CHHATTISGARH STATE
DRUG FORMULARY

2003

Government of Chhattisgarh
Department of Health and Family Welfare

Foreword

The Chhatisgarh State Drug Formulary was developed based on the model drug formulary 2002 of the World Health Organisation so as to provide the most updated and authoritative information on these drugs to all the health care providers in the state of Chhattisgarh. We have been assisted in this work by a large number of individuals and organizations whose support and encouragement we gratefully acknowledge.

This State Drug Formulary is meant to be read as complementary to two other books. One of these books is the Chhattisgarh State Essential Drug List. Such a list serves to rationalise therapy and improve effectiveness of health care only if it is accompanied by such a Stateis Drug Formulary which provides comprehensive information on all the drugs which are on the list. Health care providers who are not familiar with the problems of pharmacotherapy may be dismayed by the large list of adverse effects and precautions listed for each drug. Such caution is needed- indeed overdue. The argument that we do not encounter all these side effects in our daily practice reflects an inadequate appreciation of the problems of recognising adverse effects, of planning treatment and of the need for caution in the use of drugs. These drugs are nevertheless drugs chosen for their safety profile. The temptation to assume that a drug not on this list is safer must largely be avoided as in most cases they are likely to have more adverse effects and higher costs than these drugs.

The other book that this drug formulary must be read in conjunction with is the Standard Treatment Guidelines for Medical Officers. The STG lists an approach to diagnosis of the various symptoms in the context of medical practice as it exists in the primary and secondary health care instituions. It further gives an overview of the treatment approach in the most commonly encountered diseases. However the STG does not go into details of dosage, forrmulations, adverse effects, precautions etc which are essential for deciding on treatment. It also does not discuss the reasoning behind the choice of the appropriate drug for a given clinical context. These gaps are covered in the State Drug Formulary, which therefore also

has many aspects of standard treatment guidelines inbuilt into it. Thus these two books are best used when used together.

With the publication of these three books another important Health Sector Reform milestone under the Sector Investment Programme is achieved. The State Health Resource Center , established jointly with ActionAid India as an additional technical capacity of the Department of Health of the Government of Chhattisgarh, has been the main authors and editors of this three book set, thereby fulfilling a major commitment on its part.

The current limitation of the health system to the use of the primary health care doctor's skills to a few trivial illnesses and three or four diseases of public health importance is a serious underutilisation of existing health care resources. The publication of these books adresses this gap and represents a significant step towards achieving the state government's commitment of providing comprehensive primary health care for all it citizens.

However both SHRC and the department of health are aware that the publication of these books are necessary but not sufficient conditions for universal comprehensive primary health care. The next major step would be to introduce these three books to medical officers through a series of training workshops.

To move further on the way to "health for all" the SHRC is completing a comprehesive study that would contribute to the evolution of an action plan for workforce management, human resource development and infrastructure development. Implementin this plan would be the next step.

One step at a time.

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adapted from the
World Health Organization
Model Formulary 2002

Contents

Abbreviations

ACE angiotensin-converting enzyme
ADR adverse drug reaction
AIDS acquired immunodeficiency syndrome
AV atrioventricular
BP British Pharmacopoeia
CNS central nervous system
CSF cerebrospinal fluid
DMARD disease-modifying antirheumatic drug
ECG electrocardiogram
EEG electro-encephalogram
G6PD glucose 6-phosphate dehydrogenase
GFR glomerular filtration rate
HIV human immunodeficiency virus
HRT hormone replacement therapy
INR international normalized ratio
IP Indian Pharmacopoeia
MDI metered dose inhaler
NSAID nonsteroidal anti-inflammatory drug spp. species
SSRI selective serotonin reuptake inhibitor
USP Unites States Pharmacopeia

Itroduction : General advice to prescribers

A rational Approach to Therapeutics

Drugs need to be prescribed only when they are necessary, and in all cases the benefit to the patient of administering the medicine should be considered in relation to the risks to the patient involved. Poor prescriptions lead to ineffective and unsafe treatment, worsening or prolongation of illness, distress and harm to the patient, and higher cost to the patient and to the state.

A number of books provide undergraduates with important tools for training in the process of rational prescribing, but wide malpractice influences them into bad prescribing.

The following points kept in mind may help prescribers in using the drugs rationally.

1. Clearly define the patient's problem
2. Clearly specify the aim of therapy
3. Selecting the best therapeutic strategies

The selected strategy should be agreed in consultation with the patient; this agreement on outcome, and how it may be achieved, is termed concordance. In the modern therapeutic paradigm, a patient is a partner in the treatment and her view is important for reasonably expecting her to adhere to the therapeutic strategy.

The selected treatment can be non-pharmacological and/or pharmacological; it also needs to take into account the total cost of all therapeutic options.

(a) ***Non–pharmacological treatment***

It is very important to bear in mind that the patient does not always need a drug for treatment of the condition. Very often, health problems can be resolved by a change in life style or diet, use of physiotherapy or exercise, provision of adequate psychological support, and other non–pharmacological treatments; these have the same importance as a prescription drug, and instructions must be written, explained and monitored in the same way. A doctor's patient ear is often the best treatment!

(b) ***Pharmacological treatment- the key elements are:***

- *Selecting the correct group of drugs*
- *Selecting the drug from the chosen group*
- *Individualising drug treatment to the needs of each patient.*
- *Correct Prescription writing.*
- *Giving information, instructions and warnings*
- *Monitoring treatment*

Variation in dose response

Success in drug treatment depends not only on the correct choice of drug but on the correct dose regimen. Unfortunately, drug treatment frequently fails because the dose is too small or produces adverse effects because it is too large. This is because most texts, teachers and other drug information sources continue to recommend standard doses.

The concept of a standard or 'average' adult dose for every medicine is firmly rooted in the mind of most prescribers. After the initial 'dose ranging' studies on new drugs, manufacturers recommend a dosage that appears to produce the desired response in the majority of subjects. These studies are usually done on healthy, young male Caucasian volunteers, rather than on older men and women with illnesses and of different ethnic and environmental backgrounds. The use of standard doses in

the marketing literature suggest that standard responses are the rule, but in reality there is considerable variation in drug response. As a result many prescribed doses are far too low or too high, leading to treatment failure or toxicity. There are many reasons for this variation which include adherence (see below), drug formulation, body weight and age, composition, variation in absorption, distribution, metabolism and excretion, variation in pharmacodynamics, disease variables, genetic and environmental variables.

Adherence (compliance) with drug treatment

It is often assumed that once the appropriate drug is chosen, the prescription correctly written and the medication correctly dispensed, that it will be taken correctly and treatment will be successful. Unfortunately this is very often not the case, and physicians overlook one of the most important reasons for treatment failure — poor adherence (compliance) with the treatment plan.

There are sometimes valid reasons for poor adherence — the drug may be poorly tolerated, may cause obvious adverse effects or may be prescribed in a toxic dose. Failure to adhere with such a prescription has been described as 'intelligent noncompliance'. Bad prescribing or a dispensing error may also create a problem, which patients may have neither the insight nor the courage to question. Even with rational prescribing, failure to adhere to treatment is common. Factors may be related to the patient, the disease, the doctor, the prescription, the pharmacist or the health system and can often be avoided.

Patient reasons

In general, women tend to be more adherent than men, younger patients and the very elderly are less adherent, and people living alone are less adherent than those with partners or spouses. Specific education interventions have been shown to improve adherence. Patient failings such as illiteracy, poor eyesight or cultural attitudes (for example preference for traditional or alternative medicines and suspicion of modern medicine) may be very important in some individuals or societies. Such attitudes need to be discussed and brought in to the open.

Disease reasons

Conditions with a known worse prognosis (for example cancer) or painful conditions (for example rheumatoid arthritis) elicit better adherence rates than asymptomatic 'perceived as benign' conditions such as hypertension. Doctors need to realize that in most settings less than half of patients started for the first time on antihypertensive drug treatment are still taking it a year later. Similarly, in epilepsy, where events may occur at long intervals, adherence is notoriously unsatisfactory.

Doctor reasons

Doctors may cause poor adherence in many ways by failing to inspire confidence in the treatment offered, by giving too little or no explanation, by thoughtlessly prescribing too many medications, by making errors in prescribing, or by their overall attitude to the patient.

The doctor-patient interaction

There is considerable evidence that this is crucial to concordance. 'Satisfaction with the interview' has been consistently shown to be one of the highest predictors of good adherence. Patients are often well informed and expect a greater say in their health care. If they are in doubt or dissatisfied there are more options, including 'alternative medicines'. There is no doubt that the drug 'doctor' has a powerful effect to encourage confidence and perhaps contribute directly to the healing process.

Prescription reasons

Many aspects of the prescription may lead to non-adherence. It may be illegible or inaccurate; it may get lost; it may not be refilled as intended or instructed for a chronic disease. And it may be too complex; it has been shown that the greater the number of medications the poorer the adherence, while multiple doses also decrease adherence if more than two doses per day are given. A general guideline to follow is not more than two drugs, not more than twice a day! Side effects like drowsiness, impotence or nausea negatively influence adherence and patients may not admit to the problem.

Pharmacist reasons

Pharmacist information and advice can be a valuable source of information and reinforcement, as long as it tallies with the doctor's advice. In our setting pharmacists may play no role except passively dispensing the drug, which is really underutilizing their skills.

The health care system

The health care system may be the biggest hindrance to adherence. Long waiting times, uncaring staff, uncomfortable environment, exhausted drug supplies and so on, are all common problems in developing countries, and have a major impact on adherence. An important problem is the distance and accessibility of the clinic from the patient. Some studies have confirmed the obvious, that patients furthest from the clinic are least likely to adhere to treatment in the long term.

If there is poor patient compliance here are some tips on what you can do :

- Review the prescription to be sure it is correct.
- Limit the number of drugs and number of doses to the minimum essential.
- Spend time explaining the problem and the reason for the drug.
- Establish a good relationship with the patient, rather than a hurried or brusque manner with little eye contact.
- Explore problems, for example reading the label, knowing which drug is to be taken when etc. Asking the patient to tell it back to you showing each drug is one way.
- Insist that patients learn the names of their tablets, and review their regimen with them. Write notes for them.
- Insist that patients bring their empty medicine strips to the clinic 'for checking', so that tablet counts can be made unobtrusively.
- Communicate with the pharmacist, the nurse, the local health workers to develop teamwork and collaboration in helping and advising the patient.
- Involve the partner or another family member,
- Listen to the patient. Try to help. Do not assume that the negligence.

Adverse effects and interactions

Adverse drug reactions

An adverse drug reaction (ADR) may be defined as 'any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis, or therapy.

ADRs are therefore unwanted or unintended effects of a medicine, including idiosyncratic effects, which occur during its proper use. They differ from accidental or deliberate excessive dosage or drug maladministration.

ADRs may be directly linked to the properties of the drug in use, the so-called 'A' type reactions. An example is hypoglycaemia induced by an antidiabetic drug. ADRs may also be unrelated to the known pharmacology of the drug, the 'B' type reactions including allergic effects, for example anaphylaxis with **penicillins**.

Thalidomide marked the first recognized public health disaster related to the introduction of a new drug. It is now recognized that clinical trials, however thorough, cannot be guaranteed to detect all adverse effects likely to be caused by a drug. Health workers are thus encouraged to record and report to their national pharmacovigilance centre any unexpected adverse effects with any drug to achieve faster recognition of serious related problems. For example, from reports received in one country recently, a relationship was established between. **thioacetazone** and Stevens-Johnson syndrome when the drug was used in HIV infection, leading to the withdrawal of the drug in that country.

Major factors predisposing to adverse effects

It is well known that different patients often respond differently to a given treatment regimen.

EXTREMES OF AGE. The very old and the very young are more susceptible to ADRs.

INTERCURRENT ILLNESS. If besides the condition being treated the patient also suffers from another disease, such as kidney, liver or heart disease, special precautions are necessary to prevent ADRs. Remember also that, as well as the above factors, the genetic make-up of the individual patient may predispose to ADRs.

DRUG INTERACTIONS. (see also Appendix 1)

Drug-drug interactions are some of the commonest causes of adverse effects. When two drugs are administered to a patient, they may either act independently of each other, or interact with each other. Interaction may increase or decrease the effects of the drugs concerned and may cause unexpected toxicity. Remember that interactions which modify the effects of a drug may involve non-prescription drugs, non-medicinal chemical agents, and social drugs such as **alcohol**, **marijuana**, **and traditional remedies**, as well as certain types of food. The physiological changes in individual patients, caused by such factors as age and gender, also influence the predisposition to ADRs resulting from drug interactions.

Incompatibilities between drugs and IV fluids

Drugs should not be added to blood, amino acid solutions or fat emulsions. Certain drugs, when added to IV fluids, may be inactivated by pH changes, by precipitation or by chemical reaction. **Benzylpenicillin** and **ampicillin** lose potency after 6–8 hours if added to dextrose solutions, due to the acidity of these solutions. Some drugs bind to plastic containers and tubing, for example **diazepam** and **insulin**. **Aminoglycosides** are incompatible with **penicillins** and **heparin**. **Hydrocortisone** is incompatible with **heparin**, **tetracycline**, and **chloramphenicol**.

Adverse effects caused by traditional medicines

Patients who have been or are taking traditional herbal remedies may develop ADRs. It is not always easy to identify the responsible plant or plant constituent. Refer to the drug and toxicology information service if available and/or to suitable literature.

The effect of food on drug absorption

Food delays gastric emptying and reduces the rate of absorption of many drugs; the total amount of drug absorbed may or may not be reduced. However, some drugs are preferably taken with food, either to increase absorption or to decrease the irritant effect on the stomach.

Prescription writing

A prescription is an instruction from a prescriber to a dispenser. The prescriber is not always a doctor but can also be a paramedical worker, such as a medical assistant, a midwife or a nurse. The dispenser is not always a pharmacist, but can be a pharmacy technician, an assistant or a nurse. Every country has its own standards for the minimum information required for a prescription, and its own laws and regulations to define which drugs require a prescription and who is entitled to write it. The following guidelines will help to ensure that prescriptions are correctly interpreted and leave no doubt about the intention of the prescriber. The guidelines are relevant for primary care prescribing; they may, however, be adapted for use in hospitals or other specialist units.

Prescription form

The most important requirement is that the prescription be clear.

It should be legible and indicate precisely what should be given.

The local language is preferred.

The following details should be shown on the form.

The prescriber's name, address and telephone number. This will allow either the patient or the dispenser to contact the prescriber for any clarification or potential problem with the prescription.

Date of the prescription.: Pharmacists should not dispense drugs on prescriptions older than 6 months.

Name, form and strength of the drug. The International Nonproprietary Name of the drug should always be used. If there is a specific reason to prescribe a special brand, the trade name can be added. The pharmaceutical form (for example 'tablet', 'oral solution', 'eye ointment') should also be stated.

The strength of the drug should be stated in standard units using abbreviations that are consistent with the System Internationale (SI). 'Microgram' and 'nanogram' should not, however, be abbreviated.

Also, 'units' should not be abbreviated. Avoid decimals whenever possible. If unavoidable, a zero should be written in front of the decimal point.

Specific areas for filling in details about the patient including name, address and age.

Directions

Directions specifying the route, dose and frequency should be clear and explicit; use of phrases such as 'take as directed' or 'take as before' should be **avoided**.

For preparations which are to be taken on an 'as required' basis, the minimum dose interval should be stated together with, where relevant, the maximum daily dose. It is good practice to qualify such prescriptions with the purpose of the medication (for example 'every 6 hours as required for pain', 'at night as required to sleep').

It is good practice to explain the directions to the patient; these directions will then be reinforced by the label on the medicinal product and possibly by appropriate counselling by the dispenser. It may be worthwhile giving a written note for complicated regimens although it must be borne in mind that the patient may lose the separate note.

Quantity to be dispensed

The quantity of the medicinal product to be supplied should be stated such that it is not confused with either the strength of the product or the dosage directions.

Alternatively, the length of the treatment course may be stated (for example 'for 5 days').

