20 g /tube

Econazole nitrate lotion, 1% lotion; 30 mL/bottle

Miconazole nitrate

Indications: fungal skin infections.

Side-effects: skin irritation and some times sensitivity.

Application: apply 2 times daily. Continue treatment for further 10 days after lesions have healed. For nail infections, use tincture preparation daily.

Preparations

Miconazole nitrate cream, 1% cream; 15-20 g/tube

Miconazole nitrate lotion, 1% lotion

Miconazole nitrate tincture, 2% solution; 30 mL/bottle (**Restricted**)

13: Skin preparations

13 G.2.2: Other antifungal preparations

Nystatin

Indications: fungal skin infection due to *candida* species.

Application: apply 2-4 times daily, continue treatment for a week after lesions have healed .

Preparations

Nystatin cream, 100,000 units/g cream; 15-20 g/tube

Salicylic acid + benzoic acid (Whitfield's ointment)

Indications: fungal skin (ring-worm) infections.

Application: apply twice daily.

Preparations

Benzoic acid + salicylic acid ointment, 6% + 3% ointment (Whitfield's ointment); 25-40 g/tube

13 G.3: Parasiticial preparations

Antilice spray

A suitable preparation should be available for general use

Antilice spray; 100-120 mL/spray

Permethrin

Indications: effective for scabies and crab lice.

Cautions: avoid contact with eyes; do not use on broken or secondarily infected skin; children under 6

months, medical supervision required for cream rinse (head lice); children aged 2 months–2 years, medical supervision required for dermal cream (scabies).

Side-effects: pruritus, erythema, stinging, rashes and oedema.

Dose: Scabies, apply 5% preparation over whole body and wash off after 8–12 hours; child apply over whole body including face, neck, scalp and ears; if hands washed with soap within 8 hours of application, they should be treated again with cream; repeat application after 7 days.

Crab lice, adult over 18 years, apply 5% cream over whole body, allow to dry naturally and wash off after 12 hours or after leaving on overnight; repeat application after 7 days.

Preparations

Permethrin cream, 5%, 30 g/tube

Permethrin lotion, 1%, 59 mL bottle

13 G.4: Antiviral agents

Aciclovir (Acyclovir) (Restricted)

Indications: herpes simplex and varicella zoster infections.

Cautions: avoid contact with eyes and mucous membranes.

Side-effects: transient stinging or burning, erythema, itching or drying of the skin.

Dose: apply to lesions five times daily for 5–10 days starting at first signs of attack.

13: Skin preparations

Preparations

Aciclovir cream 5%, 2-10 g/tube

13 H: Skin disinfectants

13 H.1: Cationic surfactants and soaps

Cetrimide

Indications: skin disinfectant.

Cautions: avoid contact with eyes; avoid application on body cavities.

Side-effects: skin irritation.

Application: apply 1-2 times daily.

Preparations

Cetrimide cream, 0.5% cream; 30-50 g/tube

13 H.2: Astringents, oxidisers and dyes

Hydrogen peroxide solution

Indications: skin disinfectant, for cleansing and deodorizing wound and ulcers.

Cautions: bleaches fabrics and hair; avoid deep or large wounds.

Preparations

Hydrogen peroxide solution, 6% (20 vols); 150 mL/bottle

13 I: Antiperspirants

Aluminium chloride hexahydrate (Restricted)

Indications: hyperhidrosis.

Cautions: avoid contact with eyes or mucous membrane; avoid use on broken or irritated skin.

Application: apply at night and wash next morning. Initially daily and then less frequently as condition improves. Do not shave the area for the next 12 hours.

Preparations

Aluminium chloride hexahydrate in alcoholic basis lotion, 20% lotion; 60 mL/bottle

13 J: Depigmenting agents

Hydroquinone interferes with the formation of new melanin causing reversible depigmentation. It is indicated for the gradual bleaching of hyperpigmented skin in conditions such as melasma, freckles and senile lentigines.

Hydroquinone (Restricted)

Indications: skin hyperpigmentation.

Cautions: avoid exposure to sun light.

Application: apply 1-2 times daily to the affected skin and rub well .

Preparations

Hydroquinone cream, 4%, 30 g/tube

13: Skin preparations

13 K: Pigmenting agents

Methoxsalen (Restricted)

Indications: photo chemotherapy of vitiligo, psoriasis.

Contraindications: sensitivity to methoxsalen; aphakia; invasive squamous cell carcinoma or melanoma.

Cautions: avoid extensive exposure to sun or ultraviolet light.

Side-effects: nausea, pruritus, erythema, skin pain, nervousness, insomnia, psychological depression.

Dose: vitiligo, orally 20 mg, 2-4 hours before UVA exposure.

Psoriasis, 10-70 mg orally 2 hours before UVA radiation.

Application: apply 1% lotion topically to area of vitiligo and expose to UVA source; once a week treatment intervals are generally recommended

Preparations

Methoxsalen capsules, 10 mg cap.

Methoxsalen lotion, 0.75-1%, 25 mL bottle

Ammoidine + ammidine paint (Restricted)

Indications: topical therapy of vitiligo.

Contraindications: sensitivity to the drug.

Cautions: avoid excessive exposure to sunlight.

Side-effects: local irritation.

Application: cautiously apply to affected areas and expose to sun or ultraviolet light.

Preparations

Ammoidine + ammidine paint, 0.75 mg + 0.25 mg/mL; 30 mL paint

13 L: Topical circulatory preparations

Heparinoid (Restricted)

Indications: Superficial thrombophlebitis. Bruising. Haematoma

Cautions: Should not be used on large areas of skin, broken or sensitive skin, or mucous membranes

Dose: Apply up to 4 times a day

Preparations

Heparinoid gel, 0.3%

Heparinoid cream, 0.3%

14: Immunological Products and Vaccines

Section 14: Immunological Products and Vaccines

- Immunoglobulins
- Vaccines and antisera

14 .A: Immunoglobulins

Human immunoglobulin (Ig) preparations are commonly used now compared to the previously widely used animal types. Human immunoglobulins are of two types, normal immunoglobulin and specific immunoglobulins.

14 A.1: Normal immunoglobulin

Normal immunoglobulin (Ig) is prepared from pooled plasma obtained from at least 1,000 donors. It contains antibodies to measles, mumps, varicella, hepatitis A, and other viruses that are currently prevalent in normal individuals. Normal immunoglobulin is administered intramuscularly in certain clinical situations to prevent or modify some infectious diseases. It is indicated for the protection of susceptible contacts against hepatitis A virus, provided that the injection is given within 2 weeks of exposure. In susceptible contacts of patients with measles, especially those with immune deficiency states, the injection should be administered within 5 days of exposure. In pregnant women exposed to rubella and when therapeutic

abortion is not feasible, immunoglobulin injection is given, although congenital foetal abnormalities might develop.

Normal immunoglobulin is also given in cases of hypogammaglobulinaemia.

Cautions and side-effects of immunoglobulins include malaise, chills, fever, back pain and anaphylactic reactions. Immunoglobulin contains varying quantities of IgA; it should be used with caution in patients with IgA antibodies or selective IgA deficiencies.

Human normal immunoglobulin 16%

Dose: consult manufacturer instructions.

Preparations

Normal immunoglobulin injection, 16%; 2 mL ampoule

Human immunoglobulin

Dose: consult manufacturer instructions

Preparations

Human immunoglobulin injection, 3 g vial

Human immunoglobulin with IgM, IgA, and IgG injection, 5% preparation, 10 mL vial

Human immunoglobulin with IgM, IgA, and IgG injection, 5% preparation, 50 mL vial

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14 A.2: Specific immunoglobulins

Specific immunoglobulins are meant to contain a high level of a specific antibody. They are prepared by pooling the plasma of selected donors.

Anti-D (RH₀) immunoglobulin

Indications: in rhesus-negative women for prevention of Rh₀ (D) sensitisation to foetal rhesus-positive cells which may pass into the maternal circulation.

Cautions: administer within 72 hours following any sensitising episodes e.g. due to miscarriage, abortion or birth. If more than 72 hours period has passed, some protection can still be achieved by giving the proper dose. The dose is determined by the level of exposure to rhesus-positive blood.

Side-effects: discomfort at site of injection, anaphylactic reaction, lethargy, myalgia, elevated bilirubin level.

Dose: 250-500 micrograms (1250-2500 units) by deep intramuscular injection during the first 72 hours after exposure.

Preparations

Anti-D (RH₀) immunoglobulin injection, 250 microgram vial

Anti-varicella zoster human immunoglobulin (CDL)

Indications: Prophylaxis in high-risk individuals against infections with varicella.

Cautions: bleeding disorders; avoid intravenous administration; specific antibody (IgA) deficiency.

Side-effects: local pain and redness at the site of injection; malaise, headache and abdominal cramp.

Dose: by deep intramuscular injection, child up to 5 years 250 mg, 6-10 years 500 mg, 11-14 year 750 mg, adults 1g. A second dose required if further exposure occurs after 3 weeks.

Preparations

Varicella-zoster human immunoglobulin injection, 10%; 5 mL vial (500 mg injection)

Hepatitis B immunoglobulin (HBIG) (Restricted)

Indications: prophylaxis from infection with hepatitis B virus.

Cautions: individuals with a specific IgA deficiency; thrombocytopenia or bleeding disorders; should not be administered intravenously.

Side-effects: local pain, tenderness, angioedema, and urticaria.

Dose: intramuscular injection, adult 500 units, child under 5 years 200 units, 5-10 years 300 units

Preparations

Hepatitis immunoglobulin HBIG injection, 200-400 units/mL; 5 mL vial

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Human anti-cytomegalovirus immunoglobulin

Indications: prophylaxis in patients receiving immunosuppressive therapy.

Side-effects: facial flushing, nausea and vomiting, muscle cramps, wheezing, diaphoresis.

Dose: intravenous infusion, 150 mg/kg as a first dose then 100 mg/kg/dose on weeks 2,4,6 and 8, then 50 mg/kg/dose on weeks 12 and 16.

Preparations

Human anti-cytomegalovirus immunoglobulin injection, 50 mL vial for intravenous infusion.

Rabies immunoglobulin (human)

Indications: following exposure of non-immunised individual to an infected animal. Adjunct to rabies vaccine in high-risk areas.

Cautions: avoid intravenous administration; allergy to avian protein or chicken eggs; allergy to specific immunoglobulins.

Side-effects: local pain at site of injection; fever, urticaria.

Dose: intramuscular injection of 10 units/kg and 10 units/kg by infiltration around the wound.

Preparations

Rabies immunoglobulin injection; 150 IU/mL; 2 and 5 mL vial

Consult pharmacy about available preparation.

Tetanus immunoglobulin (human)

Indications: management of proven or suspected tetanus in non-immunised patients or when less than 3 doses of tetanus vaccine have been received.

Cautions: should be used in addition to surgical toilet, prophylactic antibiotics and tetanus vaccine; avoid intravenous administration.

Side-effects: hypersensitivity, pain, tenderness, erythema, muscle stiffness; fever, hives, angioedema, local inflammation.

Dose: intramuscular injection, prophylaxis 250 units, increased to 500 units if there is a high risk or more than 24 hours have elapsed.

Preparations

Tetanus immunoglobulin (human) injection, 250 IU/mL, 1 mL pre-filled syringe

Consult pharmacy about available preparation

14 B: Vaccines and antisera

14 B.1: Sera and antitoxins

Anti-snake venom serum polyvalent (lyophilised)

Indications: treatment of acute systemic envenoming from snakebite.

Cautions: sensitivity test should be conducted with diluted antivenom (intra-dermally, 0.02 mL of 1:100 dilution with normal saline).

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Side-effects: anaphylactic reaction.

Dose: intravenous injection or infusion, dilute with normal saline. Carefully read manufacturer's instruction.

Preparations

Anti-snake venom serum polyvalent injection, 10 mL/ampoule

Anti-scorpion venom serum

Indications: treatment of acute systemic envenoming from scorpion stings specifically when cardiovascular and neurological manifestations are evident.

Cautions: conduct a sensitivity test before full dose administration.

Side-effects: anaphylactic reaction.

Dose: usually given as a single dose.

Consult the manufacturer's instructions.

Preparations

Anti-scorpion venom serum injection

but may not be as long as that produced from natural infection. The vaccine causes sub clinical infection followed by antibody production.

Inactivated (e.g. hepatitis B and influenza) vaccines provide immunogenicity without infectivity. They are administered parenterally, but repeated doses are required to produce adequate antibodies. Booster doses, in most cases, are required. The duration of immunity varies from months to years.

Toxoids are prepared from bacterial exotoxins. Inoculation with toxoids promotes the development of antibodies. Repeated administration and booster doses are required.

Side-effects: Parenteral administration of vaccines may cause local reaction at the site of injection. Mild generalized reaction in the form of fever, malaise and headache may occur. Vaccines may contain some residual egg protein, additive antibacterials or animal serum, which could cause generalized allergic reaction.

Contra-indications: Prior allergic reactions to a specific vaccine or related vaccines are contraindication. Live attenuated vaccines are contraindicated in the following conditions:

Immunosuppressive therapy.

Immunodeficiency disorders.

Leukaemia, lymphoma or generalized malignancy.

Within three months of any injection of immunoglobulin.

14 B.2: Vaccines

Vaccines are antigenic materials that stimulate production of antibodies and other components of the immune mechanism. They may consist of live attenuated infective microorganism (virus or bacteria), inactivated forms of infective microorganism or bacterial toxoids. Live attenuated (e.g. OPV, rubella, measles, mumps or BCG) vaccines; produce immunity that is durable

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(Should be used cautiously during pregnancy because of a possible risk to the foetus.)

Indications: vaccines are indicated in the control of certain preventable infections, as is the case with the expanded programme on immunisation (EPI). Some vaccines may be used as a prophylactic measure in patients exposed to high risk of acquiring a disease (e.g. hepatitis B) or at high risk of developing complications (e.g. influenza in the elderly). Population exposed to localized outbreak of disease and those travelling to endemic areas should also be vaccinated.

in Oman in 1981 and has been repeatedly reviewed. Substantial progress has been made by EPI in the last two decades.

Immunisation coverage levels have increased substantially from 10% in 1981 to near 100% in 1995 and maintained since. This has resulted in a marked decline in EPI targeted diseases.

The followings are immunisation schedules effective in Oman. The EPI vaccines are available at the PHC levels.

14 B.2.1: Vaccines applied in the expanded programme on immunisation

The expanded programme on immunisation (EPI) was first launched

14: Immunological Products and Vaccines

A. Childhood Immunisation schedule / 2016

<i>Age</i>	<i>Vaccine</i>
At birth	BCG HBV
2 months	Hexa-1 (HBV, DTP, Hib, IPV) PCV-1
4 months	OPV-1 Hexa-2 (HBV, DTP, Hib, IPV) PCV-2
6 months	OPV-2 Hexa-3 (HBV, DTP, Hib, IPV)
9 months	Vitamin A 100, 000 IU
12 months	MMR-1 Varicella
13 months	PCV- Booster
18 months	OPV-Booster DTP-Booster MMR-2 Vitamin A 200,000 IU

B. School immunisation schedules

Class 1 (6-7 years)

<i>Vaccine</i>	<i>Immunisation</i>
OPV booster	One dose
DT booster	Give one dose to all children. (Booster dose)
Or DT (2 doses)	Or Give 2 doses at 6-8 weeks intervals if not vaccinated previously, or no doc- umentary evidence available, i.e. im- munisation card

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Class 6 (12-13 years)

<i>Vaccine</i>	<i>Immunisation</i>
Td booster	Give one booster dose for boys and girls fully immunised with DPT and/or DT.
Or	
Td (2 doses)	If not fully immunised as above or no record available, give two dose of Td at 6-8 weeks intervals.

Class 11 (17-18 years)

<i>Vaccine</i>	<i>Immunisation</i>
OPV booster	To be given to all students at this level
Td booster	Give one booster dose for students fully immunised with DPT and/or Td. If not fully immunised as above or no record available, give two dose of Td at 6-8 weeks intervals.
Or	
Td (2 doses)	

C. Females of childbearing age (15-49 years) and adult males (18 years or above)

<i>Vaccine</i>	<i>Immunisation</i>
(TT)	- If immunised, give one booster of TT every 10 years - If not immunised or immunisation status unknown, give 2 doses of TT at an interval of 4-6 weeks apart - Give 3rd dose of TT with a minimum of 6 months after the 2nd dose - Give 4th dose with a minimum interval of one year after the 3rd dose followed by a 5th dose after one year. - Subsequently give one booster dose every 10 years.
Rubella	Administer a single dose to postpartum women within 40 days after delivery if no evidence of previous vaccination documentation

Route, site and dose of EPI vaccines

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<i>Vaccine</i>	<i>Route</i>	<i>Site</i>	<i>dose</i>
BCG	Intradermal	Lt.deltoid	0.05 mL
OPV	Oral	Mouth	2drops
DPT	Intramuscular (IM)	Antero lateral thigh muscle	0.5 mL
HBV	IM	=	0.5 mL
Hib	IM	=	0.5 mL
Measles	IM	=	0.5 mL
MMR	IM	=	0.5 mL
DT	IM	Deltoid muscle	0.5 mL
Td/TT	IM	=	0.5 mL
TT	IM	=	0.5 mL
Rubella	IM	=	0.5 mL

- BCG: Bacillus Calmette-Guerin vaccine
DPT: Diphtheria-pertussis-tetanus vaccine
DT: Tetanus –diphtheria vaccine for children
HBV: Hepatitis B vaccine
Hib: Haemophilus influenzae type B vaccine
IPV: Inactivated polio vaccine
Td: Tetanus-diphtheria vaccine for adults
OPV: Oral polio vaccine
PCV7: Pneumococcal conjugate vaccine, 7-valent
TT: Tetanus toxoid
MMR: Measles, Mumps and Rubella (German measles)
-

14 B.2.2: Other vaccines

Inactivated rabies vaccine

Indications: prophylaxis immunisation to high-risk individuals; for treatment after exposure in conjunction with rabies immunoglobulin.

Dose: for prophylaxis, 2 doses with a month interval, followed by a booster dose after 6-12 months with further doses every 2-3 years.

For post-exposure treatment, a dose on day 1 (2 injections at 2 sites intramuscular or subcutaneous), followed by reinforcing doses at days 7 and 28.

Preparations

Inactivated rabies vaccine injection, single dose prefilled syringe

Hepatitis B vaccine for adults

Indications: vaccination of individuals at high risk of contracting hepatitis B.

Dose: intramuscularly, 3 doses of 20 microgram each, the 2nd dose 1 month and the 3rd dose 6 months after the first dose.

Preparations

Hepatitis B vaccine for adult injection, 20 microgram/mL single dose injection

Inactivated influenza virus vaccine

Indications: prophylaxis against influenza in adults and children

older than 6 months of age and who are at high risk (pilgrims (Omra/Hajj), health workers, ≥ 65 years and immunocompromised).

Contraindications: allergy to egg, chicken, drugs like gentamicin, formaldehyde and sodium deoxycholate.

Side-effects: mild fever, local swelling.

Dose: by intramuscular injection on annual basis, in adult and children from 36 months and above: single 0.5 mL dose, in children from 6 to 35 months: two doses of 0.25 mL each given 4 weeks apart.

Preparations

Influenza vaccine injection, in pre-filled syringe.

Note: the vaccine is manufactured every year with the strains of circulating influenza viruses.

Meningococcal (A, C, W135 and Y) vaccine

Indications: control of outbreak, routinely to pilgrims as protective measure and to individuals with high-risk exposure.

Dose: deep subcutaneous injection, 0.5 mL single dose. The dose is the same for child (>2 years) and adult.

Preparations

Meningococcal (A, C, W 135 and Y) vaccine injection, 0.5 mL vial single dose.

Pneumococcal vaccine

Indications: immunisation of susceptible individuals over the age of

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2 years with any of the following conditions: Homozygous sickle cell disease; Asplenia or severe dysfunction of the spleen; Chronic renal disease; Coeliac syndrome; Immunodeficiency or immunosuppression; Chronic heart disease; Chronic lung disease; Chronic liver disease; Diabetes mellitus.

Dose: 0.5 mL by subcutaneous or intramuscular injection

Preparations

Pneumococcal vaccine injection,
0.5 mL single dose injection

14 B.2.3: Diagnostic agents

Tuberculin

Indications: in the mantoux test as diagnostic agent for tuberculosis.

Dose: various dilutions are available (10, 100 and 1000 units / mL). Follow manufacturer instructions very carefully.

Preparations

Tuberculin purified protein derivative (PPD) 2 -3 IU (10 tests)/vial

Section 15: Anaesthesia

- General anaesthesia
- Local anaesthesia

15 A: General Anaesthesia

The state of general anaesthesia is a drug-induced total absence of perception of all sensations. The depth of anaesthesia required for surgical procedures can be achieved by a variety of drugs given alone, or more often in combinations. Intravenous anaesthetics are commonly used for induction followed by administration of inhalational anaesthetics. Specific drugs are often used to produce muscular relaxation. Such drugs may seriously interfere with spontaneous respiration.

The choice of anaesthetic is determined by the understanding of the pharmacokinetic and pharmacodynamic properties of the various drugs and the influence of the underlying pathophysiological conditions.

15 A.1: Intravenous anaesthetics

Intravenous anaesthetics are used mainly for induction of anaesthesia and may be used alone to produce anaesthesia for short surgical procedures. They produce a rapid action that might be associated with hypotension and apnoea. Adequate

resuscitation facilities should always be at hand. It should be noted that the elimination of these drugs could be delayed beyond the short anaesthetic effect.

It is important to remember that the requirements for intravenous anaesthetics vary among individuals and the recommended dose is only a guide. It could be decreased or increased according to the general conditions of the patient.

Etomidate is an induction agent associated with rapid recovery without a hangover effect. It causes less hypotension than thiopental and propofol during induction. It produces a high incidence of extraneous muscle movement, which can be minimised by an opioid analgesic or a short-acting benzodiazepine given just before induction. Pain on injection can be reduced by injecting into a larger vein or by giving an opioid analgesic just before induction. Etomidate can suppress adrenocortical function, particularly during continuous administration, and it should not be used for maintenance of anaesthesia.

Thiopental is the most widely used intravenous anaesthetic that produces a pleasant induction. It is devoid of any analgesic effect. It acts rapidly (10-30 seconds) but it may take longer (up to 2 minutes) in patients with cardiac disease or shock. Redistribution to other parts of the body accounts for the short sleep and the re-awaking of patient. Repeated doses are cumulative since

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metabolism is slow and distribution sites are saturable. Extravascular injections are painful and may cause local tissue necrosis.

Ketamine can be given both intravenously and intramuscularly. It takes 1 minute to induce a state of sedation, amnesia, immobility and analgesia. It causes an increase in muscle tone, cardiac stimulation and hallucination. Hallucination and psychotic sequelae are disadvantages that might be reduced when drugs such as diazepam are also used. It is particularly suitable for children especially when repeated use is needed. Recovery is relatively slow.

Propofol induces as rapid anaesthesia as thiopentone. Pain may be experienced at the site of injection, but rarely is followed by phlebitis or thrombosis. Anaesthesia may be maintained with continuous infusion of propofol combined with opioids and/or other inhalational anaesthetics.

There have been some reports of seizure or involuntary movement during induction or emergence from propofol-induced anaesthesia. Emergence from propofol anaesthesia is more rapid than that with thiopental even following prolonged infusion.

Etomidate

Indications: induction of general anaesthesia.

Contraindications, Cautions and Side-effects: see notes above;

avoid in acute porphyria, pregnancy, breast-feeding.

Dose: adult and child, by slow intravenous injection, 300 micrograms/kg max. total dose 60 mg; elderly 150–200 micrograms/kg; max. total dose 60 mg.

Preparations

Etomidate injection, 2 mg/mL, 10 mL ampoule

Thiopental sodium (Thiopentone sodium)

Indications: induction of general anaesthesia; general anaesthesia of short duration.

Contraindications: porphyria; airway obstruction.

Cautions and side-effects: see notes above; in oropharyngeal surgery; reduce dose in the elderly and in severe hepatic disease.

Dose: by intravenous injection, as a 2.5% solution, initially 100–150 mg for a fit premedicated adult over a period of 10–15 second. Further doses may follow if necessary after 30–60 seconds; maximum 4 mg/kg. Child, for induction 2–7 mg/kg.

Preparations

Thiopental sodium injection, Powder for reconstitution; 500 mg vial

Ketamine hydrochloride

Indications: induction and maintenance of anaesthesia.

Contraindications: hypertension; patients prone to hallucination.

Cautions and side-effects: see notes above.

Dose: intramuscular injection, 4-10 mg/kg produces 10-25 minutes of surgical anaesthesia.

Intravenous injection, 2-4.5 mg/kg over 1 minute, produces 5-10 minutes of surgical anaesthesia.

Intravenous infusion for induction in longer procedures, total dose 0.5-2 mg/kg; maintenance, 10-45 micrograms /kg/minute.

Preparations

Ketamine hydrochloride injection, 50 mg/mL, 10 mL vial

Propofol

Indications: induction and maintenance of anaesthesia.

Contraindications, cautions and side-effects: see notes above.

Dose: induction of anaesthesia, by intravenous injection or infusion, 1.5-2.5 mg/kg at a rate of 20-40 mg every 10 seconds. Child, usual dose in over 8 years, 2.5 mg/kg slowly administered.

Maintenance of anaesthesia, by intravenous injection, 25-50 mg repeated according to response. Intravenous infusion, 4-12 mg/kg/hour.

Preparations

Propofol injection, 10 mg/mL, 20 mL vial

15 A.2: Inhalational anaesthetics

Inhalational anaesthetics may be gases or volatile liquids. They are used for maintenance or induction of anaesthesia. Suitable instruments are needed to control the out-flow rate and concentration. To avoid the occurrence of hypoxia, inhalational anaesthetics are administered with oxygen.

Halothane is a potent anaesthetic with smooth induction and very little irritation. Its association with hepatotoxicity is a main disadvantage. Muscle tone is reduced, but not enough for abdominal surgery.

Isoflurane is less potent than halothane, with good muscle relaxing effect. Its association with hepatotoxicity is less than with halothane. Sevoflurane is a potent rapidly acting inhalational anaesthetic. Its low tissue and blood solubilities and high potency allow for better control of the anaesthesia depth and rapid recovery after discontinuing administration. It is rarely associated with hepatotoxicity.

In Oman, only isoflurane and sevoflurane are approved for use.

Isoflurane

Indications: general anaesthesia.

Contraindications: sensitivity to halogenated compounds.

Side-effects: respiratory depression, hypotension; see notes above.

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Dose: induction, increase gradually from 0.5% to 3% in oxygen or nitrous oxide.

Maintenance, 1-2.5% with nitrous oxide-oxygen. If oxygen is used alone an additional increase of 0.5-1% of isoflurane is needed.

Preparation

Isoflurane, 100 mL bottle

Sevoflurane

Indications: general anaesthesia.

Contraindications and cautions: sensitivity to halogenated compounds.

Side-effects: Nausea and vomiting, excitatory movements, respiratory depression, decreases in heart rate.

Dose: induction, up to 8% in oxygen or nitrous oxide-oxygen. Child, up to 7%.

Maintenance, 0.5-3%.

Preparation

Sevoflurane, 250 mL bottle

15 A.3: Antimuscarinic premedication drugs

Atropine sulphate

Indications: drying of secretions, reversal of excessive bradycardia; adjunct to neostigmine for reversal of non-depolarizing neuromuscular block; other effects see sections 1, 2 and 11.

Contraindications and cautions: cardiac disease, see section 1

Side-effects: see section 1

Dose: premedication by intravenous injection, 300-600 micrograms immediately before induction. Intramuscular injection, 300-600 micrograms 30-60 minutes before induction; Child 20 micrograms/kg.

For management of muscarinic side-effects of neostigmine in the reversal of competitive neuromuscular block, intravenously 600-1200 micrograms. (0.6-1.2 mg).

Preparations

Atropine sulphate injection, 600 micrograms/mL ampoule

Glycopyrronium bromide (CDL)

Indications, contraindications, cautions and side-effects: see under atropine sulphate

Dose: premedication and intra-operative use, intravenous or intramuscular injection 200 microgram or 5 micrograms/kg to a maximum of 400 microgram; Child, 4-8 micrograms/kg preferably by intravenous injection, to a maximum of 200 micrograms.

For management of muscarinic side-effects of neostigmine in the reversal of competitive neuromuscular block, intravenously 10-15 micrograms/kg.

Preparations

Glycopyrronium bromide injection, 200 microgram/mL ampoule

15 A.4: Muscle relaxants

The muscle relaxants used in anaesthesia are also known as neuromuscular blocking agents. They differ from those acting on the spinal cord or brain and applied in musculoskeletal disorders.

Muscle relaxants, by blocking the neuromuscular junction, allow light anaesthesia to be used with adequate relaxation of the abdomen and diaphragm. Tracheal intubation is also facilitated. Their use should always be accompanied by artificial respiration until the drug has been inactivated or antagonized.

15 A.4.1: Non-depolarising muscle relaxants

The non-depolarising muscle relaxants (also known as competitive muscle relaxant) block the neuromuscular junction by competing with acetylcholine. Neostigmine or other cholinesterase inhibitors can reverse their action. In general they belong to two groups, the aminosteroids that includes pancuronium, rocuronium and vecuronium, and the benzylisoquinolinium group, which includes atracurium, cisatracurium, gallamine and mivacurium. They can be classified according to their duration of action into short (15-30 minutes), intermediate (30-40 minutes) and long acting (60-120 minutes), although duration is dose dependent. These drugs have no analgesic or sedative effects or

being a triggering factor for malignant hyperthermia.

Pancuronium is long acting while atracurium is short and cisatracurium, rocuronium and vecuronium are intermediately acting muscle relaxants.

Atracurium besylate

Indications: muscle relaxant for surgery (short to intermediate duration).

Cautions: may cause significant histamine release leading to cardiovascular effects.

Side-effects: skin flushing, hypotension, bronchospasm, anaphylactic reactions.

Dose: intravenous injection, for adults and child over 1 month, 300-600 micrograms/kg, then 100-200 micrograms/kg as required or by intravenous infusion, 5-10 micrograms/kg /minute.

Preparations

Atracurium besylate injection, 10 mg/mL, 2.5 mL ampoules

Atracurium besylate injection, 10 mg/mL, 5 mL ampoules

Cisatracurium

Indications: muscle relaxant for surgery (intermediate duration).

Cautions: hypersensitivity to other benzylisoquinolinium compounds.

Side-effects: less frequent hypotension and bradycardia than atracurium.

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Dose: for intubation, intravenous injection, 150 micrograms/kg, maintenance, 30 micrograms /kg every 20 minutes. Child over 2 years, 100 micrograms/kg, maintenance 20 micrograms/kg every 9 minutes.

By intravenous infusion, adult and child over 2 years, initially, 3 micrograms/ kg/minute, then 1-2 micrograms/kg/minute after stabilization.

Dose reduction by up to 40% may be required when used with isoflurane.

Preparations

Cisatracurium injection, 2 mg/mL, 10 mL ampoules

Cisatracurium injection, 2 mg/mL, 30 mL ampoules

Pancuronium bromide

Indications: muscle relaxant for surgery (long duration); long-term mechanical ventilation in intensive care units.

Cautions: low plasma cholinesterase activity.

Side-effects: hypertension.

Dose: intravenous injection, 70-250 micrograms/kg; maintenance 100 micrograms/kg every 15 minutes. Child, initially, up to 6 months, 150 micrograms/kg, 7 months - 12 years 200 micrograms/kg; maintenance 100 micrograms every 6-9 minutes. Intravenous infusion, for maintenance of block, 8-10 micrograms/kg/minute. Adjusted as necessary.

Preparations

Pancuronium bromide injection, 2 mg/mL, 2 mL ampoule

Rocuronium bromide

Indications: muscle relaxant for surgery (intermediate duration and very rapid onset).

Cautions: reduce dose in renal impairment.

Side-effects: mild vagolytic effect.

Dose: intravenous injection, for intubation, 600 micrograms/kg; maintenance, 150 micrograms/kg. By intravenous infusion, 300-600 micrograms/kg/hour after an initial intravenous injection.

Preparations

Rocuronium bromide injection, 10 mg/1 mL, 5 mL vial

Vecuronium bromide

Indications: muscle relaxant for surgery (intermediate duration).

Cautions: dose adjustment in renal impairment, hepatic failure, obesity and elderly.

Side-effects: hypotension/hypertension, bronchospasm.

Dose: intravenous injection, initially 75-100 micrograms/kg, maintenance, 20-30 micrograms/kg according to response.

By intravenous infusion, 0.8-1.4 micrograms/kg/minute after an initial intravenous dose of 40-100 micrograms/kg.

Preparations

Vecuronium bromide injection, powder for reconstitution, 10 mg vial

15 A.4.2: Depolarising muscle relaxants

The depolarising agents such as suxamethonium depolarise the membrane by acting in a similar manner to acetylcholine. However, the effect is long lasting and results in blocking the transmission and neuromuscular paralysis. The degree of paralysis depends on many variables such as the type of anaesthetic used, the type of muscle affected and the intervals of drug administration.

Neostigmine does not reverse the effects of depolarising neuromuscular blocking agents. Eliminating the depolarising drug mainly by plasma pseudo-cholinesterase terminates their effect. Deficiency in this enzyme will delay the recovery and could be very dangerous if artificial respiration is not mechanically maintained.

Suxamethonium has the most rapid onset and brief duration of action. It is an ideal muscle relaxant. It should be given after induction with anaesthetics because painful muscle fasciculation precedes the muscle paralysis. Atropine premedication reduces the excessive salivation and bradycardia caused by Suxamethonium.

Suxamethonium chloride

Indications: muscle relaxation (rapid onset and short duration).

Contraindications: history of malignant hyperthermia; deficiency of plasma cholinesterase; severe liver disease.

Cautions: neuromuscular disease, cardiac and respiratory disorders, raised intra-ocular pressure; pregnancy.

Side-effects: post-operative muscle pain, hyperkalaemia, tachycardia, arrhythmia, blood pressure changes, apnoea.

Dose: intravenous injection, adult 1 mg/kg (average 0.3-1.1 mg/kg), maximum 500 mg/ hour. Child 1-2 mg/kg.