Wherever possible, the quantity should be adjusted to match the pack sizes available.

For liquid preparations, the quantity should be stated in millilitres (abbreviated as 'ml') or litres (preferably not abbreviated since the letter 'l' could be confused with the figure '1').

Narcotics and controlled substances

The prescribing of a medicinal product that is liable to abuse requires special attention and may be subject to specific statutory requirements. Practitioners may need to be authorized to prescribe controlled substances; in such cases it might be necessary to indicate details of the authority on the prescription. In particular, the strength, directions and the quantity of the controlled substance to be dispensed should be stated clearly, with all quantities written in words as well as in figures to prevent alteration. Other details such as patient particulars and date should also be filled in carefully to avoid alteration.

Section 1: Drugs used inAnaesthesia

To produce a state of prolonged full surgical anaesthesia reliably and safely, a variety of drugs is needed. Special precautions and close monitoring of the patient are required.

These drugs may be fatal if used inappro priately and should be used by non–specialized personnel only as a last resort.

Irrespective of whether a general or conduction (regional or local) anaesthetic technique is used, it is essential that facilities for intubation and mechanically assisted ventilation are available.

A full preoperative assessment is required including, if necessary, appropriate fluid replacement. Anaesthesia may be induced with an intravenous barbiturate, parenteral ketamine, or a volatile agent. Maintenance is with inhalational agents often supplemented by other drugs given intravenously. Specific drugs may be used to produce muscle relaxation. Various drugs may be needed to modify normal physiological functions or otherwise to maintain the patient in a satisfactory condition during surgery.

1.1 General anaesthetics and oxygen

1.1.1 Intravenous agents

Thiopentone sodium

Injection, powder for solution, thiopentone sodium, 0.5 g and 1 g ampoules

Uses: induction of anaesthesia prior to administration of inhalational anaesthetic; anaesthesia of short duration.

Contraindications: inability to maintain airway; hypersensitivity to barbiturates; cardiovascular disease; dyspnoea or obstructive respiratory disease; porphyria.

Precautions: local extravasation can result in extensive tissue necrosis and sloughing; intra-arterial injection causes intense pain and may result in arteriospasm; hepatic disease; pregnancy (Appendix 2);

Interactions: Appendix 1

SKILLED TASKS. Warn patient not to perform skilled tasks, for example operating machinery, driving, for 24 hours and also to avoid alcohol for 24 hours.

Dosage:

Induction, *by intravenous injection* over 10–15 seconds, ADULT 100–150 mg, followed by a further quantity if necessary according to response after 30–60 seconds; CHILD 2–7 mg/kg

RECONSTITUTION. Solutions containing 25 mg/ml should be freshly prepared by mixing 20 ml of water for injections with the contents of the 0.5-g vial, 40 ml or with the 1-g vial. Any solution made up over 24 hours previously or in which cloudiness, precipitation or crystallization is evident should be discarded.

Adverse effects: rapid injection may result in severe hypotension and hiccup; cough, laryngeal spasm, allergic reactions.

Ketamine

Injection, ketamine (as hydrochloride) 10 mg/ml, 50 mg/ml, 2 or 10-ml ampoule or vial.

Uses: induction and maintenance of anaesthesia; analgesia for painful procedures of short duration.

Contraindications: thyrotoxicosis; hypertension (including pre-eclampsia); history of cerebrovascular accident, cerebral trauma, intracerebral mass or haemorrhage or other cause of raised intracranial pressure; eye injury and increased intraocular pressure; psychiatric disorders, particularly hallucinations .

Precautions: supplementary analgesia often required in surgical procedures involving visceral pain pathways (morphine may be used but addition of nitrous oxide will often suffice); during recovery, patient must remain undisturbed but under observation; pregnancy (Appendix 2);

Interactions: Appendix 1

SKILLED TASKS. Warn patient not to perform skilled tasks, for example operating machinery or driving, for 24 hours and also to avoid alcohol for 24 hours.

Dosage:

Induction, *by intramuscular injection,* ADULT and CHILD 6–8 mg/kg (duration of anaesthesia up to 25 minutes).

By intravenous injection over at least 1 minute, ADULT and CHILD 1–4.5 mg/kg (duration of anaesthesia 5–10 minutes after 2 mg/kg dose)

By intravenous infusion of a solution containing 1 mg/ml, ADULT and CHILD total induction dose 0.5–2 mg/kg; maintenance 10–45 micrograms/kg/minute, rate adjusted according to response Analgesia, *by intramuscular injection,* ADULT and CHILD initially 4 mg/kg.

DILUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: emergence reactions during recovery possibly accompanied by irrational behaviour (effects rarely persist for more than few hours but recurrences can occur at any time within 24 hours); transient elevation of pulse rate and blood pressure common, arrhythmias have occurred; hypotension and bradycardia occasionally reported.

1.1.2 Volatile inhalational agents

Ether, anaesthetic

Volatile liquid

Uses: induction and maintenance of anaesthesia (administered from many types of vaporizers).

Contraindications: severe liver disease.

Precautions: risk of potentially fatal convulsions in febrile patients; pregnancy (Appendix 2);

Interactions: Appendix 1

FIRE HAZARD. Diathermy must not be used when ether/oxygen mixtures in use and operating theatre and its equipment should be designed to minimize risk of static discharge, particularly in hot, dry climates.

Dosage:

Induction, ADULT and CHILD, up to 15% in inspired gases Maintenance of light anaesthesia, 3–5% in air (with or without muscle relaxants); up to 10% for deep anaesthesia.

Adverse effects: transient postoperative effects include impairment of liver function and leukocytosis; nausea and vomiting; capillary bleeding.

Halothane

Volatile liquid

Uses: induction and maintenance of anaesthesia

Contraindications: history of unexplained jaundice or pyrexia following previous exposure to halothane; family history of malignant hyperthermia; raised cerebrospinal fluid pressure; porphyria.

Precautions: anaesthetic history should be carefully taken to determine previous exposure and previous reactions to halothane (at least 3 months should be allowed to elapse between each re-exposure); pregnancy and breastfeeding.

(Appendices 2 and 3); **interactions:** Appendix-1

Dosage:

Induction, using gas flow containing at least oxygen 30%, gradually increase inspired gas concentration to 2–3% (ADULT) or 1.5–2% (CHILD) Maintenance, ADULT and CHILD 0.5–1.5%

Adverse effects: arrhythmias; bradycardia; respiratory depression; hepatic damage.

1.1.3 Inhalational gases

Identification of cylinders for inhalation gases. An ISO standard (International Standard 32, Gas cylinders for medical use, 1977) requires that cylinders containing nitrous oxide should bear the name of the contents in legible and permanent characters and, preferably, also the chemical symbol N_2O. The neck, from the valve to the shoulder, should be coloured blue. Cylinders containing oxygen intended for medical use should bear the name of the contents in legible and permanent characters and, preferably, also the chemical symbol O2. The neck, from the valve to the shoulder, should be coloured white. Cylinders containing nitrous oxide and oxygen mixtures should be similarly labelled, and the neck coloured white and blue.

Nitrous oxide

Inhalation gas

Uses: maintenance of anaesthesia in combination with other anaesthetic agents (halothane, ether, or ketamine) and muscle relaxants; analgesia for obstetric practice, for emergency management of injuries, during postoperative physiotherapy and for refractory pain in terminal illness.

Contraindications: demonstrable collection of air in pleural, pericardial or peritoneal space; intestinal obstruction; occlusion of middle ear; arterial air embolism; decompression sickness; chronic obstructive airway disease, emphysema

Precautions: minimize exposure of staff; pregnancy (Appendix 2);

Interactions: Appendix 1

Dosage:

Anaesthesia, ADULT and CHILD 70% nitrous oxide mixed with at least 30% oxygen .

Analgesia, 50% nitrous oxide mixed with 50% oxygen.

Adverse effects: nausea and vomiting; after prolonged administration megaloblastic anaemia, depressed white cell formation; peripheral neuropathy.

Oxygen

Inhalation gas

Uses: to maintain an adequate oxygen tension in inhalational anaesthesia.

FIRE HAZARD. Avoid use of cautery when oxygen is used with ether; reducing valves on oxygen cylinders **must not** be greased (risk of explosion)

Precautions: interactions: Appendix 1

Dosage:

Concentration of oxygen in inspired anaesthetic gases should never be less than 21%.

Adverse effects: concentrations greater than 80% have a toxic effect on the lungs leading to pulmonary congestion, exudation and atelectasis.

1.2 Local anaesthetics

Drugs used for conduction anaesthesia (also termed local or regional anaesthesia) act by causing a reversible block to conduction along nerve fibres. Local anaesthetics are used very widely in dental practice, for brief and superficial interventions, for obstetric procedures, and for specialized techniques of regional anaesthesia calling for highly developed skills. Where patient cooperation is required the patient must be psychologically prepared to accept the proposed procedure. Facilities and equipment for resuscitation should be readily available at all times. Care must always be taken to avoid inadvertent intravascular injection.

LOCAL INFILTRATION. Many simple surgical procedures that neither involve the body cavities nor require muscle relaxation can be performed under local infiltration anaesthesia. Lowersegment caesarean section can also be performed under local infiltration anaesthesia. The local anaesthetic drug of choice is **lidocaine** 0.5% with or without epinephrine. No more than 4 mg/kg of plain lidocaine or 7 mg/kg of lidocaine with epinephrine should be administered on any one occasion. The addition of **epinephrine** (adrenaline) diminishes local blood flow, slows the rate of absorption of the local anaesthetic, and prolongs its effect. Care is necessary when using epinephrine for this purpose since, in excess, it may produce ischaemic necrosis. It should **not** be added to injections used in digits or appendages.

SURFACE ANAESTHESIA. Topical preparations of **lidocaine** are available and topical eye drop solutions of **tetracaine** (section 21.3) are used for local anaesthesia of the cornea and conjunctiva.

REGIONAL BLOCK. A regional nerve block can provide safe and effective anaesthesia but its execution requires considerable training and practice. Nevertheless, where the necessary skills are available, techniques such as axillary or ankle blocks can be invaluable. Either **lidocaine** 1% or **bupivacaine** 0.5% is suitable. Bupivacaine has the advantage of a longer duration of action.

SPINAL ANAESTHESIA. This is one of the most useful of all anaesthetic techniques and can be used widely for surgery of the abdomen and the lower limbs. It is a major procedure requiring considerable training and practice. Either **lidocaine** 5% in glucose or **bupivacaine** 0.5% in glucose can be used but the latter is often chosen because of its longer duration of action.

Bupivacaine hydrochloride

Bupivacaine is a representative local anaesthetic. Various drugs can serve as alternatives.

Injection, bupivacaine hydrochloride 5 mg/ml (0.5%), 10-ml ampoule; 5 mg/ml (0.5%) with glucose 75 mg/ml (7.5%), 4-ml ampoule.

Uses: infiltration anaesthesia; peripheral and sympathetic nerve block; spinal anaesthesia; postoperative pain relief.

Contraindications: adjacent skin infection; concomitant anticoagulant therapy; severe anaemia or heart disease; spinal or epidural anaesthesia in dehydrated or hypovolaemic patient.

Precautions: respiratory impairment; hepatic impairment; epilepsy; porphyria; myasthenia gravis; pregnancy and breastfeeding (Appendices 2 and 3);

Interactions: Appendix 1

Dosage:

Maximum cumulative safe dose for adults and children of a 0.5% solution of bupivacaine is 11.25 mg/kg Local infiltration, using 0.5% solution, ADULT up to 150 mg (up to 30 ml)

Peripheral nerve block, using 0.5% solution, ADULT up to 150 mg (up to 30 ml) .

Dental anaesthesia, using 0.5% solution, ADULT 9–18 mg (1.8–3.6 ml) spinal anaes thesia, using 0.75% solution (with glucose 7.5%), ADULT 7.5–11.25 mg (1–1.5 ml).

NOTE. Use lower doses for debilitated, elderly, epileptic, or acutely ill patients 0.75% **contraindicated** for epidural use in obstetrics.

Do not use solutions containing preservatives for spinal, epidural, caudal or intravenous regional anaesthesia.

Adverse effects: with excessive dosage or following intravascular injection, light headedness, dizziness, blurred vision, restlessness, tremors and, occasionally, convulsions rapidly followed by drowsiness, unconsciousness and respiratory failure; cardiovascular toxity includes hypotension, heart block and cardiac arrest; hypersensitivity and allergic reactions also occur; epidural anaesthesia occasionally complicated by urinary retention, faecal incontinence, headache, backache or loss of perineal sensation; transient paraesthesia and paraplegia very rare.

Lidocaine hydrochloride

Lidocaine is a representative local anaesthetic. Various drugs can serve as alternatives.

Injection, lidocaine 10 mg/ml (1%), 30-ml ampoule; 50 mg/ml (5%), 2-ml ampoule to be mixed with glucose 75 mg/ml (7.5%).

Injection with epinephrine, lidocaine hydrochloride 10 mg/ml (1%) with epinephrine 5 micrograms/ml (1 in 200 000), 30-ml ampoule

Injection with epinephrine (dental use), lidocaine hydrochloride 20 mg/ml (2%) with epinephrine 12.5 micrograms/ml (1 in 80 000), 2.2-ml dental cartridge.

Topical gel **or** ***solution***, lidocaine hydrochloride 20–40 mg/ml (2–4%).

Uses: surface anaesthesia of mucous membranes; infiltration anaesthesia; peripheral and sympathetic nerve block; dental anaesthesia; spinal anaesthesia; intravenous regional anaesthesia; arrhythmias (section 12.2)

Contraindications: adjacent skin infection; concomitant anticoagulant therapy; severe anaemia or heart disease; spinal or epidural anaesthesia in dehydrated or hypovolaemic patient.

Precautions: respiratory impairment; hepatic impairment ; epilepsy; porphyria; myasthenia gravis; pregnancy (Appendix 2); breastfeeding (Appendix 3);

Interactions: Appendix 1

Dosage:

Maximum safe doses of lidocaine for adults and children are: 1% lidocaine 4 mg/kg; 1% lidocaine +epinephrine 5 micrograms/ml (1 in 200 000) 7 mg/kg.

Plain Solutions

Local infiltration and peripheral nerve block, using 1% solution, ADULT up to 250 mg (up to 25 ml)

Surface anaesthesia of pharynx, larynx, trachea, using 4% solution, ADULT 40–200 mg (1–5 ml)

Surface anaesthesia of urethra, using 4% solution, ADULT 400 mg (10 ml)

Spinal anaesthesia, using 5% solution (with glucose 7.5%), ADULT 50–75 mg (1–1.5 ml)

Solutions containing epinephrine

Local infiltration and peripheral nerve block, using 0.5% solution with epinephrine, ADULT up to 400 mg (up to 80 ml) Local infiltration and peripheral nerve block, using 1% solution with epinephrine, ADULT up to 400 mg (up to 40 ml) Dental anaesthesia, using 2% solution with epinephrine, ADULT 20–100 mg (1–5 ml)

NOTE. Use lower doses for debilitated, elderly, epileptic, or acutely ill patients.

Do not use solutions containing preservatives for spinal, epidural, caudal or intravenous regional anaesthesia.

Adverse effects: with excessive dosage or following intravascular injection, light headedness, dizziness, blurred vision, restlessness, tremors and, occasionally, convulsions rapidly followed by drowsiness, unconsciousness and respiratory failure; cardiovascular toxicity includes hypotension, heart block and cardiac arrest; hypersensitivity and allergic reactions also occur; epidural anaesthesia occasionally complicated by urinary retention, faecal incontinence, headache, backache or loss of perineal sensation; transient paraesthesia and paraplegia very rare.

1.3 Preoperative medication and sedation

Pre-anaesthetic medication is often advisable prior to both conduction and general anaesthetic procedures. Sedatives improve the course of subsequent anaesthesia in apprehensive patients. Diazepam, promethazine and chloral are effective. **Diazepam** can be administered by mouth or by rectum. **Promethazine**, which has antihistaminic and antiemetic properties as well as a sedative effect, is of particular value in children, as is **chloral hydrate**.

Potent analgesics such as **morphine** or **pethidine** (see section 1.5 and 2.2) should be administered preoperatively to patients in severe pain or to provide analgesia during and after surgery. Sedatives should then be withheld since they may cause restlessness or confusion. Anticholinergic (more

correctly antimuscarinic) drugs such as **atropine** are additionally used prior to general anaesthetic procedures. They inhibit excessive bronchial and salivary secretions induced, in particular, by ether and ketamine. Intramuscular administration is most effective, but oral administration is more convenient in children. Lower doses should be used in cardiovascular disease or hyperthyroidism.

Atropine sulfate

Tablets, atropine sulfate 1 mg
Injection, atropine sulfate 0.6 mg / ml, 1-ml ampoule
Uses: to inhibit salivary secretions; to inhibit arrhythmias resulting from excessive vagal stimulation; to block the parasympathomimetic effects of anticholinesterases such as neostigmine; organophosphate poisoning (section 4.2.3); antispasmodic (section 17.5); mydriasis and cycloplegia (section 21.5)
Contraindications: angle-closure glaucoma; myasthenia gravis; paralytic ileus, pyloric stenosis; prostatic enlargement.
Precautions: Down syndrome, children, elderly; ulcerative colitis, diarrhoea; hyperthyroidism; heart failure, hypertension; pregnancy and breastfeeding (Appendices 2 and 3);
Interactions: Appendix 1
Dosage:
Premedication, *by mouth* 2 hours before induction, CHILD 20 micrograms/kg; *by intramuscular injection* 30–60 minutes before induction, ADULT and CHILD 20 micrograms/kg; *by intravenous injection* immediately before induction, ADULT up to max. 500 micrograms.
Inhibition of bradycardia, *by intravenous injection,* ADULT 0.4–1 mg, CHILD 10–30 micrograms/kg 24
Reversal of neuromuscular block, *by intravenous injection* 2–3 minutes before anticholinesterase, ADULT 0.6–1.2 mg, CHILD 20 micrograms/kg
Adverse effects: dry mouth; blurred vision, photophobia; flushing and dryness of skin, rash; difficulty in micturition; less commonly arrhythmias, tachycardia, palpitations; confusion (particularly in elderly); heat prostration and convulsions, especially in febrile children.

Chloral hydrate

Oral solution (Elixir), chloral hydrate 200 mg/5 ml.
Uses: preoperative sedation
Contraindications: hepatic or renal impairment; cardiac disease .
Precautions: respiratory disease; pregnancy and breastfeeding (Appendices 2 and 3);
Interactions: Appendix 1

SKILLED TASKS. Warn patient not to perform skilled tasks, for example operating machinery, driving, for 24 hours.
Dosage:
By mouth 30 minutes before surgery, ADULT 30 mg/kg (maximum 2 g); CHILD 30 mg/kg (maximum 1 g).
Adverse effects: gastric irritation; rash.

Diazepam

Drug subject to international control under the Convention on Psychotropic Substances (1971)

Diazepam is a representative benzodiazepine. Various drugs can serve as alternatives.
Tablets, diazepam 2 mg, 5 mg, 10 mg *Susp.* 2 mg/5 ml
Suppository 5 mg
Injection, diazepam 5 mg/ml, 2-ml ampoule.
Uses: premedication before major or minor surgery; sedation with amnesia for endoscopic procedures and surgery under local anaesthesia; in combination with pethidine, when anaesthetic not available, for emergency reduction of fractures; epilepsy (section 5.1); anxiety disorders (section 24.3).
Contraindications: central nervous system depression or coma; shock; respiratory depression; acute alcohol intoxication.
Precautions: elderly or debilitated patients (adverse effects more common in these groups); hepatic impairment or renal failure; chronic pulmonary insufficiency or sleep apnoea; pregnancy and breastfeeding.(Appendices 2 and 3);
Interactions: Appendix 1
SKILLED TASKS. Warn patient not to perform skilled tasks, for example operating machinery, driving, for 24 hours.
Dosage:
Premedication, *by mouth* 2 hours before surgery, ADULT and CHILD over 12 years, 5–10 mg Sedation, *by slow intravenous injection* immediately before procedure, ADULT and CHILD over 12 years, 0.2 mg/kg
ADMINISTRATION. Absorption following intramuscular injection slow and erratic; route should only be used if oral or intravenous administration not possible Slow intravenous injection into large vein reduces risk of thrombophlebitis Resuscitation equipment must be available.
Adverse effects: central nervous system effects common and include drowsiness, sedation, confusion, vertigo, and ataxia; hypotension, bradycardia, or cardiac arrest, particularly in elderly or severely ill patients; also paradoxical reactions, including irritability, excitability, hallucinations, sleep disturbances.

Promethazine hydrochloride

Promethazine is a representative sedative antihistamine. Various drugs can serve as alternatives.

Tablets, promethazine hydrochloride 10 mg, 25 mg *Oral solution* (Elixir), promethazine hydrochloride 5 mg/5 ml.

Injection, promethazine hydrochloride 25 mg/ml, 2-ml ampoule.

Uses: premedication prior to surgery; antiemetic (section 17.2).

Contraindications: child u nder 1 year; impaired consciousness due to cerebral depressants or of other origin; poryphyria.

Precautions: prostatic hypertrophy, urinary retention; glaucoma; hepatic impairment; pregnancy and breastfeeding (Appendices 2 and 3);

Interactions: Appendix 1

SKILLED TASKS. Warn patient not to perform skilled tasks, for example operating machinery, driving, for 24 hours.

Dosage:

By mouth 1 hour before surgery, CHILD over 1 year 0.5–1 mg/kg.

By deep intramuscular injection 1 hour before surgery, ADULT 25 mg

Adverse effects: drowsiness (rarely paradoxical stimulation in children); headache; anticholinergic effects such as dry mouth, blurred vision, urinary retention.

1.4 Muscle relaxants and cholinesterase inhibitors

Reserved for use in higher referral centres.

1.5 Analgesics and opioid antagonists

Opioid analgesics, **morphine** and **pethidine,** may be used to supplement general anaesthesia, usually in combination with nitrous oxide–oxy gen and a muscle relaxant. Repeated doses of intra-operative analgesics should be given with care, since respiratory depression may persist into the postoperative period. The specific opioid antagonist **naloxone** will immediately reverse this respiratory depression but the dose may need to be repeated. Other resuscitative measures must also be available. It is important to remember that naloxone will also antagonize the *analgesic* effect of opioids.

For further information on opioid analgesics, see section 2.2.

Morphine

Drug subject to international control under the Single Convention on Narcotic Drugs (1961)

Morphine is a representative opioid analgesic. Various drugs can serve as alternatives.

Injection, morphine (as hydrochloride or sulfate) 10 mg/ml, 1-ml ampoule.

Uses: adjunct during major surgery; postoperative analgesia; pain, myocardial infarction, acute pulmonary oedema (section 2.2)

Contraindications: acute respiratory depression; increased intracranial pressure, head injury or brain tumour; severe hepatic impairment; adrenocortical insufficiency; hypothyroidism; convulsive disorders; acute alcoholism, delirium tremens; diverticulitis and other spastic conditions of colon; recent surgery on biliary tract; diarrhoea due to toxins.

Precautions: asthma, emphysema, or heart failure secondary to chronic lung disease; ability to maintain airway; if used in biliary colic, antispasmodic needed; renal impairment; pregnancy (Appendix 2); breastfeeding (Appendix 3); **overdosage:** see section 4.2.2;

Interactions: Appendix 1

Dosage:

Premedication, *by subcutaneous or intramuscular injection* 1 hour before surgery, ADULT 150–200 micrograms/kg; *by. **intramuscular injection*** 1 hour before surgery, CHILD 50–100 micrograms/kg.

Intra-operative analgesia, *by intravenous injection,* ADULT and CHILD 100 micrograms/kg, repeated every 40–60 minutes as required.

Postoperative analgesia, *by intramuscular injection,* ADULT 150–300 micrograms/kg every 4 hours, CHILD 100–200 micrograms/kg; or *by intravenous infusion* ADULT 8–10 mg over 30 minutes, then 2–2.5 mg/hour.

Adverse effects: respiratory depression; anorexia, nausea, vomiting, constipation; euphoria, dizziness, drowsiness, confusion, headache; dry mouth; spasm of urinary and biliary tract; circulatory depression, hypotension, bradycardia, palpitations; miosis; allergic reactions; physical dependence.

Pethidine hydrochloride

Drug subject to international control under the Single Convention on Narcotic Drugs (1961)

Pethidine is a representative opioid analgesic. Various drugs can serve as alternatives.

Injection, pethidine hydrochloride 50 mg/ml,1-ml ampoule.

Uses: preoperative management of musculoskeletal and visceral pain; adjunct during major surgery; postoperative and obstetric analgesia; in combination with diazepam, and in the absence of other agents, for reduction of fractures and other minor interventions; pain (section 2.2).

Contraindications: increased intracranial pressure, head injury or brain tumour; severe hepatic impairment; adrenocortical insufficiency, hypothyroidism; acute respiratory depression;

convulsive disorders; acute alcoholism, delirium tremens; diarrhoea due to toxins.

Precautions: asthma, emphysema, or heart failure secondary to chronic lung disease; ability to maintain airway; renal impairment ; hepatic impairment ; pregnancy (Appendix 2); breastfeeding (Appendix 3);

Overdosage: see section 4.2.2;

Interactions: Appendix 1

Dosage:

Premedication, *by subcutaneous or intramuscular injection* 1 hour before surgery, ADULT 50–100 mg; *by intramuscular injection* 1 hour before surgery, CHILD over 1 year 1 mg/kg Intraoperative analgesia, *by slow intravenous injection,* ADULT and CHILD over 1 year 250 micrograms/kg, repeated every 40–60 minutes as required.

Postoperative analgesia, *by subcutaneous injection,* CHILD 1– 2 mg/kg; *or by intramuscular injection,* ADULT 50–150 mg every 4 hours, CHILD over 1 year 1–2 mg/kg; *or by intravenous infusion,* ADULT 15–35 mg/hour.

Obstetric analgesia, *by subcutaneous or intramuscular injection.*

ADULT 1 mg/kg, repeated as required (last dose preferably 1–3 hours before delivery to reduce neonatal depression).

NOTE. Give intravenous injections slowly over several minutes with patient recumbent to reduce hypotension and respiratory depression.

ADMINISTRATION. According to manufactu rer's directions.

Adverse effects: respiratory depression; nausea, vomiting; dizziness, drowsiness and confusion; circulatory depression, hypotension, bradycardia and palpitations; convulsions; allergic reactions; physical dependence.

Naloxone hydrochloride

Injection, naxolone hydrochloride 400 micrograms/ml, 1-ml ampoule.

Uses: to counteract respiratory depression induced by opioids during anaesthesia; opioid overdosage (see also section 4.2.2).

Precautions: dependence on opioids; cardio vascular disease.

Dosage:

Opioid-induced respiratory depression, *by intravenous injection.*

ADULT 100–200 micrograms, repeated every 2–3 minutes to obtain required response; CHILD initially 10 micrograms/kg, if no response followed by 100 micrograms/kg.

Opioid-induced respiratory depression at birth, *by subcutaneous, intramuscular, or intravenous injection,* NEONATE 10 micrograms/kg immediately after delivery.

Opioid overdosage, *by intravenous injection,* ADULT 0.4–2 mg, repeated every 2–3 minutes according to response to maximum total dose of 10 mg.

Adverse effects: nausea and vomiting; hypertension and hypotension reported; left ventricular failure; pulmonary oedema; seizures; arrhythmias such as ventricular tachycardia or fibrillation, particularly in pre-existing cardiac disease.

1.6 Blood substitutes and solutions for correcting fluid imbalance

Fluid requirements must be assessed before, during and after major surgery. Replacement fluids should correspond as nearly as possible in volume and composition to those lost. Blood transfusion is essential to restore oxygen carrying capacity when more than 15% of the circulating blood volume is lost but should be avoided whenever screening for human immunodeficiency viruses and hepatitis B virus is impracticable. Isotonic sodium chloride solution may be used for short-term volume replacement. Plasma expanders such as dextran 70 or polygeline may be useful. Provided renal function is maintained, fluid is most simply replaced by intravenous administration of **sodium chloride solution** (sodium chloride 9 mg/ml, 0.9%) or the more physiologically appropriate.

compound solution of sodium lactate. In emergency cases, there is usually an existing fluid deficit, which must be assessed and corrected before surgery. Isotonic **glucose/sodium chloride** mixtures (most commonly glucose 4%/sodium chloride 0.18%) are preferred in children to avoid the danger of sodium overload and hypoglycaemia. When fluids are administered intravenously for more than 24 hours, potassium chloride is required to prevent potassium depletion. In order to avoid serious arrhythmias, especially in patients with impaired renal function, the required dose of potassium should be determined, whenever possible, by monitoring plasma concentrations of potassium. See also sections 11.1 (plasma substitutes) and 26.2 (solutions correcting water, electrolyte, and acid-base disturbances).

Section 2: Analgesics, antipyretics,nonsteroidal antiinflammatory drugs, drugs used to treat gout, and disease-modifying antirheumatic drugs

Pain can be classified as acute or chronic. Acute pain is usually of short duration and the cause often identifiable (disease, trauma). Chronic pain persists after healing is expected to be complete, or is caused by a chronic disease. Pain may be modified by psychological factors and attention to these is essential in pain management. Drug treatment aims to modify the peripheral and central mechanisms involved in the development of pain.

Neurogenic pain generally responds poorly to conventional analgesics; treatment can be difficult and includes the use of carbamazepine (section 5.1) for trigeminal neuralgia and amitriptyline (section 24.2.1) for diabetic neuropathy and postherpetic neuralgia. Non-opioid analgesics (section 2.1) are particularly suitable for pain in musculoskeletal conditions whereas the opioid analgesics (section 2.2) are more suitable for moderate to severe visceral pain. Those non-opioid analgesics which also have anti-inflammatory actions include salicylates and NSAIDs (nonsteroidal anti-inflammatory drugs); they can reduce both pain and inflammation of chronic inflammatory disorders such as rheumatoid arthritis, but they do not alter or modify the disease process itself. For the management of rheumatoid arthritis DMARDs (disease-modifying antirheumatic drugs) may favourably influence the outcome of the disease (section 2.4). The pain and inflammation of an acute attack of gout is treated with an NSAID or colchicine (section 2.3.1); a xanthineoxidase inhibitor (section 2.3.2) is used for long-term control of gout.

2.1 Non-opioid analgesics

Non-opioid analgesics with anti-inflammatory activity include salicylates such as acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs such as ibuprofen. Non-opioid analgesics with little or no anti-in flammatory activity include paracetamol.

2.1.1 Acetylsalicylic acid

The principal effects of **acetylsalicylic acid** are anti-inflammatory, analgesic, antipyretic and antiplatelet. Oral doses are absorbed rapidly from the gastrointestinal tract; rectal absorption is less reliable but suppositories are useful in patients unable to take oral dosage forms. Acetylsalicylic acid is used for the management of mild to moderate pain such as headache, acute migraine attacks (section 7.1), transient musculoskeletal pain and dysmenorrhoea, and for reducing fever. Although it may be used in higher doses in the management of pain and inflammation of rheumatoid arthritis, other NSAIDs are preferred because they are likely

to be better tolerated. Acetylsalicylic acid is also used for its antiplatelet properties (section 12.5).

Adverse effects with analgesic doses are generally mild but include a high incidence of gastrointestinal irritation with slight blood loss, bronchospasm and skin reactions in hypersensitive patients, and increased bleeding time. Anti-inflammatory doses are associated with a much higher incidence of adverse reactions, and they also cause mild chronic salicylism which is characterized by tinnitus and deafness. Acetylsalicylic acid is contraindicated for children under 12 years, unless specifically indicated for juvenile arthritis, because of an association with Reye syndrome (encephalopathy and liver damage).