Intravenous infusion of a solution of 1-2 mg/ mL at a rate of 2-5 mg/minute. Maximum, 500 mg/hour; in child reduce infusion rate according to body weight.

Preparations

Suxamethonium chloride injection, 50 mg/ mL, 2 mL vial

15 A.5: Anti-cholinesterase used in anaesthesia

Neostigmine is used to reverse the effects of non-depolarising muscle relaxants. It is not effective in reversing the effects of depolarising muscle relaxants.

Neostigmine acts rapidly after intravenous injection. It is preferable to use atropine or glycopyrronium

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with neostigmine in order to prevent its muscarinic effects such as bradycardia and excessive salivation.

Neostigmine methyl sulphate

Indications: reversal of non-depolarising neuromuscular blockade.

Contraindications, cautions and side-effects: see notes above and section 10.B.1.

Dose: intravenous injection, 50-70 micrograms/kg, maximum 5 mg usually with atropine or glycopyrronium.

Preparations

Neostigmine methyl sulphate injection, 500 micrograms/mL, 1 mL ampoule

Neostigmine methyl sulphate injection, 500 micrograms/mL, 5 mL ampoule

Neostigmine methyl sulphate injection, 2.5 mg/mL, 5 mL ampoule

15 A.6: Antagonists for central and respiratory depressants.

Respiratory or central depression may result from anaesthetics or premedication drugs. Reversal of depression may involve various measures among which the use of drugs.

Central depression caused by benzodiazepines is reversed by flumazenil. Opioid-induced respiratory depression can be reversed by naloxone.

Doxapram is a central and respiratory stimulant but is of limited use.

Doxapram hydrochloride

Indications: reversal of post-operative respiratory depression.

Contraindications, cautions and side-effects: see section 3.E.

Dose and preparations: see section 3.E

Flumazenil

Indications: reversal of sedative effects of benzodiazepines in anaesthetic, intensive care and diagnostic procedures.

Contraindications: life threatening conditions controlled by benzodiazepines (e.g. status asthmaticus, epilepsy).

Cautions: repeated dose may be needed because of short duration; avoid rapid injection in high-risk patients; hepatic impairment; head injury (fear of convulsion).

Side-effects: nausea, vomiting and flushing; with rapid recovery, agitation, anxiety and fear.

Dose: intravenous injection, 200 micrograms over 15 seconds, then 100 micrograms at 60 seconds intervals if necessary, maximum dose 2 mg.

Preparations

Flumazenil injection, 100 micrograms/mL, 5 mL ampoule

Naloxone hydrochloride

Indications: reversal of opioid-induced respiratory depression.

Cautions: opioid physical dependence, cardiac disease.

Side-effects: precipitation of withdrawal syndrome.

Dose: intravenous injection, 100-200 micrograms; if response not adequate, 100 micrograms every 2 minutes.

Preparations

Naloxone hydrochloride injection, 400 micrograms/mL, 1 mL ampoule

15 B: Local anaesthesia

Local anaesthetics reversibly prevent the generation and conduction of nerve impulse. Their primary site of action is the nerve membrane. They affect all types of nerves and the small nerve fibres (sensory, autonomic) seem to be affected first; larger motor nerves are affected later.

Local anaesthetics have the advantage of being applied by different routes. They can be used topically on mucous membranes, injected to produce infiltration, field block, nerve block, intravenous regional (Bier's block), spinal and epidural anaesthesia.

Local anaesthetics vary widely in their potency, toxicity, duration, solubility in water and ability to penetrate mucous membranes. They are usually effective with a short onset of action (few second – few minutes) and act for a duration

of 1-2 hours. The extent of circulation at the administration site is a major factor affecting duration. Absorption of local anaesthetics into circulation eliminates their local action. Simultaneous administration of vasoconstrictor may double the duration of action. Adrenaline is generally used in concentrations of 1-200,000 in general surgery and 1-80,000 in dentistry. However, vasoconstrictors are better avoided for nerve block of digits, nose or penis, in patients with cardiac disease, and in those receiving antidepressants. Felypressin is a safer vasoconstrictor since the concentrations used with local anaesthetics do not significantly affect the heart rate or blood pressure. Adverse effects usually occur within 20-30 minutes after regional anaesthetic procedure, since plasma peak concentration is attained within this time. These include, hypotension, bradycardia, respiratory depression, cardiac arrest, and convulsion. Great care should be taken to avoid accidental intravascular injection.

Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to traumatized urethra; the drug in these conditions may be extensively absorbed and causes systemic rather than local effects.

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Bupivacaine hydrochloride

Indications: local anaesthetic (long duration and slow onset), suitable for epidural block.

Contraindications: intravenous regional anaesthesia (Bier's block).

Cautions and side-effects: see notes above.

Dose: adjust according to patient weight and nature of procedure.

Local infiltration or peripheral nerve block, 0.25% (up to 60 mL).

Epidural block;

Surgery, lumbar, 0.5% (maximum 20 mL).

Surgery, caudal, 0.5% (maximum 30 mL).

Labour, lumbar, 0.25-0.5% (maximum 12 mL).

Preparations

Bupivacaine hydrochloride injection, 0.25%, 20 mL ampoule

Bupivacaine hydrochloride injection, 0.5%, 20 mL ampoule

Bupivacaine hydrochloride + glucose injection, 0.5% (5 mg/mL) + 80 mg/mL, 4 mL (heavy) ampoule

Levobupivacaine (Restricted)

Indications: Surgical anaesthesia, acute postoperative pain, acute labour pain

Contra-indications: Application to the middle ear (can cause ototoxicity); avoid injection into infected tissues; avoid injection into inflamed tissues; complete heart block; preparations containing preservatives should not be used for caudal, epidural, or spinal block, or

for intravenous regional anaesthesia (Bier's block); should not be applied to damaged skin.

Cautions: The licensed doses stated may not be appropriate in some settings and expert advice should be sought. Cardiovascular disease; debilitated patients (consider dose reduction); elderly (consider dose reduction); epilepsy; hypovolaemia; impaired cardiac conduction; impaired respiratory function; myasthenia gravis; shock.

Side-effects: Anaemia; arrhythmias; blurred vision; cardiac arrest; convulsions; dizziness; drowsiness; feeling of inebriation; headache; lightheadedness; muscle twitching; myocardial depression (resulting in hypotension and bradycardia); nausea; numbness of the tongue and perioral region; paraesthesia (including sensations of hot and cold); peripheral vasodilatation (resulting in hypotension and bradycardia); pyrexia; restlessness; sweating; tinnitus; transient excitation (followed by depression with drowsiness, respiratory failure, unconsciousness, and coma); tremors; vomiting.

Dose: Surgical anaesthesia by peripheral nerve block 2.5–150 mg, dose administered using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution.

Surgical anaesthesia by peribulbar nerve block: 37.5–112.5 mg, dose administered using a 7.5 mg/mL (0.75%) solution.

Surgical anaesthesia by lumbar epidural: 50–150 mg, to be given over 5 minutes, dose administered using

a 5 mg/mL (0.5%) or 7.5 mg/mL (0.75%) solution.

Surgical anaesthesia by intrathecal injection: 15 mg, dose administered using a 5 mg/mL (0.5%) solution.

Surgical anaesthesia by local infiltration: 2.5–150 mg, dose administered using a 2.5 mg/mL (0.25%) solution.

Acute postoperative pain by continuous epidural infusion: 12.5–18.75 mg/ hour, dose administered using a 2.5 mg/mL (0.25%) or 1.25 mg/mL (0.125%) solution; maximum 400 mg per day.

Acute labour pain: initially by lumbar epidural: 15–25 mg every 15 minutes as required, dose administered using a 2.5 mg/mL (0.25%) solution, alternatively (by continuous epidural infusion) 5–12.5 mg/ hour, dose administered using a 1.25 mg/mL (0.125%) solution

Preparations

Levobupivacaine injection, 25 mg / 10 ml ampoule

Levobupivacaine injection, 50 mg / 10 ml ampoule

Lidocaine Hydrochloride (Lignocaine Hydrochloride)

Indications: local anaesthesia, ventricular arrhythmias see section 2.C.

Contraindications: hypovolaemia, complete heart block.

Cautions: epilepsy, bradycardia, impaired cardiac conduction, porphyria, hepatic or respiratory impairment.

Side-effects: see notes above

Dose: infiltration anaesthesia, by injection, 200 mg plain and 500 mg when mixed with adrenaline.

Nerve block, epidural and caudal 1–2% with adrenaline.

Surface anaesthesia, 2–4%.

Preparations

Lidocaine hydrochloride plain injection, 1 %, 50 mL vial

Lidocaine hydrochloride plain injection, 2%, 25–50 mL vial

Lidocaine hydrochloride plain without preservative injection, 2 %, 5 mL vial

Lidocaine hydrochloride heavy injection, 5 % , 10 mL vial

Lidocaine hydrochloride injection with adrenaline injection, 2% + 1:200,000, 20 mL vial

Lidocaine hydrochloride injection with adrenaline injection, 2% + 1:200,000, 2.2 mL dental cartridge

Lidocaine hydrochloride injection with adrenaline injection, 2% + 1:80,000, 1.8 mL dental cartridge

Lidocaine hydrochloride jelly, 2%, 20–30 g/tube

Lidocaine hydrochloride ointment, 5%, 15–35g/tube

Lidocaine hydrochloride spray, 10% preparation, 50 mL pump spray

Lidocaine hydrochloride viscous, 2% preparation

15: Anaesthesia

Prilocaine + felypressin

Indications: infiltration anaesthesia, intravenous regional anaesthesia, nerve block.

Contraindications: hypovolaemia, complete heart block, severe anaemia.

Cautions: epilepsy, bradycardia, impaired cardiac conduction, porphyria, hepatic or renal impairment.

Side-effects: see notes above

Dose: adjusted according to site of operation and response of the patient, to a maximum of 300 mg.

Preparations

Prilocaine hydrochloride + felypressin injection, 30 mg/mL + 0.54 mg/mL, 1.8 mL dental cartridge

Ethyl chloride

Ethyl chloride is applied in spray form for a rapid topical anaesthesia. Severe skin frosting may result from excessive application.

Preparation

Ethyl chloride spray; 50 – 100 mL

15 C: Sedative and analgesic perioperative drugs

Dexmedetomidine (Restricted)

Indications: Maintenance of sedation during intensive care, adjunct for sedation and general anaesthesia for certain surgical procedures.

Contra-indications: Acute cerebrovascular disorders; second- or

third-degree AV block (unless pacemaker fitted); uncontrolled hypertension.

Cautions: Abrupt withdrawal after prolonged use; bradycardia; ischaemic heart disease; malignant hyperthermia; severe cerebrovascular disease (especially at higher doses); severe neurological disorders; spinal cord injury, hepatic impairment, renal impairment, diabetes, patients on vasodilators

Side-effects: Agitation; blood pressure changes; bradycardia; changes in blood sugar; dry mouth; hyperthermia; myocardial infarction; myocardial ischaemia; nausea; tachycardia; vomiting, pleural effusion, pulmonary oedema

Dose: ICU sedation: loading dose one microgram/ kg over 10 minutes. Maintenance intravenous infusion: 0.2-1.4 microgram/ kg/ hour.

Surgical procedure sedation: loading dose one microgram/ kg over 10 minutes. Maintenance intravenous infusion: 0.6 microgram/ kg/ hour. (titrate usually to 0.2-1 microgram/ kg/ hour)

Preparations

Dexmedetomidine injection, 100 micrograms/ mL

Ketorolac (Restricted)

Indications: Short-term management (≤ 5 days) of moderate to severe acute postoperative pain only. Prophylaxis and reduction of inflammation and associated symptoms following ocular surgery

Contra-indications: With intramuscular use: active or history of gastro-intestinal bleeding; active or history of gastro-intestinal ulceration; coagulation disorders; complete or partial syndrome of nasal polyps; confirmed or suspected cerebrovascular bleeding; dehydration; following operations with high risk of haemorrhage or incomplete haemostasis; haemorrhagic diatheses; history of gastro-intestinal perforation; hypovolaemia; severe heart failure

With intravenous use: active or history of gastro-intestinal bleeding; active or history of gastro-intestinal ulceration; coagulation disorders; complete or partial syndrome of nasal polyps; confirmed or suspected cerebrovascular bleeding; dehydration; following operations with high risk of haemorrhage or incomplete haemostasis; haemorrhagic diatheses; history of gastro-intestinal perforation; hypovolaemia; severe heart failure, labour and delivery, intrathecal or epidural administration, advanced renal impairment, use as prophylactic analgesia before any major surgery, perioperative pain management in the setting of coronary artery bypass surgery

Cautions: With intramuscular use: allergic disorders; cardiac impairment (NSAIDs may impair renal function); cerebrovascular disease; coagulation defects; connective-tissue disorders; Crohn's disease (may

be exacerbated); elderly (risk of serious side-effects and fatalities); heart failure; ischaemic heart disease; peripheral arterial disease; risk factors for cardiovascular events; ulcerative colitis (may be exacerbated); uncontrolled hypertension

With intravenous use: allergic disorders; cardiac impairment (NSAIDs may impair renal function); cerebrovascular disease; coagulation defects; connective-tissue disorders; Crohn's disease (may be exacerbated); elderly (risk of serious side-effects and fatalities); heart failure; ischaemic heart disease; peripheral arterial disease; risk factors for cardiovascular events; ulcerative colitis (may be exacerbated); uncontrolled hypertension

Side-effects: With intramuscular use: alveolitis; aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible); hepatic damage; interstitial fibrosis associated with NSAIDs can lead to renal failure; pancreatitis; papillary necrosis associated with NSAIDs can lead to renal failure; pulmonary eosinophilia; Stevens-Johnson syndrome; toxic epidermal necrolysis

With intravenous use: alveolitis; aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible); hepatic

15: Anaesthesia

damage; interstitial fibrosis associated with NSAIDs can lead to renal failure; pancreatitis; papillary necrosis associated with NSAIDs can lead to renal failure; pulmonary eosinophilia; Stevens-Johnson syndrome; toxic epidermal necrolysis

Dose: (consult product literature or use the hospital protocol).

Preparations

Ketorolac injection, 30 mg / ml
ampoule

Section 16: Contrast media

- Positive contrast (radiopaque)
- Barium sulphate
- Iodinated organic compounds
- Double contrast
- Contrast media for MRI

Contrast media are agents used during visualization techniques such as X-ray including computed tomography (CT), some MRI examination or ultrasound imaging, to provide visual contrast in the pictures of different tissues and organs. They can be given orally or intravenously.

Contrast media may increase the absorption of X-rays as they pass through the body and this is described as positive contrast. A gas may also be used (air, oxygen or carbon dioxide) for visualization, this will be referred to as negative contrast. When both gas and contrast medium are used concomitantly the procedure is called double contrast.

Contrast media contain elements with high atomic numbers that absorb X-rays. The most commonly used agents are iodinated organic compounds, whose degree of radiodensity is directly proportional to their iodine content. Barium sulphate is a metal salt with an established use as a contrast medium.

The iodinated contrast media may be classified into ionic or non-ionic and additionally as monomeric or dimeric.

The ionic monomeric media such as diatrizoates (amidotrizoates) and iopodate have very high osmolality when given in concentrations suitable for radiographic visualization and this have been associated with a relatively high incidence of adverse effects. Since radiodensity depends solely on the iodine concentration, and osmolality solely upon the number of particles in a given weight of solvent, the osmolality of a particular contrast media can be reduced by using dimeric medium such as iotroxinate that contains twice the number of iodine atoms in each molecule or by the use of non-ionic medium.

The non-ionic media may be monomeric such as iohexol, iopamidol and iopromide, or dimeric such as iotrolan.

16 A: Positive contrast (radiopaque)**16 A.1: Barium sulphate**

Barium sulphate effectively coats and defines the mucous surface of the gastrointestinal tract. It is not absorbed but forms an even, homogeneous coat on the gastrointestinal mucosa without interacting with the gut secretion or producing misleading radiographic artefacts. Suitable formulations have been produced to improve its coating properties.

16: Contrast media

Barium sulphate

Indications: radiographic examination of the gastrointestinal tract.

Contraindications: should not be used in suspected GI perforation or leak.

Cautions: severely ill patients; in patients with intussusception for longer than 24 hours; history of food aspiration.

Side-effects: constipation after oral or rectal administration, obstruction and appendicitis have also been reported. Aspiration into the lung has led to pneumonitis or granuloma formation.

Dose: orally, 40 - 450 g. Rectally 150 - 750 g.

Preparations

Barium sulphate enema disposable kit

Barium sulphate suspension, 0.1%, 750 mL

Barium sulphate cup to make suspension, 177-340 g

E-Z Cat for CT scanning, 225 mL

16 A.2: Iodinated organic compounds

16 A.2.1: Monomeric ionic contrast media

Sodium diatrizoate + meglumine diatrizoate

Indications: visualization of the gastrointestinal tract.

Contraindications: sensitivity to diatrizoates; anuria; infection or

open injury at the site to be examined.

Cautions: elderly, or debilitated patients. Iodine containing contrast media may interfere with thyroid function test.

Side-effects: nausea and vomiting, flushing and sensation of warmth, various degrees of allergic reactions. Extravasation may lead tissue damage. Renal failure has been reported after intravenous administration in dehydrated patients.

Dose: the dose is dependent on the procedures to be performed.

Preparations

Sodium diatrizoate + meglumine diatrizoate injection, 10% + 66% injection

16 A.2.2: Non-ionic contrast media

Iohexol

Indications: myelography, angiography, urography, arthrography and visualization of the gastrointestinal tract and body cavities. Iohexol is also used to produce contrast enhancement during computed tomography.

Contraindications: see notes under diatrizoate

Cautions: elderly, or debilitated patients

Side-effects: see under diatrizoate; additionally when applied for myelography, severe headache, backache neck stiffness, and leg or sciatic-type pain. Mental confusion,

mild and transitory perceptual aberrations.

Dose: The choice of dose is dependent on the procedure of examination and route of administration. Iohexol is usually available as solutions containing 30.2-70.5% of iohexol which is equivalent to 140 – 350 mg iodine per mL.

Preparations

Iohexol 240 injection, 240 mg/mL, 50 mL vial

Iohexol 300 injection, 300 mg/mL, 10 mL vial

Iohexol 300 injection, 300 mg/mL, 50 mL vial

Iohexol 350 injection, 350 mg/mL, 50 mL vial

Iohexol 350 injection, 350 mg/mL, 100 mL vial

Iopromide

Indications: angiography, urography, arthrography and visualization of body cavities.

Contraindications, cautions and side-effects: *see* under diatrizoate

Dose: The choice of dose is dependent on the procedure of examination and route of administration.

Iopromide is usually available as solutions containing 31.2-76.9% of iopromide, which is equivalent to 150 – 370 mg iodine per mL.

Preparations

Iopromide injection, 499 mg/mL, 50 mL ampoule

Iopromide injection, 623 mg/mL, 50 and 100 mL ampoules

Iopromide injection, 769 mg/mL, 50 and 100 mL ampoules

Ministry of Health policy is that only one of the above non-ionic contrast media will be made available for use depending on cost

16 B: Double contraste

Sodium bicarbonate + simethicone + citric acid

Indications: adjunct preparation in double contrast radiography.

Dose: orally, 1 tablet 3 times daily and at bed time.

Preparations

Sodium bicarbonate + simethicone + citric acid tablets or granules, 2.21 g + 1.53 g + 0.04 g tablets or granules

16 C: Contrast media for MRI

Dimeglumine Gadopentetate

Indications: diagnostic use in MRI.

Contra-indications: acute and severe renal insufficiency.

Cautions: hypersensitivity, bronchial asthma, cardiovascular disease, seizure disorders, pregnancy.

Side-effects: nausea, vomiting, headache, injection site reactions.

16: Contrast media

Preparations

Dimeglumine Gadopentetate injection, 469 mg/mL, 10 mL vial

Dimeglumine Gadopentetate injection, 469 mg/mL, 15 mL vial

Gadoteric Acid

Indications: diagnostic use in MRI.

Cautions: renal impairment.

Side-effects: nausea, paraesthesia, headache.

Preparations

Gadoteric Acid injection, 0.5 mmol/mL, 10-15 mL vial

Section 17: Emergency treatment of poisoning

- Removal of poisons from gastrointestinal tract
- Treatment by specific agents

General considerations

Poisoning is the harmful effect that occurs when a toxic substance is swallowed, is inhaled, or comes in contact with the skin, eyes, or mucous membranes. However, any substance ingested in high quantities can be toxic. Common source of poisons include drugs, household products and chemicals, agricultural products, plants, industrial products and food substances.

Poisoning could be deliberate or accidental. In adult the majority of cases are deliberate self-poisoning. However, accidental poisoning is more common among children.

Substances used in self-poisoning include various categories of drugs, mainly CNS depressants, analgesics (paracetamol or aspirin), anticholinergic drugs, antidepressants, insecticides and others. Some patients use a combination of drugs.

Accidental poisoning in children involves the use of household chemicals and drugs, such as petroleum products, disinfectants, detergents, paracetamol, iron tablets or CNS depressants.

Diagnosis of poisoning

Although many cases of drug poisoning present with a clear history of drug overdosage ingestion, some patients may not willingly admit the fact or may be admitted unconscious. The diagnosis should be made through obtaining history from conscious patient or from relatives in unconscious ones. Characteristic clinical features remain the best guide to establish a correct diagnosis e.g. sweating, restlessness, and hyperventilation in salicylate poisoning; ulcerative lesions of the mouth in corrosive or pesticide poisoning; papillary dilatation and tachyarrhythmia in overdosage with tricyclic antidepressants and anticholinergic drugs.

When the clinical examination or history fail to confirm the diagnosis, chemical analysis of blood or gastric content may be helpful. Blood level may also provide quantitative assessment of the degree of poisoning.

Time should not be wasted when it is difficult to reach a diagnosis; the treating doctor should make every effort to assess the clinical condition of the patient and to initiate effective measures to maintain vital physiological functions without any delay.

Section 17: Emergency treatment of poisoning

Treatment

Although specific therapy is very useful when available, the following are important general measures in the treatment of all cases of poisoning.

Maintenance of respiration. After assessing respiration, it is important to maintain an unobstructed airway. Pull the tongue forward, remove dentures and mucus, turn the patient to one side and keep head down to prevent aspiration. An oropharyngeal tube is placed in the unconscious patient. Assess ventilation through arterial gas analysis. High concentration of oxygen is given if signs of hypoxia develop. Bronchodilators and in some cases hydrocortisone may be given when there is a significant bronchospasm. If these measures prove inadequate, mechanical ventilation should be considered.

Avoid the use of respiratory stimulant drugs as they are mostly ineffective.

Maintenance of circulation. Cardiac conduction defects and arrhythmias usually result from tissue hypoxia, metabolic disturbances or the direct effect of the poison. Hypoxia and metabolic abnormalities should be corrected. If arrhythmia persists after correction of hypoxia and metabolic disturbances, an appropriate antiarrhythmic agent should be given.

Severe hypotension (systolic blood pressure below 70 mmHg) may

lead to irreversible brain damage or renal tubular necrosis. Patients should be nursed while the head is kept downwards. Oxygen therapy should be given to correct hypoxia, and intravenous infusion should be set up whenever possible. Avoid using vasopressor agents, as they may tend to disturb the circulation to vital organs. They may be used in cases of severe hypotension resulting from an over dose of antihypertensive drugs.

Hypertension is less frequent in poisoning; it may be associated with sympathomimetic drugs.

Treatment of CNS effects. Unconscious patients need close observation and nursing. Transient short-lived convulsion does not require treatment.

Protracted or recurring convulsion should be treated with intravenous injection of diazepam. Underlying causes such as hypoxia, brain oedema, hypoglycaemia and other metabolic disturbances have to be ruled out.

Maintenance of normal body temperature. Hypothermia may result from overdoses of barbiturates or phenothiazines. Patient with coma for few hours may develop hypothermia. Accurate assessment is necessary and when confirmed, the body should be warmed by wrapping to conserve body heat.

Hyperthermia can develop in patients taking CNS stimulants or antimuscarinic drugs. Body sponging with tepid tap water is usually sufficient. Avoid using iced water.

Section 17: Emergency treatment of poisoning

17 A: Elimination and removal of poison

Removal from stomach

Prevention of further absorption of poison is achieved by emesis or gastric lavage. The danger of gastric emptying should be balanced against the danger of the ingested poison as assessed by the quantity ingested, the toxicity of the poison and the duration of ingestion. Gastric emptying is clearly unnecessary if the risk of toxicity is minimal or the patient presents too late.

Gastric lavage is of doubtful value if attempted more than 2 hour after ingestion of the poison. Emesis and gastric lavage is contraindicated in poisoning with corrosives because of the danger of perforating affected tissues and in the unconscious or drowsy for fear of aspiration. Gastric lavage is not recommended in poisoning with petroleum products as inhalation may cause severe chemical pneumonia. The gastric lavage fluid is either normal saline or tepid water given in a volume not exceeding 300 mL at a time. It should be repeated until the return fluid is clear.

Emesis can be induced with ipecacuanha mixture or by pharyngeal stimulation in both adults and children. It should only be considered if the patient is fully conscious, if the poison is neither a corrosive nor a petroleum product, if it is not adsorbed by activated charcoal, or if

gastric lavage is inadvisable or refused by patient.

Ipecacuanha mixture (C.D.L.)

Indications: induction of emesis.

Contraindications: *see* notes above

Cautions: *see* notes above

Side-effects: excessive vomiting and mucosal damage; cardiac effects if absorbed.

Dose: adult, 30 mL of ipecacuanha mixture syrup. Child 6-18 months, 10 mL, older child 15 mL, the dose is followed by a 200 mL of water. Repeated if necessary after 30 minutes.

Preparations

Ipecacuanha emetic mixture syrup

Prevention of absorption and elimination after absorption

Many poisons are effectively adsorbed on activated charcoal and their absorption in the stomach is reduced. The sooner an oral activated charcoal is given the better and it could still be effective 1 hour after ingestion of the poison.

Repeated oral doses of activated charcoal enhance the elimination of some drugs after being absorbed such as carbamazepine, phenobarbital, quinine, theophylline and dapsone. The usual dose is 50 g initially, followed by 50 g every 4 hours.

Section 17: Emergency treatment of poisoning

When the above measures are not effective and the poison is absorbed, other techniques have to be considered such as acidifying or alkalizing the urine, peritoneal or haemodialysis for dialyzable toxins.

Other techniques may be applied such as alkaline or acid diuresis, haemodialysis, or peritoneal dialysis

Activated charcoal

Indications: prevention of absorption of toxic substances; selective active elimination (*see notes above*).

Dose: for reduction of absorption, orally, adult 50 g, child 25g. For active elimination 50 g every 4 hours.

Preparations

Activated charcoal powder; 50 g/pack

Activated charcoal granules; 50 g/pack

17 B: Treatment by specific agents

Paracetamol poisoning

Ingestion of 10-15 g (20-30 tablets) of paracetamol may cause serious hepatocellular necrosis. Liver damage is maximal 3-4 days after ingestion and may lead to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death.

Antidotes such as acetylcysteine may protect the liver if given within 24 hours of ingestion.

Patient should be assessed at hospital for the level of serum paracetamol and further measures are considered accordingly.

Acetylcysteine

Indications: paracetamol overdose.

Cautions: asthma.

Side-effects: rashes, anaphylaxis.

Dose: by intravenous infusion, in 5% glucose intravenous infusion, initial dose 150 mg/kg in 200 mL over 15 minutes, followed by 50 mg/kg in 500 mL over 4 hours, then 100 mg/kg in 1000 mL over 16 hours.

Preparations

Acetylcysteine injection, 200 mg/mL, 10 mL ampoule

Hypnotics and anxiolytics poisonings

Overdose of benzodiazepines taken alone cause drowsiness, ataxia, dysarthria and occasionally minor and short-lived depression of consciousness and coma in severe cases. Serious sequelae of overdose are rare because of the high safety index of benzodiazepines.

Expert assessment is needed before the use of flumazenil. Special caution should be taken in patients dependent on benzodiazepine because of the possibility of convulsion.

Section 17: Emergency treatment of poisoning

Flumazenil

Indications, side-effects and dose: see sec 15A.6.

Iron and heavy metals poisoning

Deferoxamine mesilate (Desferri-oxamine mesilate)

Indications: iron poisoning.

Cautions: avoid Prochlorperazine (can cause coma due to a synergistic action between the two drugs).

Side-effects: anaphylactic reaction and hypotension, more frequent with rapid intravenous administration.

Dose: continuous intravenous infusion up to 15 mg/kg/hour; maximum 80 mg/kg in 24 hours.

Preparations

Deferoxamine mesilate injection, 500 mg vial

Dimercaprol (British Anti-Lewisite-BAL) (C.D.L)

Indications: poisoning with antimony, arsenic, bismuth, mercury, gold; adjunct to sodium calcium edetate in lead poisoning.

Contraindications: not indicated for iron, cadmium or selenium poisoning; hepatic impairment.

Cautions: hypertension, renal impairment, elderly, pregnancy and breast-feeding.

Side-effects: nausea and vomiting, headache, tremor, rhinorrhoea & lachrymation; hypertension and tachycardia.

Dose: intramuscularly, 2.5–3 mg/kg every 4 hours for 2 days, 2–4 times on the third day, then 1–2 times daily for 10 days or until recovery.

Preparations

Dimercaprol injection, 50 mg/mL, 2 mL ampoule

Sodium calcium edetate (C.D.L)

Indications: heavy metal poisoning especially lead.

Cautions: renal impairment.

Side-effects: nausea, cramp; renal impairment in overdosage.

Dose: intravenous infusion with sodium chloride 0.9% or dextrose 5% intravenous solutions, 40 mg/kg twice daily for up to 5 days, repeated if necessary.

Preparations

Sodium calcium edetate injection, 200 mg/mL, 5 mL ampoule

Pesticide poisoning

Poisoning with organophosphorus compound is very common. The insecticides are prepared with organic solvents that can be absorbed through intact skin, the bronchi and the gut. Their main effect is the inhibition of cholinesterase enzyme and hence prolonging the effects of acetylcholine. Atropine will help prevent the excessive muscarinic effects of acetylcholine and it can be given in a dose of 2 mg as atro-

Section 17: Emergency treatment of poisoning

pine sulphate intravenously or intramuscularly every 20-30 minutes until signs of atropinisation are seen.

Pralidoxime helps to reactivate the cholinesterase enzyme and should be used in conjunction with atropine but it is only effective if given within 24 hours of exposure.

Pralidoxime mesilate

Indications: adjunct to atropine in the treatment of organophosphorus poisoning.

Contraindications: poisoning with neostigmine or other carbamate compounds

Cautions: renal impairment, myasthenia gravis.

Side-effects: drowsiness, dizziness, disturbances of vision, nausea, tachycardia, headache, hyperventilation, and muscular weakness, laryngospasm.

Dose: by slow intravenous injection, 30 mg/kg initially followed by 1-2 further doses if necessary; maximum 12 g in 24 hours.

Preparations

Pralidoxime mesilate injection, 200 mg/mL, 5 mL ampoule

Contraindications: severe renal impairment.

Cautions: repeated injections may result in severe anaemia.

Side-effects: headache, dizziness, nausea and vomiting.

Dose: by intravenous injection of 1% solution, 1-4 mg/kg over 10 minutes.

Preparations

Methylthioninium chloride injection, 1% solution, 10 mL ampoule

Sodium thiosulphate

Indications: poisoning with cyanides adjunct to other therapies; poisoning with nitroprusside, cisplatin and bromate.

Dose: 12.5 grams given by slow intravenous route over 10 minutes.

Preparations

Sodium thiosulphate injection, 25% solution

Other poisoning

Methylthioninium chloride (Methylene blue)

Indications: poisoning with drugs or toxins inducing methaemoglobinemia.

Appendix 1: Drug interactions

The use of more than one drug to achieve therapeutic objective or treat co-existing diseases is a common and essential clinical practice. Such concurrent use increases the possibility of an interaction between drugs.

A potential drug interaction refers to the possibility that one drug may alter the intensity of pharmacological effects of another drug simultaneously used. The net result may be enhanced or diminished effects of one or both of the drugs or the appearance of a new effect that is not seen with either drug alone.

Interactions may be either **pharmacokinetic** (alteration of the absorption, distribution or elimination of one drug by another) or **pharmacodynamic** (such as the interaction between agonist and antagonist on the receptor site).

The most important drug interactions occur with drugs that have serious side-effects and a low therapeutic index, so that a small change in drug concentration can have significant adverse consequences.

Pharmacokinetic drug-drug interaction

Drugs may interact at any point during their absorption, distribution, metabolism or excretion. The result will be an increase or decrease in the concentration of drugs

at the site of action. As individuals vary in their rates of disposition of any given drug, the magnitude of an interaction that alters pharmacokinetic parameters is not always predictable but can be very significant.

Interactions involving absorption: Drug absorption can be impeded by an interaction with food or with other drugs. Antacids for example, may delay or even prevent the absorption of many drugs. Drugs altering gastric motility may delay absorption, though this is of little clinical significance unless a high peak plasma concentration is required.

Interactions involving distribution: Drugs bind to plasma protein with variable degree. The binding sites are non-specific and one drug can displace another on the same binding site. Such an interaction leads to a shift in plasma concentration of the unbound and effective fraction of the drug. This only produces a detectable effect if the drug is extensively bound to plasma protein and not very widely distributed throughout the body. Such an interaction rarely produces more than a transient potentiation because this increased concentration of the free drug results in an increased rate of elimination

Interactions involving metabolism:

Interactions involving drug metabolism can increase or decrease the amount of drug available for action

Appendix 1: Drug interactions

by inhibition or induction of metabolism, respectively. Interactions may occur among administered drugs or between drugs and dietary component (e.g. grapefruit juice) or other chemicals (cigarette smoking, alcohol). The effect of enzyme induction or inhibition is more obviously seen with drugs given orally; as such drugs undergo enterohepatic circulation.

Interactions involving excretion:

Drugs eliminated through the kidney may interact at the active transport site at the distal tubules, where for example, probenecid inhibits the excretion of penicillin leading to a higher plasma concentration.