Acetylsalicylic acid

Tablets, acetylsalicylic acid 300 mg
Dispersible tablets, acetylsalicylic acid 300 mg
Suppositories, acetylsalicylic acid 150 mg, 300 mg

Uses: mild to moderate pain including dysmenorrhoea, headache; pain and inflammation in rheumatic disease and other musculoskeletal disorders (including juvenile arthritis); pyrexia; also acute migraine attack (section 7.1); antiplatelet (section 12.5)

Contraindications: hypersensitivity (including asthma, angioedema, urticaria or rhinitis) to acetylsalicylic acid or any other NSAID; children under 12 years (Reye syndrome) unless for juvenile arthritis (Still disease); gastrointestinal ulceration; haemophilia and other bleeding disorders; gout.

Precautions: asthma, allergic disease; impaired renal or hepatic function (Appendices 4 and 5); pregnancy (Appendix 2); breastfeeding (Appendix 3); elderly; to avoid risk of haemorrhage do not administer within 7 days of surgery; G6PDdeficiency; dehydration;

Interactions: see Appendix 1

Dosage:

Mild to moderate pain, pyrexia, *by mouth* with or after food, ADULT 300–900 mg every 4–6 hours if necessary; maximum 4 g daily; CHILD Contraindicated under 12 years.

Mild to moderate pain, pyrexia, *by rectum*, ADULT 600–900 mg inserted every 4 hours if necessary; maximum 3.6 g daily; CHILD contraindicated under 12 years.

Inflammatory arthritis, *by mouth* with or after food, ADULT 4–8 g daily in divided doses in acute conditions; up to 5.4 g daily may be sufficient in chronic conditions.

Juvenile arthritis, *by mouth* with or after food, CHILD up to 130 mg/kg body weight daily in 5–6 divided doses in acute conditions; 80–100 mg/kg body weight daily in divided doses for maintenance.

Adverse effects: generally mild and infrequent for lower doses,

but common with anti-inflammatory doses; gastrointestinal discomfort or nausea, ulceration with occult bleeding (occasionally major haemorrhage); also other haemorrhage (including subconjunctival); hearing disturbances such as tinnitus (rarely deafness), vertigo, confusion, hypersensitivity reactions (angioedema, bronchospasm and rash); increased bleeding time; rarely oedema, myocarditis, blood disorders (particularly thrombocytopenia).

2.1.2 Paracetamol

Paracetamol is similar in analgesic and antipyretic efficacy to acetylsalicylic acid. It is used for mild to moderate pain including headache and acute migraine attacks (section 7.1) and for reducing fever, including post-im munization pyrexia. Paracetamol is particularly useful in patients in whom salicylates or other NSAIDs are contraindicated, such as asthmatics and those with a history of peptic ulcer, or for children under the age of 12 years in whom salicylates are contraindicated because of the risk of Reye syndrome. It is generally preferred to acetylsalicylic acid, particularly in the elderly, because it is less irritant to the stomach. Unlike acetylsalicylic acid and other NSAIDs, paracetamol has little anti-inflammatory activity which limits its usefulness for longterm treatment of pain associated with inflammation; however it is useful in the management of osteoarthritis, a condition with only a small inflammatory component. In normal doses adverse effects are rare, but overdosage with a single dose of 10–15 g is particularly dangerous because it may cause hepatocellular necrosis and, less frequently, renal tubular necrosis.

Paracetamol

Tablets, paracetamol 500 mg
Dispersible tablets, paracetamol 120 mg, 500 mg
Oral solution, paracetamol 120 mg/5 ml, 250 mg/5 ml *Suppositories*, paracetamol 60 mg, 100 mg, 125 mg, 250 mg, 500 mg.

Uses: mild to moderate pain including dysmenorrhoea, headache; pain relief in osteoarthritis and soft tissue lesions; pyrexia including post-immunization pyrexia; also acute migraine attack (section 7.1)

Precautions: hepatic impairment ; renal impairment; alcohol dependence; pregnancy and breastfeeding (Appendices 2 and 3); **overdosage:** see section 4.2.1;

Interactions: see Appendix 1

Dosage:

Post-immunization pyrexia, *by mouth*, INFANT 2–3 months, 60 mg followed by a second dose, if necessary, 4–6 hours later; warn parents to seek medical advice if pyrexia persists after second dose.

Mild to moderate pain, pyrexia, *by mouth,* ADULT 0.5–1 g every 4–6 hours, maximum 4 g daily; CHILD 3 months–1 year 60–120 mg, 1–5 years 120–250 mg, 6–12 years 250–500 mg, these doses may be repeated every 4–6 hours if necessary (maximum 4 doses in 24 hours).

Mild to moderate pain, pyrexia, *by rectum,* ADULT 0.5–1g; CHILD 1–5 years 125–250 mg, 6–12 years 250–500 mg; doses inserted every 4–6 hours if necessary, maximum 4 doses in 24 hours.

NOTE. Infants under the age of 3 months should not be given paracetamol unless advised by a doctor; a dose of 10 mg/kg (5 mg/kg if jaundiced) is suitable .!

Adverse effects: rare, but rashes, blood disorders; acute pancreatitis reported after prolonged use; **important:** liver damage (and less frequently renal damage) following over dosage

2.1.3 NSAIDs (nonsteroidal anti-inflammatory drugs)

NSAIDs, including **ibuprofen**, have analgesic, anti-inflammatory and antipyretic properties. In single doses NSAIDs have analgesic activity comparable to that of paracetamol. In regular full dosage, they have a lasting analgesic and anti-inflammatory effect, which makes them useful for continuous or regular pain due to inflammation. Differences in anti-inflammatory activity between different NSAIDs are small but there is considerable variation in individual patient response and in the incidence and type of adverse effects. Ibuprofen has fewer adverse effects than other NSAIDs but its anti-inflammatory properties are weaker. Ibuprofen is used in the treatment of mild to moderate pain and in the management of pain and inflammation in rheumatoid arthritis and juvenile arthritis. It may also be of value in the less well-defined conditions of back pain and soft-tissue disorders. Ibuprofen is also used to reduce pain and fever in children. With all NSAIDs caution should be exercised in the treatment of the elderly, in allergic disorders, during pregnancy and breastfeeding. In patients with renal, cardiac or hepatic impairment, the dose should be kept as low as possible and renal function should be monitored. NSAIDs should not be given to patients with active peptic ulceration and used with caution in those with a history of the disease. The commonest adverse effects are generally gastrointestinal including nausea, vomiting, diarrhoea, dyspepsia; hypersensitivity reactions including anaphylaxis,bronchospasm, rash; also fluid retention.

Ibuprofen

Ibuprofen is a representative nonsteroidal anti-inflammatory drug (NSAID).

Various drugs can serve as alternatives.

Tablets, ibuprofen 200 mg, 400 mg, 600 mg, 800 mg

Oral suspension, ibuprofen 100 mg/5 ml

Uses: pain and inflammation in rheumatic disease and other musculoskeletal disorders including juvenile arthritis; mild to moderate pain including dysmenorrhoea, headache; fever and pain in children; also acute migraine attack (section 7.1).

Contraindications: hypersensitivity (including asthma, angioedema, urticaria or rhinitis) to acetylsalicylic acid or any other NSAID; active peptic ulceration .

Precautions: renal and hepatic impairment (Appendices 4 and 5); history of peptic ulceration; cardiac disease; elderly; pregnancy and breastfeeding (Appendices 2 and 3); coagulation defects; allergic disorders;

Interactions: see Appendix 1

Dosage:

Mild to moderate pain, pyrexia, inflammatory musculoskeletal disorders, *by mouth* with or after food, ADULT 1.2–1.8 g daily in 3–4 divided doses, increased if necessary to maximum 2.4 g daily; maintenance dose of 0.6–1.2 g daily may be sufficient

Juvenile arthritis, *by mouth* with or after food, CHILD over 7 kg, 30–40 mg/kg body weight daily in 3–4 divided doses.

Fever and pain in children (not recommended for child under 7 kg body weight), *by mouth* with or after food, 20–30 mg/kg body weight daily in divided doses *or* 1–2 years 50 mg 3–4 times daily, 3–7 years 100 mg 3–4 times daily, 8–12 years 200 mg 3–4 times daily.

Adverse effects: gastrointestinal disturbances including nausea, diarrhoea, dyspepsia, gastrointestinal haemorrhage; hypersensitivity reactions including rash, angioedema, bronchospasm; headache, dizziness, vertigo, tinnitus, photosensitivity, haematuria; fluid retention, renal failure; rarely hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, visual disturbances, erythema multiforme (Stevens-Johnson syndrome), toxic dermal necrolysis (Lyell syndrome), colitis, aseptic meningitis.

2.2 Opioid analgesics

Morphine and **pethidine** are opioid analgesics which are effective in relieving moderate to severe pain, particularly of visceral origin; there is a large variation in patient response.

Weaker opioids such as **codeine** are suitable for mild to moderate pain.

Morphine remains the most valuable analgesic for severe pain.

In addition to pain relief it confers a state of euphoria and mental detachment; repeated administration may cause dependence and tolerance, but this should not be a deterrent in the control of pain in terminal illness (see also section 8.4). In normal doses common adverse effects include nausea, vomiting, constipation and drowsiness; larger doses produce respiratory depression and hypotension.

Pethidine produces prompt but short-acting analgesia; it is less constipating than morphine, but even in high doses it is less effective. A neurotoxic metabolite, norpethidine, accumulates during repeated administration and can cause central nervous system excitation, including myoclonus and seizures. These adverse effects together with the short duration of analgesic action make pethidine unsuitable for severe, continuing pain. It is used for analgesia in labour; however other opioid analgesics such as morphine are often preferred.

Codeine is an opioid analgesic much less potent than morphine and much less liable, in normal doses, to produce adverse effects including dependency. It is effective for mild to moderate pain but is too constipating for long-term use.

Morphine salts

Drug subject to international control under the Single Convention on Narcotic Drugs (1961)

Morphine is a representative opioid analgesic. Various drugs can serve as alternatives.

Tablets, morphine sulfate 10 mg.

Oral solution, morphine hydrochloride or sulfate 10 mg/5 ml.

Injection, morphine sulfate 10 mg/ml, 1-ml am poule.

Uses: severe pain (acute and chronic); my ocardial infarction, acute pulmonary oedema; also adjunct during major surgery and postoperative analgesia (section 1.5).

Contraindications: acute respiratory depression, acute alcoholism, where risk of paralytic ileus; acute abdomen; raised intracranial pressure or head injury (interferes with respiration, also affects pupillary responses vital for neurological assessment); avoid injection in phaeochromocytoma.

Precautions: renal and hepatic impairment (Appendices 4 and 5); reduce dose or avoid in elderly and debilitated; dependence (severe withdrawal symptoms if withdrawn abruptly); hypothyroidism; convulsive disorders; decreased respiratory reserve and acute asthma; hypotension; prostatic hypertrophy; pregnancy and breastfeeding (Appendices 2 and 3); **overdosage:** see section 4.2.2;

Interactions: see Appendix 1

Dosage :

Acute pain, *by subcutaneous injection* (not suitable for oedematous patients) *or by intramuscular injection* ADULT 10 mg every 4 hours if necessary (15 mg for heavier wellmuscled patients); INFANT up to 1 month 150 micrograms/kg body weight, 1–12 months 200 micrograms/kg body weight; CHILD 1–5 years 2.5–5 mg, 6–12 years 5–10 mg.

Chronic pain, *by mouth or by subcutaneous injection* (not suitable for oedematous patients) *or by intramuscular injection* 5–20 mg regularly every 4 hours; dose may be increased according to need; oral dose should be approximately double corresponding intramuscular dose.

Myocardial infarction, *by slow intravenous injection* (2 mg/minute), 10 mg followed by a further 5–10 mg if necessary; elderly or debilitated patients, reduce dose by half.

Acute pulmonary oedema, *by slow intravenous injection* (2 mg/minute), 5–10 mg .

NOTE. The doses stated above refer equally to morphine sulfate and hydrochloride

Adverse effects: nausea, vomiting (particularly in initial stages) constipation; drowsiness; also dry mouth, anorexia, spasm of urinary and biliary tract; bradycardia, tachycardia, palpitations, euphoria, decreased libido, rash, urticaria, pruritus, sweating, headache, facial flushing, vertigo, postural hypo-tension, hypothermia, hallucinations, confusion, dependence, miosis; larger doses produce respiratory depression and hypotension.

Pethidine hydrochloride

Drug subject to international control under the Single Convention on Narcotic Drugs (1961)

Pethidine is a representative opioid analgesic. Various drugs can serve as alternatives.

Tablets, pethidine hydrochloride 50 mg, 100 mg

Injection, pethidine hydrochloride 50 mg/ml, 1-ml ampoule.

Uses: moderate to severe pain; also adjunct during major surgery and postoperative analgesia, obstetric analgesia (section 1.5).

Contraindications: severe renal impairment; acute respiratory depression, acute alcoholism, where risk of paralytic ileus; acute abdomen; raised intracranial pressure or head injury (interferes with respiration, also affects pupillary responses vital for neurological assessment); avoid injection in phaeochromocytoma (risk of pressor response to histamine release).

Precautions: not suitable for severe continuing pain; hepatic impairment , moderate renal impairment ; reduce dose or avoid in elderly and debilitated; dependence (severe withdrawal symptoms if withdrawn abruptly); hypothyroi-

dism; convulsive disorders; asthma and decreased respiratory reserve; hypo tension; prostatic hypertrophy; pregnancy (Appendix 2); breastfeeding (Appendix 3); **overdosage:** see section 4.2.2;1

Interactions: see Appendix 1

Dosage:

Acute pain, *by mouth*, ADULT 50–150 mg every 4 hours; CHILD 0.5–2 mg/kg body weight *By subcutaneous or intramuscular injection* ADULT 25–100 mg, repeated after 4 hours; CHILD *by intramuscular injection*, 0.5–2 mg/kg body weight *By slow intravenous injection*, 25–50 mg, repeated after 4 hours.

Adverse effects: nausea, vomiting (particularly in initial stages), constipation; drowsiness; also dry mouth, anorexia, spasm of urinary and biliary tract; bradycardia, tachycardia, palpitations, euphoria, decreased libido, rash, urticaria, pruritus, sweating, headache, facial flushing, vertigo, postural hypotension, hypothermia, hallucinations, confusion, dependence, miosis; larger doses produce respiratory depression and hypotension;

Important: convulsions reported in overdosage.

2.3 Drugs used in gout

Reserved for use in higher referral centres.

2.4 DMARDs (disease-modifying antirheu matic drugs)

The process of cartilage and bone destruction which occurs in rheumatoid arthritis may be reduced by the use of a diverse group of drugs known as DMARDs (disease-modifying antirheumatic drugs). DMARDs include antimalarials (chloroquine, hydroxychloroquine), penicillamine, sulfasalazine, immunosuppressants (azathioprine, cyclophosphamide, metho trexate) and gold compounds.

Treatment should be started early in the course of the disease, before joint damage starts. DMARDs do not produce an immediate therapeutic effect but require 4–6 months of treatment for a full response. Their long term use is limited by toxicity and loss of efficacy. If one drug does not lead to objective benefit within 6 months, it should be discontinued and a different DMARD substituted. Adverse reactions with DMARDs frequently occur and may be life threatening; careful monitoring is needed to avoid severe toxicity. Blood disorders (bone marrow suppression) can occur during treatment with many DMARDs; blood counts should be carried out before and during treatment, and patients should

be advised to report without delay any unexplained symptom such as bleeding, bruising, purpura, infection, sore throat or fever. It has been suggested that combinations of DMARDs may be more effective than single drugs but increased toxicity may be a problem; whether used alone or in combination, they should be prescribed only by specialists to ensure that they are used safely and to best advantage.

The antimalarial **chloroquine** is less effective than most other DMARDs, but as it is generally better tolerated it may be preferred in the treatment of mild rheumatoid arthritis. Chloroquine should not be used for psoriatic arthritis. Because longterm therapy can result in retinopathy ophthalmological examinations should be conducted before and during treatment.