Pharmacodynamic drug-drug interactions

Due to the limitation in quantity of the receptor sites, drugs of similar or antagonistic pharmacological nature may interact on the same receptors. The interaction may be due to competition on the receptor sites or occur between drugs acting on the same physiological system. In general, such interactions are predictable due to the knowledge of pharmacological properties of the drug. Their occurrence is to a greater or lesser extent in most patients who use the interacting drugs.

The following is a list of drugs or therapeutic groups of drugs and

their potentially significant interactions alphabetically arranged.

Abacavir

Methadone: abacavir possibly reduces plasma concentration of methadone

Phenobarbital: plasma concentration of abacavir possibly reduced by phenobarbital

Phenytoin: plasma concentration of abacavir possibly reduced by phenytoin

Rifampicin: plasma concentration of abacavir possibly reduced by rifampicin

Tipranavir: plasma concentration of abacavir reduced by tipranavir

ACE Inhibitors

Adrenergic Neurone Blockers: enhanced hypotensive effect

Alcohol: enhanced hypotensive effect

Alpha-blockers: enhanced hypotensive effect

Alprostadil: enhanced hypotensive effect

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect

Anxiolytics and hypnotics: enhanced hypotensive effect

Beta-blockers: enhanced hypotensive effect

Calcium-channel Blockers: enhanced hypotensive effect

Ciclosporin: increased risk of hyperkalaemia

Corticosteroids: antagonism of hypotensive effect

Diazoxide: enhanced hypotensive effect

Diuretics: enhanced hypotensive effect (can be extreme)

Diuretics, Potassium-sparing: risk of severe hyperkalaemia

Epoetin: antagonism of hypotensive effect and increased risk of hyperkalaemia

Heparins: increased risk of hyperkalaemia

Hydralazine: enhanced hypotensive effect

Insulin: hypoglycaemic effect possibly enhanced

Lithium: ACE inhibitors reduce excretion of lithium (increased plasma-lithium concentration)

Metformin: hypoglycaemic effect possibly enhanced

Methyldopa: enhanced hypotensive effect

Nitrates: enhanced hypotensive effect

Nitroprusside: enhanced hypotensive effect

NSAIDs: antagonism of hypotensive effect, increased risk of renal impairment

Oestrogens: antagonism of hypotensive effect

Phenothiazines: enhanced hypotensive effect

Potassium Salts: risk of severe hyperkalaemia

Sulphonylureas: hypoglycaemic effect possibly enhanced

Acetazolamide

See under diuretics

Aciclovir

Note: Interactions do not apply to topical aciclovir preparations

Ciclosporin: increased risk of nephrotoxicity

Mycophenolate: plasma concentration of aciclovir increased by mycophenolate, *Also* plasma concentration of inactive metabolite of mycophenolate increased

Probenecid: excretion of aciclovir reduced by probenecid (increased plasma concentration)

Tacrolimus: possible increased risk of nephrotoxicity when aciclovir given with tacrolimus

Adalimumab

Abatacept: increased risk of side-effects when adalimumab given with abatacept

Anakinra: avoid concomitant use of adalimumab with anakinra

Vaccines: avoid concomitant use of adalimumab with live vaccines

Adefovir

Tenofovir: avoidance of adefovir advised by manufacturer

Adenosine

Dipyridamole: effect of adenosine enhanced and extended by dipyridamole (important risk of toxicity)

Theophylline: anti-arrhythmic effect of adenosine antagonised by theophylline

Also, see under Anti-arrhythmic

Appendix 1: Drug interactions

Adrenaline

See under sympathomimetics

Alendronic acid

See under bisphosphonates

Allopurinol

Amoxicillin: increased risk of rash

Ampicillin: increased risk of rash

Azathioprine: effects of azathioprine enhanced with increased toxicity, reduce dose when given with allopurinol

Captopril: increased risk of toxicity especially in renal impairment

Ciclosporin: plasma-ciclosporin concentration possibly increased (risk of nephrotoxicity)

Coumarins: anticoagulant effect possibly enhanced

Mercaptopurine: effects of mercaptopurine enhanced with increased toxicity, reduce dose when given with allopurinol

Theophylline: plasma-theophylline concentration possibly increased

Alpha-blockers

ACE Inhibitors: enhanced hypotensive effect

Adrenergic neurone blockers: enhanced hypotensive effect

Alcohol: enhanced hypotensive effect

Alprostadil: enhanced hypotensive effect

Anaesthetics, General: enhanced hypotensive effect

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect

Antipsychotics: enhanced hypotensive effect

Anxiolytics and Hypnotics: enhanced hypotensive and sedative effects

Beta-blockers: enhanced hypotensive effect; increased risk of first-dose hypotensive effect of post-synaptic alpha-blockers such as prazosin

Calcium-channel Blockers: enhanced hypotensive effect; increased risk of first-dose hypotensive effect of post-synaptic alpha-blockers such as prazosin

Corticosteroids: antagonism of hypotensive effect

Diazoxide: enhanced hypotensive effect

Diuretics: enhanced hypotensive effect; increased risk of first-dose hypotensive effect of post-synaptic alpha-blockers such as prazosin

Hydralazine: enhanced hypotensive effects

Levodopa: enhanced hypotensive effect

Methyldopa: enhanced hypotensive effect Nitrates: enhanced hypotensive effect

NSAIDs: antagonism of hypotensive effect

Oestrogens: antagonism of hypotensive effect

Alprostadil

Antihypertensives: enhanced hypotensive effects

Amantadine

Appendix 1: Drug interactions

Antimuscarinics: increased risk of antimuscarinic side-effects

Antipsychotics: increased risk of extrapyramidal side-effects

Bupropion: increased risk of side-effects

Domperidone: increased risk of extrapyramidal side-effects

Memantine: increased risk of CNS toxicity

Methyldopa: increased risk of extrapyramidal side-effects

Metoclopramide: increased risk of extrapyramidal side-effects

Tetrabenazine: increased risk of extrapyramidal side-effects

Aminoglycosides

Antibacterial: increased risk of nephrotoxicity with vancomycin

Antifungals: increased risk of nephrotoxicity with amphotericin

Bisphosphonates: increased risk of hypocalcaemia

Ciclosporin: increased risk of nephrotoxicity

Diuretics: increased risk of ototoxicity with loop diuretics

Muscle relaxant: effects of non-depolarising muscle relaxant enhanced

Aminosalicylates

Azathioprine: possible increased risk of leucopenia

Mercaptopurine: possible increased risk of leucopenia

Amiodarone

Amiodarone has a long half-life and a possible interaction might take place with other drugs weeks after the treatment with it has stopped.

Anti-arrhythmics: enhanced effects

Anticoagulants: enhanced effects

Antidepressants: increased risk of ventricular arrhythmias with tricyclic antidepressants

Antipsychotics: increased risk of ventricular arrhythmias

Beta-blockers: increased risk of bradycardia, AV block, and myocardial depression

Calcium channel blockers: increased risk of bradycardia, AV block, and myocardial depression with diltiazem and verapamil

Cardiac glycosides: increased plasma level of digoxin

Diuretics: cardiac toxicity increased if hypokalaemia develops

Ivabradine: increased risk of ventricular arrhythmias when amiodarone given with ivabradine

Amitriptyline

See under antidepressants

Amoxicillin

See under penicillin

Amphotericin

Aminoglycosides: increased risk of nephrotoxicity when amphotericin given with aminoglycosides

Appendix 1: Drug interactions

Antifungals: Imidazole effects of amphotericin possibly antagonised by imidazoles

Antifungals, Triazole effects of amphotericin possibly antagonised by triazoles

Cardiac Glycosides: hypokalaemia caused by amphotericin increases cardiac toxicity with cardiac glycosides

Ciclosporin: increased risk of nephrotoxicity when amphotericin given with ciclosporin

Corticosteroids: increased risk of hypokalaemia when amphotericin given with corticosteroids —avoid concomitant use unless corticosteroids needed to control reactions

Diuretics: Loop or Thiazide increased risk of hypokalaemia

Pentamidine Isetionate: possible increased risk of nephrotoxicity

Polymyxins: increased risk of nephrotoxicity when amphotericin given with polymyxins

Tacrolimus: increased risk of nephrotoxicity when amphotericin given with tacrolimus

Vancomycin possible increased risk of nephrotoxicity

Ampicillin

See under penicillin

Anaesthetics, General

Alpha-blockers: enhanced hypotensive effect

Antidepressants, Tricyclic: increased risk of arrhythmias and hypotension

Antipsychotics: enhanced hypotensive effect when general anaesthetics given with antipsychotics

Anxiolytics and Hypnotics: enhanced sedative effect

Antihypertensives: enhanced hypotensive effect

Argatroban: increased risk of haemorrhage when anticoagulants given with intravenous diclofenac and ketorolac avoid concomitant use.

Calcium-channel Blockers: enhanced hypotensive effect

Cytotoxics: nitrous oxide increases antifolate effect of methotrexate

Dopaminergics: increased risk of arrhythmias when volatile liquid general anaesthetics given with levodopa

MAOIs: because of their hazardous interactions, MAOIs should normally be stopped 2 weeks before surgery

Methylphenidate: increased risk of hypertension when volatile liquid general anaesthetics given with methylphenidate

Muscle Relaxants: increased risk of myocardial depression and bradycardia when propofol given with suxamethonium; volatile liquid general anaesthetics enhance effects of non-depolarising muscle relaxants and suxamethonium; ketamine enhances effects of atracurium

Nitrates: enhanced hypotensive effect

Nitroprusside: enhanced hypotensive effect

Appendix 1: Drug interactions

Sympathomimetics: manufacturer of isoflurane advises avoid concomitant use with sympathomimetics (risk of ventricular arrhythmias); increased risk of arrhythmias when volatile liquid general anaesthetics given with adrenaline (epinephrine) or noradrenaline (norepinephrine); increased risk of hypertension when volatile liquid general anaesthetics given with methylphenidate

Vancomycin: hypersensitivity-like reactions can occur with concomitant intravenous vancomycin

Verapamil: enhanced hypotensive effect and AV delay

Anaesthetics, Local

Including lignocaine (lidocaine), bupivacaine & levobupivacaine

Anti-arrhythmics: increased risk of myocardial depression

Propranolol: increased risk of bupivacaine and lignocaine toxicity

Analgesics

See under individual drugs, aspirin, NSAIDs, opioids and paracetamol

Angiotensin-II Receptor Antagonists

ACE Inhibitors: increased risk of hyperkalaemia when

Adrenergic Neurone Blockers: enhanced hypotensive effect

Alcohol: enhanced hypotensive effect
Aldesleukin: enhanced hypotensive effect

Alpha-blockers: enhanced hypotensive effect

Alprostadil: enhanced hypotensive effect

Anaesthetics: General enhanced hypotensive effect

Antipsychotics: enhanced hypotensive effect

Anxiolytics and Hypnotics: enhanced hypotensive effect

Baclofen: enhanced hypotensive effect

Beta-blockers: enhanced hypotensive effect

Calcium-channel Blockers: enhanced hypotensive effect

Ciclosporin: increased risk of hyperkalaemia

Clonidine: enhanced hypotensive effect

Corticosteroids: hypotensive effect of angiotensin-II receptor antagonists antagonised by corticosteroids

Diazoxide: enhanced hypotensive effect
Diuretics: enhanced hypotensive effect

Drospirenone: risk of hyperkalaemia

Epoetin: antagonism of hypotensive effect and increased risk of hyperkalaemia

Heparin: increased risk of hyperkalaemia
Hydralazine: enhanced hypotensive effect

Levodopa: enhanced hypotensive effect
Lithium: angiotensin-II receptor antagonists reduce excretion of lithium (increased plasma concentration)

Appendix 1: Drug interactions

MAOIs: hypotensive effect of angiotensin-II receptor antagonists possibly enhanced by MAOIs

Methyldopa: enhanced hypotensive effect Minoxidil: enhanced hypotensive effect

Moxisylyte (thymoxamine): enhanced hypotensive effect

Moxonidine: enhanced hypotensive effect when angiotensin-II receptor antagonists given with moxonidine

Nitrates: enhanced hypotensive effect NSAIDs: increased risk of renal impairment, *Also* hypotensive effect antagonised

Oestrogens: hypotensive effect of angiotensin-II receptor antagonists antagonised by oestrogens

Potassium Salts: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with potassium salts Includes salt substitutes

Sodium Nitroprusside: enhanced hypotensive effect

Tacrolimus: increased risk of hyperkalaemia

Tizanidine: enhanced hypotensive effect

Antacids

Generally, antacids should not be taken at the same time as other drugs. Impairment of absorption is likely to take place.

Anti-arrhythmic

Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other anti-arrhythmics

Antimalarials: avoidance of amiodarone advised by manufacturer of artemether with lumefantrine (risk of ventricular arrhythmias); avoidance of flecainide advised by manufacturer of artemether with lumefantrine (risk of ventricular arrhythmias)

Antipsychotics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with antipsychotics that prolong the QT interval

Beta-blockers: increased myocardial depression

Bupivacaine: increased myocardial depression

Fingolimod: possible increased risk of bradycardia when fingolimod given with amiodarone, disopyramide or dronedarone

Levobupivacaine: increased myocardial depression

Prilocaine: increased myocardial depression

Ropivacaine: increased myocardial depression

Tropisetron: caution with anti-arrhythmics advised by manufacturer of tropisetron (risk of ventricular arrhythmias) Anticholinergics: *See under* antimuscarinic

Antibacterial

See under individual drugs

Antidepressants, SSRI

Alcohol: possibly enhanced sedative effect

Appendix 1: Drug interactions

Antibacterials: ciprofloxacin inhibits metabolism of duloxetine—avoid concomitant use

Antidepressants (tricyclic): plasma concentration of some tricyclics increased by SSRI

Antiepileptics: antagonism (convulsive threshold lowered)

Antimalarials: avoidance of antidepressants advised by manufacturer of artemether with lumefantrine

Barbiturates: antagonism (convulsive threshold lowered)

Beta-blockers: plasma concentration of metoprolol increased by citalopram; plasma concentration of metoprolol possibly increased by paroxetine, avoid concomitant use in cardiac insufficiency.

Coumarins: anticoagulant effect possibly enhanced

Lithium: increased risk of CNS effects (lithium toxicity reported)

MAOIs: CNS effects of SSRIs increased by MAOIs (risk of serious toxicity)

Methylthioninium: risk of CNS toxicity when SSRI-related antidepressants given with methylthioninium—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration)

Tramadol: increased risk of CNS toxicity

Antidepressants, Tricyclic

Adrenaline: hypertension and arrhythmias (but local anaesthetics with adrenaline appear to be safe)

Alcohol: enhanced sedative effect

Amiodarone: increased risk of ventricular arrhythmias (avoid concomitant use)

Anaesthetics, (general): increased risk of arrhythmias and hypotension

Antidepressants, SSRI: plasma concentration of some tricyclics increased by SSRIs

Antiepileptics: antagonism (convulsive threshold lowered)

Antihistamines: increased antimuscarinic and sedative effects

Antimuscarinics: increased antimuscarinic side-effects

Antipsychotics: increased plasma-tricyclic concentrations; possibly increased risk of ventricular arrhythmias

Anxiolytics and hypnotics: enhanced sedative effect

Barbiturates: antagonism of anti-convulsant effect (convulsive threshold lowered); metabolism of tricyclics possibly accelerated (reduced plasma concentration)

Carbamazepine: possibly accelerated metabolism of tricyclics (reduced plasma concentration; reduced antidepressant effect)

Disopyramide: increased risk of ventricular arrhythmias

Diuretics: increased risk of postural hypotension

Flecainide: increased risk of ventricular arrhythmias

Appendix 1: Drug interactions

MAOIs: CNS excitation and hypertension with MAOIs; tricyclics should not be started until 2 weeks after stopping MAOI (3 weeks if starting clomipramine or imipramine); MAOI should not be started until at least 7-14 days after stopping tricyclic (3 weeks in the case of clomipramine or imipramine)

Nitrates: reduced effect of sublingual nitrates (owing to dry mouth)

Noradrenaline (norepinephrine): hypertension and arrhythmias

Oestrogens: antagonism of antidepressant effect but side-effects possibly increased due to increased plasma concentrations of tricyclics

Opioid Analgesics: possibly increased sedation

Phenothiazines: increased antimuscarinic side-effects

Phenytoin: possibly reduced plasma-tricyclic concentration

Procainamide: increased risk of ventricular arrhythmias

Quinidine: increased risk of ventricular arrhythmias

Rifampicin: plasma concentrations of tricyclics possibly reduced (reduced antidepressant effect)

Thioridazine: increased risk of ventricular arrhythmias (avoid concomitant use)

Tramadol: increased risk of CNS toxicity

Verapamil: possibly increased plasma concentration of tricyclic

Anticoagulants

See under individual drugs argatroban, fondaparinux, ivaroxaban and warfarin

Antidiabetics

Include, insulins as well

Alcohol: enhanced hypoglycaemic effect; increased risk of lactic acidosis when metformin given with alcohol

Analgesics: effects of sulfonylureas possibly enhanced by NSAIDs

Anabolic Steroids: hypoglycaemic effect possibly enhanced

Beta-blockers: masking of warning signs of hypoglycaemia such as tremor

Antibacterials: hypoglycaemic effect of acarbose possibly enhanced by neomycin; effects of sulfonylureas enhanced by chloramphenicol; metabolism of sulfonylureas possibly accelerated by rifamycins (reduced effect); effects of sulfonylureas rarely enhanced by sulfonamides and trimethoprim; hypoglycaemic effect of sulfonylureas possibly enhanced by tetracyclines;

Anticoagulants: exenatide possibly enhances anticoagulant effect of warfarin; hypoglycaemic effect of sulfonylureas possibly enhanced by coumarins,

Antifungals: plasma concentration of sulfonylureas increased by fluconazole and miconazole; hypoglycaemic effect of gliclazide enhanced by miconazole; plasma

concentration of sulfonylureas possibly increased by voriconazole

Corticosteroids: antagonism of hypoglycaemic effect

Diazoxide: hypoglycaemic effect antagonised by Diazoxide

Diuretics, Loop: antagonism of hypoglycaemic effect

Diuretics, Thiazide and related compounds: antagonism of hypoglycaemic effect

Lipid regulating Drugs: hypoglycaemic effect of acarbose possibly enhanced by colestyramine; plasma concentration of glibenclamide

possibly increased by fluvastatin; may be improved glucose tolerance and an additive effect when insulin or sulfonylureas given with fibrates

Lithium: may occasionally impair glucose tolerance

MAOIs: possibly enhanced hypoglycaemic effect

Oestrogens: antagonism of hypoglycaemic effect

Progestogens: antagonism of hypoglycaemic effect

Testosterone: Hypoglycaemic effect possibly enhanced

Antiepileptics

See under individual drugs, carbamazepine, Clonazepam, chlor-methiazole, lamotrigine, phenytoin, phenobarbitone, sodium valproate

Antifungals

Imidazole and triazole

Imidazole antifungals include, clotrimazole, ketoconazole and miconazole; Triazole antifungals include fluconazole, voriconazole and itraconazole.

Antacids: reduce absorption of itraconazole and ketoconazole

Anti-arrhythmics: plasma concentration of quinidine increased by itraconazole and miconazole

Antibacterials: rifampicin accelerates fluconazole, itraconazole, voriconazole and ketoconazole metabolism. Plasma concentration of ketoconazole may be reduced by isoniazid. Plasma concentration of itraconazole increased by clarithromycin. Triazoles possibly increase plasma

concentration of rifabutin

Anticoagulants: warfarin effects enhanced by imidazole and Triazole antifungals; manufacturer of rivaroxaban advises avoid concomitant use with itraconazole; plasma concentration of rivaroxaban increased by ketoconazole—avoid concomitant use; manufacturer of rivaroxaban advises avoid concomitant use with voriconazole

Antidepressants: avoidance of triazoles advised by manufacturer of .reboxetine; fluconazole possibly increases plasma concentration of amitriptyline and nortriptyline; plasma concentration of voriconazole reduced by .St John's wort avoid concomitant use

Antidiabetics: plasma concentration of sulphonylureas increased by

Appendix 1: Drug interactions

fluconazole, voriconazole and miconazole

Antiepileptics: effects of phenytoin enhanced by fluconazole and miconazole. Plasma concentration of itraconazole and ketoconazole reduced by phenytoin. Voriconazole increases plasma concentration of phenytoin, also phenytoin reduces plasma concentration of Voriconazole. Fluconazole possibly increases plasma concentration of carbamazepine; plasma concentration of voriconazole possibly reduced by carbamazepine and phenobarbital.

Antifungals, others: possible antagonism of amphotericin effect

Antihistamines: astemizole and terfenadine metabolism inhibited

Antimalarials: avoidance of imidazoles advised by manufacturer of artemether with lumefantrine; avoidance of triazoles advised by manufacturer of artemether with lumefantrine

Antimuscarinic: reduced absorption of ketoconazole

Antivirals: plasma concentration of zidovudine increased by fluconazole. Plasma concentration of voriconazole reduced by Ritonavir. Triazoles possibly increase plasma concentration of saquinavir. Fluconazole increases plasma concentration of zidovudine.

Anxiolytics and hypnotics: prolonged sedative effects of midazolam and diazepam

Calcium-channel blockers: plasma concentration of felodipine and other analogues increased

Cardiac glycosides: plasma concentration of digoxin increased by itraconazole

Ciclosporin: plasma concentration of ciclosporin increased

Clopidogrel: fluconazole, itraconazole and voriconazole possibly reduce antiplatelet effect of clopidogrel

Colchicine: itraconazole possibly increases risk of colchicine

Corticosteroids: itraconazole possibly inhibits metabolism of corticosteroids and methylprednisolone; itraconazole increases the plasma concentration of inhaled and oral budesonide; itraconazole increases plasma concentration of inhaled fluticasone

Cytotoxics: itraconazole may inhibit metabolism of vincristine

Diuretics: plasma concentration of fluconazole increased by hydrochlorothiazide

Domperidone: possible increased risk of ventricular arrhythmias when itraconazole or voriconazole

Everolimus: plasma concentration of everolimus possibly increased by voriconazole and itraconazole

Ivabradine: fluconazole increases plasma concentration of ivabradine—reduce initial dose of ivabradine; itraconazole possibly increases plasma concentration of ivabradine—avoid concomitant use; ketoconazole increases plasma

concentration of ivabradine—avoid concomitant use.

Lipid-regulating drugs: increased risk of myopathy with simvastatin and atorvastatin

Oestrogens and progestogens: possible contraceptive failure with imidazole and triazole antifungals

Opioids: Alfentanil metabolism inhibited by ketoconazole

Retinoids: fluconazole and voriconazole possibly increase risk of tretinoin toxicity

Sirolimus: fluconazole, itraconazole and voriconazole possibly increase plasma concentration of sirolimus

Tacrolimus: fluconazole, itraconazole and voriconazole increase plasma concentration of tacrolimus

Theophylline: plasma concentration increased by fluconazole

Ulcer-healing drugs: H₂-receptor antagonists and proton pump inhibitors reduce absorption of ketoconazole and itraconazole. Sucralfate reduces absorption of ketoconazole. voriconazole

possibly increases plasma concentration of esomeprazole and omeprazole

Antihistamines

Non-sedating antihistamines show less sedative interactions; they do not potentiate the effects of alcohol

Alcohol: enhanced sedative effects

Antacids: reduced absorption

Anti-arrhythmics: avoid concomitant use

Antibacterials: possibility of increased plasma loratidine concentration with erythromycin

Antidepressants: MAOIs and tricyclics increase antimuscarinic and sedative effects

Antifungals: possibility of increased plasma loratidine concentration with ketoconazole

Antimuscarinics: increased antimuscarinic side-effects

Antipsychotics: avoid concomitant use with terfenadine- increased risk of ventricular arrhythmias

Antivirals: possibility of increased plasma loratidine concentration

Anxiolytics and hypnotics: enhanced sedative effects

Beta-blockers: sotalol may increase the risk of ventricular arrhythmias with non-sedating antihistamines

Betahistidine: enhanced sedative effects

Antihypertensive drugs

See under individual drugs

Antimalarials

See under individual drugs

Antimuscarinics

Many drugs have antimuscarinic effects. Effects such as dry mouth, urine retention, constipation and blurred vision may be augmented when two drugs with antimuscarinic effects are used concomitantly. In the elderly, confusion is a notable interaction

Appendix 1: Drug interactions

Alcohol: sedative effect of hyoscine enhanced

Anti-arrhythmics: atropine delays absorption of mexiletine; increased antimuscarinic effects with disopyramide

Antidepressants: increased antimuscarinic side-effects with tricyclics and MAOIs

Antifungals: reduced absorption of ketoconazole

Antihistamines: increased antimuscarinic effects

Antipsychotics: increased antimuscarinic effects

Antivirals: plasma concentration of solifenacin possibly increased by ritonavir

Dopaminergics: absorption of levodopa possibly reduced

Metoclopramide and domperidone: antimuscarinics antagonize gastrointestinal effects

Antiplatelet drugs

See under individual drugs

Antipsychotics

Avoid concomitant use with drugs that may induce agranulocytosis such as carbamazepine, co-trimoxazole, chloramphenicol, sulphonamide, penicillamine or cytotoxics

ACE inhibitors: severe postural hypotension with chlorpromazine and possibly other phenothiazines

Alcohol: enhanced sedative effects

Anaesthetics: enhanced hypotensive effects

Analgesics: enhanced hypotensive and sedative effects with opioid analgesics

Antacids: reduced absorption

Anti-arrhythmics: increased risk of ventricular arrhythmias with thioridazine

Antibacterials: rifampicin enhances haloperidol metabolism (reduced plasma haloperidol concentration)

Antidepressants: increased plasma concentration and antimuscarinic effects on administration of tricyclics with phenothiazines and possibly with fluoxetine; fluoxetine increases plasma concentration of olanzapine and haloperidol

Antiepileptics: antagonism; carbamazepine accelerates the metabolism of haloperidol, olanzapine, and risperidone

Antihypertensives: enhanced hypotensive effects; increased risk of extrapyramidal effects with methyl-dopa

Antimalarials: manufacturer of artemether with lumefantrine advises avoid concomitant use with antipsychotics

Antimuscarinics: antimuscarinic side-effects of phenothiazines increased

Antipsychotics (other): increased risk of ventricular arrhythmias with thioridazine and other phenothiazines

Antivirals: plasma concentration of quetiapine possibly increased by darunavir—manufacturer of quetiapine advises avoid concomitant use

Appendix 1: Drug interactions

Anxiolytics and hypnotics: enhanced sedative effects; buspirone increases plasma concentration of haloperidol

Beta-blockers: phenothiazines increases risk of ventricular arrhythmias with sotalol

Cabergoline: hypoprolactinaemic and antiparkinsonian effects of cabergoline antagonised by antipsychotics

Deferasirox: manufacturer of deferasirox advises avoid concomitant use with clozapine

Diuretics: hypokalaemia increases risk of ventricular arrhythmias with thioridazine

Dopaminergics: antagonism of effects

Everolimus: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

Gefitinib: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

Lapatinib: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

Lithium: increased risk of neurotoxicity with phenothiazines, haloperidol and clozapine

Metoclopramide and domperidone: increased risk of extrapyramidal effects

Sorafenib: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

Ulcer-healing drugs: cimetidine enhances effects of antipsychotics

Antivirals

See under individual drugs

Anxiolytics and Hypnotics

Alcohol: enhanced sedative effects

Anaesthetics, general: enhanced sedative

Analgesics: opioids enhance sedative effects

Antibacterials: clarithromycin and erythromycin

Inhibit metabolism of midazolam with profound sedation; rifampicin inhibit metabolism of diazepam and possibly other benzodiazepine

Antidepressants: enhanced sedative effects

Antiepileptics: plasma phenytoin concentrations fluctuate by diazepam, possibly other benzodiazepines

Antifungals: itraconazole, ketoconazole and fluconazole increase plasma concentration of midazolam

Antihistamines: enhanced sedative effects

Antihypertensives: enhanced hypotensive effects

Antipsychotics: enhanced sedative effects

Antivirals: increased risk of enhanced and prolonged sedative effects and respiratory depression

Calcium-channel blockers: enhanced effect of midazolam

Apraclonidine

Antidepressants: manufacturer of apraclonidine advises avoid con-

Appendix 1: Drug interactions

comitant use with MAOIs, tricyclic-related antidepressants and tricyclics

Sympathomimetics: manufacturer of apraclonidine advises avoid concomitant use with sympathomimetics.

Aprepitant

Contraceptives: aprepitant possibly causes contraceptive failure of hormonal contraceptives containing oestrogens (alternative contraception recommended); aprepitant possibly causes contraceptive failure of hormonal contraceptives containing progestogens (alternative contraception recommended)

Argatroban

Analgesics: increased risk of haemorrhage when anticoagulants given with intravenous diclofenac and ketorolac avoid concomitant use.

Anticoagulants: increase risk of haemorrhage when given with other anticoagulants including Rivaroxaban (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)

Artemether + lumefantrine

Antidepressants: avoidance of antidepressants advised by manufacturer of artemether with lumefantrine

Antiarrhythmics: avoidance of amiodarone advised by manufacturer of artemether with lumefantrine (risk

of ventricular arrhythmias); avoidance of flecainide advised by manufacturer of artemether with lumefantrine (risk of ventricular arrhythmias)

Antimalarials: avoidance of antimalarials advised by manufacturer of artemether with lumefantrine

Antipsychotics: manufacturer of artemether with lumefantrine advises avoid concomitant use with antipsychotics

Antivirals: plasma concentration of artemether with lumefantrine reduced by efavirenz

Beta-blockers: manufacturer of artemether with lumefantrine advises avoid concomitant use with

metoprolol; manufacturer of artemether with lumefantrine advises avoid concomitant use with sotalol

Antibacterials: avoidance of macrolides advised by manufacturer of artemether with lumefantrine; avoidance of quinolones advised by manufacturer of artemether with lumefantrine

Antifungals: avoidance of imidazoles advised by manufacturer of artemether with lumefantrine; avoidance of triazoles advised by manufacturer of artemether with lumefantrine

Aspirin

Other analgesics: increased risk of side-effects with other NSAIDs

Antacids: aspirin excretion increased in alkaline urine

Anticoagulants: increased risk of bleeding due to antiplatelet effect

Appendix 1: Drug interactions

Antidepressants: increased risk of bleeding when aspirin given with SSRIs

Antiplatelet: increased risk of bleeding

Corticosteroids: increased risk of gastro-intestinal bleeding and ulceration

Cytotoxic: increased risk of toxicity with methotrexate

Diuretics: antagonism of Spironolactone diuretic effect

Metoclopramide and domperidone: enhanced effect of aspirin

Uricosurics: effects of probenecid and sulphapyrazone reduced

Atenolol

See Beta-blockers

Atomoxetine:

Amiodarone: increased risk of ventricular arrhythmias

Antidepressants: possible increased risk of convulsions

Antidepressants, Tricyclic: increased risk of ventricular arrhythmias

Antipsychotics: increased risk of ventricular arrhythmias when atomoxetine given with antipsychotics that prolong the QT interval

Bupropion: possible increased risk of convulsions

Disopyramide: increased risk of ventricular arrhythmias

Diuretics: risk of ventricular arrhythmias with atomoxetine increased by hypokalaemia caused by diuretics

Erythromycin: increased risk of ventricular arrhythmias when atomoxetine given with parenteral erythromycin

Fluoxetine: metabolism of atomoxetine possibly inhibited by fluoxetine

MAOIs: atomoxetine should not be started until 2 weeks after stopping MAOIs, Also MAOIs should not be started until at least 2 weeks after stopping atomoxetine

Methadone: increased risk of ventricular arrhythmias

Moxifloxacin: increased risk of ventricular arrhythmias

Paroxetine: metabolism of atomoxetine possibly inhibited by paroxetine

Procainamide: increased risk of ventricular arrhythmias

Salbutamol: Increased risk of cardiovascular side-effects when atomoxetine given with parenteral salbutamol

Sotalol: increased risk of ventricular arrhythmias

Tramadol: possible increased risk of convulsions

Atorvastatin:

See under statins

Atracurium

See Muscle Relaxants

Atropine

See antimuscarinics

Azathioprine

Appendix 1: Drug interactions

ACE Inhibitors: increased risk of leucopenia

Allopurinol: increased risk of toxicity

Antibacterials: increased risk of haematological toxicity with co-trimoxazole

Anticoagulants: anticoagulant effect of warfarin possibly reduced

Azithromycin

See under erythromycin

Baclofen

See under muscle relaxants

Barbiturates

Alcohol: enhances sedative effects

Anti-arrhythmics: metabolism of disopyramide and quinidine increased

Antibacterials: metabolism of chloramphenicol, doxycycline and metronidazole increased

Anticoagulants: metabolism of warfarin accelerated; phenobarbital plasma concentration of rivaroxaban possibly reduced by phenobarbital—manufacturer of rivaroxaban advises monitor for signs of thrombosis

Antidepressants: antagonism of anticonvulsant effect

Antiepileptics: enhanced sedative and anticonvulsant effects

Antipsychotics: antagonism of anticonvulsant effect

Calcium-channel blockers: effect reduced

Ciclosporin: metabolism of ciclosporin accelerated

Corticosteroids: metabolism of corticosteroids accelerated

Oestrogens and progestogens: metabolism of gestrinone, Tibolone and oral contraceptives accelerated

Bendamustine

Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

Benzodiazepines

See anxiolytics and hypnotics

Benzylopenicillin

See penicillins

Beta-blockers

Systemic absorption of topically applied preparation to the eye may take place.

Alcohol: enhanced hypotensive effect

Alpha blockers: enhanced hypotensive effect when beta-blockers are given with alpha-blockers, also increased chance of first dose hypotension with post-synaptic alpha blockers such as prazosin.

Alprostadil: enhanced hypotensive effect

Anaesthetics, local: increased risk of bupivacaine toxicity with propranolol

Analgesics: NSAIDs antagonise hypotensive effect

Anti-arrhythmics: increased risk of myocardial depression and bradycardia

Antibacterials: metabolism of bisoprolol and accelerated by rifampicin. Plasma concentration of metoprolol reduced by rifampicin.

Antidepressants: enhanced hypotensive effects with MAOIs; risk of ventricular arrhythmias associated with sotalol increased by tricyclics; plasma concentration of metoprolol increased by citalopram; Plasma concentration of metoprolol possibly increased by paroxetine, avoid concomitant use in cardiac insufficiency.