Sulfasalazine has a beneficial anti inflammatory effect and is considered by some rheumatologists to be a first-line DMARD, but it is poorly tolerated by about 25 per cent of patients. Adverse reactions include blood disorders (bone marrow suppression), hepatotoxicity, skin reactions and gastrointestinal disturbances.

Methotrexate, an immunosuppressant, is considered to be a first-line DMARD; at the low doses used for rheumatoid arthritis it is well tolerated but there remains the risk of blood disorders (bone marrow suppression) and of hepatic and pulmonary toxicity. Other immunosuppressant drugs, including. **cyclophosphamide** and **azathioprine**, are generally reserved for use in patients with severe disease who have failed to respond to other DMARDs, especially in those with extra-cellular manifestations such as vasculitis. Immunosuppressants are used in psoriatic arthritis. Adverse reactions include blood disorders, alopecia, nausea and vomiting.

Penicillamine is not a first-line drug and its use is limited by a significant incidence of adverse effects including blood disorders (bone marrow suppression), proteinuria and rash.

Corticosteroids (section 18.1) are potent anti-inflammatory drugs but their place in the treatment of rheumatoid arthritis remains controversial. Their usefulness is limited by adverse effects and their use should be controlled by specialists. Corticosteroids are usually reserved for use in patients with severe disease which has failed to respond to other antirheumatics, or where there are severe extra-articular effects such as vasculitis. Corticosteroids are also used to control disease activity during initial therapy with DMARDs. Although corticosteroids are associated with bone loss this appears to be dose-related; recent studies have suggested that a low dose of a corticosteroid started during the first two years of moderate to severe rheumatoid arthritis may reduce the rate of bone destruction. The smallest effective

dose should be used, such as oral prednisolone 7.5 mg daily for 2–4 years only, and at the end of treatment the dose should be tapered off slowly to avoid possible long term adverse effects. Relatively high doses of a corticosteroid, with cyclophosphamide, may be needed to control vasculitis.

Chloroquine salts

Tablets, chloroquine sulfate 200 mg; chloroquine phosphate 250 mg .

NOTE. Chloroquine base 150 mg is approximately equivalent to chloroquine sulfate 200 mg or chloroquine phosphate 250 mg.

Uses: rheumatoid arthritis (including juvenile arthritis); also malaria (section 6.4.3)

Contraindications: psoriatic arthritis.

Precautions: monitor visual acuity throughout treatment; warn patient to report immediately any unexplained visual disturbances; hepatic impairment; renal impairment pregnancy and breastfeeding (Appendices 2 and 3); neurological disorders including epilepsy; severe gastrointestinal disorders; G6PD deficiency; elderly; may exacerbate psoriasis and aggravate myasthenia gravis; porphyria;

Interactions: see Appendix 1

Dosage:

Administered on expert advice.

Rheumatoid arthritis, *by mouth*, ADULT chloroquine base 150 mg daily; maximum 2.5 mg/kg body weight daily; CHILD chloroquine base up to 3 mg/kg body weight daily.

NOTE. To avoid excessive dosage in obese patients the dose of chloroquine should be calculated on the basis of lean body weight.

Adverse effects: gastrointestinal disturbances, headache, skin reactions (rash, pruritus); less frequently ECG changes, convulsions, visual changes, retinal damage, keratopathy, ototoxicity, hair depigmentation, alopecia, discoloration of skin and mucous membranes; rarely blood disorders (including thrombocytopenia, agranulocytosis, aplastic anaemia); mental changes (including emotional disturbances, psychosis), myopathy (including cardiomyopathy), acute generalised exanthematous pustulosis, exfoliative dermatitis, erythema multiforme Stevens Johnson syndrome) and hepatic damage; **important**: arrhythmias and convulsions in overdosage.

Methotrexate

Tablets, methotrexate 2.5 mg

Uses: severe rheumatoid arthritis which has failed to respond to penicillamine or chloroquine; also malignant disease (section8.2)

Contraindications: pregnancy and breastfeeding (Appendices 2 and 3); immunodeficiency syndromes; significant pleural effusion or ascites.

Precautions: monitor throughout treatment including blood counts and hepatic and renal function tests; renal and hepatic impairment (avoid if severe, see also Appendices 4 and 5); reduce dose or withdraw if acute infection develops; for woman or man, contraception during and for at least 6 months after treatment; peptic ulceration, ulcerative colitis, diarrhoea, ulcerative stomatitis; advise patient to avoid self-medication with salicylates or other NSAIDs; warn patient to report immediately any unexplained symptoms including bleeding, bruising, purpura, infection, sore throat or fever; warn patient with rheumatoid arthritis to report cough or dyspnoea;

Interactions: see Appendix 1

Dosage:

Administered on expert advice

Rheumatoid arthritis, *by mouth*, ADULT 7.5 mg once *weekly* (as a single dose *or* divided into 3 doses of 2.5 mg given at intervals of 12 hours), adjusted according to response; maximum total. *weekly* dose 20 mg .

Adverse effects: blood disorders (bone marrow suppression), liver damage, pulmonary toxicity; gastrointestinal disturbances — if stomatitis and diarrhoea occur, stop treatment; renal failure, skin reactions, alopecia, osteoporosis, arthralgia, myalgia, ocular irritation, precipitation of diabetes.

Sulfasalazine

Tablets (gastro-resistant), sulfasalazine 500 mg

Uses: severe rheumatoid arthritis; also ulcerative colitis and Crohn disease (section 17.4).

Contraindications: hypersensitivity to salicylates and sulphonamides; severe renal impairment; children.

Precautions: monitor during first 3 months of treatment including blood counts and hepatic and renal function tests; renal impairment ; pregnancy and breastfeeding (Appendices 2 and 3); history of allergy; G6PD deficiency; slow acetylator status; porphyria; warn patient to report immediately any unexplained symptoms including bleeding, bruising, purpura, infection, sore throat or fever;

Interactions: see Appendix 1

Dosage:

Administered on expert advice.

Rheumatoid arthritis, *by mouth* as gastro-resis tant tablets, ADULT initially 500 mg daily, increased by 500 mg at intervals of 1 week to a maximum of 2–3 g daily in divided doses.

Adverse effects: nausea, diarrhoea, headache, loss of ppetite; fever; blood disorders (including Heinz body anaemia, megaloblastic anaemia, leukopenia, neutropenia, thrombocytopenia); hypersensitivity reactions (including rash, urticaria, erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, epidermal necrolysis, pruritus, photosensitization, anaphylaxis, serum sickness, interstitial nephritis, lupus erythematosus-like syndrome); lung complications (including eosinophilia, fibrosing alveolitis); ocular complications (including periorbital oedema); stomatitis, parotitis; ataxia, aseptic meningitis, vertigo, tinnitus, alopecia, peripheral neuropathy, insomnia, depression, hallucinations; kidney reactions (including proteinuria, crystalluria, haematuria); oligospermia; rarely acute pancreatitis, hepatitis; urine may be coloured orange; some soft contact lenses may be stained.

Section 3:Antiallergics and drugs used in anaphylaxis

3.1 Antiallergics and drugs used in anaphylaxis

The H1-receptor antagonists are generally referred to as antihistamines. They inhibit the wheal, pruritus, sneezing and nasal secretion responses that characterize allergy. Antihistamines thus relieve the symptoms of allergic reactions, such as urticaria, allergic rhinitis, and allergic conjunctivitis; they also control pruritus in skin disorders, such as eczema. Antihistamines are used to treat drug allergies, food allergies, insect stings and some of the symptoms of anaphylaxis and angioedema. Drug treatment and other supportive care should not be delayed in critically ill patients (see Allergic Emergencies below). Specific precipitants should be sought and if identified, further exposure avoided and desensitization considered.

Drowsiness and sedation are particular disadvantages of the early antihistamines and the patient should be warned against driving or operating machinery. Other central nervous depressants, including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytics and neuroleptics, may enhance the sedative effects of antihistamines. Since antihistamines interfere with skin tests for allergy, they should be stopped at least one week before conducting a skin test.

Chlorphenamine is a typical sedative antihistamine. Newer antihistamines do not cause significant sedation. In practice, all antihistamines are equally effective in relieving the symptoms of allergic reactions and differ mainly in the intensity of sedative and anticholinergic (more correctly antimuscarinic) effects. Selection of an antihistamine should thus be based on the intended therapeutic use, the adverse reaction profile, and the cost.

Corticosteroids, such as **dexamethasone**, **hydrocortisone**, or **prednisolone**, suppress or prevent almost all symptoms of inflammation associated with allergy. The route of administration depends on the particular type of allergic condition. For example, for a mild allergic skin reaction, the best therapy may be the use of a corticosteroid ointment or cream. If the skin reaction does not respond to topical corticosteroid therapy, it may be necessary to give a corticosteroid orally.

Allergic reactions of limited duration and with mild symptoms, such as urticaria or allergic rhinitis, usually require no treatment. If on the other hand, symptoms become persistent, antihistamines constitute the mainstay of treatment. However, oral corticosteroids may be required for a few days in an acute attack of urticaria or for severe skin reactions. Oral corticosteroids are also used to relieve severe exacerbations in chronic urticaria, but long-term use should be avoided.

Corticosteroids may be used topically to reduce inflammation in allergic rhinitis but should only be used systemically for this condition when symptoms are disabling.

Adverse effects associated with long-term use of corticosteroids include inhibition of growth in children, disturbances of electrolyte balance leading to oedema, hypertension and hypokalaemia, with osteoporosis, spontaneous fractures, skin thinning, increased susceptibility to infection, mental disturbances and diabetes mellitus. For further information on the disadvantages of corticosteroids, see section 18.1.

Allergic emergencies

Anaphylactic shock and conditions such as angioedema are medical emergencies that can result in cardiovascular collapse and/or death. They require prompt treatment of possible laryngeal oedema, bronchospasm or hypo tension. Atopic individuals are particularly susceptible. Insect bites and certain foods including eggs, fish, peanuts and nuts are also a risk for sensitized persons. Therapeutic substances particularly associated with anaphylaxis include blood products, vaccines, hyposensitizing (allergen) preparations, antibiotics (especially penicillins), iron injections, heparin, and neuromuscular blocking drugs. Acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs NSAIDs) may cause bronchoconstriction in leuko triene-sensitive patients. In the case of drug allergy, anaphylaxis is more likely to occur after parenteral administration. Resuscitation facilities should always be available when injecting a drug associated with a risk of anaphylactic reactions.

First-line treatment of a severe allergic reaction includes administering epinephrine (adrenaline), keeping the airway open (with assisted respiration if necessary), and restoring blood pressure. Epinephrine (adrenaline) should immediately be given by intramuscular injection to produce vasoconstriction and bronchodilation and injections should be repeated every 10 minutes until blood pressure and pulse have stabilized. If there is cardiovascular shock with inadequate circulation, epinephrine (adrenaline) must be given cautiously by slow intravenous injection of a dilute solution.

An antihistamine such as chlorphenamine is a useful adjunctive treatment given after epinephrine (adrenaline) injection and continued for 24 to 48 hours to reduce the severity and duration of symptoms and to prevent relapse. An intravenous corticosteroid such as hydrocortisone has an onset of action that is delayed by several hours but should be given to help prevent later deterioration in severely affected patients.

Further treatment of anaphylaxis may include intravenous fluids, oxygen, an intravenous vasopressor such as dopamine, intravenous aminophylline or injected or nebulized bronchodilator, such as salbutamol.

Steps in anaphylaxis:

1. Sympathomimetic

Epinephrine (adrenaline) *by intramuscular injection* using epinephrine injection 1 in 1000, ADULT and ADOLESCENT, 500 micrograms (0.5 ml); INFANT under 6 months 50 micrograms (0.05 ml); CHILD 6 months–6 years 120 micrograms (0.12 ml), 6–12 years 250 micrograms (0.25 ml).

NOTE. The above doses may be repeated several times if necessary at 5- minute intervals, according to blood pressure, pulse, and respiratory function If circulation inadequate, *by slow intravenous injection* using epinephrine injection 1 in 10 000 (given at a rate of 1 ml/minute), ADULT 500 micrograms (5 ml); CHILD 10 micrograms/kg (0.1 ml/kg), given over several minutes

2. Vital functions

Maintain an open airway; give oxygen by mask, restore blood pressure (lay patient flat, raise feet).

3. Antihistamine

such as chlorphenamine *by slow intravenous injection* over 1 minute, ADULT 10–20 mg, repeated if required (maximum total dose 40 mg in 24 hours)

4. Corticosteroids

such as hydrocortisone *by slow intravenous injection*, ADULT 100–300 mg; CHILD up to 1 year, 25 mg; 1–5 years, 50 mg; 6–12 years, 100 mg.

5. Intravenous fluids

start infusion with sodium chloride (0.5–1 litre during the first hour).

6. If the patient has asthma

like symptoms, give salbutamol 2.5–5 mg by nebulization or aminophylline 5 mg/kg by intravenous injection over at least 20 minutes.

Antihistamine

Chlorphenamine maleate

Chlorphenamine is a representative sedative antihistamine. Various drugs can serve as alternatives.

Tablets, chlorphenamine maleate 4 mg.

Oral solution (Elixir), chlorphenamine maleate 2 mg/5 ml.

Injection, chlorphenamine maleate 10 mg/ml, 1-ml ampoule.

Uses: symptomatic relief of allergy, allergic rhinitis (hay fever) and conjunctivitis, urticaria, insect stings and pruritus of allergic origin; adjunct in the emergency treatment of anaphylactic shock and severe angioedema.

Contraindications: prostatic enlargement, urinary retention; ileus or pyloric stenosis; glaucoma; child under 1 year.

Precautions: pregnancy and breastfeeding(Appendices 2 and 3); renal and hepatic impairment (Appendices 4 and 5);

Interactions: Appendix 1

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving.

Dosage:

By mouth, ADULT 4 mg every 4–6 hours (maximum 24 mg daily); CHILD not recommended under 1 year, 1–2 years 1 mg twice daily, 2–5 years 1 mg every 4–6 hours (maximum 6 mg daily), 6–12 years 2 mg every 4–6 hours (maximum 12 mg daily).

By subcutaneous, intramuscular, or slow intravenous injection over 1 minute, ADULT 10–20 mg, repeated if required (maximum 40 mg in 24 hours); *by subcutaneous injection* CHILD 87.5 micrograms/kg, repeated if necessary up to 4 times daily.

Adverse effects: drowsiness (rarely paradoxical stimulation with high doses, or in children or elderly), hypotension, headache, palpitations, psychomotor impairment, urinary retention, dry mouth, blurred vision, gastrointestinal disturbances; liver dysfunction; blood disorders; also rash and photosensitivity reactions, sweating and tremor, hypersensitivity reactions (including bronchospasm, angiodema, anaphylaxis); injections may be irritant.

Sympathomimetic

Epinephrine (adrenaline)

Injection, epinephrine (as hydrochloride or hydrogen tartrate) 1 mg/1 ml; 1- ml ampoule.

Uses: severe anaphylactic reaction; severe angioedema; cardiac arrest (section 12.2).

Precautions: hyperthyroidism, hypertension, diabetes mellitus, ischaemic heart disease, arrhythmias, cerebrovascular disease, elderly.

Interactions: Appendix 1

Dosage:

Caution: Different dilutions of epinephrine injection are used for different routes of administration.

Intramuscular or subcutaneous injection use 1:1000 epinephrine injection, see Steps in Anaphylaxis for doses.

Slow intravenous injection use 1:10 000 epinephrine injection. This route should be reserved for severely ill patients when there is doubt about the adequacy of circulation and absorption from the intramuscular site, see Steps in Anaphylaxis for doses.

Adverse effects: tachycardia and arrhythmias, hypertension, tremor, anxiety, sweating, nausea, vomiting, weakness, dizziness, pulmonary oedema have all been reported; headache common.

Corticosteroids

Dexamethasone

Dexamethasone is a representative corticosteroid. Various drugs can serve as alternatives.

Tablets, dexamethasone 500 micrograms, 4 mg

Injection, dexamethasone phosphate (as sodium salt), 4 mg/ml, 1-ml ampoule.