Antihypertensives: enhanced hypotensive effect

Antimalarials: manufacturer of artemether with lumefantrine advises avoid concomitant use with metoprolol or sotalol.

Antipsychotics: risk of ventricular arrhythmias associated with sotalol increased by phenothiazines

Anxiolytics and hypnotics: enhanced hypotensive effect

Calcium-channel blockers: increased risk of bradycardia and AV block with diltiazem; severe hypotension with nifedipine; asystole, severe hypotension and heart failure with verapamil

Cardiac glycosides: increased AV block and bradycardia

Corticosteroids: antagonise hypotensive effects

Diuretics: enhanced hypotensive effect

Fingolimod: possible increased risk of bradycardia when fingolimod given with beta-blockers

Ivabradine: increased risk of ventricular arrhythmias when sotalol given with ivabradine

Oestrogens and progestogens: oestrogens and combined oral contraceptives antagonize hypotensive effect

Sympathomimetics: severe hypertension with adrenaline, noradrenaline and possible with dobutamine

Betahistine

Antihistamines: antagonism (on theoretical basis)

Betamethasone

See corticosteroids

Bethanechol

See parasympathomimetics

Bezafibrate

See fibrates

Bicalutamide

Anticoagulants: bicalutamide possibly enhances anticoagulant effect of coumarins.

Biguanides

See antidiabetics

Bile Acids

Antacids: absorption of bile acids possibly reduced by antacids

Colestipol: absorption of bile acids possibly reduced by colestipol

Colestyramine: absorption of bile acids possibly reduced by colestyramine

Appendix 1: Drug interactions

Oestrogens: elimination of cholesterol in bile increased when bile acids given with oestrogens

Bismuth chelate

See tripotassium

Bisoprolol

See under beta-blockers

Bisphosphonates

Antacids: reduced absorption

Antibacterials: increased risk of hypocalcaemia with aminoglycosides

Calcium salt: reduced absorption

Iron: reduced absorption

Bleomycin

Cisplatin: increased pulmonary toxicity

Also, see cytotoxics

Bortezomib:

Ketoconazole: plasma concentration of bortezomib increased by ketoconazole

Also, see under cytotoxics

Brimonidine

Antidepressants, Tricyclic: manufacturer of brimonidine advises avoid concomitant use with tricyclics

MAOIs: manufacturer of brimonidine advises avoid concomitant use with MAOIs

Bromazepam

See anxiolytics and hypnotics

Bromocriptine

Alcohol: reduced tolerance to bromocriptine

Antibacterials: erythromycin increases risk of toxicity

Antipsychotics: antagonism of hypoprolactinaemic and antiparkinsonian effects

Metoclopramide and domperidone: antagonism of hypoprolactinaemic effect

Sympathomimetics: increased risk of toxicity with bromocriptine and phenylpropanolamine

Budesonide

See under corticosteroids

Bupivacaine

See local anaesthetics

Buspirone

See anxiolytics and hypnotics

Busulfan

Itraconazole: metabolism of busulfan inhibited by itraconazole (increased risk of toxicity)

Metronidazole: plasma concentration of busulfan increased by metronidazole (increased risk of toxicity)

Paracetamol: metabolism of intravenous busulfan possibly inhibited by paracetamol (manufacturer of

intravenous busulfan advises caution within 72 hours of paracetamol)

Phenytoin: plasma concentration of busulfan possibly reduced by phenytoin

Tioguanine: increased risk of hepatotoxicity

Also, see cytotoxics

Cabergoline

Antibacterials: plasma concentration of cabergoline increased by erythromycin; plasma concentration of cabergoline possibly increased by macrolides

Antipsychotics: hypoprolactinaemic and antiparkinsonian effects of cabergoline antagonised by antipsychotics

Domperidone: hypoprolactinaemic effect of cabergoline possibly antagonised by domperidone

Methyldopa: antiparkinsonian effect of dopaminergics antagonised by methyldopa

Metoclopramide: hypoprolactinaemic effect of cabergoline antagonised by metoclopramide

Calcium salts

Antibacterials: reduced absorption of ciprofloxacin and tetracyclines

Cardiac glycosides: large intravenous injection of calcium can precipitate arrhythmias.

Calcium-channel blockers

Grapefruit juice significantly increases plasma concentration of dihydropyridine calcium-channel blockers and verapamil

ACE Inhibitors: enhanced hypotensive effect

Alcohol: enhanced hypotensive effect

Alpha-blockers: enhanced hypotensive effect; increased risk of first-dose hypotensive effect of post-synaptic alpha-blockers such as prazosin

Alprostadil: enhanced hypotensive effect

Anaesthetics, General: enhanced hypotensive effect; verapamil increases hypotensive effects and risk of AV delay

Anti-arrhythmics: amiodarone-induced risk of AV Block, bradycardia and myocardial depression increased by diltiazem and verapamil

Antibacterials: rifampicin increases metabolism; erythromycin inhibits metabolism of calcium channel blockers

Antidepressants: diltiazem and verapamil increase plasma concentration of tricyclics

Antiepileptics: effect of carbamazepine enhanced by diltiazem and verapamil

Antifungals: possibly increased negative inotropic effects of itraconazole

Antihypertensives: enhanced hypotensive effects

Appendix 1: Drug interactions

Antipsychotics: enhanced hypotensive effect

Anxiolytics and Hypnotics: enhanced hypotensive effect; diltiazem and verapamil inhibit metabolism of midazolam

Beta-blockers: enhanced hypotensive effect; increased risk of bradycardia and AV block with diltiazem; severe hypotension, asystole and heart failure with verapamil

Cardiac glycosides: plasma concentration of digoxin increased

Corticosteroids: antagonism of hypotensive effect

Diuretics: enhanced hypotensive effect

Everolimus: plasma concentration of both drugs may increase when everolimus given with verapamil

Fingolimod: possible increased risk of bradycardia when fingolimod given with diltiazem or verapamil

Ivabradine: diltiazem increases plasma concentration of ivabradine—avoid concomitant use; verapamil increases plasma concentration of ivabradine—avoid concomitant use

Lenalidomide: plasma concentration of lenalidomide possibly increased by verapamil

NSAIDs: antagonism of hypotensive effect

Theophylline: possibly enhanced theophylline effect (possibly increased plasma-theophylline concentration)

Capecitabine

See Fluorouracil

Capreomycin

Other antibacterials: increased risk of nephrotoxicity and ototoxicity with aminoglycosides and vancomycin

Cytotoxics: increased risk of nephrotoxicity and ototoxicity with cisplatin

Captopril

See under ACE inhibitors

Carbamazepine

Acetazolamide: acetazolamide increases plasma-carbamazepine concentration

Alcohol: possibly enhanced CNS side-effects of carbamazepine

Antibacterials: effect of doxycycline reduced; clarithromycin and erythromycin increase plasma-carbamazepine concentration

Anticoagulants: accelerated metabolism of coumarins (reduced anticoagulant effect)

Antidepressants, Tricyclic: possibly accelerated metabolism of tricyclics (reduced plasma concentration; reduced antidepressant effect)

Antipsychotics: antagonism of anticonvulsant effect (convulsive threshold lowered)

Calcium-channel Blockers (dihydropyridines): probably reduced effect of dihydropyridine

Ciclosporin: accelerated metabolism (reduced plasma-ciclosporin concentration)

Appendix 1: Drug interactions

Corticosteroids: accelerated metabolism of corticosteroids (reduced effect)

Diuretics: increased risk of hyponatraemia

Hormone antagonists: danazol inhibits metabolism of carbamazepine

Oestrogens and progestogens: carbamazepine enhances metabolism of oral contraceptives

Rivaroxaban: plasma concentration possibly reduced by carbamazepine—manufacturer of rivaroxaban advises monitor for signs of thrombosis

Vitamins: carbamazepine possibly increases vitamin D requirements

Carbonic anhydrase inhibitors

See diuretics

Cardiac glycosides

ACE inhibitors: possibly increases plasma concentration of digoxin

Acetazolamide: Increased toxicity if hypokalaemia occurs

Anti-arrhythmics: plasma concentration of digoxin increased by amiodarone

Antifungals: increased toxicity if hypokalaemia occurs with amphotericin

Antimalarials: raise plasma concentration of digoxin

Beta-blockers: increased AV block and bradycardia

Calcium –Channel blockers: plasma concentration of digoxin increased by diltiazem and verapamil

Calcium Salts: large intravenous doses of calcium can precipitate arrhythmias

Corticosteroids: increased risk of hypokalaemia

Diuretics: increased toxicity if hypokalaemia occurs

Lenalidomide: possibly increases plasma concentration of digoxin

NSAIDs: possibly exacerbation of heart failure, reduced GFR, and increased plasma-cardiac glycoside concentrations

Carvedilol

See beta-blockers

Caspofungin

Ciclosporin: plasma concentration of caspofungin increased by ciclosporin (manufacturer of caspofungin recommends monitoring liver enzymes)

Corticosteroids: plasma concentration of caspofungin possibly reduced by dexamethasone

Tacrolimus: caspofungin reduces plasma concentration of tacrolimus

Cefaclor

See cephalosporins

Cefalaxin (cephalexin)

See cephalosporins

Cefixime

See cephalosporins

Cefotaxime

See cephalosporins

Appendix 1: Drug interactions

Cefradine

See cephalosporins

Ceftazidime

See cephalosporins

Ceftriaxone

See cephalosporins

Cefuroxime

See cephalosporins

Celecoxib

See under NSAIDs

Cephalosporins

Antacids: reduced absorption

Diuretics: loop diuretics may increase nephrotoxicity

Uricosurics: excretion of cephalosporins reduced by probenecid

Cetirizine

See antihistamines

Chloral hydrate

See anxiolytics and hypnotics

Chloramphenicol

Anticoagulants: anticoagulant effect enhanced

Antidiabetics: effects of sulphonylureas enhanced

Antiepileptics: increased plasma concentration of phenytoin

Ciclosporin: plasma concentration of ciclosporin possibly increased

Chloroquine and Hydroxychloroquine

Agalsidase Alfa and Beta: chloroquine and hydroxychloroquine possibly inhibit effects of agalsidase alfa and beta

Amiodarone: increased risk of ventricular arrhythmias

Antacids: absorption of chloroquine and hydroxychloroquine reduced by antacids

Antiepileptics: possible increased risk of convulsions

Ciclosporin: chloroquine and hydroxychloroquine increase plasma concentration of ciclosporin (increased risk of toxicity)

Cimetidine: metabolism of chloroquine and hydroxychloroquine inhibited by cimetidine (increased plasma concentration)

Digoxin: chloroquine and hydroxychloroquine possibly increase plasma concentration of digoxin

Kaolin: absorption of chloroquine and hydroxychloroquine reduced by kaolin

Lanthanum: absorption of chloroquine and hydroxychloroquine possibly reduced by lanthanum (give at least 2 hours apart)

Laronidase: chloroquine and hydroxychloroquine possibly inhibit effects of laronidase (manufacturer of laronidase advises avoid concomitant use)

Mefloquine: increased risk of convulsions when chloroquine and hydroxychloroquine given with mefloquine

Moxifloxacin: increased risk of ventricular arrhythmias when chloroquine and hydroxychloroquine given with moxifloxacin

Neostigmine: chloroquine and hydroxychloroquine have potential to increase symptoms of myasthenia gravis and thus diminish effect of neostigmine

Pyridostigmine: chloroquine and hydroxychloroquine have potential to increase symptoms of myasthenia gravis and thus diminish effect of pyridostigmine

Chlorpheniramine

See antihistamines

Chlorpromazine

See antipsychotics

Ciclosporin

ACE Inhibitors: Increased risk of hyperkalaemia

Allopurinol: plasma-ciclosporin concentration possibly increased (risk of nephrotoxicity)

Antibacterials: increased risk of nephrotoxicity with aminoglycosides and quinolones,

Anti-arrhythmics: amiodarone possibly increases plasma concentration of ciclosporin

Antidepressants: carbamazepine and phenytoin increase metabolism of ciclosporin

Antifungals: increased risk of nephrotoxicity with amphotericin

Antimalarials: chloroquine increases plasma ciclosporin concentration

Calcium-channel blockers: diltiazem, verapamil increase plasma ciclosporin concentration

Caspofungin: plasma concentration of caspofungin increased by ciclosporin (manufacturer of caspofungin recommends monitoring liver enzymes)

Corticosteroids: high dose methylprednisolone increases plasma ciclosporin concentration (risk of convulsion)

Cytotoxics: increases risk of neurotoxicity, and nephrotoxicity

Diuretics, Potassium-sparing: increased risk of hyperkalaemia

Everolimus plasma concentration of everolimus increased by ciclosporin

Lenalidomide: plasma concentration of lenalidomide possibly increased by ciclosporin

Lipid regulating drugs: increased risk of myopathy with statins; possible increased risk of renal impairment with fibrates

NSAIDs: increased risk of nephrotoxicity

Oestrogens and progestogens: progestogens inhibits metabolism of ciclosporin

Potassium salts: increased risk of hyperkalaemia

Vaccines: avoid use of live vaccines with immunosuppressant drugs

Appendix 1: Drug interactions

Cimetidine

See H₂-antihistamines

Cinacalcet

Hormone Antagonists: cinacalcet possibly inhibits metabolism of tamoxifen to active metabolite

Ciprofloxacin

See quinolones

Cisatracurium

See muscle relaxants

Cisplatin

See platinum compounds

Citalopram

See antidepressants

Clarithromycin

See erythromycin

Clindamycin

Parasympathomimetics: antagonism of effects of neostigmine and pyridostigmine

Clodronate

See Bisphosphonates

Clomethiazole

See antiepileptics

Clomipramine

See antidepressants

Clonazepam

See anxiolytics and hypnotics

Clonidine

ACE Inhibitors: enhanced hypotensive effect

Adrenaline: (epinephrine) possible risk of hypertension

Adrenergic Neurone Blockers: enhanced hypotensive effect

Alcohol: enhanced hypotensive effect
Aldesleukin: enhanced hypotensive effect

Alpha-blockers: enhanced hypotensive effect

Alprostadil: enhanced hypotensive effect

Anaesthetics, General: enhanced hypotensive effect

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect

Antidepressants, Tricyclic: hypotensive effect of clonidine antagonised by tricyclics, *Also* increased risk of hypertension on clonidine withdrawal

Anxiolytics and Hypnotics: enhanced hypotensive effect

Baclofen: enhanced hypotensive effect

Beta-blockers: increased risk of withdrawal hypertension when clonidine given with beta-blockers (withdraw beta-blockers several days before slowly withdrawing clonidine)

Calcium-channel Blockers: enhanced hypotensive effect

Captopril: previous treatment with clonidine possibly delays antihypertensive effect of captopril

Corticosteroids: hypotensive effect of clonidine antagonised by corticosteroids

Appendix 1: Drug interactions

Diazoxide: enhanced hypotensive effect

Diuretics: enhanced hypotensive effect
Hydralazine: enhanced hypotensive effect

Levodopa: enhanced hypotensive effect
MAOIs: enhanced hypotensive effect

Methyldopa: enhanced hypotensive effect

Methylphenidate: serious adverse events reported with concomitant use of clonidine and methylphenidate

Minoxidil: enhanced hypotensive effect

Moxisylyte (thymoxamine): enhanced hypotensive effect

Moxonidine: enhanced hypotensive effect

Nitrates: enhanced hypotensive effect
Noradrenaline (norepinephrine): possible risk of hypertension

NSAIDs: hypotensive effect of clonidine antagonised by NSAIDs

Oestrogens: hypotensive effect of clonidine antagonised by oestrogens

Phenothiazines: enhanced hypotensive effect

Sodium Nitroprusside: enhanced hypotensive effect

Tizanidine: enhanced hypotensive effect

Clopidogrel

Analgesics: increased risk of bleeding when given with NSAIDs or aspirin

Anticoagulants: increased risk of bleeding

Proton pump inhibitors: esomeprazole and omeprazole reduce the antiplatelet effect of clopidogrel

Clotrimazole

See antifungals

Clozapine

Amprenavir: plasma concentration of clozapine possibly increased by amprenavir

Antidepressants, Tricyclic possibly increased antimuscarinic side-effects

Antimuscarinics: increased risk of antimuscarinic side-effects

Azapropazone: avoid concomitant use of clozapine with azapropazone (increased risk of agranulocytosis)

Carbamazepine: metabolism of clozapine accelerated by carbamazepine (reduced plasma concentration), *Also* avoid concomitant use of drugs with substantial potential for causing agranulocytosis

Chloramphenicol: avoid concomitant use of clozapine with chloramphenicol (increased risk of agranulocytosis)

Cimetidine: effects of clozapine possibly enhanced by cimetidine

Ciprofloxacin: plasma concentration of clozapine increased by ciprofloxacin

Citalopram: plasma concentration of clozapine possibly increased by citalopram (increased risk of toxicity)

Appendix 1: Drug interactions

Cytotoxics: avoid concomitant use of clozapine with cytotoxics (increased risk of agranulocytosis)

Erythromycin: plasma concentration of clozapine possibly increased by erythromycin (possible increased risk of convulsions)

Flecainide: increased risk of arrhythmias when clozapine given with flecainide

Fluoxetine: plasma concentration of clozapine increased by fluoxetine

Flupentixol: avoid concomitant use of clozapine with depot formulation of flupentixol as cannot be withdrawn quickly if neutropenia occurs

Fluphenazine: avoid concomitant use of clozapine with depot formulation of fluphenazine as cannot be withdrawn quickly if neutropenia occurs

Fluvoxamine: plasma concentration of clozapine increased by fluvoxamine

Haloperidol: avoid concomitant use of clozapine with depot formulation of haloperidol as cannot be withdrawn quickly if neutropenia occurs

Lithium: increased risk of extrapyramidal side-effects and possibly neurotoxicity MAOIs: clozapine possibly increases CNS effects of MAOIs

Omeprazole: plasma concentration of clozapine possibly reduced by omeprazole

Paroxetine: plasma concentration of clozapine increased by paroxetine

Penicillamine: avoid concomitant use of clozapine with penicillamine (increased risk of agranulocytosis)

Phenytoin: metabolism of clozapine accelerated by phenytoin (reduced plasma concentration)

Pipotiazine: avoid concomitant use of clozapine with depot formulation of pipotiazine as cannot be withdrawn quickly if neutropenia occurs

Rifampicin: plasma concentration of clozapine possibly reduced by rifampicin

Risperidone: avoid concomitant use of clozapine with depot formulation of risperidone as cannot be withdrawn quickly if neutropenia occurs

Ritonavir: plasma concentration of clozapine increased by ritonavir (increased risk of toxicity)—avoid concomitant use

Sertraline: plasma concentration of clozapine increased by sertraline

Sulphonamides: avoid concomitant use of clozapine with sulphonamides (increased risk of agranulocytosis)

Venlafaxine: plasma concentration of clozapine increased by venlafaxine

Zuclopenthixol: avoid concomitant use of clozapine with depot formulation of zuclopenthixol as cannot be withdrawn quickly if neutropenia occurs

Also see antipsychotics

Co-amoxiclav

See penicillins

Colchicine

Ciclosporin: increased risk of nephrotoxicity and myotoxicity toxicity

Clarithromycin: increased risk of colchicine toxicity

Erythromycin: increased risk of colchicine toxicity w

Statins: possible increased risk of myopathy

Colecalciferol

See under vitamins

Colestyramine (cholestyramine)

Absorption of other drugs will be affected if taken simultaneously with colestyramine. It is advisable to take other drugs 1 hour before or 4-6 hours after colestyramine.

Colistin

Aminoglycosides: increased risk of nephrotoxicity

Capreomycin: increased risk of nephrotoxicity

Teicoplanin: increased risk of nephrotoxicity and ototoxicity

Vancomycin: increased risk of nephrotoxicity and ototoxicity

Also, see under Polymyxins

Contraceptives, oral

Antibacterials: rifampicin enhances metabolism of oral combined or

progestogen only contraceptive resulting in reduced contraceptive effect; broad-spectrum antibiotics possibly reduce contraceptive effects

Anticoagulants: antagonism of anticoagulant effects

Antiepileptics: carbamazepine and phenytoin accelerate metabolism of combined and progestogen only contraceptives

Antifungals: griseofulvin accelerates metabolism

Aprepitant: causes contraceptive failure of hormonal contraceptives containing oestrogens (alternative contraception recommended); causes contraceptive failure of hormonal contraceptives containing progestogens (alternative contraception recommended)

Corticosteroids

The following interactions do not generally apply to topically applied corticosteroids

Antibacterials: rifampicin accelerates metabolism of corticosteroids; erythromycin inhibits metabolism

Anticoagulants: corticosteroids may enhance or reduce anticoagulant effect of coumarins (warfarin)

Antidiabetics: antagonism of hypoglycaemic effects

Antiepileptics: accelerate metabolism of corticosteroids

Antifungals: increased risk of hypokalaemia when corticosteroids given with amphotericin; metabolism of corticosteroids and

Appendix 1: Drug interactions

methylprednisolone possibly inhibited by itraconazole; plasma concentration of inhaled and oral (and possibly also intranasal and rectal) budesonide increased by itraconazole; plasma concentration of inhaled fluticasone increased by itraconazole; dexamethasone

possibly reduces plasma concentration of caspofungin

Antivirals: dexamethasone possibly reduces plasma concentration of indinavir, lopinavir, saquinavir and telaprevir; plasma concentration of inhaled and intranasal fluticasone increased by ritonavir

increased risk of adrenal suppression; plasma concentration of budesonide (including inhaled, intranasal, and rectal budesonide) possibly increased by ritonavir—increased risk of adrenal suppression; plasma concentration of corticosteroids possibly increased by ritonavir—increased risk of adrenal suppression

Antihypertensives: antagonism of hypotensive effect

Cardiac glycosides: increased risk of toxicity if hypokalaemia induced by corticosteroids

Caspofungin: plasma concentration of caspofungin possibly reduced by dexamethasone

Ciclosporin: plasma-ciclosporin concentration increased by prednisolone; ciclosporin increases plasma concentration of prednisolone.

Diuretics: antagonism of diuretic effect; increased risk of hypokalaemia

NSAIDs: increased risk of gastrointestinal bleeding and ulceration

Theophylline: increased risk of hypokalaemia

Co-trimoxazole and trimethoprim

Anti-arrhythmics: co-trimoxazole increases the risk of ventricular arrhythmias with amiodarone.

Anticoagulants: effect of coumarin and warfarin enhanced

Antidiabetics: effects of sulphonylurea compounds may be enhanced.

Antiepileptics: antifolate effect increased; plasma phenytoin concentration increased

Antimalarials: risk of antifolate effects increased with pyrimethamine
Ciclosporin: increased risk of nephrotoxicity

Cytotoxics: increased antifolate effect with methotrexate; methotrexate toxicity increased

Vaccines: high doses of corticosteroids impair immune response to vaccines, avoid concomitant use with live vaccines

Cyclopentolate

See under Antimuscarinics

Cyclophosphamide and ifosfamide

Anticoagulants: ifosfamide possible enhances effects of warfarin

Appendix 1: Drug interactions

Suxamethonium: possible enhancement of muscle relaxant effect

Cycloserine

Alcohol: increased risk of seizure

Antibacterials: increased risk of CNS toxicity with isoniazid

Antiepileptics: increased risk of toxicity of phenytoin

Cytotoxics

Clozapine: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis);

Digoxin: cytotoxics reduce absorption of digoxin tablets

Cytotoxics, others: plasma concentration of everolimus increased by imatinib; possible increased risk of neutropenia when lapatinib given with docetaxel; increased risk of neutropenia when lapatinib given with paclitaxel; sorafenib possibly increases plasma concentration of doxorubicin and irinotecan; sorafenib increases plasma concentration of docetaxel

Phenytoin: cytotoxics possibly reduce absorption of phenytoin

Also, see under individual drugs

Danazol

Anticoagulants: effects of warfarin enhanced

Antiepileptics: inhibits metabolism of carbamazepine

Ciclosporin: increased plasma-ciclosporin concentration

Dantrolene

See under muscle relaxants

Dapsone

Antibacterials: plasma concentration reduced by rifampicin

Probenecid: dapsone excretion reduced

Darunavir

Antibacterials: plasma concentration of quinine possibly increased by darunavir (increased risk of toxicity)

Antivirals: plasma concentration of darunavir reduced by efavirenz (adjust dose—consult product literature); plasma concentration of darunavir reduced by lopinavir—avoid concomitant use

Antimalarials: rifampicin significantly reduces plasma concentration of darunavir—avoid concomitant use

Antimaligants: darunavir possibly increases plasma concentration of everolimus—manufacturer of everolimus advises avoid concomitant use.

Antipsychotics: plasma concentration of quetiapine possibly increased by darunavir—manufacturer of quetiapine advises avoid concomitant use

Dasatinib

Famotidine: plasma concentration of dasatinib possibly reduced by famotidine

Appendix 1: Drug interactions

Rifampicin: metabolism of dasatinib accelerated by rifampicin

Simvastatin: dasatinib possibly increases plasma concentration of simvastatin

Also, see under cytotoxics

Deferasirox

Antacids: absorption of deferasirox possibly reduced by antacids containing aluminium

Antibacterials: plasma concentration of deferasirox reduced by rifampicin

Antidiabetics: deferasirox increases plasma concentration of repaglinide

Antipsychotics: manufacturer of deferasirox advises avoid concomitant use with clozapine.

Anxiolytics and Hypnotics: deferasirox possibly reduces plasma concentration of midazolam.

Muscle Relaxants: manufacturer of deferasirox advises avoid concomitant use with tizanidine .

Theophylline: deferasirox increases plasma concentration of theophylline (consider reducing dose of theophylline)

Desferrioxamine

Antipsychotics: avoid Prochlorperazine (on theoretical basis)

Desmopressin

Analgesics: effect of desmopressin is potentiated by Indomethacin

Dexamethasone

See under corticosteroids

Diazepam

See under anxiolytics and hypnotics

Diclofenac

See under NSAIDs

Didanosine

Allopurinol: plasma concentration of didanosine possibly increased by allopurinol

Ganciclovir: plasma concentration of didanosine possibly increased by ganciclovir

Hydroxycarbamide: increased risk of toxicity when didanosine given with hydroxycarbamide

Ribavirin: increased risk of side-effects Stavudine: increased risk of side-effects

Tenofovir: plasma concentration of didanosine increased by tenofovir (increased risk of toxicity)

Tipranavir: plasma concentration of didanosine reduced by tipranavir

Digoxin

See under cardiac glycosides

Diltiazem

See under calcium-channel blockers

Dimenhydrinate

See under antihistamines

Diphenhydramine

See under antihistamines

Dipyridamole

Antiarrhythmic: effects of adenosine enhanced

Anticoagulant: effect enhanced due to antiplatelet action of dipyridamole

Antiplatelets: increased risk of bleeding

Disodium etidronate

See under bisphosphonates

Disodium pamidronates

See under bisphosphonates

Disopyramide

Anti-arrhythmics (others): increased risk of myocardial depression; amiodarone increases risk of ventricular arrhythmias

Antibacterials: plasma concentration of disopyramide reduced by rifampicin but increased by erythromycin or clarithromycin

Antidepressants: increased risk of ventricular arrhythmias with tricyclics

Antihistamines: increased risk of ventricular arrhythmias

Antipsychotics: increased risk of ventricular arrhythmias

Beta blockers: increased myocardial depression

Diuretics

ACE inhibitors and angiotensin II antagonists: enhanced hypotensive

effects; risk of severe hypokalaemia with potassium sparing diuretics

Analgesics: diuretics increase risk of NSAIDs nephrotoxicity; notably Indomethacin antagonises diuretic effect; Indomethacin and may be other NSAIDs increase risk of hyperkalaemia with potassium sparing diuretics

Anti-arrhythmics: cardiac toxicity of anti-arrhythmics increased if diuretics produce hypokalaemia

Antibacterials: loop diuretics increase the nephrotoxicity of and ototoxicity of aminoglycosides and

Antidepressants: increased risk of postural hypotension

Antiepileptics: increased risk of hyponatraemia with carbamazepine

Antihypertensives: enhanced hypotensive effect

Antipsychotics

Cardiac glycosides: increased toxicity if hypokalaemia occurs with loop diuretics and thiazides; effect enhanced with spironolactone

Ciclosporin: increased risk of hyperkalaemia with potassium sparing diuretics

Lithium: lithium excretion reduced

Potassium salts: hyperkalaemia with potassium sparing diuretics

Theophylline: increased risk of hypokalaemia

Dobutamine

See under sympathomimetics

Docetaxel

Appendix 1: Drug interactions

Ciclosporin: in vitro studies suggest a possible interaction between docetaxel and ciclosporin (consult docetaxel product literature)

Erythromycin: in vitro studies suggest a possible interaction between docetaxel and erythromycin (consult docetaxel product literature)

Ketoconazole: in vitro studies suggest a possible interaction between docetaxel and ketoconazole (consult docetaxel product literature)

Sorafenib: plasma concentration of docetaxel increased by sorafenib

Also, see cytotoxics

Domperidone

Antimuscarinics: antagonism of effects on gastrointestinal activity

Bromocriptine: possible antagonism of hypoprolactinaemic effect

Cabergoline: hypoprolactinaemic effect of cabergoline possibly antagonised by domperidone

Dopamine

See under sympathomimetics

Doxapram

Theophylline: possible increase in CNS stimulation

Doxazosin

See under alpha-blockers

Doxorubicin

Ciclosporin: increased risk of neurotoxicity

Doxycycline

See under tetracyclines

Drotrecogin Alfa

Heparin: manufacturer of drotrecogin alfa advises avoid concomitant use with high doses of heparin

Duloxetine

See under antidepressants SSRI

Dydrogesterone

See under progesterone

Efavirenz

Amprenavir: efavirenz reduces plasma concentration of amprenavir

Antimalarials: plasma concentration of artemether with lumefantrine reduced by efavirenz

Aripiprazole: efavirenz possibly reduces plasma concentration of aripiprazole —Atazanavir: efavirenz reduces plasma concentration of atazanavir

Atorvastatin: efavirenz reduces plasma concentration of atorvastatin

Carbamazepine: plasma concentration of both drugs reduced when efavirenz given with carbamazepine

Caspofungin: efavirenz possibly reduces plasma concentration of caspofungin —Clarithromycin: increased risk of rash

Darunavir: efavirenz reduces plasma concentration of darunavir

Diltiazem: efavirenz reduces plasma concentration of diltiazem

Appendix 1: Drug interactions

Ergot Alkaloids: increased risk of ergotism
Grapefruit Juice: plasma concentration of efavirenz possibly increased by grapefruit juice

Indinavir: efavirenz reduces plasma concentration of indinavir

Itraconazole: efavirenz reduces plasma concentration of itraconazole

Lopinavir: efavirenz reduces plasma concentration of lopinavir

Maraviroc: efavirenz possibly reduces plasma concentration of maraviroc —Methadone: efavirenz reduces plasma concentration of methadone

Midazolam: increased risk of prolonged sedation

Nevirapine: plasma concentration of efavirenz reduced by nevirapine

Oestrogens: efavirenz possibly reduces contraceptive effect of oestrogens

Pimozide: efavirenz possibly increases plasma concentration of pimozide (increased risk of ventricular arrhythmias—avoid concomitant use)

Posaconazole: efavirenz reduces plasma concentration of posaconazole

Pravastatin: efavirenz reduces plasma concentration of pravastatin

Rifabutin: efavirenz reduces plasma concentration of rifabutin

Rifampicin: plasma concentration of efavirenz reduced by rifampicin

Ritonavir: toxicity of efavirenz increased by ritonavir, monitor liver function tests

Saquinavir: efavirenz significantly reduces plasma concentration of saquinavir

Sertraline: efavirenz reduces plasma concentration of sertraline

Simvastatin: efavirenz reduces plasma concentration of simvastatin

St John's Wort: plasma concentration of efavirenz reduced by St John's wort

Voriconazole: efavirenz reduces plasma concentration of voriconazole, Also plasma concentration of efavirenz increased

Eformoterol (formoterol)

See under sympathomimetics

Enalapril

See under ACE inhibitors

Enflurane

See under general anaesthetics

Entacapone

Anticoagulants: anticoagulant effect of warfarin enhanced by entacapone

Ephedrine

See under sympathomimetics

Erlotinib

Capecitabine: plasma concentration of erlotinib possibly increased by capecitabine. (Capecitabine is a prodrug of fluorouracil)

Coumarins: increased risk of bleeding

Appendix 1: Drug interactions

Ketoconazole: metabolism of erlotinib inhibited by ketoconazole (increased plasma concentration)

NSAIDs: increased risk of bleeding
Rifampicin: metabolism of erlotinib accelerated by rifampicin (reduced plasma concentration)

Tobacco: plasma concentration of erlotinib reduced by tobacco smoking

Ertapenem

Antiepileptics: sodium valproate-carbapenems reduce plasma concentration of sodium valproate—avoid concomitant use

Erythromycin and other macrolides

Analgesics (opioid): plasma concentration of alfentanil increased by erythromycin

Anti-arrhythmics: plasma concentration of disopyramide increased by erythromycin

Anticoagulants: effects of warfarin enhanced by erythromycin and possibly by other macrolides

Antiepileptics: erythromycin and clarithromycin inhibit carbamazepine metabolism

Antihistamines: erythromycin possibly increases plasma-loratidine concentration

Antimalarials: avoidance of macrolides advised by manufacturer of artemether with lumefantrine

Anxiolytics and hypnotics: clarithromycin and erythromycin inhibit metabolism of midazolam resulting in profound sedation

Cabergoline: plasma concentration of cabergoline increased by erythromycin

Ciclosporin: macrolides inhibit ciclosporin metabolism

Everolimus: plasma concentration of everolimus possibly increased by clarithromycin; plasma concentration of everolimus increased by erythromycin

Ivabradine: clarithromycin possibly increases plasma concentration of ivabradine—avoid concomitant use; increased risk of ventricular arrhythmias when erythromycin given with ivabradine—avoid concomitant use

Lenalidomide: plasma concentration of lenalidomide possibly increased by clarithromycin (increased risk of toxicity)

Lipid-regulating drugs: erythromycin and clarithromycin increase risk of myopathy with simvastatin and atorvastatin; clarithromycin increases plasma concentration of atorvastatin

Theophylline: erythromycin and clarithromycin inhibit metabolism of Theophylline

Esmolol

See under beta-blockers

Esomeprazole

See under proton pump inhibitors

Estradiol

See under Oestrogens

Etanercept

Appendix 1: Drug interactions

Abatacept: increased risk of side-effects

Anakinra: increased risk of side-effects when etanercept given with anakinra

Vaccines: avoid concomitant use of etanercept with live vaccines

Ethinylestradiol

See under contraceptives

Ethosuximide

Antibacterials: isoniazid increases plasma concentrations

Antidepressants: antagonism

Antiepileptics (other): potentiation of effects with excessive sedation

Antimalarials: mefloquine antagonises anticonvulsant effect; chloroquine reduces convulsive threshold

Antipsychotics: antagonism

Etidronate

See under bisphosphonates

Etomidate

See under Anaesthetics, General

Etonogestrel

See under Progestogens

Etoricoxib

See under NSAIDs

Everolimus

Antibacterials: plasma concentration of everolimus possibly increased by clarithromycin; plasma

concentration of everolimus increased by erythromycin; plasma concentration of everolimus reduced by rifampicin

Antifungals: plasma concentration of everolimus possibly increased by voriconazole and itraconazole

Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

Antivirals: plasma concentration of everolimus possibly increased by darunavir, indinavir, ritonavir, atazanavir and saquinavir

Calcium-channel Blockers: plasma concentration of both drugs may increase when everolimus given with verapamil

Ciclosporin: plasma concentration of everolimus increased by ciclosporin

Cytotoxics: plasma concentration of everolimus increased by imatinib (consider reducing the dose of everolimus)

Grapefruit Juice: manufacturer of everolimus advises avoid concomitant use with grapefruit juice

Exemestane

Rifampicin: plasma concentration of exemestane possibly reduced by rifampicin

Fenofibrate

See under fibrates

Fentanyl

See under opioid analgesics

Appendix 1: Drug interactions

Ferrous salts

See under Iron

Fibrates

Anticoagulants: enhancement of effects of warfarin

Ciclosporin: possible increased risk of renal impairment with fenofibrate

Lipid-regulating drugs (other): increased risk of myopathy with statins

Filgrastim

Fluorouracil: neutropenia possibly exacerbated when filgrastim given with fluorouracil

Finasteride

No clinically important reaction reported

Fingolimod

Anti-arrhythmics: possible increased risk of bradycardia when fingolimod given with amiodarone, disopyramide or dronedarone

Antiepileptics: plasma concentration of fingolimod reduced by carbamazepine

Beta-blockers: possible increased risk of bradycardia when fingolimod given with beta-blockers

Calcium-channel Blockers: possible increased risk of bradycardia when fingolimod given with diltiazem or verapamil

Flecainide

Anti-arrhythmics (other): amiodarone increases plasma-flecainide concentration (increased risk of ventricular arrhythmias); increased myocardial depression with any other anti-arrhythmics

Antidepressants: fluoxetine increases plasma-flecainide concentration; increased risk of arrhythmias with tricyclics

Antimalarials: increased plasma-flecainide concentration with quinine

Beta-blockers: increased myocardial depression and bradycardia

Calcium-channel blockers: increased myocardial depression and asystole with verapamil

Diuretics: cardiac toxicity increased if hypokalaemia occurs

Flucloxacillin

See penicillins

Fluconazole

See under antifungals (imidazole and triazole)

Fludrocortisone

See under corticosteroids

Flunarizine

Alcohol: excessive sedation

Anxiolytics and hypnotics: excessive sedation

Fluorouracil

Anticoagulants: possible enhancement of warfarin effect

Fluoxetine

Appendix 1: Drug interactions

See under antidepressants

Flupenthixol

See under antipsychotics

Fluphenazine

See under antipsychotics

Flutamide

Anticoagulants: effect of warfarin enhanced

Fluticasone

See under corticosteroids

Fluvastatin

See statins

Folates

Sulfasalazine: absorption of folic acid possibly reduced by sulfasalazine

Phenobarbital: folates possibly reduce plasma concentration of phenobarbital

Phenytoin: folates possibly reduce plasma concentration of phenytoin

Primidone: folates possibly reduce plasma concentration of primidone

Folic Acid

See folates

Fondaparinux

Analgesics: increased risk of haemorrhage when anticoagulants are given with intravenous diclofenac (avoid concomitant use); increased

risk of hemorrhage when anticoagulants given with ketorolac (avoid concomitant use)

Formoterol (eformoterol)

See under sympathomimetics

Furosemide

See under diuretics

Fusidic Acid

Atorvastatin: possible increased risk of myopathy

Ritonavir: plasma concentration of both drugs increased

Simvastatin: increased risk of myopathy

Gabapentin

Antacids: absorption of gabapentin reduced by antacids Gabapentin belongs to Antiepileptics and will have the following interactions:

Antidepressants, SSRI: anticonvulsant effect of antiepileptics antagonised by SSRIs

Antidepressants, Tricyclic: anticonvulsant effect of antiepileptics antagonised by tricyclics

Chloroquine and Hydroxychloroquine: possible increased risk of convulsions

MAOIs: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs

Mefloquine: anticonvulsant effect of antiepileptics antagonised by mefloquine

St John's Wort: avoid concomitant use

Appendix 1: Drug interactions

Ganciclovir

Didanosine: ganciclovir possibly increases plasma concentration of didanosine

Imipenem with Cilastatin: increased risk of convulsions

Lamivudine: avoidance of intravenous ganciclovir advised by manufacturer of lamivudine

Mycophenolate: plasma concentration of ganciclovir possibly increased by mycophenolate , Also plasma concentration of inactive metabolite of mycophenolate possibly increased

Probenecid: excretion of ganciclovir reduced by probenecid (increased plasma concentration and risk of toxicity)

Tacrolimus: possible increased risk of nephrotoxicity when ganciclovir given with tacrolimus I

Zidovudine: profound myelosuppression

Gefitinib

Antibacterials: plasma concentration of gefitinib reduced by rifampicin

Anticoagulants: gefitinib possibly enhances anticoagulant effect of warfarin

Antiepileptics: manufacturer of gefitinib advises avoid concomitant use with carbamazepine, phenobarbital and phenytoin

Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

Ulcer-healing Drugs: plasma concentration of gefitinib reduced by ranitidine

Gentamicin

See under aminoglycosides

Glibenclamide

See under antidiabetics

Gliclazide

See under antidiabetics

Glimepiride

See under antidiabetics

Glyceryl trinitrate

See under nitrates

Griseofulvin

Contraceptives (oral): metabolism of oral contraceptives accelerated

Haloperidol

See under antipsychotics

Halothane

See under general anaesthetics

Heparin

ACE Inhibitors: increased risk of hyperkalaemia

Aliskiren: increased risk of hyperkalaemia Heparin has the following interaction information:

Angiotensin-II Receptor Antagonists: increased risk of hyperkalaemia

Aspirin: anticoagulant effect of heparins enhanced by aspirin

Clopidogrel: increased risk of bleeding
Diclofenac: increased risk of haemorrhage when heparins given with intravenous diclofenac (avoid concomitant use, including low-dose heparin)

Dipyridamole: anticoagulant effect of heparins enhanced by dipyridamole

Drotrecogin Alfa: avoidance of concomitant use of high doses of heparin with drotrecogin alfa advised by manufacturer of drotrecogin alfa literature

Glyceryl Trinitrate: anticoagulant effect of heparins reduced by infusion of glyceryl trinitrate

Iloprost: anticoagulant effect of heparins possibly enhanced by iloprost

Ketorolac: increased risk of haemorrhage when heparins given with ketorolac (avoid concomitant use, including low-dose heparin)

NSAIDs: possible increased risk of bleeding when heparins given with NSAIDs

Histamine H₂-antagonists

Cimetidine inhibits activity of cytochrome P450 and thereby slows the metabolism of many drugs. Ranitidine does not inhibit hepatic cytochrome P450 and therefore has little effect on drug metabolism

5HT₁ Agonists

Duloxetine: possible increased serotonergic effects

St John's Wort: increased serotonergic effects

Hydralazine

ACE inhibitors: enhanced hypotensive effect

Anaesthetics: enhanced hypotensive effect

Analgesics: NSAIDs antagonise hypotensive effect

Corticosteroids: antagonise hypotensive effect

Hydrochlorothiazide

See under diuretics

Hydrocortisone

See under corticosteroids

Hydromorphone

See under opioid analgesics

Hydroxycarbamide

Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

Didanosine: increased risk of toxicity

Stavudine: increased risk of toxicity

Also, see under cytotoxics

Hydroxychloroquine

Appendix 1: Drug interactions

See under chloroquine and hydroxychloroquine

Hydroxyprogesterone hexanoate

See under Progestogens

Hydroxyzine

See under antihistamine

Hyoscine

See under antimuscarinics

Ibuprofen

See under NSAIDs

Ifosfamide

See under cyclophosphamide

Imatinib

Carbamazepine: plasma concentration of imatinib reduced by carbamazepine

Ciclosporin: imatinib possibly increases plasma concentration of ciclosporin

Ketoconazole: plasma concentration of imatinib increased by ketoconazole

Levothyroxine (thyroxine): imatinib possibly reduces plasma concentration of levothyroxine (thyroxine)

Oxcarbazepine: plasma concentration of imatinib reduced by oxcarbazepine

Phenytoin: plasma concentration of imatinib reduced by phenytoin

Rifampicin: plasma concentration of imatinib reduced by rifampicin

Simvastatin: imatinib increases plasma concentration of simvastatin

St John's Wort: plasma concentration of imatinib reduced by St John's wort

Warfarin: manufacturer of imatinib advises replacement of warfarin with a heparin (possibility of enhanced warfarin effect)

Also, see under cytotoxics

Imipramine

See under antidepressants

Indinavir

Alprazolam: increased risk of prolonged sedation

Amiodarone: indinavir possibly increases plasma concentration of amiodarone

Aripiprazole: indinavir possibly inhibits metabolism of aripiprazole

Artemether with Lumefantrine: avoid concomitant use of indinavir with artemether/lumefantrine

Atazanavir: avoid concomitant use of indinavir with atazanavir

Atorvastatin: possible increased risk of myopathy

Atovaquone: plasma concentration of indinavir possibly reduced by atovaquone

Barbiturates: plasma concentration of indinavir possibly reduced by barbiturates

Carbamazepine: plasma concentration of indinavir possibly reduced by carbamazepine

Appendix 1: Drug interactions

Cilostazol: indinavir possibly increases plasma concentration of cilostazol

Darifenacin: avoidance of indinavir advised by manufacturer of darifenacin

Darunavir: plasma concentration of both drugs increased

Dexamethasone: plasma concentration of indinavir possibly reduced by dexamethasone

Efavirenz: plasma concentration of indinavir reduced by efavirenz

Eletriptan: indinavir increases plasma concentration of eletriptan (risk of toxicity)

Methysergide: increased risk of ergotism when indinavir given with ergotamine and methysergide

Fesoterodine: manufacturer of fesoterodine advises dose reduction when indinavir given with fesoterodine

Flecainide: indinavir possibly increases plasma concentration of flecainide (increased risk of ventricular arrhythmias)

Itraconazole: plasma concentration of indinavir increased by itraconazole

Ketoconazole: metabolism of indinavir inhibited by ketoconazole

Maraviroc: indinavir increases plasma concentration of maraviroc

Midazolam: indinavir possibly increases plasma concentration of midazolam (risk of prolonged sedation)

Nelfinavir: combination of indinavir with nelfinavir may increase

plasma concentration of either drug (or both)

Nevirapine: plasma concentration of indinavir reduced by nevirapine

Phenytoin: plasma concentration of indinavir possibly reduced by phenytoin

Pimozide: indinavir possibly increases plasma concentration of pimozide (increased risk of ventricular arrhythmias)

Primidone: plasma concentration of indinavir possibly reduced by primidone

Rifabutin: indinavir increases plasma concentration of rifabutin , *Also* plasma concentration of indinavir decreased (reduce dose of rifabutin and increase dose of indinavir)

Rivaroxaban: manufacturer of rivaroxaban advises avoid concomitant use with indinavir

Rifampicin: metabolism of indinavir accelerated by rifampicin (reduced plasma concentration)

Ritonavir: plasma concentration of indinavir increased by ritonavir

Rosuvastatin: possible increased risk of myopathy when indinavir given with rosuvastatin

Saquinavir: indinavir increases plasma concentration of saquinavir

Sertindole: indinavir increases plasma concentration of sertindole (increased risk of ventricular arrhythmias)

Sildenafil: indinavir increases plasma concentration of sildenafil

Appendix 1: Drug interactions

Simvastatin: increased risk of myopathy

St John's Wort: plasma concentration of indinavir reduced by St John's wort

Telithromycin: avoidance of concomitant indinavir in severe renal and hepatic impairment

Tolterodine: avoidance of indinavir advised by manufacturer of tolterodine

Vardenafil: indinavir increases plasma concentration of vardenafil

Indomethacin

See under NSAIDs

Infliximab

Abatacept: increased risk of side-effects

Anakinra: avoid concomitant use

Vaccines: avoid concomitant use of infliximab with live vaccines

Insulins

See under antidiabetics

Interferons

Vaccines: manufacturer of interferon gamma advises avoid concomitant use with vaccines

Telbivudine: increased risk of peripheral neuropathy when interferon alfa given with telbivudine

Theophylline: interferon alfa inhibits metabolism of theophylline (increased plasma concentration)

Ipratropium

See under antimuscarinics

Irinotecan

Atazanavir: metabolism of irinotecan possibly inhibited by atazanavir (increased risk of toxicity)

Carbamazepine: plasma concentration of irinotecan and its active metabolite reduced by carbamazepine

Ketoconazole: plasma concentration of irinotecan reduced by ketoconazole (but concentration of active metabolite of irinotecan increased)

Phenobarbital: plasma concentration of irinotecan and its active metabolite reduced by phenobarbital

Phenytoin: plasma concentration of irinotecan and its active metabolite reduced by phenytoin

Sorafenib: plasma concentration of irinotecan possibly increased by sorafenib

St John's Wort: metabolism of irinotecan accelerated by St John's wort (reduced plasma concentration)

Also, see under cytotoxics

Iron

Antacids: reduces absorption of oral iron salts

Antibacterials: tetracyclines reduce oral iron salt absorption; absorption of ciprofloxacin reduced by oral iron salts

Isoflurane

See under anaesthesia

Isoniazid

Anaesthesia: possible potentiation of hepatotoxicity with isoflurane

Antibacterials (other): increased CNS toxicity with cycloserine
Antiepileptics: metabolism of carbamazepine, ethosuximide and phenytoin inhibited; hepatotoxicity of isoniazid possibly increased with carbamazepine

Isoprenaline

See under sympathomimetics

Isosorbide

See under nitrates

Isotretinoin

See under retinoids

Itraconazole

See under antifungals (imidazole and triazole)

Ivabradine

Anti-arrhythmics: amiodarone increased risk of ventricular arrhythmias when amiodarone given with ivabradine

Antibacterials: clarithromycin possibly increases plasma concentration of ivabradine—avoid concomitant use; increased risk of ventricular arrhythmias when erythromycin given with ivabradine—avoid concomitant use

Antifungals: fluconazole increases plasma concentration of ivabradine—reduce initial dose of ivabradine; itraconazole possibly increases plasma concentration of ivabradine—avoid concomitant use; ketoconazole increases plasma

concentration of ivabradine—avoid concomitant use.

Antimalarials: increased risk of ventricular arrhythmias when mefloquine given with ivabradine.

Antivirals: ritonavir possibly increases plasma concentration of ivabradine—avoid concomitant use.

Beta-blockers: increased risk of ventricular arrhythmias when sotalol given with ivabradine.

Calcium channel blockers: diltiazem increases plasma concentration of ivabradine—avoid concomitant use; verapamil increases plasma concentration of ivabradine—avoid concomitant use

Ketamine

See under anaesthesia

Ketoconazole

See under antifungals (imidazole and triazole)

Labetalol

See under beta-blockers

Lamivudine

Emtricitabine: avoidance of lamivudine advised by manufacturer of emtricitabine

Foscarnet: manufacturer of lamivudine advises avoid concomitant use with foscarnet

Ganciclovir: manufacturer of lamivudine advises avoid concomitant use of intravenous ganciclovir

Appendix 1: Drug interactions

Trimethoprim: plasma concentration of lamivudine increased by trimethoprim (as co-trimoxazole)

Lamotrigine

Antidepressants: antagonism of anticonvulsant effect

Antiepileptics (other): potentiation of effects, increased sedation

Antimalarials: mefloquine antagonises anticonvulsant effect

Lapatinib

Antibacterials: manufacturer of lapatinib advises avoid concomitant use with rifabutin and rifampicin

Antiepileptics: plasma concentration of lapatinib reduced by carbamazepine; manufacturer of lapatinib advises avoid concomitant use with phenytoin

Antifungals: manufacturer of lapatinib advises avoid concomitant use with itraconazole and voriconazole

Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

Antivirals: manufacturer of lapatinib advises avoid concomitant use with ritonavir and saquinavir

Cytotoxics: possible increased risk of neutropenia when lapatinib given with docetaxel; increased risk of neutropenia when lapatinib given with paclitaxel

Grapefruit Juice: manufacturer of lapatinib advises avoid concomitant use with grapefruit juice

Ulcer-healing Drugs: absorption of lapatinib possibly reduced by histamine H₂-antagonists and proton pump inhibitors

Leflunomide

Note: Increased risk of toxicity with other haematotoxic and hepatotoxic drugs

Antibacterials: plasma concentration of active metabolite of leflunomide possibly increased by rifampicin

Anticoagulants: leflunomide possibly enhances anticoagulant effect of warfarin

Antidiabetics: leflunomide possibly enhances hypoglycaemic effect of tolbutamide

Antiepileptics: leflunomide possibly increases plasma concentration of phenytoin

Cytotoxics: risk of toxicity when leflunomide given with methotrexate.

Lipid-regulating Drugs: the effect of leflunomide is significantly decreased by colestyramine (enhanced elimination)

Vaccines: avoid concomitant use of leflunomide with live vaccines.

Lenalidomide

Antibacterials: plasma concentration of lenalidomide possibly increased by clarithromycin (increased risk of toxicity)

Calcium-channel Blockers: plasma concentration of lenalidomide possibly increased by verapamil (increased risk of toxicity)

Cardiac Glycosides: lenalidomide possibly increases plasma concentration of digoxin

Ciclosporin: plasma concentration of lenalidomide possibly increased by ciclosporin (increased risk of toxicity)

Levetiracetam

Antidepressants, SSRI: anticonvulsant effect of antiepileptics antagonised by SSRIs

Antidepressants, Tricyclic: anticonvulsant effect of antiepileptics antagonised by tricyclics

Chloroquine and Hydroxychloroquine: possible increased risk of convulsions

MAOIs: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs

Mefloquine: anticonvulsant effect of antiepileptics antagonised by mefloquine

St John's Wort: avoid concomitant use of antiepileptics with St John's wort

Levodopa

Anaesthetics: risk of arrhythmias with halothane, isoflurane and other volatile anaesthetics

Antidepressants: hypertensive crises with MAO inhibitors

Antihypertensives: potentiation of hypotensive effect

Antipsychotics: antagonism of effect

Iron: absorption of levodopa may be reduced

Levofloxacin

Amiodarone: increased risk of ventricular arrhythmias

Antacids: absorption of levofloxacin reduced by antacids

Coumarins: levofloxacin possibly enhances anticoagulant effect of coumarins

Iron: absorption of levofloxacin reduced by oral iron

Phenindione: levofloxacin possibly enhances anticoagulant effect of phenindione

Sucralfate: absorption of levofloxacin reduced by sucralfate

Zinc: absorption of levofloxacin reduced by zinc

Also, see under quinolones

Levonorgestrel

See under progesterone

Lignocaine (Lidocaine)

Interactions are less likely when Lidocaine is used topically.

Anti-arrhythmics (other): increased myocardial depression

Beta-blockers: increased risk of myocardial depression; increased risk of lignocaine toxicity with propranolol

Lisinopril

See under ACE inhibitors

Linezolid

Antidepressants: MAOIs can cause increased risk of hypertension and CNS excitation when given with

Appendix 1: Drug interactions

other MAOIs (avoid for at least 2 weeks after stopping previous MAOIs and then start at a reduced dose);

Adrenaline: risk of hypertensive crisis when MAOIs given with adrenaline (epinephrine)

Atomoxetine: after stopping MAOIs do not start atomoxetine for 2 weeks, also MAOIs should not be started until at least 2 weeks after stopping atomoxetine

Antiepileptics: avoidance for 2 weeks after stopping MAOIs advised by manufacturer of carbamazepine, also antagonism of anti-convulsant effect

Antipsychotics: CNS effects of MAOIs possibly increased by clozapine

Dopaminergics: risk of hypertensive crisis when MAOIs given with co-careldopa, avoid co-careldopa for at least 2 weeks after stopping MAOIs; avoid concomitant use of non-selective MAOIs with entacapone

Ephedrine: risk of hypertensive crisis when MAOIs given with ephedrine, avoid ephedrine for at least 2 weeks after stopping MAOIs

Sympathomimetics: risk of hypertensive crisis when MAOIs given with dopamine

Liraglutide

See under Antidiabetics

Lithium

ACE inhibitors: lithium excretion reduced

Analgesics: NSAIDs reduce lithium excretion
Antidepressants: SSRI increase risk of CNS toxicity
Antihypertensives: neurotoxicity may occur with methyl dopa
Antipsychotics: increased risk of extrapyramidal effects
Diuretics: lithium excretion reduced

Loperamide

Desmopressin: loperamide increases plasma concentration of oral desmopressin

Lopinavir

In combination with ritonavir as Kaletra® (ritonavir is present to inhibit lopinavir metabolism and increase plasma-lopinavir concentration)—see Also Ritonavir

Amprenavir: lopinavir reduces plasma concentration of amprenavir, effect on lopinavir plasma concentration not predictable

Aripiprazole: lopinavir possibly inhibits metabolism of aripiprazole

Artemether with Lumefantrine: avoid concomitant use of lopinavir with artemether/lumefantrine

Atorvastatin: possible increased risk of myopathy

Carbamazepine: plasma concentration of lopinavir possibly reduced by carbamazepine

Chlorphenamine (chlorpheniramine): lopinavir possibly increases plasma concentration of chlorphenamine (chlorpheniramine)

Appendix 1: Drug interactions

Cilostazol: lopinavir possibly increases plasma concentration of cilostazol

Darifenacin: avoidance of lopinavir advised by manufacturer of darifenacin

Darunavir: plasma concentration of lopinavir increased by darunavir (Also plasma concentration of darunavir reduced)

Dexamethasone: plasma concentration of lopinavir possibly reduced by dexamethasone

Efavirenz: plasma concentration of lopinavir reduced by efavirenz

Flecainide: lopinavir possibly increases plasma concentration of flecainide (increased risk of ventricular arrhythmias)

Lidocaine (lignocaine): lopinavir possibly increases plasma concentration of lidocaine (lignocaine)

Maraviroc: lopinavir increases plasma concentration of maraviroc

Nelfinavir: plasma concentration of lopinavir reduced by nelfinavir , Also plasma concentration of active metabolite of nelfinavir increased

Nevirapine: plasma concentration of lopinavir possibly reduced by nevirapine

Phenobarbital: plasma concentration of lopinavir possibly reduced by phenobarbital

Phenytoin: plasma concentration of lopinavir possibly reduced by phenytoin

Primidone: plasma concentration of lopinavir possibly reduced by primidone

Rifampicin: plasma concentration of lopinavir reduced by rifampicin
Rivaroxaban: manufacturers advise avoid concomitant use of rivaroxaban with lopinavir

Rosuvastatin: possible increased risk of myopathy when lopinavir given with rosuvastatin

Saquinavir: lopinavir increases plasma concentration of saquinavir
Sertindole: lopinavir increases plasma concentration of sertindole (increased risk of ventricular arrhythmias)

Simvastatin: possible increased risk of myopathy when lopinavir given with simvastatin

Sirolimus: lopinavir possibly increases plasma concentration of sirolimus

St John's Wort: plasma concentration of lopinavir reduced by St John's wort —Telithromycin: avoidance of concomitant lopinavir in severe renal and hepatic impairment advised by manufacturer of telithromycin

Tenofovir: lopinavir increases plasma concentration of tenofovir

Tipranavir: plasma concentration of lopinavir reduced by tipranavir

Tolterodine: avoidance of lopinavir advised by manufacturer of tolterodine

Loratidine

See under antihistamines

Lorazepam

Appendix 1: Drug interactions

Valproate: plasma concentration of lorazepam possibly increased by valproate

Lorazepam: belongs to Benzodiazepines and will have the following interactions:

Cimetidine: metabolism of benzodiazepines inhibited by cimetidine (increased plasma concentration)

Disulfiram: metabolism of benzodiazepines inhibited by disulfiram (increased sedative effects)

Fluvoxamine: plasma concentration of some benzodiazepines increased by fluvoxamine

Levodopa: benzodiazepines possibly antagonise effects of levodopa

Moxonidine: sedative effects possibly increased when benzodiazepines given with moxonidine

Olanzapine: increased risk of hypotension, bradycardia and respiratory depression when parenteral benzodiazepines given with intramuscular olanzapine

Phenytoin: benzodiazepines possibly increase or decrease plasma concentration of phenytoin

Rifampicin: metabolism of benzodiazepines possibly accelerated by rifampicin (reduced plasma concentration)

Sodium Oxybate: benzodiazepines enhance effects of sodium oxybate (avoid concomitant use)

Theophylline: effects of benzodiazepines possibly reduced by theophylline

Lorazepam belongs to Anxiolytics and Hypnotics and will have the following interactions:

ACE Inhibitors: enhanced hypotensive effect when anxiolytics and hypnotics given with ACE inhibitors

Adrenergic Neurone Blockers: enhanced hypotensive effect when anxiolytics and hypnotics given with adrenergic neurone blockers

Alcohol: increased sedative effect when anxiolytics and hypnotics given with alcohol

Alpha-blockers: enhanced hypotensive and sedative effects when anxiolytics and hypnotics given with alpha-blockers

Anaesthetics, General: increased sedative effect when anxiolytics and hypnotics given with general anaesthetics

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when anxiolytics and hypnotics given with angiotensin-II receptor antagonists

Antidepressants, Tricyclic: increased sedative effect when anxiolytics and hypnotics given with tricyclics

Antidepressants, Tricyclic (related): increased sedative effect when anxiolytics and hypnotics given with tricyclic-related antidepressants

Antihistamines: increased sedative effect when anxiolytics and hypnotics given with antihistamines

Appendix 1: Drug interactions

Antipsychotics: increased sedative effect when anxiolytics and hypnotics given with antipsychotics

Baclofen: increased sedative effect when anxiolytics and hypnotics given with baclofen

Beta-blockers: enhanced hypotensive effect when anxiolytics and hypnotics given with beta-blockers
Since systemic absorption may follow topical application of beta-blockers to the eye the possibility of interactions, in particular, with drugs such as verapamil should be borne in mind

Calcium-channel Blockers: enhanced hypotensive effect when anxiolytics and hypnotics given with calcium-channel blockers

Dihydropyridine: calcium-channel blockers include amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, and nisoldipine

Clonidine: enhanced hypotensive effect when anxiolytics and hypnotics given with clonidine

Diazoxide: enhanced hypotensive effect when anxiolytics and hypnotics given with diazoxide

Diuretics: enhanced hypotensive effect when anxiolytics and hypnotics given with diuretics

Hydralazine: enhanced hypotensive effect when anxiolytics and hypnotics given with hydralazine

Lofexidine: increased sedative effect when anxiolytics and hypnotics given with lofexidine

Methyldopa: enhanced hypotensive effect when anxiolytics and hypnotics given with methyldopa

Minoxidil: enhanced hypotensive effect when anxiolytics and hypnotics given with minoxidil

Mirtazapine: increased sedative effect when anxiolytics and hypnotics given with mirtazapine

Moxonidine: enhanced hypotensive effect when anxiolytics and hypnotics given with moxonidine

Nabilone: increased sedative effect when anxiolytics and hypnotics given with nabilone

Nitrates: enhanced hypotensive effect when anxiolytics and hypnotics given with nitrates

Opioid Analgesics: increased sedative effect when anxiolytics and hypnotics given with opioid analgesics

Ritonavir: plasma concentration of anxiolytics and hypnotics possibly increased by ritonavir

Sodium Nitroprusside: enhanced hypotensive effect when anxiolytics and hypnotics given with sodium nitroprusside

Tizanidine: increased sedative effect when anxiolytics and hypnotics given with tizanidine

Losartan

See under ACE inhibitors and angiotensin II antagonists

Appendix 1: Drug interactions

Macrolides

See under erythromycin and other macrolides

Magnesium salts

Calcium-channel blockers: profound hypotension with nifedipine and intravenous magnesium sulphate in pre-eclampsia

Maprotiline

See under antidepressants

Medroxyprogesterone

See under progesterone

Mefenamic acid

See under NSAIDs

Mefloquine

Anti-arrhythmics: increased risk of ventricular arrhythmias with amiodarone and quinidine

Antiepileptics: antagonism of anti-convulsant effect

Antipsychotics: increased risk of ventricular arrhythmias

Ivabradine: increased risk of ventricular arrhythmias when mefloquine given with ivabradine.

Megestrol

See under progestogens

Melphalan

Ciclosporin: increased risk of nephrotoxicity

Nalidixic Acid: increased risk of melphalan toxicity

Also, see under cytotoxics

Mercaptopurine

Allopurinol: enhancement of effect
Antibacterials: increased haematological toxicity with co-trimoxazole and trimethoprim

Meropenem

Probenecid: excretion of meropenem reduced by probenecid (manufacturers of meropenem advise avoid concomitant use)

Valproate: meropenem reduces plasma concentration of valproate

Mesalazine

See under aminosalicylates

Metoprolol

See under beta-blockers

Metformin

See under antidiabetics

Methadone

See under Opioid analgesics

Methotrexate

Anaesthetics: antifolate effect increased by N₂O

Analgesics: excretion reduced by aspirin and other NSAIDs

Antibacterials: antifolate effect increased by co-trimoxazole and trimethoprim; excretion reduced by penicillin

Ciclosporin: increased toxicity

Corticosteroids: increased risk of haematological toxicity

Proton pump inhibitors: decrease the excretion of methotrexate (increased risk of toxicity)

Appendix 1: Drug interactions

Retinoids: Acitretin increases plasma-methotrexate concentration
Uricosurics: excretion reduced by probenecid

Methyldopa

Anaesthetics: enhanced hypotensive effects

Analgesics: NSAIDs antagonise the hypotensive effect

Antidepressants: enhanced hypotensive effects

Cabergoline: antiparkinsonian effect of dopaminergics antagonised by methyldopa

Corticosteroids: antagonism of hypotensive effect

Lithium: neurotoxicity may occur without increased plasma-lithium concentration

Methylphenidate

Isoflurane: increased risk of hypertension when volatile liquid general anaesthetics given with methylphenidate

Methylprednisolone

See under corticosteroids

Metoclopramide

Antimuscarinic: antagonism of effect on gastrointestinal tract

Antipsychotics: increased risk of extrapyramidal effects

Cabergoline: hypoprolactinaemic effect of cabergoline antagonised by metoclopramide

Dopaminergics: antagonism of hypoprolactinaemic effect of bromocriptine

Metronidazole

Alcohol: disulfiram-like reaction (alcohol intolerance)

Anticoagulants: effect of warfarin enhanced

Antiepileptics: metabolism of phenytoin inhibited

Barbiturates: metabolism of metronidazole enhanced

Mexiletine

Analgesics: opioids delay absorption

Anti-arrhythmics (other): increased myocardial depression

Antihistamines: increased risk of ventricular arrhythmias

Mianserin

Antiepileptics: antagonism

Miconazole

See under antifungals (imidazole and triazole)

Midazolam

See under anxiolytics and hypnotics

Milrinone

Anagrelide: avoidance of milrinone advised by manufacturer of anagrelide

Minocycline

See under tetracyclines

Appendix 1: Drug interactions

Montelukast

Phenobarbital: plasma concentration of montelukast reduced by phenobarbital

Primidone: plasma concentration of montelukast reduced by primidone

Morphine

See opioid analgesics

Moxifloxacin

Amiodarone: increased risk of ventricular arrhythmias

Antacids: absorption of moxifloxacin reduced by antacids

Antidepressants, Tricyclic: increased risk of ventricular arrhythmias

Atomoxetine: increased risk of ventricular arrhythmias

Chloroquine and Hydroxychloroquine: increased risk of ventricular arrhythmias Disopyramide: increased risk of ventricular arrhythmias

Erythromycin: increased risk of ventricular arrhythmias

Haloperidol: increased risk of ventricular arrhythmias

Iron: absorption of moxifloxacin reduced by oral iron

Mefloquine: increased risk of ventricular arrhythmias

Mizolastine: increased risk of ventricular arrhythmias

Nilotinib: avoidance of moxifloxacin advised by manufacturer of nilotinib

Pentamidine: Isetionate increased risk of ventricular arrhythmias

Phenothiazines: increased risk of ventricular arrhythmias

Pimozide: increased risk of ventricular arrhythmias

Procainamide: increased risk of ventricular arrhythmias

Quinine: increased risk of ventricular arrhythmias

Sertindole: increased risk of ventricular arrhythmias

Sotalol: increased risk of ventricular arrhythmias

Sucralfate: absorption of moxifloxacin reduced by sucralfate

Zinc: absorption of moxifloxacin reduced by zinc

Also, see under quinolones

Muscle relaxants

Anti-arrhythmics: lignocaine prolongs suxamethonium effect

Antibacterials: effect of non-depolarising muscle relaxants enhanced by aminoglycosides Antiepileptics: effect of non-depolarising muscle relaxants antagonised by carbamazepine and phenytoin

Calcium-channel blockers: nifedipine and verapamil enhance effect of non-depolarising muscle relaxant

Parasympathomimetics: enhance effect of suxamethonium but antagonize effect of non-depolarising muscle relaxants

Appendix 1: Drug interactions

Mycophenolate

Aciclovir: mycophenolate increases plasma concentration of aciclovir

Antacids: absorption of mycophenolate reduced by antacids

Colestyramine: absorption of mycophenolate reduced by colestyramine

Ganciclovir: mycophenolate possibly increases plasma concentration of ganciclovir

Iron: absorption of mycophenolate reduced by oral iron

Metronidazole: bioavailability of mycophenolate possibly reduced by metronidazole

Norfloxacin: bioavailability of mycophenolate possibly reduced by norfloxacin

Rifampicin: plasma concentration of active metabolite of mycophenolate reduced by rifampicin

Sevelamer: plasma concentration of mycophenolate possibly reduced by sevelamer

Also, see under cytotoxics

Mycophenolate Mofetil

See under mycophenolate

Mycophenolate Sodium

See under mycophenolate

Mycophenolic Acid

See under mycophenolate

Nabumetone

See under NSAIDs

Nadolol

See under beta-blockers

Nalbuphine

See under opioid analgesics

Nalidixic acid

See under quinolones

Naproxen

See under NSAIDs

Naratriptan

See under 5HT₁ Agonists

Neomycin

See under aminoglycosides

Neostigmine

See under parasympathomimetics

Netilmicin

See under aminoglycosides

Nevirapine

Amprenavir: nevirapine possibly reduces plasma concentration of amprenavir

Aripiprazole: nevirapine possibly reduces plasma concentration of aripiprazole — Atazanavir: nevirapine possibly reduces plasma concentration of atazanavir

Caspofungin: nevirapine possibly reduces plasma concentration of caspofungin — Efavirenz: nevirapine reduces plasma concentration of efavirenz

Appendix 1: Drug interactions

Fluconazole: plasma concentration of nevirapine increased by fluconazole

Indinavir: nevirapine reduces plasma concentration of indinavir

Ketoconazole: nevirapine reduces plasma concentration of ketoconazole

Lopinavir: nevirapine possibly reduces plasma concentration of lopinavir

Methadone: nevirapine possibly reduces plasma concentration of methadone

Oestrogens: nevirapine accelerates metabolism of oestrogens

Progestogens: nevirapine accelerates metabolism of progestogens (reduced contraceptive effect)

Rifabutin: nevirapine possibly increases plasma concentration of rifabutin

Rifampicin: plasma concentration of nevirapine reduced by rifampicin

St John's Wort: plasma concentration of nevirapine reduced by St John's wort

Warfarin: nevirapine may enhance or reduce anticoagulant effect of warfarin

Nifedipine

See under calcium-channel blockers

Nimodipine

See under calcium-channel blockers

Nitrates

Hypotensive interaction will be encountered with drugs that have the tendency to lower blood pressure

Anticoagulants: excretion of heparin increased by glyceryl trinitrate infusion

Antimuscarinics: dry mouth may cause a delay in absorption of sublingual glyceryl trinitrate

Sildenafil: hypotensive effect significantly enhanced

Nitrazepam

See under anxiolytics and hypnotics

Nitrofurantoin

Uricosurics: probenecid reduces excretion of nitrofurantoin

Nizatidine

See under histamine H₂-antagonists

Noradrenaline

See under sympathomimetics

Norethisterone

See under progesterone

Norgestrel

See under progesterone

NSAIDs

ACE Inhibitors: antagonism of hypotensive effect; increased risk of renal impairment

Analgesics (other): avoid concomitant use of NSAIDs with

Appendix 1: Drug interactions

NSAIDs or aspirin (increased side-effects); avoid concomitant use of NSAIDs with ketorolac (increased side-effects and haemorrhage); ibuprofen possibly reduces antiplatelet effect of aspirin.