Uses: adjunct in the emergency treatment of anaphylaxis; shortterm suppression of inflammation in allergic disorders; for other indications see section 18.1.

Contraindications: untreated systemic infection (unless condition life-threatening); administration of live virus vaccines.

Precautions: increased susceptibility to and severity of infection; activation or exacerbation of tuberculosis, amoebiasis, strongyloidiasis; risk of severe chickenpox in nonimmune patient (varicella-zoster immunoglobulin required if exposed to chickenpox); avoid exposure to measles (normal immunoglobulin possibly required if exposed); diabetes mellitus; peptic ulcer; hypertension; for further precautions relating to long-term use of corticosteroids see section 18.1.

Dosage:

By mouth, ADULT and CHILD, usual range 0.5–10 mg daily as a single dose in the morning.47

By slow intravenous injection or infusion, ADULT 0.5–20 mg; CHILD 200–500 micrograms/kg

Adverse effects: nausea, dyspepsia, malaise, hiccups; hypersensitivity reactions including anaphylaxis; perineal irritation after intravenous administration; for adverse effects associated with long-term corticosteroid treatment see section 18.1

Hydrocortisone

Powder for injection, hydrocortisone (as sodium succinate), 100-mg vial.

Uses: adjunct in the emergency treatment of anaphylaxis; inflammatory skin conditions (section 13.3); inflammatory bowel disease (section 17.4); adrenocortical insufficiency (section 18.1)

Contraindications: not relevant to emergency use but for contra-indications relating to long-term use see section 18.1

Precautions: not relevant to emergency use but for precautions relating to long-term use see section 18.1

Dosage:

Anaphylactic emergency, *by slow intravenous injection* as a single dose, see Steps in Anaphylaxis.

Prednisolone

Prednisolone is representative corticosteroid. Various drugs can serve as alternatives

Tablets, prednisolone 5 mg.

Uses: short-term suppression of inflammation in allergic disorders; longer-term suppression (section 18.1); malignant disease (section 8.3); eye (section 21.2)

Contraindications: untreated systemic infection; administration of live virus vaccines

Precautions: increased susceptibility to and severity of infection; activation or exacerbation of tuberculosis, amoebiasis, strongyloidiasis; risk of severe chickenpox in nonimmune patient (varicella-zoster immunoglobulin required if exposed to chickenpox); avoid exposure to measles (normal immunoglobulin possibly required if exposed); diabetes mellitus; peptic ulcer; hypertension; for further precautions relating to long-term use of corticosteroids see section 18.1

Dosage:

By mouth, ADULT and CHILD, initially up to 10–20 mg daily as a single dose in the morning (in severe allergy up to 60 mg daily as a short course of 5–10 days).

Adverse effects: nausea, dyspepsia, malaise, hiccups; hypersensitivity reactions including anaphylaxis; for adverse effects associated with long-term corticosteroid treatment see section

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Section 4: Antidotes and other substances used in poisonings

These notes are only guidelines and it is strongly recommended that poisons information centres be consulted in cases where there is doubt about the degree of risk or about appropriate management.

4.1 General care and non-specific treatment

All patients who show features of poisoning should generally be admitted to hospital. Patients who have taken poisons with delayed actions should also be admitted, even if they appear well; delayed-action poisons include acetylsalicylic acid, iron, lithium, paracetamol, paraquat, tricyclic antidepressants and warfarin. This also applies to modified-release preparations.

However, it is often impossible to establish with certainty the identity of the poison and the size of the dose but information on the nature of the poison may be useful for carrying out symptomatic management. Few patients require active removal of the poison.

Most patients must be treated symptomatically and monitored.

Particular care must be given to maintenance of respiration and blood pressure. Assisted ventilation may be required. Cardiac conduction defects and arrhythmias often respond to correction of underlying hypoxia or acidosis. Hypothermia which may develop in patients who have been unconscious for some hours is best treated by wrapping the patient in blankets to conserve body heat. Convulsions which are prolonged or recurrent may be controlled by intravenous diazepam. In some situations removal of the poison from the stomach by gastric lavage may be appropriate (see below). Activated charcoal can bind many poisons in the stomach and therefore prevent absorption. Active elimination techniques such as repeated administration of activated charcoal can enhance the elimination of some drugs after they have been absorbed (see below). Other techniques to enhance elimination of poisons after their absorption are only practical in hospital and are only suitable for a small number of patients and only to a limited number of poisons. Methods include haemodialysis and haemoperfusion. Alkalinization of urine can be used to increase the elimination of salicylates. Forced alkaline diuresis is no longer recommended.

Gastric lavage

The dangers of attempting to empty the stomach have to be balanced against the toxicity of the ingested poison, as assessed by the quantity ingested, the inherent toxicity of the poison, and the time since ingestion. Gastric emptying is clearly unnecessary if the risk of toxicity is small or if the

patient presents too late. Emptying the stomach may be of value if undertaken within 1–2 hours after ingestion. The main risk is with inhalation of stomach contents and gastric lavage should not be undertaken in drowsy or comatose patients without assistance of an anaesthetist so that the airway can be protected by a cuffed endotracheal tube. Gastric lavage must not be attempted after corrosive poisoning or for petroleum products.

Emesis

Emesis induced by **ipecacuanha** has been widely used in adults and children but its use is controversial. It should only be considered if the patient is fully conscious, if the poison ingested is neither corrosive nor a petroleum distillate, if the poison is not adsorbed by activated charcoal or, if gastric lavage is inadvisable or refused.

Prevention of absorption

Given by mouth **activated charcoal** can bind many poisons in the stomach, thereby reducing their absorption. The sooner it is given, the more effective it is, but it may be effective for as long as 2 hours after ingestion. It may be effective several hours after poisoning with modified-release preparations or drugs with anticholinergic (antimuscarinic) properties. It is safe and particularly useful for prevention of absorption of poisons which are toxic in small amounts, for example, antidepressants. Furthermore, repeated doses of activated charcoal enhance the faecal elimination of some drugs (that undergo enterohepatic or enteroenteric recycling) several hours after ingestion and after they have been absorbed, for example phenobarbitone, theophylline.

4.2 Specific antidotes

4.2.1 Paracetamol posioning

To be referred to medical college after first aid

4.2.2 Opioid poisoning

Opioids cause varying degrees of coma, respiratory depression and pinpoint pupils. **Naloxone** is a specific antidote indicated if there is coma or bradypnoea. Naloxone has a shorter duration of action than many opioids so close monitoring and repeated injections are required depending on respiratory rate and depth of coma. The effects of some opioids such as buprenorphine are only partially reversed by naloxone. Acute withdrawal syndromes may be

precipitated by the use of naloxone in patients with a physical dependence on opioids or in overdosage with large doses; a withdrawal syndrome may occur in neonates of opioid-dependent mothers.

Naloxone hydrochloride

Injection (Solution for injection), naloxone hydrochloride 400 micrograms/ml, 1-ml ampoule.

Uses: opioid overdosage; postoperative respiratory depression (section 1.5).

Precautions: physical dependence on opioids or other situations where acute withdrawal syndrome may be precipitated (see above); pregnancy (Appendix 2); breastfeeding (Appendix 3); cardiovascular disease.

Dosage:

Overdosage of opioids, *by intravenous injection*, ADULT 0.8– 2 mg repeated at intervals of 2–3 minutes to a maximum of 10 mg, if respiratory function does not improve, question diagnosis; CHILD 10 micrograms/kg; a subsequent dose of 100 micrograms/kg if no response NOTE. Naloxone hydrochloride may be administered in the same doses by intramuscular or subcutaneous injection, but only if the intravenous route is not feasible (slower onset of action).

Adverse effects: nausea, vomiting, sweating; hypertension, tremor, convulsions, hyperventilation; cardiac arrest.

4.2.3 Organophosphate and carbamate poisoning

Initial treatment of organophosphate or carbamate poisoning includes prevention of further absorption by emptying the stomach by gastric lavage, moving patient to fresh air supply, removing contaminated clothing and washing contaminated skin. A clear airway must be maintained. Organophosphates inhibit cholinesterases and thus prolong the effects of acetylcholine. **Atropine** will reverse the muscarinic effects of acetylcholine and is used (in conjunction with oximes such as pralidoxime) with additional symptomatic treatment.

Additional treatment for carbamate poisoning is generally symptomatic and supportive. **Atropine** may be given but may not be required because of the rapidly reversible type of cholinesterase inhibition produced (oximes should not be given).

Atropine sulfate

Injection (Solution for injection), atropine sulfate 1 mg/ml, 1-ml ampoule.

Uses: organophosphate and carbamate poisoning; premedication (section 1.3); antispasmodic (section 17.5); mydriasis and cycloplegia (section 21.5).

Precautions: children, elderly, Down syndrome; angle-closure glaucoma; myasthenia gravis; gastrointestinal disorders; prostatic enlargement; cardiac disorders; pyrexia; pregnancy (Appendix 2); breastfeeding (Appendix 3);
Interactions: Appendix 1
Dosage:
Organophosphate poisoning, *by intramuscular or intravenous injection* (depending on severity of poisoning), ADULT 2 mg every 20–30 minutes until the skin becomes flushed and dry and tachycardia develops

Section 5: Anticonvulsants/ Antiepileptics

5.1 Control of epilepsy

Treatment should always be started with a single drug, but the choice of an anticonvulsant can only be made on an individual basis and will depend on the efficacy of the drug and the patient's tolerance of treatment. If one drug fails to control the seizures after it has been used in full therapeutic dosage for an adequate period, or if it is not well tolerated, it should be gradually substituted with another. If monotherapy is ineffective, two drugs should be given in combination and several regimens may need to be tried before the most appro priate is found.

Initial dose of the drug of choice should be determined on the basis of the degree of urgency, the size and age of the patient. It should be increased gradually until an effective response is obtained. All antiepileptics commonly produce neurological adverse effects at too high a dose, and should be monitored for the earliest signs to help in accurate dose titration. Where the necessary laboratory facilities exist, it can be useful to measure plasma concentrations as an aid to dose adjustment or to determine whether the patient is complying with treatment. Non-compliance because of inappropriate dosing and overdosing is a major impediment to effective antiepileptic treatment. Patients should ideally remain under supervision throughout treatment.

WITHDRAWAL. Treatment is normally continued for a minimum of two years after the last seizure. Withdrawal should be extended over a period of several months since abrupt withdrawal can lead to complications such as status epilepticus. Abrupt discontinuation is therefore never warranted. Many adult patients relapse once treatment is withdrawn and it may be justified to continue treatment indefinitely, particularly when the patient's livelihood or lifestyle can be endangered by recurrence of a seizure.

PREGNANCY AND BREASTFEEDING. Untreated epilepsy during pregnancy may cause harm to the fetus; there is therefore no justification for abrupt withdrawal of treatment although withdrawal of therapy may be an option if the patient has been seizure-free for at least 2 years; resumption of treatment may be considered after the first trimester. If antiepileptics are continued in pregnancy, monotherapy with the lowest effective dose is preferred, with adjustment made to take account of changes in plasma levels associated with pregnancy. There is an increased risk of birth defects with the use of anticonvulsants, particularly **carbamazepine**, **valproic acid** and **phenytoin**.

However, if there is good seizure control, there is probably no advantage in changing pregnant patients' antiepileptic drugs. In view of the risks of neural tube and other defects, patients

who may become pregnant should be informed of the risks and referred for advice, and pregnant patients should be offered counselling and antenatal screening. To counteract the risk of neural tube defects, adequate **folate** supplements are advised for women before and during pregnancy. In view of the risk of neonatal bleeding associated with **carbamazepine**, **phenobarbitone** and **phenytoin**, prophylactic **phytomenadione (vitamin K1)** is recommended for the neonate and the mother before delivery. Antiepileptic drugs can be continued during breastfeeding (see also Appendix 3).

DRIVING. Regulations are in place in many countries which may, for example, restrict driving by patients with epilepsy to those whose seizures are controlled. Further, antiepileptic drugs may cause CNS depression, particularly in the early stages of treatment and patients affected by adverse effects such as drowsiness or dizziness should not operate machinery or drive.

Choice of antiepileptic in management of convulsive disorders

GENERALIZED TONIC-CLONIC, SIMPLE PARTIAL AND COMPLEX PARTIAL SEIZURES. **Carbamazepine**, **phenobarbitone**, **phenytoin**, and **valproic acid**are widely used in the treatment of these conditions. However, each of these drugs is associated with dose-related and idiosyncratic adverse effects and monitoring of haematological and hepatic function is often advised, particularly for carbamazepine and va;proic acid.

ABSENCE SEIZURES. Both **ethosuximide** and **valproic acid** are widely used in the treatment of absence seizures (petit mal) and are usually well tolerated. However, ethosuximide can, rarely, cause lupus erythematosus and psychoses which call for immediate, but cautious, discontinuation. Absence seizures are commonly associated with tonic-clonic seizures and valproic acid is preferred since it is effective in both disorders.

TONIC SEIZURES, ATONIC SEIZURES AND ATYPICAL ABSENCE SEIZURES. **Phenobarbitone** or **phenytoin** is widely used for tonic seizures, **valproic acid**or **clonazepam** for atonic seizures, and **clonazepam** for atypical absence seizures.

MYOCLONIC SEIZURES. **Valproic acid** is widely used and most effective for juvenile myoclonic seizures. However, both valproic acidand this type of seizure are associated with a high relapse rate and it is often necessary to continue therapy indefinitely. Other myoclonic seizures are often resistant to treatment and some do not have an epileptic basis. **Valproic**

acid or **clonazepam** can be of value in this case and other antiepileptic drugs may be useful in intractable cases. Both drugs are generally well accepted, although tolerance to clonazepam has been reported.

INFANTILE SPASM (INFANTILE MYOCLONIC EPILEPSY). Infantile spasms, which are often associated with severe brain damage, can be resistant to antiepileptic drugs. **Clonazepam** is sometimes of value in resistant cases.

FEBRILE CONVULSIONS. Febrile convulsions usually respond to sponging with tepid water and antipyretics such as paracetamol. Rectal **diazepam** is needed for severe attacks. Prolonged treatment is advisable when first seizures occur during the first 18 months of life, when the child has evident neurological abnormalities or has had previous prolonged or focal convulsions. **Phenobarbitone** is used for this purpose but careful clinical monitoring and dosage adjustment are necessary to minimize the risk of adverse effects. **Valproic acid**, although also effective, is not recommended because of the greater risk of hepatotoxicity in this age group. Alternatively, intermittent prophylaxis with rectal diazepam during febrile episodes can also be effective.

Status epilepticus

Status epilepticus is a medical emergency which carries a high mortality rate. Maintenance of the airway and assisted ventilation are crucial even when the seizures are controlled, since the drugs used in its management may also depress respiration. Unresponsive patients require intensive care. Intravenous **diazepam** or **clonazepam** is often effective. Diazepam, which is rapid-acting, should be administered first and should be followed immediately by a loading dose of **phenytoin** which has a longer-acting effect. When cannulation is impossible, diazepam may be administered rectally as a solution (absorption from suppositories is too slow for treatment of status epilepticus). Intravenous **phenobarbitone** is also effective but is more likely to cause respiratory depression; it is used in refractory cases but should be avoided in patients who have recently received oral phenobarbitone. Rectal paraldehyde may also be used; it causes little respiratory depression and is therefore useful where facilities for resuscitation are poor. If seizures continue despite treatment, general anaesthesia may be required. The underlying cause must be identified and remedied in all cases.

Carbamazepine

Tablets, carbamazepine 100 mg, 200 mg, 400 mg;
Syrup 20 mg / ml.

Uses: generalized tonic-clonic and partial seizures; trigeminal neuralgia; bipolar disorder (section 24.2.2).

Contraindications: atrioventricular conduction abnormalities; history of bone-marrow depression; porphyria.