Antibacterials: indometacin possibly increases plasma concentration of amikacin and gentamicin in neonates; plasma concentration of celecoxib and diclofenac reduced by rifampicin; possible increased risk of convulsions when NSAIDs given with quinolones

Anticoagulants: anticoagulant effect seriously enhanced by NSAIDs; increased risk of haemorrhage when anticoagulants are given with intravenous diclofenac (avoid concomitant use); increased risk of haemorrhage when anticoagulants given with ketorolac (avoid concomitant use); NSAIDs possibly enhance anticoagulant effect of coumarins; possible increased risk of bleeding when NSAIDs given with dabigatran or heparins

Antidepressants: increased risk of bleeding when NSAIDs given with SSRIs

Antidiabetics: effect of sulphonylureas possibly enhanced by NSAIDs

Antiepileptics: effect of phenytoin possibly enhanced by NSAIDs

Antihypertensives: antagonism of hypotensive effect

Antiplatelet drugs: increased risk of bleeding

Antivirals: increased risk of toxicity with zidovudine

Cardiac glycosides: NSAIDs may exacerbate heart failure, reduce GFR and increase plasma-glycoside concentration

Ciclosporin: increased risk of nephrotoxicity

Cytotoxics: NSAIDs probably reduce excretion of methotrexate (increased risk of toxicity); increased risk of bleeding when NSAIDs given with erlotinib

Diuretics: risk of nephrotoxicity of NSAIDs increased

Lithium: excretion of lithium reduced

Tacrolimus: possible increased risk of nephrotoxicity when NSAIDs given with tacrolimus; increased risk of nephrotoxicity when ibuprofen given with tacrolimus

Uricosurics: Probenecid delays NSAIDs excretion

Appendix 1: Drug interactions

Octreotide

Bromocriptine: octreotide increases plasma concentration of bromocriptine

Ciclosporin: octreotide reduces plasma concentration of ciclosporin

Cimetidine: octreotide possibly delays absorption of cimetidine

Insulin: octreotide possibly reduces requirements for insulin

Metformin: octreotide possibly reduces requirements for metformin

Repaglinide: octreotide possibly reduces requirements for repaglinide

Sulphonylureas: octreotide possibly reduces requirements for sulphonylureas

Oestrogens

See under contraceptives

Olanzapine

See under antipsychotics

Olsalazine

See under aminosalicylates

Omeprazole

See under proton pump inhibitors

Opioid analgesics

Anti-arrhythmics: delay absorption of mexiletine

Antidepressants: CNS excitation or depression if opioids are used with MAO inhibitors; tramadol increases risk of CNS toxicity with SSRIs and tricyclics; possibly increased sedation with tricyclics

Antiepileptics: effect of tramadol and methadone decreased by carbamazepine

Antipsychotics: enhanced sedative and hypotensive effect

Metoclopramide and domperidone: antagonism of gastro-intestinal effects

Orphenadrine

See under antimuscarinics

Oxaliplatin

See under platinum compounds

See under cytotoxics

Oxymetazoline

See under sympathomimetics

Oxytocin

Anaesthetics: inhalational anaesthetics possibly reduce oxytocin effect

Prostaglandins: enhanced uterotonic effect

Pancreatin

Antidiabetics: hypoglycaemic effect of acarbose reduced

Pancuronium

See under muscle relaxants

Panitumumab

Antipsychotics: avoid concomitant use of cytotoxic with clozapine (increased risk of agranulocytosis)

Vaccine: risk of generalized infection when monoclonal antibodies given with live vaccine

Paracetamol

Anticoagulants: prolonged use of paracetamol possibly enhances warfarin effect

Metoclopramide and domperidone: paracetamol absorption accelerated

Parasympathomimetics

Antibacterials: aminoglycosides and clindamycin antagonize the effect of neostigmine

Antimuscarinics: antagonism

Beta-blockers: propranolol antagonizes effects of neostigmine and pyridostigmine

Muscle relaxants: effect of suxamethonium enhanced

Paroxetine

See under antidepressants

Pegfilgrastim:

See under filgrastim

Peginterferon alfa

See under interferons

Penicillamine

Antacids: reduce absorption of penicillamine

Iron: reduce absorption of penicillamine

Penicillins

Allopurinol: increased risk of rash with concomitant use of penicillins

Uricosurics: excretion of penicillins reduced with probenecid

Pentamidine isethionate

Anti-arrhythmics: increased risk of ventricular arrhythmias

Antipsychotics: increased risk of ventricular arrhythmias with thioridazine

Pethidine

See under opioid analgesics

Phenobarbitone

See under barbiturates

Phenoxybenzamine

See under alpha-blockers

Phenoxyethylpenicillin

See under penicillins

Phentolamine

See under alpha-blockers

Phenytoin

Analgesics: plasma-phenytoin concentration increased by aspirin

Anti-arrhythmics: amiodarone increases plasma-phenytoin concentration; phenytoin decreases plasma concentration of disopyramide, mexiletine and quinidine

Antibacterials: plasma-phenytoin concentration increased by chloramphenicol, clarithromycin, isoniazid and metronidazole; plasma-phenytoin concentration reduced by rifampicin

Anticoagulants: metabolism of warfarin accelerated; plasma concentration of rivaroxaban possibly

Appendix 1: Drug interactions

reduced by phenytoin—manufacturer of rivaroxaban advises monitor for signs of thrombosis

Antidepressants: antagonism of anticonvulsive effect; fluoxetine increase plasma-phenytoin concentration

Antiepileptics (other): potentiation of sedative effect

Antimalarials: mefloquine antagonises anticonvulsive effect; chloroquine reduced convulsive threshold

Antipsychotics: antagonism of anticonvulsant effect

Calcium-channel blockers: diltiazem and nifedipine increase plasma-phenytoin concentration

Ciclosporin: metabolism of ciclosporin accelerated

Corticosteroids: metabolism of corticosteroids accelerated

Oestrogens: metabolism of oestrogens, tibolone and oral contraceptives, accelerated

Proton pump inhibitors: effect of phenytoin enhanced by omeprazole and esomeprazole

Physostigmine

See under parasympathomimetics

Phytomenadione

See under vitamins

Pilocarpine

See under parasympathomimetics

Piperacillin

See under penicillins

Pirenidone

Antibacterials: ciprofloxacin increases plasma concentration of pirenidone

Platinum Compounds

Aminoglycosides: increased risk of nephrotoxicity and possibly of ototoxicity Capreomycin: increased risk of nephrotoxicity and ototoxicity

Diuretics: increased risk of nephrotoxicity and ototoxicity

Polymyxins: increased risk of nephrotoxicity and possibly of ototoxicity

Polymyxins

Aminoglycosides: increased risk of nephrotoxicity

Amphotericin: increased risk of nephrotoxicity

Capreomycin: increased risk of nephrotoxicity

Ciclosporin: increased risk of nephrotoxicity

Diuretics, Loop: increased risk of ototoxicity Muscle Relaxants, non-depolarising: polymyxins enhance effects of non-depolarising muscle relaxants

Neostigmine: polymyxins antagonise effects of neostigmine

Platinum Compounds: increased risk of nephrotoxicity and possibly

Appendix 1: Drug interactions

of ototoxicity Pyridostigmine: polymyxins antagonise effects of pyridostigmine

Suxamethonium: polymyxins enhance effects of suxamethonium

Vancomycin: increased risk of nephrotoxicity

Potassium salts

ACE inhibitors: increased risk of hyperkalaemia

Ciclosporin: increased risk of hyperkalaemia

Diuretics: hyperkalaemia with potassium sparing diuretics

Pravastatin

See under statins

Prazosin

See under alpha-blockers

Prednisolone

See under corticosteroids

Primaquine

Artemether with Lumefantrine: avoidance of antimalarials advised by manufacturer of artemether/lumefantrine

Mepacrine: plasma concentration of primaquine increased by mepacrine (increased risk of toxicity)

Procainamide

ACE inhibitors: increased risk of toxicity with Captopril especially in the presence of renal impairment

Anti-arrhythmics (other): increased myocardial depression

Antidepressants: increased risk of ventricular arrhythmias with tricyclics

Antipsychotics: increased risk of ventricular arrhythmias

Muscle relaxants: muscle relaxant effect enhanced

Procarbazine

Alcohol: disulfiram-like effect

Prochlorperazine

See under antipsychotics

Procyclidine

See under antimuscarinics

Progestogens

Antibacterials: metabolism accelerated by rifampicin

Anticoagulants: progestogens may enhance or reduce anticoagulant effect of coumarins

Antiepileptics: metabolism of progestogens accelerated by carbamazepine, phenobarbital, phenytoin (reduced contraceptive effect)

Ciclosporin: increased ciclosporin plasma concentration

Proguanil

Artemether with Lumefantrine: avoidance of antimalarials advised by manufacturer of artemether/lumefantrine

Magnesium Salts: (oral) absorption of proguanil reduced by oral magnesium salts (as magnesium trisilicate)

Appendix 1: Drug interactions

Pyrimethamine: increased antifolate effect
Warfarin: isolated reports that proguanil may enhance anticoagulant effect of warfarin

Promethazine

See under antihistamines

Propofol

See under anaesthetics

Propranolol

See under beta-blockers

Proton pump inhibitors

Anticoagulants: effect of warfarin possibly enhanced by omeprazole and esomeprazole

Antiepileptics: effect of phenytoin enhanced by omeprazole and esomeprazole

Clopidogrel: esomeprazole and omeprazole reduce the antiplatelet effect of clopidogrel

Cytotoxics: proton pump inhibitors possible reduce the excretion of methotrexate (increased risk of toxicity).

Pseudoephedrine

See under sympathomimetics

Pyridostigmine

See under parasympathomimetics

Pyridoxine

See under vitamins

Pyrimethamine

Antibacterials: increased antifolate effect with sulphonamides

Antiepileptics: increased antifolate effect and antagonism of anticonvulsant effect of phenytoin

Cytotoxics: increased antifolate effect with methotrexate

Quetiapine

Antifungals, Imidazole: plasma concentration of quetiapine possibly increased by imidazoles (reduce dose of quetiapine)

Antifungals, Triazole: plasma concentration of quetiapine possibly increased by triazoles (reduce dose of quetiapine)

Carbamazepine: metabolism of quetiapine accelerated by carbamazepine (reduced plasma concentration)

Macrolides: plasma concentration of quetiapine possibly increased by macrolides

Phenytoin: metabolism of quetiapine accelerated by phenytoin (reduced plasma concentration)

Also, see under antipsychotics

Quinidine

Anti-arrhythmics (other): avoid concomitant use of amiodarone

Antibacterials: rifampicin accelerates metabolism

Antidepressants: increased risk of ventricular arrhythmias with tricyclics

Antifungal: plasma concentration increased by itraconazole and miconazole

Antimalarials: increased risk of ventricular arrhythmias with mefloquine

Antipsychotics: increased risk of ventricular arrhythmias

Calcium-channel blockers: nifedipine reduces plasma-quinidine concentration; verapamil increases plasma-quinidine concentration

Cardiac glycosides: plasma concentration of digoxin increased

Diuretics: quinidine toxicity increased if hypokalaemia occurs with diuretics

Muscle relaxants: muscle relaxant effect enhanced

Quinine

Anti-arrhythmics: plasma-concentration of flecainide increased; increased risk of ventricular arrhythmias with amiodarone increased

Antipsychotics: increased risk of ventricular arrhythmias

Antivirals: plasma concentration of quinine possibly increased by darunavir (increased risk of toxicity)

Cardiac glycosides: plasma concentration of digoxin increased

Quinolones

Analgesics: possible increased risk of convulsion with NSAIDs

Anticoagulants: anticoagulant effect of warfarin enhanced by ciprofloxacin and nalidixic acid

Antidepressants: ciprofloxacin inhibits metabolism of duloxetine—avoid concomitant use

Antimalarials: avoidance of quinolones advised by manufacturer of arte-mether with lumefantrine

Ciclosporin: increased risk of nephrotoxicity

Pirfenidone: ciprofloxacin increases plasma concentration of pirfenidone

Theophylline: possible increased risk of convulsion

Ranitidine

See under Histamine H₂-antagonists

Remifentanyl

See under opioid analgesics

Retinoids

Antibacterials: possible increased risk of benign intracranial hypertension with acitretin and tretinoin

Anticoagulants: acitretin possibly reduces the effect of warfarin

Antifungals: fluconazole and voriconazole possibly increase risk of tretinoin toxicity

Cytotoxic: acitretin increases plasma concentration of methotrexate

Oral contraceptives: acitretin possibly reduces the efficacy of low oestrogen oral contraceptives

Ribavirin

Didanosine: increased risk of side-effects

Stavudine: ribavirin possibly inhibits effects of stavudine

Zidovudine: increased risk of anaemia

Rifabutin

See under Rifamycins

Appendix 1: Drug interactions

Rifampicin

See under Rifamycins

Rifamycins

Anti-arrhythmics: reduced plasma concentration of disopyramide, mexiletine and quinidine

Antibacterials (other): plasma concentration of chloramphenicol reduced; plasma concentration of dapsone reduced increased risk of side-effects including

neutropenia when rifabutin given with .azithromycin; rifamycins reduce plasma concentration of

clarithromycin and dapsone; plasma concentration of rifabutin increased by .clarithromycin;

plasma concentration of rifabutin possibly increased by erythromycin; rifampicin possibly reduces

plasma concentration of tinidazole and trimethoprim; rifampicin

reduces plasma concentration of doxycycline; rifampicin

accelerates metabolism of chl ramphenicol; increased risk of

hepatotoxicity when rifampicin given with .isoniazid; rifampicin

reduces plasma concentration of linezolid; metabolism of sunitinib

accelerated by rifampicin

Anticoagulants: metabolism of warfarin accelerated; rifampicin reduces plasma concentration of rivaroxaban—manufacturer of rivaroxaban advises monitor for signs of thrombosis.

Antidiabetics: metabolism of sulphonylureas possibly accelerated

Antiepileptics: metabolism of phenytoin accelerated; plasma concentration of carbamazepine reduced. Rifabutin reduces plasma concentration of carbamazepine; rifampicin reduces plasma concentration of lamotrigine; plasma concentration of rifampicin possibly reduced by phenobarbital; rifamycins accelerate metabolism of phenytoin

Antifungals: plasma concentration of rifabutin increased by fluconazole ; rifampicin accelerates metabolism of fluconazole; rifabutin and rifampicin reduce plasma concentration of itraconazole; plasma concentration of rifabutin increased by .voriconazole, also

rifabutin reduces plasma concentration of voriconazole; rifampicin

reduces plasma concentration of voriconazole; rifampicin initially

increases and then reduces plasma concentration of caspofungin

Antimalarials: avoidance of rifampicin advised by manufacturer of

piperazine with artemisinin; rifampicin reduces plasma concentration of

.mefloquine avoid concomitant use; rifampicin reduces plasma

concentration of quinine

Antipsychotics: rifampicin accelerates metabolism of haloperidol

Antivirals: rifampicin significantly reduces plasma concentration of da-runavir—avoid concomitant

use; plasma concentration of rifabutin reduced by efavirenz

Appendix 1: Drug interactions

; rifampicin reduces plasma concentration of efavirenz; rifampicin reduces plasma concentration of ritonavir; plasma concentration of rifabutin increased by ritonavir

Beta blockers: metabolism of bisoprolol accelerated by rifampicin; plasma concentration of metoprolol reduced by rifampicin.

Calcium-channel blockers: metabolism of most calcium-channel blockers accelerated

Ciclosporin: metabolism accelerated

Corticosteroids: rifamycins accelerate metabolism of corticosteroids

Deferasirox: plasma concentration of deferasirox reduced by rifampicin

Everolimus: plasma concentration of everolimus reduced by rifampicin

Gefitinib: plasma concentration of gefitinib reduced by rifampicin

Lapatinib: manufacturer of lapatinib advises avoid concomitant use with rifabutin and rifampicin

Lipid regulating drugs: metabolism of fluvastatin accelerated

Oestrogens and progestogens: metabolism accelerated (reduced effect of oral contraceptives)

Sirolimus: rifabutin and rifampicin reduce plasma concentration of sirolimus

Sorafenib: plasma concentration of sorafenib reduced by rifampicin

Tacrolimus: rifabutin possibly reduces plasma concentration

of tacrolimus; rifampicin reduces plasma concentration of tacrolimus

Risperidone

See under antipsychotics

Ritodrine

See under sympathomimetics, Beta₂

Ritonavir

Alfuzosin: ritonavir possibly increases plasma concentration of alfuzosin

Alprazolam: ritonavir possibly increases plasma concentration of alprazolam (risk of extreme sedation and respiratory depression)

Amiodarone: ritonavir increases plasma concentration of amiodarone (increased risk of ventricular arrhythmias)

Amprenavir: ritonavir increases plasma concentration of amprenavir

Antidepressants, SSRI: ritonavir possibly increases plasma concentration of SSRIs

Antidepressants, Tricyclic: ritonavir possibly increases plasma concentration of tricyclics

Antihistamines, Non-sedating: ritonavir possibly increases plasma concentration of non-sedating antihistamines

Antipsychotics: ritonavir possibly increases plasma concentration of antipsychotics

Anxiolytics and Hypnotics: ritonavir possibly increases plasma

Appendix 1: Drug interactions

concentration of anxiolytics and hypnotics

Aprepitant: ritonavir possibly increases plasma concentration of aprepitant

Aripiprazole: ritonavir possibly inhibits metabolism of aripiprazole

Artemether with Lumefantrine: avoid concomitant use of ritonavir with artemether/lumefantrine

Atorvastatin: possible increased risk of myopathy

Azithromycin: ritonavir possibly increases plasma concentration of azithromycin

Bosentan: ritonavir possibly increases plasma concentration of bosentan

Budesonide: ritonavir increases plasma concentration of inhaled and intranasal budesonide

Buprenorphine: ritonavir possibly increases plasma concentration of buprenorphine

Bupropion: ritonavir increases plasma concentration of bupropion (risk of toxicity)

Buspirone: ritonavir increases plasma concentration of buspirone (increased risk of toxicity)

Calcium-channel Blockers: ritonavir possibly increases plasma concentration of calcium-channel blockers

Carbamazepine: ritonavir possibly increases plasma concentration of carbamazepine

Ciclosporin: ritonavir possibly increases plasma concentration of ciclosporin

Cilostazol: ritonavir possibly increases plasma concentration of cilostazol

Clarithromycin: ritonavir increases plasma concentration of clarithromycin

Clozapine: ritonavir increases plasma concentration of clozapine (increased risk of toxicity)

Corticosteroids: ritonavir possibly increases plasma concentration of corticosteroids

Coumarins: ritonavir possibly enhances anticoagulant effect of coumarins

Darifenacin: avoidance of ritonavir advised by manufacturer of darifenacin

Dexamethasone: ritonavir possibly increases plasma concentration of dexamethasone

Dexamfetamine: ritonavir possibly increases plasma concentration of dexamfetamine

Dextropropoxyphene: ritonavir increases plasma concentration of dextropropoxyphene (risk of toxicity)

Diazepam: ritonavir possibly increases plasma concentration of diazepam (risk of extreme sedation and respiratory depression)

Digoxin: ritonavir possibly increases plasma concentration of digoxin

Disopyramide: ritonavir possibly increases plasma concentration of disopyramide (increased risk of toxicity)

Efavirenz: ritonavir increases toxicity of efavirenz , monitor liver function tests

Appendix 1: Drug interactions

Eletriptan: ritonavir increases plasma concentration of eletriptan (risk of toxicity)

Eplerenone: ritonavir increases plasma concentration of eplerenone

Erythromycin: ritonavir possibly increases plasma concentration of erythromycin

Fentanyl: ritonavir increases plasma concentration of fentanyl

Fesoterodine: manufacturer of fesoterodine advises dose reduction when ritonavir given with fesoterodine

Flecainide: ritonavir possibly increases plasma concentration of flecainide (increased risk of ventricular arrhythmias)

Fluconazole: plasma concentration of ritonavir increased by fluconazole

Flurazepam: ritonavir possibly increases plasma concentration of flurazepam (risk of extreme sedation and respiratory depression)

Fluticasone: ritonavir increases plasma concentration of inhaled and intranasal fluticasone

Fusidic Acid: plasma concentration of both drugs increased when ritonavir given with fusidic acid

Indinavir: ritonavir increases plasma concentration of indinavir

Itraconazole: combination of ritonavir with itraconazole may increase plasma concentration of either drug (or both)

Ivabradine: ritonavir possibly increases plasma concentration of ivabradine

Ketoconazole: combination of ritonavir with ketoconazole may increase plasma concentration of either drug (or both)

Lercanidipine: avoidance of ritonavir advised by manufacturer of lercanidipine

Methadone: ritonavir reduces plasma concentration of methadone

Midazolam: ritonavir possibly increases plasma concentration of midazolam (risk of prolonged sedation)

Morphine: ritonavir possibly reduces plasma concentration of morphine

Nelfinavir: combination of ritonavir with nelfinavir may increase plasma concentration of either drug (or both)

Nilotinib: avoidance of ritonavir advised by manufacturer of nilotinib

NSAIDs: ritonavir possibly increases plasma concentration of NSAIDs

Oestrogens: ritonavir accelerates metabolism of oestrogens (reduced contraceptive effect)

Olanzapine: ritonavir reduces plasma concentration of olanzapine

Paclitaxel: ritonavir increases plasma concentration of paclitaxel

Paroxetine: ritonavir possibly reduces plasma concentration of paroxetine

Pethidine: ritonavir reduces plasma concentration of pethidine, but increases plasma concentration of toxic metabolite of pethidine

Appendix 1: Drug interactions

Phenindione: ritonavir possibly enhances anticoagulant effect of phenindione

Phenytoin: plasma concentration of ritonavir possibly reduced by phenytoin, *Also* plasma concentration of phenytoin possibly affected

Pimozide: ritonavir increases plasma concentration of pimozide (increased risk of ventricular arrhythmias)

Piroxicam: ritonavir increases plasma concentration of piroxicam (risk of toxicity) Prednisolone: ritonavir possibly increases plasma concentration of prednisolone

Propafenone: ritonavir increases plasma concentration of propafenone (increased risk of ventricular arrhythmias)

Rifabutin: ritonavir increases plasma concentration of rifabutin (increased risk of toxicity)

Rifampicin: plasma concentration of ritonavir possibly reduced by rifampicin

Rivaroxaban: plasma concentration of rivaroxaban increased by ritonavir—avoid concomitant use

Rosuvastatin: possible increased risk of myopathy when ritonavir given with rosuvastatin

Saquinavir: ritonavir increases plasma concentration of saquinavir

Sertindole: ritonavir increases plasma concentration of sertindole (increased risk of ventricular arrhythmias)

Sildenafil: ritonavir significantly increases plasma concentration of sildenafil Simvastatin: increased

risk of myopathy when ritonavir given with simvastatin

Solifenacin: ritonavir increases plasma concentration of solifenacin

St John's Wort: plasma concentration of ritonavir reduced by St John's wort

Tacrolimus: ritonavir possibly increases plasma concentration of tacrolimus

Tadalafil: ritonavir increases plasma concentration of tadalafil

Telithromycin: avoidance of concomitant ritonavir in severe renal and hepatic impairment advised by manufacturer of telithromycin

Theophylline: ritonavir accelerates metabolism of theophylline (reduced plasma concentration)

Tolbutamide: ritonavir possibly increases plasma concentration of tolbutamide

Tolterodine: avoidance of ritonavir advised by manufacturer of tolterodine

Trazodone: side-effects possibly increased when ritonavir given with trazodone

Vardenafil: ritonavir possibly increases plasma concentration of vardenafil Voriconazole: ritonavir reduces plasma concentration of voriconazole

Warfarin: ritonavir may enhance or reduce anticoagulant effect of warfarin

Zolpidem: ritonavir possibly increases plasma concentration of zolpidem (risk of extreme sedation and respiratory depression)

Rivaroxaban

Analgesics: increased risk of haemorrhage when intravenous diclofenac given with anticoagulants (avoid concomitant use, including low-dose heparins)

Antibacterials: rifampicin reduces plasma concentration of rivaroxaban—manufacturer of rivaroxaban advises monitor for signs of thrombosis

Anticoagulants: increased risk of haemorrhage when other anticoagulants given with rivaroxaban (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency); increased risk of haemorrhage when ketorolac given with anticoagulants (avoid concomitant use, including low-dose heparins).

Antiepileptics: plasma concentration of rivaroxaban possibly reduced by carbamazepine—manufacturer of rivaroxaban advises monitor for signs of thrombosis; plasma concentration of rivaroxaban possibly reduced by phenytoin—manufacturer of rivaroxaban advises monitor for signs of thrombosis; phenobarbital plasma concentration of rivaroxaban possibly reduced by phenobarbital—manufacturer of rivaroxaban advises monitor for signs of thrombosis

Antifungals: manufacturer of rivaroxaban advises avoid concomitant use with itraconazole; plasma concentration of rivaroxaban increased

by ketoconazole—avoid concomitant use; manufacturer of rivaroxaban advises avoid concomitant use with voriconazole

Antivirals: manufacturer of rivaroxaban advises avoid concomitant use with indinavir; manufacturers advise avoid concomitant use of rivaroxaban with lopinavir. Note: In combination with ritonavir as Kaletra® (ritonavir is present to inhibit lopinavir metabolism and increase plasma-lopinavir concentration)—see also Ritonavir; plasma concentration of rivaroxaban increased by ritonavir—avoid concomitant use

Rizatriptan

Methysergide: increased risk of vasospasm

MAOIs: risk of CNS toxicity

Moclobemide: risk of CNS toxicity

Propranolol: plasma concentration of rizatriptan increased by propranolol

Also, see under 5HT₁ agonists

Salbutamol

See under sympathomimetics, (β_2 -agonists)

Salmeterol

See under sympathomimetics, (β_2 -agonists)

Selegiline

Antidepressants: increase CNS toxicity

Appendix 1: Drug interactions

Methyldopa: antiparkinsonian effect antagonised by methyldopa
Moclobemide: avoid concomitant use

Oestrogens: plasma concentration of selegiline increased by oestrogens (increased risk of toxicity)

Paroxetine: increased risk selegiline given with citalopram (especially if dose of selegiline exceeds 10 mg daily)

Dopamine: risk of hypertensive crisis

Entacapone: max. dose of 10 mg selegiline advised by manufacturer of entacapone if used concomitantly

Escitalopram: caution with selegiline advised by manufacturer

Fluoxetine: increased risk of hypertension and CNS excitation

Fluvoxamine: increased risk of hypertension and CNS excitation

Levodopa: selegiline enhances effects and increases toxicity of hypertension and CNS excitation

Pethidine: hyperpyrexia and CNS toxicity

Progestogens: plasma concentration of selegiline increased by progestogens (increased risk of toxicity)

Sertraline: increased risk of hypertension and CNS excitation

Sevelamer

Ciclosporin: sevelamer possibly reduces plasma concentration of

ciclosporin Ciprofloxacin: sevelamer reduces bioavailability of ciprofloxacin

Mycophenolate: sevelamer possibly reduces plasma concentration of mycophenolate

Tacrolimus: sevelamer possibly reduces plasma concentration of tacrolimus

Thyroid Hormones: sevelamer possibly reduces absorption of levothyroxine

Vitamins: sevelamer reduces absorption of calcitriol (give at least 1

Appendix 1: Drug interactions

hour before or 3 hours after sevelamer)

Sildenafil

Alpha-blockers: enhanced hypotensive effect

Amlodipine: enhanced hypotensive effect when sildenafil given with amlodipine

Amprenavir: plasma concentration of sildenafil possibly increased by amprenavir

Atazanavir: side-effects of sildenafil possibly increased by atazanavir

Bosentan: plasma concentration of sildenafil reduced by bosentan

Cimetidine: plasma concentration of sildenafil increased by cimetidine

Clarithromycin: plasma concentration of sildenafil possibly increased by clarithromycin

Erythromycin: plasma concentration of sildenafil increased by erythromycin

Grapefruit Juice: plasma concentration of sildenafil possibly increased by grapefruit juice

Indinavir: plasma concentration of sildenafil increased by indinavir

Itraconazole: plasma concentration of sildenafil increased by itraconazole

Ketoconazole: plasma concentration of sildenafil increased by ketoconazole

Nelfinavir: plasma concentration of sildenafil possibly increased by

nelfinavir
Nicorandil: sildenafil significantly enhances hypotensive effect of nicorandil

Nitrates: sildenafil significantly enhances hypotensive effect of nitrates

Ritonavir: plasma concentration of sildenafil significantly increased by ritonavir

Saquinavir: plasma concentration of sildenafil possibly increased by saquinavir

Telithromycin: plasma concentration of sildenafil possibly increased by telithromycin

Simvastatin

See under statins

Sirolimus

Atazanavir: plasma concentration of sirolimus possibly increased by atazanavir

Ciclosporin: plasma concentration of sirolimus increased by ciclosporin

Clarithromycin: plasma concentration of sirolimus increased by clarithromycin — Diltiazem: plasma concentration of sirolimus increased by diltiazem

Erythromycin: plasma concentration of both drugs increased when sirolimus given with erythromycin

Grapefruit Juice: plasma concentration of sirolimus increased by grapefruit juice

Itraconazole: plasma concentration of sirolimus increased by itraconazole

Appendix 1: Drug interactions

Ketoconazole: plasma concentration of sirolimus increased by ketoconazole

Lopinavir: plasma concentration of sirolimus possibly increased by lopinavir

Miconazole: plasma concentration of sirolimus increased by miconazole

Posaconazole: plasma concentration of sirolimus possibly increased by posaconazole

Rifabutin: plasma concentration of sirolimus reduced by rifabutin

Rifampicin: plasma concentration of sirolimus reduced by rifampicin

Telithromycin: plasma concentration of sirolimus increased by telithromycin

Verapamil: plasma concentration of both drugs increased when sirolimus given with verapamil

Voriconazole: plasma concentration of sirolimus increased by voriconazole

Sitagliptin

See under Antidiabetics

Sodium benzoate

Corticosteroids: effects of sodium benzoate possibly reduced by corticosteroids

Haloperidol: effects of sodium benzoate possibly reduced by haloperidol

Probenecid: excretion of conjugate formed by sodium benzoate possibly reduced by probenecid

Valproate: effects of sodium benzoate possibly reduced by valproate

Sodium phenylbutyrate

Corticosteroids: effects of sodium phenylbutyrate possibly reduced by corticosteroids

Haloperidol: effects of sodium phenylbutyrate possibly reduced by haloperidol

Probenecid: excretion of conjugate formed by sodium phenylbutyrate possibly reduced by probenecid

Valproate: effects of sodium phenylbutyrate possibly reduced by valproate

Sodium valproate

Antidepressants: antagonism of anticonvulsant effect

Antibacterials: carbapenems reduce plasma concentration of sodium valproate—avoid concomitant use

Antimalarials: mefloquine antagonises anticonvulsant effect; chloroquine reduces convulsive threshold

Antipsychotics: antagonism of anticonvulsant effect

Solifenacin

See under Antimuscarinics

Sorafenib

Antibacterials: bioavailability of sorafenib reduced by neomycin; plasma concentration of sorafenib reduced by rifampicin

Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

Cytotoxics: sorafenib possibly increases plasma concentration

Appendix 1: Drug interactions

of doxorubicin and irinotecan; sorafenib increases plasma concentration of docetaxel

Spironolactone

See under diuretics

Statins

Grapefruit juice increases plasma concentration of simvastatin

Antibacterials: metabolism of fluvastatin accelerated by rifampicin; clarithromycin and erythromycin increase risk of myopathy with simvastatin; clarithromycin increases plasma concentration of atorvastatin.

Anticoagulants: effect of warfarin enhanced by simvastatin; atorvastatin may transiently reduce the effect of warfarin.

Antifungals: imidazole and triazole derivatives increase the risk of myopathy with simvastatin and atorvastatin; avoid atorvastatin with ketoconazole.

Ciclosporin: increased risk of myopathy with simvastatin (avoid concomitant use)

Lipid-regulating drugs (other): increased risk of myopathy with fibrates and nicotinic acid

Stavudine

Didanosine: increased risk of side-effects

Doxorubicin: effects of stavudine possibly inhibited by doxorubicin

Hydroxycarbamide: increased risk of toxicity

Ribavirin: effects of stavudine possibly inhibited by ribavirin

Zidovudine: effects of stavudine possibly inhibited by zidovudine

Streptomycin

See under aminoglycosides

Sucralfate

Anticoagulants: absorption of warfarin possibly reduced

Antiepileptics: reduced absorption of phenytoin

Sulfadoxine

See under co-trimoxazole and trimethoprim

Sulfasalazine (Sulphasalazine)

See under aminosaliclates

Sulphonylureas

See under antidiabetics

Sumatriptan

See under 5HT₁ Agonists

Sunitinib

Antibacterials: metabolism of sunitinib accelerated by rifampicin (reduced plasma concentration)

Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

Antivirals: avoidance of sunitinib advised by manufacturer

Appendix 1: Drug interactions

of boceprevir.

Suxamethonium

See under muscle relaxants

Sympathomimetics

Anaesthetics: risk of arrhythmias if adrenaline is given with inhalational liquid anaesthetics such as halothane and isoflurane

Antidepressants: risk of hypertension with tricyclics

Beta-blockers: severe hypertension with adrenaline and noradrenaline, possible with dobutamine

Corticosteroids: ephedrine accelerates metabolism dexamethasone

Oxytocin: risk of hypertension

Sympathomimetics (β_2 -agonists)

Antihypertensives: acute hypertension reported with salbutamol infusion and methyldopa

Corticosteroids: increased risk of hypokalaemia if high doses of corticosteroids are used with β_2 -agonists

Diuretics: increased risk of hypokalaemia when used with high doses of β_2 -agonists

Tacrolimus

Aciclovir: possible increased risk of nephrotoxicity

Aminoglycosides: increased risk of nephrotoxicity

Amphotericin: increased risk of nephrotoxicity

Angiotensin-II Receptor Antagonists: increased risk of hyperkalaemia

Antifungals, Imidazole: plasma concentration of tacrolimus possibly increased by imidazoles

Antifungals, Triazole: plasma concentration of tacrolimus possibly increased by triazoles

Atazanavir: plasma concentration of tacrolimus possibly increased by atazanavir

Caspofungin: plasma concentration of tacrolimus reduced by caspofungin

Chloramphenicol: plasma concentration of tacrolimus possibly increased by chloramphenicol

Ciclosporin: tacrolimus increases plasma concentration of ciclosporin (increased risk of nephrotoxicity)

Clarithromycin: plasma concentration of tacrolimus increased by clarithromycin

Danazol: plasma concentration of tacrolimus possibly increased by danazol

Diltiazem: plasma concentration of tacrolimus increased by diltiazem

Diuretics, Potassium-sparing and Aldosterone Antagonists: increased risk of hyperkalaemia

Erythromycin: plasma concentration of tacrolimus increased by erythromycin

Ethinylestradiol: plasma concentration of tacrolimus possibly increased by ethinylestradiol

Felodipine: plasma concentration of tacrolimus possibly increased by felodipine

Appendix 1: Drug interactions

Fluconazole: plasma concentration of tacrolimus increased by fluconazole

Ganciclovir: possible increased risk of nephrotoxicity

Grapefruit Juice: plasma concentration of tacrolimus increased by grapefruit juice

Ibuprofen: increased risk of nephrotoxicity Itraconazole: plasma concentration of tacrolimus increased by itraconazole

Ketoconazole: plasma concentration of tacrolimus increased by ketoconazole

Nelfinavir: plasma concentration of tacrolimus possibly increased by nelfinavir

Nicardipine: plasma concentration of tacrolimus possibly increased by nicardipine

Nifedipine: plasma concentration of tacrolimus increased by nifedipine

NSAIDs: possible increased risk of nephrotoxicity

Oestrogens: tacrolimus possibly inhibits metabolism of oestrogens

Omeprazole: plasma concentration of tacrolimus possibly increased by omeprazole

Phenobarbital: plasma concentration of tacrolimus reduced by phenobarbital

Phenytoin: plasma concentration of tacrolimus reduced by phenytoin, *Also* plasma concentration of phenytoin possibly increased

Posaconazole: plasma concentration of tacrolimus increased by posaconazole

Potassium Salts: increased risk of hyperkalaemia

Progestogens: tacrolimus possibly inhibits metabolism of progestogens

Quinupristin: with Dalfopristin plasma concentration of tacrolimus increased by quinupristin/dalfopristin

Rifampicin: plasma concentration of tacrolimus reduced by rifampicin

Ritonavir: plasma concentration of tacrolimus possibly increased by ritonavir

Saquinavir: plasma concentration of tacrolimus increased by saquinavir

Sevelamer: plasma concentration of tacrolimus possibly reduced by sevelamer

St John's Wort: plasma concentration of tacrolimus reduced by St John's wort —Telithromycin:

plasma concentration of tacrolimus possibly increased by telithromycin Vancomycin: possible increased risk of nephrotoxicity

Verapamil: plasma concentration of tacrolimus possibly increased by verapamil

Voriconazole: plasma concentration of tacrolimus increased by voriconazole

Tamoxifen

Anticoagulants: effect of warfarin enhanced

Appendix 1: Drug interactions

Cinacalcet: possibly inhibits metabolism of tamoxifen to active metabolite (avoid concomitant use)

Tamsulosin

See under alpha-blockers

Teicoplanin

Antibacterials: increased risk of ototoxicity and nephrotoxicity with aminoglycosides

Temozolomide

Valproate: plasma concentration of temozolomide increased by valproate

Also, see under cytotoxics

Tenofovir

Adefovir: avoid concomitant use with adefovir

Atazanavir: tenofovir reduces plasma concentration of atazanavir, *Also* plasma concentration of tenofovir possibly increased

Cidofovir: combination of tenofovir with cidofovir may increase plasma concentration of either drug (or both)

Didanosine: tenofovir increases plasma concentration of didanosine (increased risk of toxicity)

Antacids: in tablet formulation may affect absorption of other drugs

Lopinavir: plasma concentration of tenofovir increased by lopinavir

Tenoxicam

See under NSAIDs

Terazosin

See under alpha-blockers

Terbinafine

Antibacterials: enhanced metabolism by rifampicin

Oral contraceptives: reports of breakthrough bleeding

Terbutaline

See under sympathomimetics, β_2

Testosterone

Anticoagulants: effect of warfarin enhanced

Antidiabetics: hypoglycaemic effect possibly enhanced

Tetracosactrin

See under corticosteroids

Tetracyclines

Antacids: reduced absorption

Antiepileptics: metabolism of doxycycline enhanced by carbamazepine and phenytoin

Calcium salts: reduced absorption of tetracyclines

Ciclosporin: doxycycline possibly increases plasma-ciclosporin concentration

Dairy products: reduce absorption (except for doxycycline and minocycline)

Retinoids: possible increased risk of benign intracranial hypertension with tetracyclines

Theophylline

Anaesthetics: increased risk of arrhythmias with halothane; increased risk of convulsion with Ketamine

Antibacterials: increased risk of convulsion with ciprofloxacin; plasma concentration of theophylline increased by ciprofloxacin, clarithromycin, erythromycin and isoniazid; rifampicin reduces plasma-theophylline concentration

Antifungals: plasma-theophylline possible increased by fluconazole and ketoconazole

Antiplatelets: ticlopidine increases plasma-theophylline concentration

Calcium channel blockers: plasma-theophylline concentration increased

Corticosteroids: increased risk of hypokalaemia

Deferasirox: increases plasma concentration of theophylline

Diuretics: increased risk of hypokalaemia

Lithium salts: lithium excretion accelerated

Thiopentone

See under anaesthetics

Thioridazine

See under antipsychotics

Thyroid hormones

Antibacterials: rifampicin enhances metabolism of thyroxine

Anticoagulants: effect of warfarin enhanced

Antiepileptics: carbamazepine, phenobarbitone and phenytoin enhanced metabolism of thyroid hormones

Tiaprofenic acid

See under NSAIDs

Tibolone

Antibacterials: rifampicin accelerates metabolism

Antiepileptics: carbamazepine, phenobarbitone and phenytoin accelerate metabolism

Ticlopidine

Analgesics: increased risk of bleeding with NSAIDs

Anticoagulants: increased risk of bleeding

Ciclosporin: reduced plasma-ciclosporin concentration

Tigecycline

Anticoagulants: tigecycline possibly enhances anticoagulant effect of coumarins

Timolol

See under beta-blockers

Tiotropium

See under antimuscarinics

Tirofiban

Iloprost: increased risk of bleeding when tirofiban given with iloprost

Appendix 1: Drug interactions

Tobramycin

See under aminoglycosides

Tocilizumab

Vaccines: avoid concomitant use of tocilizumab with live vaccines

Tolterodine

Amiodarone: increased risk of ventricular arrhythmias

Amprenavir: manufacturer of tolterodine advises avoid concomitant use

Clarithromycin: manufacturer of tolterodine advises avoid concomitant use

Disopyramide: increased risk of ventricular arrhythmias

Erythromycin: manufacturer of tolterodine advises avoid concomitant use

Flecainide: increased risk of ventricular arrhythmias

Indinavir: manufacturer of tolterodine advises avoid concomitant use

Itraconazole: manufacturer of tolterodine advises avoid concomitant use

Ketoconazole: manufacturer of tolterodine advises avoid concomitant use

Lopinavir: manufacturer of tolterodine advises avoid concomitant use

Nelfinavir: manufacturer of tolterodine advises avoid concomitant use

Procainamide: increased risk of ventricular arrhythmias

Ritonavir: manufacturer of tolterodine advises avoid concomitant use

Saquinavir: manufacturer of tolterodine advises avoid concomitant use

Sotalol: increased risk of ventricular arrhythmias

Also, see under antimuscarinics

Topiramate

Carbamazepine: plasma concentration of topiramate often reduced by carbamazepine

Glibenclamide: topiramate possibly reduces plasma concentration of glibenclamide

Lithium: topiramate possibly affects plasma concentration of lithium

Oestrogens: topiramate accelerates metabolism of oestrogens

Phenytoin: topiramate increases plasma concentration of phenytoin (*Also* plasma concentration of topiramate reduced)

Progestogens: topiramate accelerates metabolism of progestogens

Also, see under antiepileptics

Tramadol

See under opioid analgesics

Tretinoin

See under retinoids

Triamcinolone

See under corticosteroids

Trifluoperazine

See under antipsychotics

Trimethoprim

Appendix 1: Drug interactions

Antimalarials: increased risk of antifolate effect with pyrimethamine

Ciclosporin: increased risk of nephrotoxicity

Cytotoxics: increased risk of haematological toxicity with azathioprine and mercaptopurine; antifolate effect of methotrexate increased

Triprolidine

See under antihistamines

Tropicamide

See under antimuscarinics

Ursodeoxycholic Acid

Ciclosporin: ursodeoxycholic acid increases absorption of ciclosporin

Also, see under bile Acids

Vaccines

Abatacept: avoid concomitant use

Adalimumab: avoid concomitant use

Anakinra: avoid concomitant use

Corticosteroids: immune response to vaccines impaired by high doses of corticosteroids

Efalizumab: live or live-attenuated vaccines should be given 2 weeks before efalizumab or withheld until 8 weeks after discontinuation

Etanercept: avoid concomitant use

Infliximab: avoid concomitant use

Interferon Gamma: avoidance of vaccines advised by manufacturer of interferon gamma

Leflunomide: avoid concomitant use

Phenytoin: influenza vaccine enhances effects of phenytoin

Theophylline: influenza vaccine possibly increases plasma concentration of theophylline

Warfarin: influenza vaccine possibly enhances anticoagulant effect of warfarin

Valaciclovir

See under aciclovir

Valganciclovir

See under ganciclovir

Valsartan

See under Angiotensin-II Receptor Antagonists

Vancomycin

Antibacterials (other): increased of ototoxicity and nephrotoxicity with aminoglycosides

Cytotoxics: increased risk of ototoxicity and nephrotoxicity with cisplatin

Diuretics: increased risk of ototoxicity with loop diuretics

Vecuronium

See under muscle relaxants

Verapamil

See under calcium-channel blockers

Vigabatrin

Antiepileptics (other): enhanced effects, increased sedation and reduction in plasma concentration

Appendix 1: Drug interactions

Antimalarials: antagonism of anticonvulsant effect with mefloquine

Vildagliptin

See under Antidiabetics

Vinblastine

Erythromycin: toxicity of vinblastine increased by erythromycin

Posaconazole: metabolism of vinblastine possibly inhibited by posaconazole (increased risk of neurotoxicity)

Also, see under cytotoxics

Vincristine

Itraconazole: metabolism of vincristine possibly inhibited by itraconazole (increased risk of neurotoxicity)

Nifedipine: metabolism of vincristine possibly inhibited by nifedipine

Posaconazole: metabolism of vincristine possibly inhibited by posaconazole (increased risk of neurotoxicity)

Also, see under cytotoxics

Vitamins

Anticoagulants: warfarin effect antagonised by vitamin K

Antiepileptics: vitamin D requirement increased

Diuretics: increased risk of hypercalcaemia if vitamin D and thiazides are given together

Retinoids: risk of hypervitaminosis A with vitamin A given concomitantly with retinoids

Sevelamer: reduces absorption of calcitriol (give at least 1 hour before or 3 hours after sevelamer)

Voriconazole

See under Antifungals

Warfarin

Alcohol: enhanced anticoagulant effect with large amounts of alcohol

Analgesics: enhanced anticoagulant effect

Anion-exchange resins: may enhance or reduce anticoagulant effects

Anti-arrhythmics: amiodarone and quinidine enhance anticoagulant effect

Antibacterials: rifampicin reduced anticoagulant effect; anticoagulant effect enhanced by chloramphenicol, ciprofloxacin, co-trimoxazole, erythromycin, metronidazole and sulphonamides; anticoagulant effect possibly enhanced by clarithromycin, nalidixic acid, neomycin and trimethoprim. Tigecycline possibly enhances anticoagulant effect of coumarins

Antidepressants: SSRIs possibly enhance anticoagulant effect

Antiepileptics: anticoagulant effect reduced by carbamazepine and phenobarbitone; anticoagulant effect increased by valproate; phenytoin may increase or decrease the anticoagulant effect

Appendix 1: Drug interactions

Antifungals: anticoagulant effect reduced by griseofulvin; anticoagulant effect enhanced by fluconazole, itraconazole, ketoconazole and miconazole

Antiplatelets: increased risk of bleeding

Barbiturates: anticoagulant effect reduced

Corticosteroids: anticoagulant effect possibly altered

Cytotoxics: anticoagulant effect possibly enhanced by ifosfamide and fluorouracil; azathioprine possibly enhances the anticoagulant effect; gefitinib possibly enhances anticoagulant effect of warfarin

Entacapone: anticoagulant effect of warfarin enhanced by entacapone

Hormone antagonists: danazol, tamoxifen and flutamide possibly enhance anticoagulant effect

Lipid-regulating drugs: fibrates and simvastatin enhance anticoagulant effect, atorvastatin reduced the anticoagulant effect transiently

Oral contraceptives: anticoagulant effect reduced testosterone: anticoagulant effect enhanced

Rivaroxaban: increased risk of haemorrhage when other anticoagulants given with rivaroxaban (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency).

Thyroid hormones: anticoagulant effect enhanced

Ulcer-healing drugs: omeprazole enhances anticoagulant effect

Vitamins: vitamin K reduces warfarin anticoagulant effect

Zidovudine

Analgesics: increased risk of haematological toxicity with NSAIDs

Antibacterials: clarithromycin tablets reduces absorption of zidovudine

Antivirals (other): profound myelosuppression with Ganciclovir

Uricosurics: probenecid increases plasma-zidovudine concentration and risk of toxicity

Zinc

Antibacterials: zinc reduces absorption of ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin, norfloxacin; tetracyclines (give at least 2 hours apart)

Calcium Salts: absorption of zinc reduced by calcium salts.

Iron: absorption of zinc reduced by oral iron, also absorption of oral iron reduced by zinc

Penicillamine: absorption of zinc reduced by penicillamine, also absorption of penicillamine reduced by zinc

Zoledronic Acid

See under bisphosphonates

Zolmitriptan

Cimetidine: metabolism of zolmitriptan inhibited by cimetidine

Appendix 1: Drug interactions

Ergotamine and Methysergide: increased risk of vasospasm

Fluvoxamine: metabolism of zolmitriptan possibly inhibited by fluvoxamine

Moclobemide: risk of CNS toxicity

Quinolones: metabolism of zolmitriptan possibly inhibited by quinolones

Also, see under 5HT1

Zuclopenthixol

See under antipsychotics

Drug induced hepatotoxicity:

Drugs are an important cause of liver injury. This is the most common reason cited for withdrawal of an approved drug. Risk factors for drug induced hepatotoxicity include age (common in elderly), sex (common in females), liver disease, alcohol ingestion, genetic factors, the presence of other comorbidities and drug formulations (long acting drugs may cause more injury than short acting drugs).

Some drugs are directly toxic: with these, injury is generally characteristic for the drug, begins within hours of exposure, and is dose-related. *E.g. Acetaminophen (Paracetamol).*

Other drugs produce damage only rarely and only in susceptible people; the injury generally first occurs within a few weeks but occasionally may be delayed for several months after drug exposure. This injury is not dose-related. These reactions are rarely allergic; they are more accurately described as idiosyncratic. *E.g. Halothane, Isoniazid and Methyldopa.*

Metabolic drug interactions:

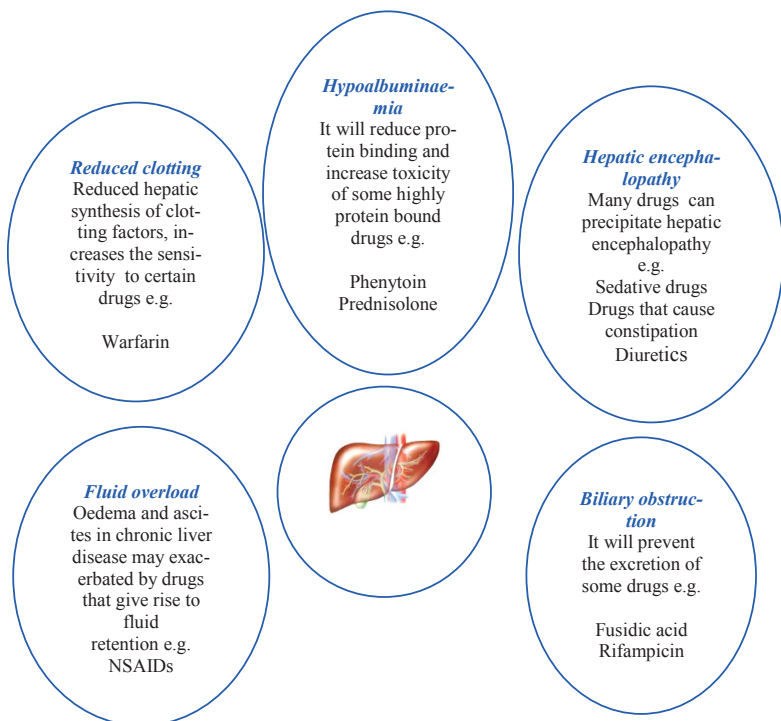
Cytochrome P-450 enzymes are haemoproteins located in the smooth endoplasmic reticulum of the liver. At least 50 enzymes have been identified, and based on structure; they are categorized into 10 groups, with groups 1, 2, and 3 being the most important in drug metabolism. Each P-450 enzyme can metabolize many drugs. Drugs that share the same P-450 specificity for biotransformation may competitively inhibit each other, resulting in drug interactions. Several drugs can induce and inhibit the P-450 enzyme (*see table*)

Liver enzyme inducers	Liver enzyme Inhibitors
Phenobarbital	Amiodarone
Phenytoin	Cimetidine
Carbamazepine	Erythromycin
Primidone	Grape fruit
Ethanol/ Alcohol	Isoniazid
Glucocorticoids	Ketoconazole
Rifampicin	Metronidazole
Griseofulvin	Sulfonamides
Quinine	Quinidine
Omeprazole -Induces P-450 1A2	Omeprazole - Inhibits P-450 2C8

Appendix 2: Drug Induced Hepatotoxicity

The majority of drugs are metabolised by the liver and under normal circumstances there is considerable reserve. If, however, the metabolic capacity of the liver is markedly reduced (e.g. in different liver diseases), the metabolism of the drug will be reduced.

Hepatic insufficiency also affects the action of different drugs through other mechanisms, *see* the diagram.



Creatinine clearance provides a measure of renal function and can be used to classify renal insufficiency. For some medications doses are adjusted according to severity of renal impairment.

Creatinine clearance (CrCl) calculation for adult:

From 24 hour urine collection:

- Creatinine clearance (mL/min) =
$$\frac{\text{Urine creatinine } (\mu\text{mol/L}) \times \text{Urine volume (mL)}}{\text{Serum creatinine } (\mu\text{mol/L}) \times \text{time (min)}}$$

Cockcroft and Gault formula:

- Creatinine clearance (mL/min) =
$$\frac{(140 - \text{age in years}) \times \text{body weight in kg} \times F}{\text{Serum creatinine } (\mu\text{mol/L})}$$

F = 1.04 for women, 1.23 for men

Creatinine clearance (CrCl) calculation for a child over 1 year:

- *Approximate Creatinine clearance*

$$(\text{mL/minute}/1.73 \text{ m}^2) = \frac{40 \times \text{height (cm)}}{\text{Serum creatinine } (\mu\text{mol/L})}$$

Creatinine clearance (CrCl) calculation for a neonate:

- *Approximate Creatinine clearance*

$$(\text{mL/minute}/1.73 \text{ m}^2) = \frac{30 \times \text{height (cm)}}{\text{Serum creatinine } (\mu\text{mol/L})}$$

Appendix 3: Kidney and Drugs

The definitions of mild, moderate and severe renal impairment are as follows:

Severity of renal impairment	CrCl (mL/min)
Mild	20-50
Moderate	10-20
Severe	Less than 10

Renal dysfunction secondary to medications is common. Renal toxicity can be classified into three:

Pre-renal toxicity: this occurs when drugs alter renal blood flow.

Intrarenal toxicity: medications can have direct injury to cells and tissues through different mechanisms e.g.

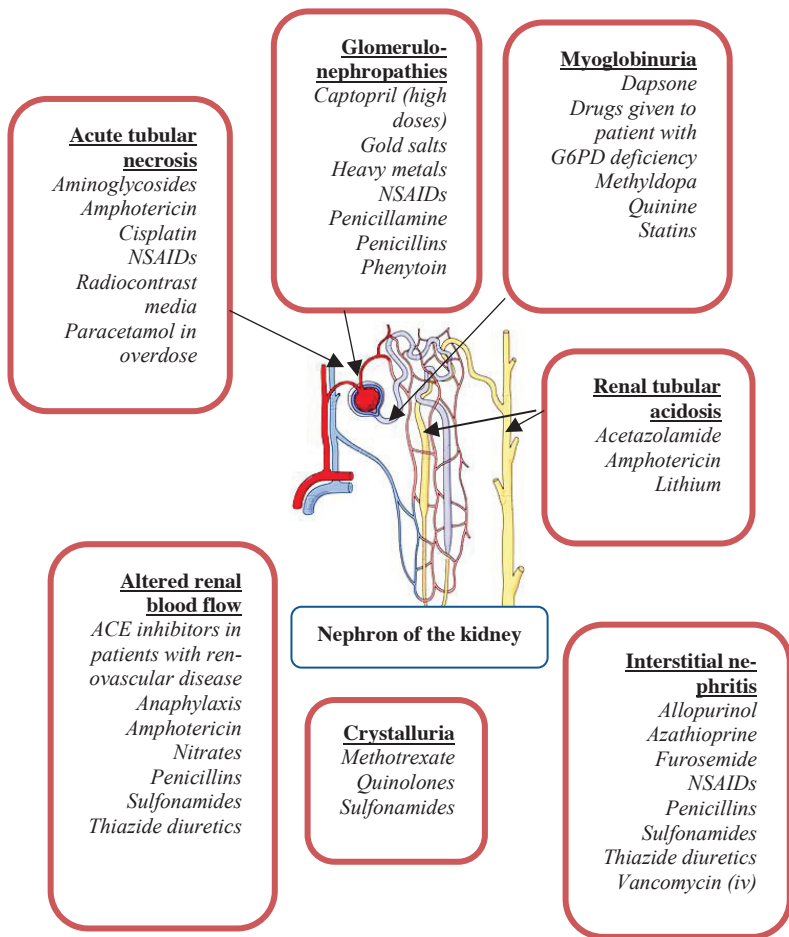
- Acute Tubular Necrosis
- Glomerulonephropathies
- Interstitial Nephritis
- Renal tubular acidosis
- Myoglobinuria.

Postrenal toxicity: occurs by obstruction of renal excretion by drugs inducing crystalluria or nephrolithiasis.

As it is impossible to list all drugs associated with nephrotoxicity, the diagram next page will summarize the mechanisms of injury associated with particularly common drugs

Note: this illustration modified from Oxford handbook of practical drug therapy. Duncan Richards, Jeffry Aronson (Ed). Oxford University Press. UK. 20

Appendix 3: Kidney and Drugs



Appendix 4: Drugs and Blood Donation

Blood donation is extremely important because it is the only way to maintain sufficient blood supplies for medical treatment.

Certain drugs (primarily Non-Steroidal Anti-Inflammatory Drugs ‘NSAIDs’ which affect platelets function) should be stopped for some days prior blood donation. *See the table below for more details*

Medications affect platelet function for 48 hours	Medications affect platelet function for 5 days
Acetoclofenac	Aspirin
Acematacin	Azapropazone
Diclofenac	Diiflunisal
Fenoprofen	Fenbufen
Flurbiprofen	Nabumetone
Ibuprofen	Naproxen
Indometacin (Indomethacin)	Phenylbutazone
Ketoprofen	Piroxicam
Ketorolac	Sodium salicylate
Mefenamic acid	Tenoxicam
Tiaprofenic acid	
Tolmetin	

Note:

Other medicines which are used in varies conditions are not mentioned as these conditions might themselves disqualify a person from donating blood permanently or temporarily. E.g. Atenolol in poorly controlled high blood pressure.

Some of the above NSAIDs are not available from or approved for use by Ministry of Health

Appendix 5: Drugs and G6PD Deficiency

Below is a list for the common drugs and agents known to cause oxidative reactions and should be avoided in patients with G6PD deficiency.

Note:

- *Not all the drugs are approved by MOH.*
- *Susceptibility to the hemolytic risk from drugs varies; thus, a drug found to be safe in some G6PD deficiency individuals may not be equally safe in others.*
- *List of other agents that can lead to hemolysis in patients with G6PD deficiency could be found in the following link :*
<http://www.g6pd.org/favism/english/index.mv?pgid=avoid>

Name of the medicine in alphabetical order	Risk Level (Definite/ Possible)
Aspirin ¹	Possible (acceptable up to a dose at least 1 g daily)
Chloroquine	Possible (acceptable in acute malaria)
Dapsone	Definite
Menadiol Sodium Sulfate	Possible
Tetramethylthionine Chloride (methylene blue)	Definite
Niridazole	Definite
Nitrofurantoin	Definite
Pamaquine	Definite
Primaquine	Definite
Probenecid	Possible
Quinolones ²	Definite
Quinidine	Possible (acceptable in acute malaria)
Quinine	Possible (acceptable in acute malaria)
Rasburicase	Possible
Sulphonamides ³ (including co-trimoxazole)	Definite

Name of some foods and chemicals associated with haemolysis in patients with G6PD deficiency

Blueberries Fava beans Henna application especially in infants Lentils Naphthalene, (Pure as in mothball) Red wine Soya products Tonic water can cause problems but usually not Vitamin K Ascorbic acid (in very high doses)

¹Other Antipyretics and analgesics with susceptibility to hemolytic risk include:

- Acetanilide
- Acetophenetidin
- Antipyrine
- Aminopyrine

²Quinolones:

- Ciprofloxacin
- Moxifloxacin
- Nalidixic acid
- Norfloxacin
- Ofloxacin

Appendix 5: Drugs and G6PD Deficiency

³ Sulphonamides

- Furaltadone
- Furazolidone
- N-Acetylsulfanilamide
- Nitofurantoin
- Nitrofurazone
- Salicylazosulfapyridine
- Sulfacetamide
- Sulfamethoxypyridazine
- Sulfanilamide
- Sulfapyridine
- Sulfisoxazole



Fava beans

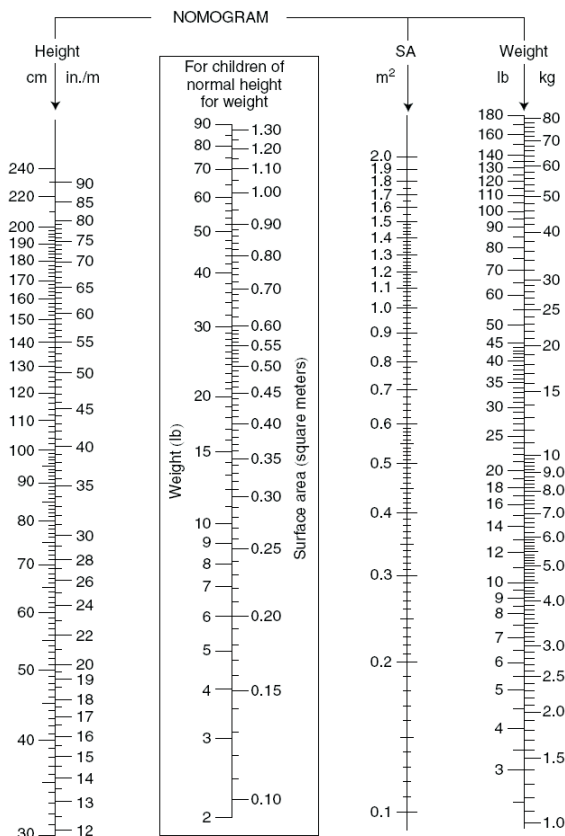
Body surface area (BSA):

Body surface area is recommended as the principle basis for drug dosages in paediatric age group than body weight since many physiological phenomena correlate better with body surface area.

BSA calculation by using child-BSA-nomogram:

- Get the child weight and height.
- Find the weight in the right column and the height in the left column.
- Place a straightedge on the nomogram so the weight and height are connected.
- The point where the straightedge crosses the centre column denotes the body's surface area in square meters.

Appendix 6: Body Surface Area (BSA)



Note: Nomogram modified from data of E. Boyd by C.D. West; from Behrman, R.E., Kliegman, R.M., & Jenson, H.B. (eds.). (2000). *Nelson textbook of pediatrics* (16th ed.). Philadelphia: W.B. Saunders.