Precautions: hepatic impairment ; renal impairment; cardiac disease (see also Contraindications); skin reactions (see Adverse effects); history of blood disorders (blood counts before and during treatment); glaucoma; pregnancy (**important** see notes above; Appendix 2); breastfeeding (see notes above; Appendix 3); avoid sudden withdrawal;

Interactions: Appendix 1

BLOOD, HEPATIC OR SKIN DISORDERS. Patients or their carers should be told how to recognize signs of blood, liver or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising or bleeding develop. Leukopenia which is severe, progressive and associated with clinical symptoms requires withdrawal (if necessary under cover of suitable alternative).

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving; see also notes above.

Dosage:

Generalized tonic-clonic seizures, partial seizures, *by mouth*, ADULT initially 100 mg twice daily, increased gradually according to response to usual maintenance dose of 0.8–1.2 g daily in divided doses; ELDERLY reduce initial dose; CHILD 10–20 mg/kg daily in divided doses.

Trigeminal neuralgia, *by mouth*, ADULT initially 100 mg 1–2 times daily increased gradually according to response; usual dose 200 mg 3–4 times daily with up to 1.6 g daily in some patients.

NOTE. Plasma concentration for optimum response 4–12 mg/litre (17–50 micromol/litre).

Adverse effects: dizziness, drowsiness, headache, ataxia, blurred vision, diplopia (may be associated with high plasma levels); gastrointestinal intolerance including nausea and vomiting, anorexia, abdominal pain, dry mouth, diarrhoea or constipation; commonly, mild transient generalized erythematous rash (withdraw if worsens or is accompanied by other symptoms); leukopenia and other blood disorders (including thrombocytopenia, agranulocytosis and aplastic anaemia); cholestatic jaundice, hepatitis, acute renal failure, Stevens-Johnson syndrome (erythema multiforme), toxic epidermal necrolysis, alopecia, thromboembolism, arthralgia, fever, proteinuria, lymph node enlargement, arrhythmias, heart block and heart failure, dyskinesias, paraesthesia, depression, impotence, male infertility, gynaecomastia, galactorrhoea, aggression, activation of psychosis, photosensitivity, pulmonary hypersensitivity, hyponatraemia, oedema, disturbances of bone metabolism with osteomalacia also reported; confusion and agitation in elderly.

Diazepam

Drug subject to international control under the Convention on Psychotropic Substances (1971)

Diazepam is a representative benzodiazepine anticonvulsant. Various drugs can serve as alternatives

Injection (Solution for injection),diazepam 5 mg/ml, 2-ml ampoule

Susp. 2mg/ 5 ml

Suppository 5 mg.

Uses: status epilepticus; emergency management of recurrent seizures; febrile convulsions; seizures associated with poisoning and drug withdrawal; adjunct in acute alcohol withdrawal; premedication (section 1.3); anxiety disorders (section 24.3)

Contraindications: respiratory depression; acute pulmonary insufficiency; sleep apnoea; severe hepatic impairment; myasthenia gravis.

Precautions: respiratory disease, muscle weakness, history of alcohol or drug abuse, marked personality disorder; pregnancy (see notes above; Appendix 2); breastfeeding (see notes above; Appendix 3); reduce dose in elderly or debilitated and in hepatic impairment (avoid if severe, Appendix 5), renal impairment ; avoid prolonged use and abrupt withdrawal; when given intravenously facilities for reversing respiratory depression with mechanical ventilation must be at hand (see below); porphyria;

Interactions: Appendix 1

PRECAUTIONS FOR INTRAVENOUS INFUSION. Intravenous infusion of diazepam is potentially hazardous (especially if prolonged) calling for close and constant observation and best carried out in a specialist centre with intensive care facilities. Prolonged intravenous infusion requires special caution according to manufacturer's directions

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving; see also notes above .

Dosage:

Status epilepticus or emergency management of recurrent epileptic seizures, *by slow intravenous injection* (at rate of 5 mg/minute), ADULT 10–20 mg, repeated if necessary after 30–60 minutes; may be followed *by intravenous infusion* to maximum 3 mg/kg over 24 hours; *by slow intravenous injection*, CHILD 200 to 300 micrograms/kg (*or* 1 mg per year of age); *by rectum* as suppository, ADULT and CHILD over 10 kg, 0.5 mg/kg; ELDERLY 0.25 mg (1/4th of supp.)/ kg; repeated if necessary every 12 hours; if convulsions not controlled, other measures should be instituted.

Febrile convulsions (preferred treatment), *by rectum* as solution, CHILD over 10 kg, 0.5 mg/kg (maximum 10 mg), with dose repeated if necessary Febrile convulsions (alternative treatment), *by slow intravenous injection*, CHILD 0.2 to 0.3 mg/kg (*or* 1 mg per year of age).

Drug or alcohol withdrawal, *by slow intravenous injection* (at rate of 5 mg/minute), ADULT 10 mg; higher doses may be required depending on severity of symptoms Seizures associated with poisoning, *by slow intravenous injection* (at rate of 5 mg/minute), ADULT 10–20 mg.

Adverse effects: drowsiness and lightheadedness the next day; confusion and ataxia (especially in the elderly); amnesia; dependence; paradoxical increase in aggression; muscle weakness; occasionally headache, vertigo, salivation changes, gastrointestinal disturbances, rashes, visual disturbances, dysarthria, tremor, changes in libido, incontinence, urinary retention; blood disorders and jaundice; raised liver enzymes; hypotension and apnoea, pain and hrombophlebitis (with injection)

Phenobarbitone

Drug subject to international control under the .Convention on Psychotropic Substances (1971).

Tablets, phenobarbitone 15 mg, 30 mg, 60 mg, 100 mg.

Syrup, phenobarbitone 20mg/5 ml.

Injection (Concentrate for solution for injection), phenobarbitone sodium 200 mg/ml.

Uses: generalized tonic-clonic seizures; partial seizures; neonatal seizures; febrile convulsions; status epilepticus (see notes above)

Contraindications: porphyria; absence seizures

Precautions: elderly, debilitated, children (may cause behavioural changes); impaired renal function or hepatic function , respiratory depression (avoid if severe); pregnancy (see notes above; Appendix 2); breastfeeding (see notes above; Appendix 3); avoid sudden withdrawal;

Interactions: Appendix 1

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving; see also notes above.

Dosage:

Generalized tonic-clonic seizures, partial seizures, *by mouth*, ADULT 60–180 mg at night; CHILD up to 8 mg/kg daily

Febrile convulsions, *by mouth*, CHILD up to 8 mg/kg daily.

Neonatal seizures, *by intravenous injection* (dilute injection 1 in 10 with water for injections), NEONATE 5–10 mg/kg every 20–30 minutes up to plasma concentration of 40 mg/litre

Status epilepticus, *by intravenous injection* (dilute injection 1 in 10 with water for injections), ADULT 10 mg/kg at a rate of not more than 100 mg/minute (up to maximum total dose of 1 g); CHILD 5–10 mg/kg at a rate of not more than 30 mg/minute

NOTE. For therapeutic purposes phenobarbitone and phenobarbitone sodium may be considered equivalent in effect. Plasma concentration for optimum response 15–40 mg/litre (65–170 micromol/litre).

Adverse effects: sedation, mental depression, ataxia, nystagmus; allergic skin reactions including rarely, exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome (erythema multiforme); paradoxical excitement, restlessness and confusion in the elderly; irritability and hyperactivity in children; megaloblastic anaemia (may be treated with folic acid); osteomalacia; status epilepticus (on treatment withdrawal); hypotension, shock, laryngospasm and apnoea (with intravenous injection) .

Phenytoin sodium

Tablets, phenytoin sodium 25 mg, 50 mg, 100 mg

Capsules & kapseals, phenytoin sodium 25 mg, 100 mg

Injection (Solution for injection), phenytoin sodium 50 mg/ml, 5-ml ampoule

Syrup, *suspension* 25 mg/ml, 100 ml bottle .

Uses: generalized tonic-clonic seizures; partial seizures; status epilepticus

Contraindications: porphyria; avoid parenteral use in sinus bradycardia, sino-atrial block, second- and third-degree heart block, Stokes-Adams syndrome.

Precautions: hepatic impairment (reduce dose; Appendix 5); pregnancy (**important,** see notes above; Appendix 2); breastfeeding (see notes above; Appendix 3); diabetes mellitus; monitor blood counts; hypotension and heart failure (caution with parenteral use); intravenous administration—resuscitation facilities must be available; injection solution alkaline (irritant to tissues);

Interactions: Appendix 1

BLOOD OR SKIN DISORDERS. Patients or their carers should be told how to recognize signs of blood or skin disorders and advised to seek immediate medical attention if symptoms such as sore throat, rash, mouth ulcers, bruising or bleeding develop. Leukopenia which is severe, progressive or associated with clinical symptoms requires withdrawal (if necessary under cover of suitable alternative)

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving; see notes above.

Dosage:

Generalized tonic-clonic seizures, partial seizures, *by mouth*, ADULT initially 3–4 mg/kg daily (as a single dose *or* in 2 divided doses), increased gradually by 25 mg at intervals of 2 weeks as necessary (with plasma-phenytoin concentration monitoring); usual dose 200–500 mg daily; CHILD initially 5 mg/kg daily in 2 divided doses; usual dose range 4–8 mg/kg daily (maximum 300 mg).

NOTE. Plasma concentration for optimum response 10–20 mg/litre (40–80 micromol/litre).

PATIENT ADVICE. Preferably taken with or after food.

Status epilepticus, *by slow intravenous injection or by intravenous infusion* (with blood pressure and ECG monitoring), ADULT

15 mg/kg at a rate of not more than 50 mg/minute, as a loading dose; maintenance doses of about 100 mg *by mouth* or *by slow intravenous injection* should be given thereafter at intervals of 6–8 hours, monitored by measurement of plasma concentrations; rates and dose reduced according to weight; CHILD 15 mg/kg as a loading dose at rate of 0.5–1.5 mg/kg/minute; NEONATE 15–20 mg/kg as a loading dose at rate of 1–3 mg/kg/minute .

DILUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: gastric intolerance, headache, sleeplessness, agitation (during initial phase); sedation, confusion, blurred vision, ataxia, nystagmus, diplopia, slurred speech, cerebellarvestibular symptoms, behavioural disorders, hallucinations, hyperglycaemia (may be signs of overdosage); gingival hyperplasia, acne, coarse facies, hirsutism, fever, hepatitis, neurological changes (peripheral neuropathy, choreiform movements, impaired cognition, increased seizure frequency); osteomalacia, rickets (associated with reduced plasma calcium levels); lymph-node enlargement; rashes (discontinue; if mild re-introduce cautiously, but discontinue if recurrence); very rarely, Stevens-Johnson syndrome (erythema multiforme), systemic lupus erythematosus, toxic epidermal necrolysis; rarely blood disorders including megaloblastic anaemia (may be treated with folic acid), leukopenia, thrombocytopenia, agranulocytosis with or without bone marrow depression; intravenous administration— cardiovascular and CNS depression (particularly if administered too rapidly) with arrhythmias, hypotension and cardiovascular collapse, alterations in respiratory function (including respiratory collapse).

Sodium valproic acid

Gastro-resistant tablets (Enteric-coated tablets), sodium valproic acid 100 mg, 200 mg, 500 mg.

Syrup *(liquid, oral solution)* 200 mg/5 ml .

Uses: generalized tonic-clonic seizures; partial seizures; atonic seizures; absence seizures; myoclonic seizures; acute mania (section 24.2.2)

Contraindications: active liver disease, family history of severe hepatic dysfunction; pancreatitis; porphyria.

Precautions: monitor liver function before and during first 6 months of therapy, especially in patients at most risk (children under 3 years of age, those with metabolic disorders, degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation, or multiple antiepileptic therapy); ensure no undue potential for bleeding before starting and before major surgery or

anticoagulant therapy; renal impairment ; pregnancy. (**important** see notes above; Appendix 2 (neural tube screening)); breastfeeding (see notes above; Appendix 3); systemic lupus erythematosus; false-positive urine tests for ketones; avoid sudden withdrawal;

Interactions: Appendix 1

BLOOD OR HEPATIC DISORDERS. Patients their carers should be told how to recognize signs of blood or liver disorders, and advised to seek immediate medical attention if symptoms including loss of seizure control, malaise, weakness, anorexia, lethargy, oedema, vomiting, abdominal pain, drowsiness, jaundice, or spontaneous bruising or bleeding develop.

SKILLED TASKS. Restrictions on driving in patients with epilepsy, see notes above.

Dosage:

Generalized tonic-clonic seizures, partial seizures, absence seizures, atonic seizures; myoclonic seizures, *by mouth*, ADULT initially 600 mg daily in 2 divided doses, preferably after food, increased by 200 mg daily at 3-day intervals to maximum of 2.5 g daily in divided doses; usual maintenance dose 1–2 g daily (20–30 mg/kg daily); CHILD up to 20 kg, initially 20 mg/kg daily in divided doses, may be increased provided plasma concentrations monitored (above 40 mg/kg daily also monitor clinical chemistry and haematological parameters); CHILD over 20 kg, initially 400 mg daily in divided doses, increased until control (usually in range of 20–30 mg/kg daily); maximum 35 mg/kg daily.

NOTE. Plasma concentrations in therapeutic range of 40–100 mg/litre (280 to 700 micromol/litre); not generally considered useful in assessing control, but higher levels associated with increased incidence of adverse effects; indicator of compliance, dose change or co-medication.

Adverse effects: gastrointestinal irritation, nausea, increased appetite and weight gain, hyperammonaemia; ataxia, tremor; transient hair loss (regrowth may be curly); oedema, thrombocytopenia, inhibition of platelet aggregation; impaired hepatic function and rarely fatal hepatic failure (see Precautions withdraw treatment immediately if malaise, weakness, lethargy, oedema, abdominal pain, vomiting, anorexia, jaundice, drowsiness or loss of seizure control); sedation reported and also increased alertness; behavioural disturbances; rarely pancreatitis (measure plasma amylase if acute abdominal pain), leukopenia, pancytopenia, red cell hypoplasia, fibrinogen reduction; irregular periods, amenorrhoea, gynaecomastia, hearing loss, Fanconi syndrome, dementia, toxic epidermal necrolysis, Stevens-Johnson syndrome (erythema multiforme) and vasculitis reported

Section 6: Anti-infective drugs

6.1 Anthelminthics

6.1.1 Intestinal anthelminthics

Cestode infections (tapeworms) include intestinal taeniasis and cysticercosis, hymenolepiasis (dwarf tapeworm), diphyllobothriasis and echinococcosis (hydatid disease). Cysticercosis is a systemic infection caused by the larval form (cysticercus) of *Taenia solium*.

Neurocysticercosis occurs when the infection involves the brain. In man, echinococcosis is due to the larval stage of *Echinococcus granulosus* or *E. multilocularis*. The larvae (oncospheres) develop by expansion (cystic echinococcosis) or tumour-like infiltration (alveolar echinococcosis), respectively, in the liver, lungs, or other organs.

TAENIASIS. In taeniasis, **praziquantel** is well tolerated and extensively absorbed and kills adult intestinal taenia worms in a single dose. Praziquantel also kills *T. solium* cysticerci when taken for 14 days in high doses. It thus offers the prospect of a cure for neurocysticercosis, which has been treatable only by surgery, anti-inflammatory corticosteroids and anticonvulsants. However, because dying and disintegrating cysts may induce localized cerebral oedema, treatment with praziquantel must always be undertaken in a hospital setting. In addition, a corticosteroid is usually given to reduce the inflammatory response. **Albendazole** also kills neurocysticerci when given daily for one month; a corticosteroid or an antihistamine is also given to reduce any inflammatory reaction. Cestode infections, due to *T. solium*, occurring duringpregnancy should always be treated immediately (with praziquantel, but not with albendazole) because of the risk of cysticercosis.

ECHINOCOCCOSIS. In echinococcosis, although surgery is still the treatment of choice for operable cystic disease due to *Echinococcus granulosus* **albendazole** may be of value as adjunctive therapy. Alveolar echinococcosis due to *E. multilocularis* requires both surgery and long-term treatment with either mebendazole or albendazole to inhibit metastatic spread.