Therapeutic drug monitoring (TDM)

Therapeutic drug monitoring (TDM) is defined as the use of drug measurements in body fluids as an aid to the management of patients receiving specific drugs. It plays an important role in facilitating optimization of therapy where the pharmacological response can not be established easily by clinical means or by laboratory markers, and so drug efficacy or toxicity is difficult or impossible to be assessed

Criteria for valid TDM:

- For drugs with poor correlation between dose and clinical response
- For drugs with narrow concentration interval between toxic and therapeutic effect
- Where there are no good clinical markers of effects (e.g. BP, blood glucose, INR and lipid profile)
- There is a good correlation between plasma concentration and effect

Generally the list of drugs which fulfill these criteria is small and only those drugs which are frequently monitored will be mentioned in this appendix

1. Analgesics

Indications for TDM

- Paracetamol (Acetaminophen) poisoning: *see* section 17 B
- Acetylsalicylic acid (Aspirin) poisoning

Paracetamol (Acetaminophen)

Clinical use: *see* section 4 D

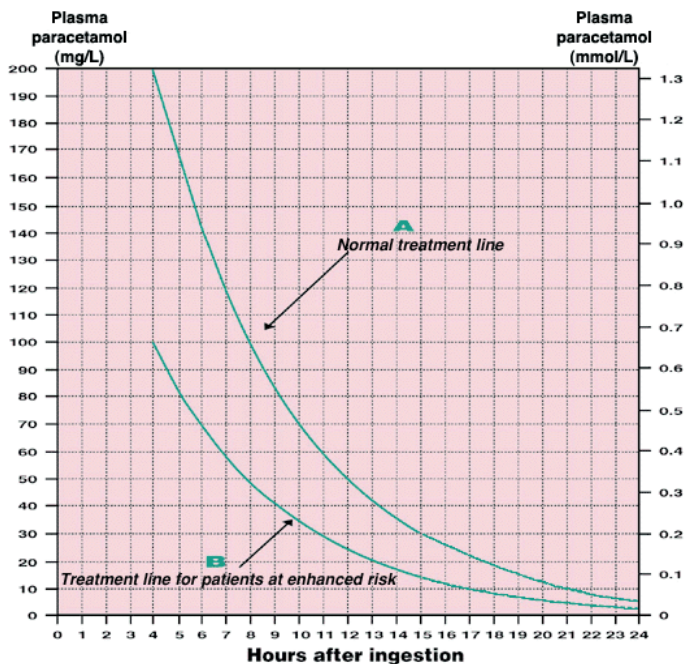
Recommended sampling time: 1 hour after a dose for a peak

Target therapeutic range: no age limit, 10 to 20 mg/L (66-132 $\mu\text{mol/L}$)

Toxic levels: ≥ 200 mg/L (1320 $\mu\text{mol/L}$) 4 hour post ingestion
 ≥ 50 mg/L (330 $\mu\text{mol/L}$) 12 hour post ingestion)

Appendix 7: Therapeutic drug monitoring

The diagram shows when the treatment with an antidote such as N-Acetyl-cysteine should be started in relation to plasma-paracetamol concentration and time of ingestion



Acetylsalicylic acid (Aspirin)

Clinical use: *see* section 4D

Recommended sampling time: 1 to 3 hours after an oral dose (formulation dependent)

Target therapeutic range: no age limit, 150 -300 mg/L(1085-2170 $\mu\text{mol/L}$) (for anti-inflammatory dose)

N.B: therapeutic range is usually lower if the drug is used for analgesia

Toxic levels: > 300 mg/L(2170 $\mu\text{mol/L}$)

2. Antibiotics

Indications for TDM

- Patients on long term therapy
- Patients with renal impairment
- Monitoring is essential in infants, the elderly, in obesity, in cystic fibrosis or if high doses are being used

Amikacin

Clinical uses: *see* section 5 A

Recommended sampling time: peak 0.5-1 hour after the end of 30 minute infusion (1 hour after IM dose), trough level is measured, immediately before next dose

Target therapeutic range: peak is (20-30 mg/L) and trough is (<5 mg/L)

Gentamicin:

Clinical uses: *see* section 5 A

Recommended sampling time: peak 0.5-1 hour after the end of 30 minute infusion (1 hour after IM dose), trough level is measured, immediately before next dose

Target therapeutic range: peak is (5-10 mg/L) and trough is (<2 mg/L)

Once daily Gentamicin:

The rationale for pulse dosing of gentamicin is based on the following factors:

Appendix 7: Therapeutic drug monitoring

- Relatively easy, straightforward initial dosing
- Enhanced efficacy due to higher peak levels
- Enhanced safety due to shorter effective exposure time
- Convenience for both patients and doctors/nurses
- Likely on-time administration
- A much reduced need for serum aminoglycoside levels (reduced cost)

Exclusion criteria for once daily aminoglycoside dosing:

1. Pregnancy
2. Patients with extensive burn (>20% of body surface area)
3. Patients with severe liver disease (e.g. ascites)
4. Patients with severe renal disease ($\text{CrCl} < 30 \text{ mL/min}$)
5. Patients with neutropoenia
6. Patients with enterococcal endocarditis
7. Patients with Gram positive infections (when the aminoglycoside is used for synergy).
8. Children < 12 years

Guidelines for the pulse dosing of gentamicin:

1. First determine the creatinine clearance (CrCl): for (CrCl) calculation see appendix 3
2. Usually dosage is 5-7 mg/kg, unless the patient is more than 20% of ideal body weight (morbid obesity), the dosing weight should be calculated as follows:

Appendix 7: Therapeutic drug monitoring

Dosing weight (Adjusted Body Weight) = Ideal body weight in kg + 0.4
(Actual body weight - Ideal body weight)

Ideal Body Weight (men) = $50 + 2.3 (\text{Height (inches)} - 60)$

Ideal Body Weight (women) = $45.5 + 2.3 (\text{Height (inches)} - 60)$

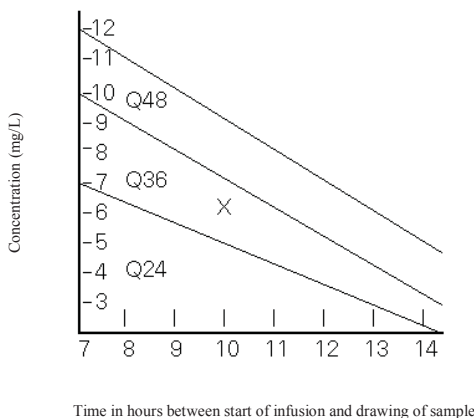
* 1 inch = 2.54 cm

3. The calculated dose is diluted in 100 ml of isotonic saline and infused over 0.5-1 hour
4. The initial dosing interval is determined by the creatinine clearance (CrCl):

CrCl (mL/min)	> 60	40-60	20-40	< 20
Dosing interval	24 hrs	36 hrs	48 hrs	Consultation is needed

5. To determine the proper dosing interval, the reported level is plotted on a special graph (Hartford nomogram), which is applicable to gentamicin. *See next page*
 6. Obtain a single serum level after first dose, 8 hrs after start of infusion
 7. Evaluate on the nomogram, if the level falls in area 24hrs, 36hrs or 48hrs, the interval should be every 24, 36 or 48 hrs respectively
 8. If the point is on the line, choose the longer interval
 9. If the point is above the nomogram, stop scheduled treatment. Do serial levels to determine the time of next dose (< 2 mg/L)
- * Laboratory analytical limit of detection is 2 mg/L

Appendix 7: Therapeutic drug monitoring



Hartford Hospital Once Daily Dose Nomogram for Gentamicin

Vancomycin

Clinical uses: see section 5 A

Recommended sampling time: trough level is usually measured, immediately prior to next dose

Target therapeutic range: (5-10 mg/L)

N.B: trough level is higher for less sensitive strains of methicillin resistant staphylococcus aureus

3. Antiepileptics (Anticonvulsants)

Indications for TDM

- On initial therapy to check if the desired dose is achieved
- During intravenous therapy in status epileptics
- Unexpected deterioration in seizure control
- As an adjunct to the diagnosis of toxicity
- When interacting drugs are added or withdrawn
- During pregnancy

Carbamazepine

Clinical use: *see* section 4.E

Recommended sampling time: usually trough levels

Target therapeutic range: no age limit, 4-10 mg/L (17-42 $\mu\text{mol/L}$)

Phenobarbital (Phenobarbitone)

Clinical use: *see* section 4.E

Recommended sampling time: trough or peak due to long half life

Target therapeutic range:

Age ≤ 12 yrs 15 - 20 mg/L (65-85 $\mu\text{mol/L}$)

Age > 12 yrs 15 - 40 mg/L (65-170 $\mu\text{mol/L}$)

Phenytoin

Clinical use: *see* section 4.E

Recommended sampling time: usually trough levels

Target therapeutic range:

Age ≤ 3 months 6-14 mg/L (24-56 $\mu\text{mol/L}$)

Age > 3 months 10-20 mg/L (40-80 $\mu\text{mol/L}$)

Valproic acid (Sodium valproate)

Clinical use: *see* section 4.E

Recommended sampling time: usually trough levels

Target therapeutic range: no age limit, 50-100 mg/L (350-700 $\mu\text{mol/L}$)

4. Antineoplastics

Methotrexate

Appendix 7: Therapeutic drug monitoring

Indications for TDM

- Only required for high dose therapy to identify patients at risk of toxicity and as a guide to the dose and timing of Leucovorin (Calcium folinate) rescue

Clinical use: *see* section 8 A

Recommended sampling time: initial sample (in the first 24 hours) to calculate half life, 24 hours post-infusion and 48 hours post-infusion

If the levels are found to be high (see toxic levels below) or in the presence of clinical risk factors (e.g. renal impairment, pleural effusion or ascites), methotrexate levels should be monitored daily to achieve concentration < 0.01 $\mu\text{mol/L}$

Target therapeutic range: a recommended therapeutic range for methotrexate has not been well defined. The minimum cytotoxic concentration (threshold level) is 4.5 $\mu\text{g/L}$ (0.01 $\mu\text{mol/L}$)

Toxic levels:

- 24 hours post-infusion $\geq 2250 \mu\text{g/L}$ ($\geq 5 \mu\text{mol/L}$)
- 48 hours post-infusion $\geq 225 \mu\text{g/L}$ ($\geq 0.5 \mu\text{mol/L}$)

5. Bronchodilators

Indications for TDM

- Optimizing dosage
- Diagnosis of Theophylline toxicity

Theophylline

Clinical use: *see* section 3 A

Recommended sampling time: both peak and trough are useful.

For intravenous infusion:

Prior to intravenous infusion

30 minutes after loading dose

4-6 hours after beginning of continuous infusion therapy or before next infusion

For oral product with rapid release properties:

Peak: 2 hours after administration

Trough: immediately before next dose

Appendix 7: Therapeutic drug monitoring

For oral product with sustained release properties:

Peak: 4-8 hours after administration

Trough: immediately before next dose

Target therapeutic range: 8-20 mg/L (45-110 $\mu\text{mol/L}$)

6. Cardiac agents

Indications for TDM

- When there is an initial poor response to treatment
- In helping to confirm digoxin toxicity (careful clinical examination remains the most important tool)
- To decide if continued therapy is justified

Digoxin

Clinical use: see section 2 A

Recommended sampling time: peak level (8-24 hours) after dose

Target therapeutic range: no age limit, 0.8-2.0 $\mu\text{g/L}$ (1.0-2.6 nmol/L)

Toxic levels: > 3.0 $\mu\text{g/L}$ (> 3.8 nmol/L)

N.B: it is recommended to measure both plasma digoxin and potassium. Hypokalaemia sensitizes the myocardium to the action of digoxin and so can precipitate or aggravate toxicity.

7. Immunosuppressants:

Indications for TDM

- Solid organ transplantation to predict toxicity or rejection

Ciclosporin:

Clinical use: see section 8 B

Recommended sampling time: 2 hours post dose

Target therapeutic range: 100-400 $\mu\text{g/L}$ (83-332 nmol/L) Therapeutic range varies depending upon organ transplant type, the length of period post transplantation and concomitant drug therapy

Post renal transplant

Appendix 7: Therapeutic drug monitoring

Period	Therapeutic range ($\mu\text{g/L}$)
1 month	1500-2000
2 months	≤ 1500
3 months	≤ 1300
4-6 months	≤ 1100
7- 12 months	≤ 900
>12 months	≤ 300

Post liver transplant

Period	Therapeutic range ($\mu\text{g/L}$)
0-3 months	≤ 1000
4-6 months	≤ 800
> 6 months	≤ 600

Sirolimus

Clinical use: *see* section 8 B

Recommended sampling time: trough concentration

Target therapeutic range:

When given with ciclosporin, during the three months following transplantation, target level is 4-12 $\mu\text{g/L}$

When ciclosporin is discontinued, target level is recommended to be increased to 12-20 $\mu\text{g/L}$

Tacrolimus

Clinical use: *see* section 8 B

Recommended sampling time: trough concentration

Target therapeutic range: no age limit

Trough level: 8-15 $\mu\text{g/L}$

Long term Rx: 3-8 $\mu\text{g/L}$

8. Psychoactive agents

Indications for TDM

- Optimizing dosage
- Diagnosis of lithium toxicity

Appendix 7: Therapeutic drug monitoring

Lithium

Clinical use: *see* section 4. B

Recommended sampling time: trough (12 hours after evening dose)

Target therapeutic range:

In acutely manic patients: 0.9-1.4 mmol/L

In patients on maintenance therapy: 0.6-1.2 mmol/L

Toxic levels: > 2.0 mmol/L

Conversion factors:

To convert from (mg/L to $\mu\text{mol/L}$)

Multiply the number of mg/L by the conversion factor

Drug	Conversion Factor
Acetaminophen/ Paracetamol	6.61
Acetylsalicylic acid (Aspirin):	7.24
Amikacin:	1.71
Gentamicin:	2.09
Vancomycin:	0.69
Carbamazepine:	4.23
Phenobarbital (Phenobarbital):	4.31
Phenytoin:	3.96
Valproic acid:	6.93
Methotrexate:	2.20
Theophylline:	5.55

To convert from ($\mu\text{g/L}$ to nmol/L)

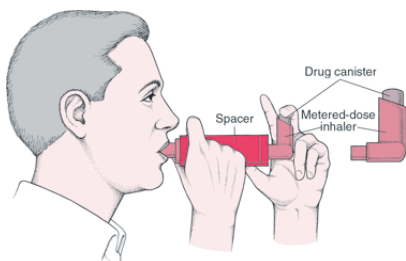
Multiply number of micrograms per mL by the conversion factor

Drug	Conversion Factor
Ciclosporin	0.83
Digoxin:	1.28

Appendix 7: Therapeutic drug monitoring

References:

1. *Therapeutic drug monitoring and laboratory medicine*. Mike Hallworth; Ian Watson (Ed). 2nd edition. ACB venture publications. London, UK. 2008
2. *Therapeutic drug monitoring-clinical guide*. William E.Evans; Michael; Oellerich,David W.Holt (Ed). Abbott laboratories. 1994
3. *Sultan Qaboos University Hospital Antibiotic Handbook*. Scrimger E.M (Ed). 6th edition. Sultan Qaboos University Hospital. Sultanate of Oman. 2003
4. *Pulse dosing of aminoglycosides*. Nasr Anaizi.
<http://www.thedrugmonitor.com/oda.html>
5. *Therapeutic ranges*. Royal Hospital. Sultanate of Oman. 2008



Guide to use metered dose inhaler (MDI):

- Remove MDI cap.
- Hold inhaler upright.
- Shake the inhaler vigorously.
- Breathe out slowly and completely.
- Put the inhaler in your mouth between closed lips (held vertically) and tilt head back slightly.
- Start to breathe in slowly.
- While starting to breathe in, immediately depress canister once.
- Breathe in slowly and deeply until your lungs are full.
- Remove inhaler with mouth closed.
- Hold your breath for 10 seconds.
- Breathe out / relax.
- For a 2nd inhalation wait 20-30 seconds and repeat the same steps.
- Clean the mouthpiece with dry and clean tissue.

Appendix 8: Drug Administration

- Put the cap back to the inhaler.

A spacer can be used with an MDI; it requires less hand-breath co-ordination and decreases oral candidiasis with inhaled corticosteroids.

Steps :

- Shake inhaler and insert it in one side of the spacer, insert the mouthpiece in the opposite side.
- Place mouthpiece in mouth and exhale gently.
- Depress canister once.
- Breathe in slowly and deeply and hold breath for 10 seconds or
- Breathe in and out normally through the spacer for 4 breaths.
- Remove spacer from mouth.
- Relax.
- For a 2nd inhalation wait 20-30 seconds and repeat the same steps.
- Wash spacer but drip dry, DO NOT dry with a cloth (causes static electricity build up which can attract drug droplets)

N.B: for children, a face mask is attached to the spacer instead of the mouth piece and it should be placed over mouth and nose.

Other common inhaler devises:

Dry powder inhalers:

These types of inhaler do not have a gas propellant to push the drug out of a canister. Instead, each dose contains a tiny amount of drug in a powder form that the patient can suck in. Various devices are made by different companies. Each has a different method of providing the correct amount of powder for each dose. Some types are shown below.

Accuhaler



Turbohaler





Eye drops:

1. Wash your hands and remove any contact lenses.
2. Do not touch the dropper opening.
3. Look upward.
4. Pull the lower eyelid down to make a gutter.
5. Bring the dropper as close to the gutter as possible without touching it or the eye.
6. Apply the prescribed amount of drops in the gutter.
7. Close the eye for about two minutes. Do not shut eye too tight.
8. Excess fluid can be removed with a tissue.
9. If more than one drop is prescribed or another kind of eye drop is used wait at least five minutes before applying the next drops.
10. Eye-drops may cause a burning feeling but this should not last for more than a few minutes. If it does last longer consult a doctor or pharmacist.

In children:

1. Wash your hands thoroughly.
2. Do not touch the edge of the dropper to keep it clean.
3. Let the child lie straight on his back.
4. The child's eye should be closed.
5. Drip the prescribed dose at the eye angle close to the nose.
6. Keep the head straight for one minute.
7. Always keep the droppers clean and closed.
8. Do not use any type of droppers after four weeks from the date the dropper was opened.

Appendix 8: Drug Administration

Eye ointment:

1. Wash your hands thoroughly.
2. Do not touch the edge of the tube to avoid contamination.
3. Look upward and move your head slightly backward.
4. Hold the tube and pull the lower eyelid downward with your other hand.
5. Put the upper end of the tube near the opened eyelid and apply the prescribed amount of ointment.
6. Close the eye gently for two minutes.
7. Wipe the excessive amount of ointment with a clean tissue.
8. Clean the upper end of the tube with a clean tissue and keep it tightly closed.
9. Do not use the ointment after four weeks from the date the tube was opened.

Ear drops:

1. Warm up the ear dropper for two minutes by grasping it with hand. Do not use hot water tap as there is no way to control temperature.
2. Move the head aside or lie it down on any side.
3. Pull the earlobe gently to widen the ear opening.
4. Apply the prescribed amount of drops in the ear.
5. Wait for five minutes before you apply drops in the other ear.
6. Clean the upper end of the dropper with a clean tissue.
7. Always keep the dropper clean and closed.
8. Do not use any type of droppers after four weeks from the date the dropper was opened.
9. Do not use gauze to close ear canal after applying the drops unless recommended by doctor.
10. Ear-drops should not burn or sting longer than a few minutes.

Appendix 8: Drug Administration

Nasal drops:

1. Blow the nose.
2. Sit down and gently tilt head backward as far as possible or lie down with a pillow under the shoulders; keep head straight.
3. Insert the dropper one centimetre into the nostril.
4. Apply the number of drops prescribed.
5. Pinch nose and immediately afterward tilt head forward as far as possible. (The rationale behind this position is to get the liquid to spread over all the inside surface including the upper surface of the nose.)

N.B: if this position is inconvenient e.g. patient is obese, lying on a bed with head hanging back over the edge for two minutes is an alternative.

6. Sit up after a few seconds, the drops will then drip into the pharynx.
7. Repeat the procedure for the other nostril, if necessary.
8. Rinse the dropper with boiled water.

Nasal spray:

1. Blow your nose.
2. Sit down with the head slightly moved forward.
3. Shake the nasal spray.
4. Insert the upper end of the nebulizer inside the nostril.
5. Close the other nostril and mouth.
6. Press the nasal spray and inhale slowly.
7. Keep the upper end away from the nose and put your head between your knees.
8. Breathe through the mouth.
9. Repeat the same steps in the other nostril, if necessary.
10. Clean the upper end of the nasal spray and keep it closed.

Rectal suppository:

1. If necessary, go the toilet to empty your bowels.
2. Wash your hands.
3. Remove any foil or plastic wrapping from the suppository.
4. If the suppository is too soft let it harden first by cooling it (fridge) then remove covering.
5. Moisten the suppository with cold water.
6. Lie on one side with one leg straight and the other is bent.
7. Gently insert the suppository, tapered end first, into the back passage (the rectum).
8. Remain lying down for several minutes.
9. Wash your hands.
10. Try not to have a bowel movement during the first hour (unless suppository is a laxative).

Appendix 8: Drug Administration

Rational application of topical treatments:

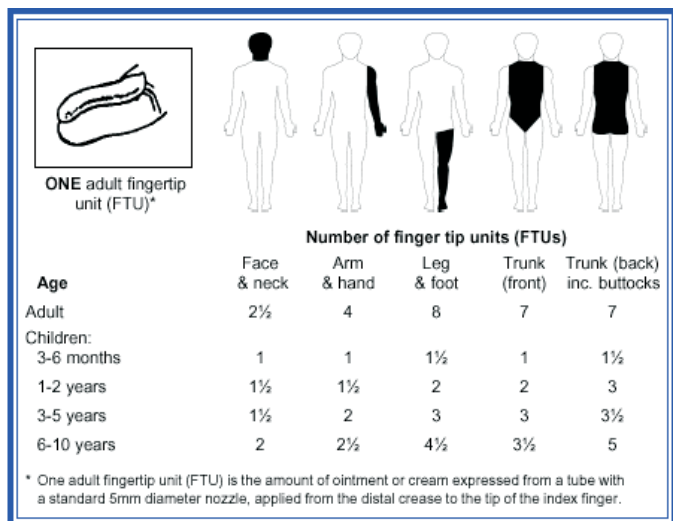
Unlike many other creams and ointments, it is important to get the dose right when using topical steroids. This is why a standard measure is often used, a fingertip unit. One fingertip unit (FTU) is the amount of topical steroid that is squeezed out from a standard tube along an adult's fingertip. (This assumes the tube has a standard 5 mm nozzle.) A finger tip is from the very end of the finger to the first crease in the finger. One FTU is enough to treat an area of skin twice the size of the flat of an adult's hand with the fingers together.



Two FTUs are about the same as 1 g of topical steroid. Therefore, for example, say you treat an area of skin the size of eight adult hands. You will need four FTUs for each dose (This is 2 g per dose). If the dose is once a day, then a 30 g tube should last about 15 days of treatment.

Appendix 8: Drug Administration

The following gives a rough guide:



N.B: for more details, refer to Pharmaco-logical newsletter volume 1, No. 2, issued by Directorate of Rational Use of Medicines

Appendix 8: Drug Administration

Insulin injection techniques



1-Wash your hands



2-If you are taking cloudy insulin, roll the bottle between your hands until it is uniformly cloudy.
Never shake a bottle



3-Wipe the top of the insulin bottle with alcohol swab



4-Draw air into the syringe by pulling out one the plunger to the approximate dose



5-Push the needle through the centre of the rubber top of the insulin bottle.

-Push the air into the insulin bottle.

-Turn the insulin bottle and syringe upside down.

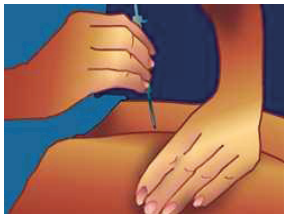
-Pull the plunger down about 5 units past your dose. If there are no bubbles, push the top of the plunger tip up to the line which marks your exact dose.

-If there are air bubbles, tap the syringe until they float to the top, then eliminate them out as you push the plunger tip to your exact dose.



6-Clean the injection site with an alcohol swab. Move the swab in a circular motion. Start from the centre and move outward. Allow the alcohol to dry for a few seconds.

Appendix 8: Drug Administration



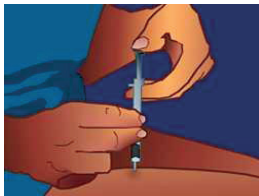
7-Carefully pick up the syringe without allowing the needle to touch anything.

Gently pinch up a two inch fold of skin. With one quick motion, inject the needle into the skin.

The usual injection angle is between 45 and 90 degrees.



9-When finished with the injection, hold an alcohol swab at the injection site. Pull the needle straight out of the skin and gently wipe the site with the alcohol swab. ***Do not massage the area.***



8-Release the fold of skin. Use one hand to hold the barrel of the syringe steady, and with the other hand push on the plunger to inject the insulin. The injection of the insulin should be completed in 3 to 5 seconds.

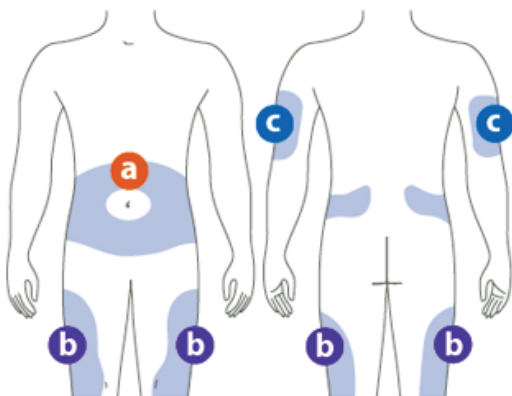
10-Destroy the syringe by clipping off the needle with an insulin needle clipper, or very carefully break off the needle. Drop the unusable syringe into an empty re-sealable household container such as a coffee can or bleach bottle. When the container is full, seal the lid securely and deposit in the trash.

Appendix 8: Drug Administration

It is essential to rotate the site of insulin injection. DO NOT use the same site repeatedly.

This illustration shows the common sites for insulin injections:

- a- The abdomen
- b- The upper buttocks or hips, and the outer side of the thighs
- c- The back of the upper arms



Recommended injection sites

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Glossary of Scientific Terms and Abbreviations

(Most of the following acronyms, words or symbols appear in the ONF text. Only a few recurrent medical words appear here. For further assistance consult a good medical dictionary.)

©	Copyright
®	Signifies a commercial or brand name product e.g. Actifed® <i>see also</i> TM
3TC	Lamivudine – an antiviral drug – a nucleoside reverse transcriptase inhibitor - NRTI
5-HT	5-Hydroxytryptamine or Serotonin
Ab	Antibody
ac	before food or meals
ACE	Angiotensin-converting enzyme
ACTH	Adrenocorticotrophic hormone
ADH	Antidiuretic hormone (vasopressin)
ADR(s)	Adverse drug reaction(s)
AF	Atrial Fibrillation
Ag	Antigen
AIDS	Acquired immunodeficiency syndrome
APTT	Activated partial thromboplastin time (used for heparin monitoring)
ARB	Angiotensin receptor blocker
ARI	Acute respiratory infections
ATPase	Adenosine triphosphatase enzyme
AV	Atrio-ventricular
BAL	British anti Lewisite or dimercaprol
BCG	Bacillus Calmette Guérin (attenuated strain of TB bacillus - <i>Mycobacterium bovis</i>)
bd	twice a day
BMI	Body mass index (ratio of weight to height)
BSA	Body surface area

Glossary of Terms and Abbreviations

cAMP	Cyclic Adenosine Monophosphate
CAPD	Continuous ambulatory peritoneal dialysis
CAT	Computerised axial tomography
CAT scan	Computerised axial tomography scan (multiple X-rays turned into images)
CCF	Congestive cardiac failure
CDC	Central Drug Committee
CDL	Complimentary Drug List
CFC	Chlorofluorocarbon
CG	Chorionic gonadotrophin
cGMP	Cyclic Guanosine Monophosphate
chronotropic	rate of cardiac contraction
CI	Contraindications
COAD	Chronic obstructive airways disease
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenase enzyme e.g. COX-1 or COX-2
CPR	Cardio-pulmonary resuscitation
CrCl	Creatinine clearance
CRF	Chronic renal failure
CRP	C-reactive protein (blood marker for inflammation)
CS	Cephalosporins
CSF	Cerebro-spinal fluid
CT	Computerized tomography
DI	Drug Information
DMARDs	Disease Modifying Antirheumatic Drugs
DNA	Deoxyribonucleic acid
DPP-4 inhibitors	Dipeptidyl peptidase 4 inhibitors
DPT or DTP	Diphtheria Pertussis Tetanus
DVT	Deep vein thrombosis
EC or ec	Enteric coated (or gastric acid-resistant)

Glossary of Terms and Abbreviations

ECG	Electro-cardiogram (EKG in US)
EEG	Electro-encephalogram
eGFR	Estimated glomerular filtration rate
EP	Extra pyramidal
EPI	Expanded programme on immunisation
f/c	film coated
FEV ₁	Forced expiratory volume in first second
FSH	Follicle stimulating hormone
FTU	fingertip unit
G6PD	Glucose-6-phosphate dehydrogenase
GFR	Glomerular filtration rate
GI	Gastro-intestinal
GORD	Gastro-oesophageal reflux disease (or GERD in US)
GLP-1 Receptor Agonists	Glucagon-Like Peptide 1 Receptor Agonists
GTN	Glyceryl trinitrate
HAART	Highly active antiretroviral therapy
HBIG	Hepatitis B Immunoglobulin
HBV	Hepatitis B vaccine
HCG	Human chorionic gonadotrophin
HCV	Hepatitis C vaccine
HDL	High density lipoprotein
HFA	Hydrofluoroalkane
Hib	<i>Haemophilus influenzae</i> type B
HIV	Human immunodeficiency virus
HRT	Hormone Replacement Therapy
HTN	Hypertension
IA i/a	Intra-articular – injection into a joint
Iatrogenic	Drug induced

Glossary of Terms and Abbreviations

IBS	Irritable bowel syndrome
IDDM	Insulin Dependent Diabetes Mellitus
Ig	Immunoglobulin e.g. IgE or IgG or IgM, etc
IGT	Impaired glucose tolerance
IM, im or i/m	Intramuscular
IMCI	Integrated management of childhood illnesses (guidelines)
INCB	International Narcotic Control Board
INH	Isoniazid
inotropic	force of cardiac contraction
INR	International normalised ratio (prothrombin time {PT} ratio in blood-coagulation)
IOP	Intra-ocular pressure
ISA	Intrinsic sympathomimetic activity
IV, iv or i/v	Intravenous
LA	Long acting
LDL	Low density lipoprotein
LH	Luteinising hormone
LMWH	Low molecular weight heparins (fractionated heparin)
mAB	Monoclonal antibody
MAOI	Mono Amine Oxidase Inhibitors
MCT	Medium chain triglycerides
MDI	Metered dose inhaler
MDRD	Modification of Diet in Renal Disease
MI	Myocardial Infarction
MMR	Mumps Measles Rubella
MR or m/r	Modified Release
MRI	Magnetic resonance imaging
MRSA	Methicillin Resistant Staphylococcus aureus
MSA	Membrane stabilising activity

Glossary of Terms and Abbreviations

NIDDM	Non Insulin Dependent Diabetes Mellitus
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NPH	Isophane Insulin (<u>N</u> eutral <u>P</u> rotamine <u>H</u> agedorn)
NRTI	Nucleoside reverse transcriptase inhibitor
NSAIDs	Non Steroidal Anti-Inflammatory Drugs
OCP	Oral Contraceptive Pills
od	each day
OPV	Oral polio vaccine
ORS	Oral Rehydration Salts
ORT	Oral Rehydration Therapy
OTC	Over the counter
PaCO ₂	Arterial carbon dioxide tension
PaO ₂	Arterial oxygen tension
pc	after food or meals
PEG	Polyethylene Glycol
PET	Positron emission tomography
PI	Protease inhibitor
po	Orally or by mouth
PPI	Proton Pump Inhibitors
PRN	as required or as necessary
PSVT	Paroxysmal supraventricular tachycardia
PT	Prothrombin time
PUD	Peptic ulcer disease
qid or qds	four times a day
qnh	every n hours (n represents any number e.g. usually 4, 6, 8 or 12)
QRST inter- val	electrocardiographic period of ventricular electrical activity
rINN	Recommended International Non-proprietary Name
RBS	Random blood sugar (level)

Glossary of Terms and Abbreviations

RNA	Ribonucleic acid
SA	Sustained action
SC or sc	Subcutaneous
SOS	if necessary
spp	species
SR or S/R	Sustained release
SSRIs	Selective Serotonin Re-uptake Inhibitors
Stat	At once
STD	Sexually transmitted disease
STG	Standard Treatment Guidelines
T ₃	Tri-iodothyronine
T ₄	Thyroxine or Tetra-iodothyronine
TB	Tuberculosis
TCA	Tricyclic antidepressant drug
TD or Td	Tetanus and Diphtheria (vaccine)
TDM	Therapeutic drug monitoring
TENS	Transcutaneous electrical nerve stimulator (electrically controlled pain relief)
TGs	Triglycerides
TIA	Transient ischaemic attack
tid or tds	three times a day
™	Signifies a trade mark for a commercial/brand name product
TNF	Tumour necrosis factor
TPA	Tissue plasminogen activator
TPN	Total Parenteral Nutrition
TRH	Thyrotrophin releasing hormone
TT	Tetanus Toxoid
TTS	Transdermal therapeutic system
UF-heparin	Unfractionated heparin
URTI	Upper respiratory tract infection

Glossary of Terms and Abbreviations

UTI	Urinary tract infection
UVA	Ultraviolet light in the A range of frequency (long-wavelength)
VIP	Vaso-active intestinal polypeptide
VLDL	Very low density lipoprotein
VRE	Vancomycin resistant enterococcae
VRSA	Vancomycin resistant <i>Staphylococcus aureus</i>
VT	Ventricular tachycardia

Useful Acronyms

BNF	British National Formulary
DGMS	Directorate General of Medical Supplies
DGPA&DC	Directorate General of Pharmaceutical Affairs and Drug Control
DRUM	Directorate of Rational Use of Medicine
FDA	Food and Drugs Administration
INRUD	International Network for the Rational Use of Drugs
MoH	Ministry of Health
ONF	Oman National Formulary
OR or RO	Omani Rials
RDU	Rational Drug Use
RUM	Rational Use of Medicines
WHO	World Health Organisation

Suspected Adverse Drug Reactions (ADRs) & Drug Related Problems Reporting Form
Drugs / Herbal Medicines / Health Products / Biological Products[illegible]

3 Suspected Reaction(s)/ Error/ Quality Problem

Description of Reaction(s) / Error(s) / Quality Problem(s):	Date of Onset:	/	/	20	
	Date Stopped:	/	/	20	
	Outcome of Reaction:				
	Recovered ☐	Recovering ☐	No Improvement ☐	Fatal ☐ Unknown ☐	
	Seriousness of reaction:				
	Patient died ☐	Life-threatening ☐	Permanently Disability ☐	Hospitalization ☐	Congenital Abnormality ☐
	Other ☐				
Additional Notes (medical history, test results, allergies, dechallenge, rechallenge, pregnancy etc. Attach papers if necessary)					

4 Reporter Details

Name:	
Specialty:	
Address:	
Tel No:	Email:
Signature:	Date:

Kindly submit the report to:

Pharmacovigilance & Drug Information Department
Directorate General of Pharmaceutical Affairs & Drug Control, Ministry of Health
P.O.BOX: 393, Muscat, P.C: 100, Sultanate of Oman
Phone: 24602177, Ext: 7688/7689/7690, Fax: 24602287; Email: mohphar@omantel.net.om

Guidelines for Reporting

This form can be used by: • Physician. • Pharmacist. • Dentist. • Nurses. • Other healthcare providers.	Use this form to report adverse drug reactions, medication errors & quality problems from: • Drugs • Herbal Medicines • Health Products • Biological Products (e.g. Vaccines)

Confidentiality: Reporter's and patient's identity are held in strict confidence by Pharmacovigilance & Drug Information Department, information provided by the reporter will be strictly protected and will not be used in any way against him / her.

Adverse Drug Reaction (ADR) is a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

Medication Error: is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient (prescribing, dispensing, storing, preparation and administration of a medicine).

Quality Problems:

- ☐ Suspected counterfeit product.
- ☐ Suspected contamination.
- ☐ Suspected pharmaceutical defects
- ☐ Product non-compliant with specification (chemical/ physical/ microbial)
- ☐ Poor packaging or labeling.
- ☐ Therapeutic failure.
- ☐ Others.....

Number of samples affected in the batch

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