In *animal* studies, albendazole has been found to be teratogenic. It is contraindicated for the treatment of cestode infections in pregnancy; pregnancy should be excluded before treatment with albendazole (non-hormonal contraception during and for 1 month after treatment). For single dose or short-term use in pregnancy, see 6.1.1.2.

Albendazole

Tablets *(some chewable),* albendazole 400 mg .
Suspension 200 mg/ 5 ml .

Uses: *Echinococcus multilocularis* and *E. granulosus* infections prior to or not amenable to surgery; neurocysticercosis; nematode infections (sections 6.1.1.2 and 6.1.1.3); filariasis (6.1.2.2)

Contraindications: pregnancy (Appendix 2; see notes above and Precautions).

Precautions: liver function tests and blood counts before treatment and twice during each cycle; exclude pregnancy before starting treatment (non-hormonal contraception during and for 1 month after treatment); breastfeeding

Dosage:

Cystic echinococcosis, *by mouth*, ADULT over 60 kg, 800 mg daily in 2 divided doses for 28 days followed by 14 tablet-free days; ADULT less than 60 kg, 15 mg/kg daily in two divided doses (to a maximum daily dose of 800 mg) for 28 days followed by 14 tablet-free days; up to 3 courses may be given.

Alveolar echinococcosis, *by mouth*, ADULT as for cystic echinococcosis, but treatment cycles may need to be continued for months or years.

Neurocysticercosis, *by mouth*, ADULT over 60 kg, 800 mg daily in 2 divided doses for 8–30 days; ADULT less than 60 kg, 15 mg/ kg daily in two divided doses (to a maximum daily dose of 800 mg) for 8 to 30 days.

Adverse effects: gastrointestinal disturbances, headache, dizziness; increases in liver enzymes; reversible alopecia; rash; fever; leukopenia and rarely, pancytopenia; allergic shock if cyst leakage; convulsions and meningism in cerebral disease.

Praziquantel

Tablets, praziquantel 600 mg.

Uses: *Taenia saginata, T. solium, Hymenolepis nana* and *Diphyllobothrium latum* infections; trematode infections (sections 6.1.3.1 and 6.1.3.2).

Contraindications: ocular cysticercosis.

Precautions: neurocysticercosis (corticosteroid cover with monitoring, in hospital); pregnancy (Appendix 2); breastfeeding (avoid during and for 72 hours after treatment);

Interactions: Appendix 1

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving.

Dosage:

Taenia saginata and *T. solium* infections, *by mouth*, ADULT and CHILD over 4 years 5–10 mg/kg as a single dose.

Hymenolepis nana infection, *by mouth*, ADULT and CHILD over 4 years, 15–25 mg/kg as a single dose.

Diphyllobothrium latum infection, *by mouth,* ADULT and CHILD over 4 years, 10–25 mg/kg as a single dose .

Cysticercosis, *by mouth*, ADULT and CHILD over 4 years, 50 mg/kg daily in 3 divided doses for 14 days with prednisolone (or similar corticosteroid) given 2–3 days before and throughout treatment period .

Dermal cysticercosis, *by mouth,* ADULT and CHILD over 4 years, 60 mg/kg daily in 3 divided doses for 6 days.

Adverse effects: abdominal discomfort, nausea, vomiting, malaise; headache, dizziness, drowsiness; rarely hypersensitivity reactions including fever, urticaria, pruritus, eosinophilia (may be due to dead and dying parasites); in neurocysticercosis, headache, hyperthermia, seizures, intracranial hypertension (inflammatory response to dead and dying parasites in CNS).

6.1.1.2 Intestinal nematode infections

Intestinal nematode infections include ascariasis, hookworm infection, trongyloidiasis, enterobiasis, trichuriasis, trichostrongyliasis and capillariasis.

HOOKWORM INFECTIONS. Hookworm infections are caused by *Ancylostoma duodenale* (ancylostomiasis) and *Necator americanus* (necatoriasis); they are a major cause of iron deficiency anaemia in the tropics and sub-tropics. Ideally all cases of hookworm infection should be treated. However, when this is impracticable, priority should be given to women in second- and third- trimester pregnancy, children and debilitated patients. In hookworm, broad-spectrum anthelminthics are preferred wherever other nematode infections are endemic. Albendazole is effective.

In *animal* studies, **albendazole has** been found to be teratogenic. Albendazole should not be used during the first trimester of pregnancy to treat nematode infections. Both drugs are contraindicated for the treatment of cestode infections in pregnancy (see section 6.1.1.1).

Patients with iron-deficiency anaemia caused by hookworm infection require supplementary iron salts and should receive ferrous sulfate (200 mg for adults daily) for at least 3 months after the haemoglobin concentration of 12 g/100 ml is obtained.

ASCARIASIS. Ascariasis is an infection, usually of the small intestine, caused by *Ascaris lumbricoides* (roundworm). Single doses the broadspectrum anthelminthics **albendazole** is effective.

STRONGYLOIDIASIS. Strongyloidiasis is an infection of the small intestine caused by *Strongyloides stercoralis*. All infected

patients should be treated. **Albendazole** 400 mg, administered for 3 consecutive days is well tolerated by both adults and children aged over 2 years and it may eradicate up to 80% of infections.

ENTEROBIASIS. Enterobiasis is an infection of the large intestine caused by *Enterobius vermicularis* (pinworm, threadworm). All household members should be treated concurrently with a single dose of **albendazole**. Since reinfection readily occurs, at least one further dose should be given 2–4 weeks later.

TRICHURIASIS. Trichuriasis is an infection of the large intestine caused by *Trichuris trichiura*. Chemotherapy is required whenever symptoms develop or when faecal samples are found to be heavily contaminated (up to 10 000 eggs per gram). A single dose of **albendazole** (400 mg) can be effective in mild to moderate infections; heavier infections require a 3-day course.

TRICHOSTRONGYLIASIS. Trichostrongyliasis is an infection of the small intestine caused by *Trichostrongylus* spp. In symptomatic trichostrongyliasis, a single dose **albendazole** (400 mg) is effective.

Albendazole

Tablets *(some chewable),* albendazole 400 mg

Uses: ascariasis, hookworm infections, strongyloidiasis, enterobiasis, trichuriasis, trichostrongyliasis, and capillariasis; cestode infections (section 6.1.1.1); tissue nematode infections (section 6.1.1.3); filariasis (6.1.2.2).

Precautions: pregnancy (see notes above and Appendix 2; also section 6.1.1.1)

Dosage:

Ascariasis, hookworm infections, enterobiasis, and trichostrongyliasis, *by mouth*, ADULT and CHILD over 2 years, 400 mg as a single dose Trichuriasis, *by mouth*, ADULT and CHILD over 2 years, 400 mg as a single dose (for moderate infections) or 400 mg daily for 3 days (severe infections) Strongyloidiasis, *by mouth*, ADULT and CHILD over 2 years, 400 mg daily for 3 days

Adverse effects: gastrointestinal discomfort, headache; adverse effects associated with use in cestode infections (section 6.1.1.1).

6.1.1.3 Tissue nematode infections

Tissue nematode infections include dracunculiasis, trichinellosis, cutaneous larva migrans, visceral larva migrans, anisakiasis and angiostrongyliasis.

DRACUNCULIASIS. Dracunculiasis (dracontiasis, guinea-worm infection) is caused by infection with *Dracunculus*

medinensis, acquired through drinking water containing larvae that develop in small freshwater crustaceans. **Metronidazole** (25 mg/kg daily for 10 days, with a daily maximum of 800 mg for children) provides rapid symptomatic relief. It also weakens the anchorage of the worms in the subcutaneous tissues, and they can then be removed by traction. However, since it has no effect on the larvae of pre-emergent worms, it does not immediately prevent transmission.

TRICHINELLOSIS. Trichinellosis (trichinosis) is caused by infection with the larvae of *Trichinella spiralis*. Each case of confirmed or even suspected trichinellosis infection should be treated in order to prevent the continued production of larvae. In both adults and children, **albendazole** (400 mg for 3 days) is effective. Prednisolone (40–60 mg daily) may be needed to alleviate the allergic and inflammatory symptoms.

CUTANEOUS LARVA MIGRANS. Cutaneous larva migrans (creeping eruption) is caused by infection with larvae of animal hookworms, usually *Ancylostoma braziliense* and *A. caninum* which infect cats and dogs. **Albendazole** in a single dose of 400 mg is effective.

6.1.2 Antifilarials

Lymphatic filariasis

Lymphatic filariasis is caused by infection with *Wuchereria bancrofti* (bancroftian filariasis), *Brugia malayi* or *B. timori* (brugian filariasis). Occult filariasis (tropical pulmonary eosinophilia) is a clinical variant of *W. bancrofti* infection. Individual treatment with **diethy lcarbamazine** which has both microfilaricidal and macrofilaricidal activity is effective. Total cumulative dosages of 72 mg/kg are generally recommended for *Wuchereria bancrofti* infections with half this dose used for *Brugia malayi* and *B. timori* infections. In all cases treatment should be initiated with smaller doses for 2–3 days to avoid the danger of immunological reactions. Rigorous hygiene to the affected limbs with adjunctive measures to minimize infection and promote lymph flow are important for reducing acute episodes of inflammation.

Albendazole 600 mg with either diethylcarbamazine or ivermectin may be used for long periods of time every year in areas endemic for filaria.

Trials in India and China have shown that the consistent use for 6–12 months of table salt containing diethylcarbamazine 0.1% can eliminate *W. bancrofti;* a concentration of 0.3% for 3–4 months may be required where *B. malayi* is endemic.

Diethylcarbamazine citrate

Tablets, diethylcarbamazine citrate 50 mg, 100 mg, 250 mg;
Syrup, 120 mg/ 5 ml, 50 mg / 5 ml (paediatric)

Uses: systemic lymphatic filariasis and occult filariasis;

Contraindications: pregnancy (delay treatment until after delivery)

Precautions: renal impairment (reduce dose;); cardiac disorders; other severe acute disease delay diethylcarbamazine treatment until after recovery.

Dosage:

Lymphatic filariasis (bancroftian), *by mouth*, ADULT and CHILD over 10 years, 6 mg/kg daily, preferably in divided doses after meals, for 12 days; CHILD under 10 years, half the adult dose;

Mass treatment control programmes, ADULT and CHILD over 10 years, 6 mg/kg in divided doses over 24 hours, once a year; CHILD under 10 years, half the adult dose.

Lymphatic filariasis (brugian), *by mouth*, ADULT and CHILD over 10 years, 3–6 mg/kg, preferably in divided doses after meals, for 6–12 days; CHILD under 10 years, half the adult dose.

Mass treatment control programmes, ADULT and CHILD over 10 years, 3–6 mg/kg in divided doses over 24 hours, 6 times at weekly or monthly intervals; CHILD under 10 years, half the adult dose.

Occult filariasis, *by mouth*, ADULT 8 mg/kg daily for 14 days, repeated as necessary if symptoms return .

NOTE. The above dose regimens are intended only as a guide, since many countries have developed specific treatment regimens.

Adverse effects: headache, dizziness, drowsiness, nausea and vomiting; immuno logical reactions, within a few hours of the first dose, subsiding by fifth day of treatment, including fever, headache, joint pain, dizziness, anorexia, malaise, transient haematuria, urticaria, vomiting, asthma in asthmatics (similar to Mazzotti reaction—see section 6.1.2.3) induced by disintegrating microfilariae; nodules (palpable subcutaneously and along spermatic cord—formed by recently killed worms); transient lymphangitis and exacerbation of lymphoedema.

6.2 Antibacterials

6.2.1 Beta-lactam drugs

Beta-lactam antibiotics including penicillins, Cephalosporins and carbapenems share a common structure; they are bactericidal, their mechanism of action resulting from inhibition of peptidoglycan, a mucopeptide in bacterial cell walls.

Benzylpenicillin and **phenoxymethylpenicillin** are active against susceptible strains of Gram-positive bacteria and Gramnegative bacteria, spirochaetes, and actinomycetes, but are inactivated by penicillinase and other beta-lactamases.

Benzathine benzylpenicillin is a long-acting preparations which slowly release benzylpenicillin on injection. A range of penicillins with improved stability to gastric acid and penicillinases have been produced by substitution of the 6-amino position of 6-aminopenicillanic acid.

Cloxacillin is an isoxazoyl penicillin which is resistant to staphylococcal penicillinase. Broad-spectrum penicillins such as **ampicillin** are acid-stable and active against Gram-posi tive and Gram-negative bacteria, but are inactivated by penicillinase.

Beta-lactamase inhibitors such as **clavulanic acid** are often necessary to provide activity against beta-lactamases produced by a wide range of both Gram-negative and Grampositive bacteria, but the treatment for such proven patients is best done by referral to higher centres.

Cephalosporins are classified by generation, with the first generation agents having Gram-positive and some Gramnegative activity; the second generation drugs have improved Gram-negative activity and the third generation Cephalosporins have a wider spectrum of activity, although may be less active against Gram-positive bacteria than first generation drugs, but they are active against Gram-negative Enterobacteriaceae and *Pseudomonas aeruginosa*.

Carbapenems are semisynthetic derivatives of *StreptomycesL cattleya*. They have a broad spectrum of activity and are stable to most penicillinases. They should be reserved for severe infections resistant to other antibiotics. Penicillins may cause encephalopathy due to cerebral irritation. This rare, but serious adverse effect may result from very high doses or in severe renal failure. Penicillins should not be given by intrathecal injection because they can cause encephalopathy which may be fatal.

HYPER SENSITIVITY. The most important adverse effect of penicillins is hypersensitivity which causes rashes and, occasionally anaphylaxis, which can be fatal. A careful history should be taken with regard to previous allergic reactions. If rashes develop, another antimicrobial should be substituted. Patients who are allergic to one penicillin will be allergic to them all and about 10% of penicillin-sensitive patients will be allergic to Cephalosporins and other beta-lactams. However, very few penicillin-allergic patients are at risk of anaphylaxis; a penicillin should not be withheld unnecessarily for severe infections; however, facilities should be available for treating anaphylaxis.

6.2.1.1 Benzylpenicillins and phenoxymethylpenicillin

Benzylpenicillin remains an important and useful antibiotic but it is inactivated by bacterial beta-lactamases. It is effective for many streptococcal, (including pneumococcal), gonococcal and meningococcal infections and also for anthrax, diphtheria, gas gangrene, leptospirosis, tetanus and treatment of Lyme disease in children. Pneumococci, meningococci and gonococci often have decreased sensitivity to penicillin and benzylpenicillin is no longer the first choice for pneumococcal meningitis. Benzylpenicillin is given by injection as it is inactivated by gastric acid and absorption from the intestinal tract is low. Depot preparations are used when therapeutic concentrations need to be sustained for several hours. Benzathine benzylpenicillin- Provides a tissue depot from which the drug is slowly absorbed over a period of 12 hours to several days. They are the preferred choice for the treatment of syphilis or yaws.

Phenoxymethylpenicillin is suitable for oral administration; it has a similar spectrum of activity but is less effective than benzylpenicillin. It should not be used for serious infections because absorption can be unpredictable and plasma concentrations variable.

Benzylpenicillin

Injection (Powder for solution for injection), benzylpenicillin sodium vial (1 lakh units, 3 lakh units)

Uses: pneumonia; throat infections; otitis media; Lyme disease in children; streptococcal endocarditis; meningococcal meningitis; necrotizing enterocolitis; necrotizing fasciitis; leptospirosis; neurosyphilis; anthrax; actinomycosis; brain abscess; gas gangrene; cellulitis; osteomyelitis.

Contraindications: penicillin hypersensitivity (see notes above); avoid intrathecal route (see notes above)

Precautions: history of allergy (see notes above); renal failure ; heart failure; pregnancy and breastfeeding (Appendices 2 and 3);

Interactions: Appendix 1

Dosage:

Mild to moderate infections due to sensitive organisms, *by intramuscular injection or by slow intravenous injection or by intravenous infusion*, ADULT 1 million- 4 million units daily in 2–4 divided doses, with higher doses in severe infections and duration of treatment depending on disease (see also below); NEONATE 80,000 units/ kg daily in 2 divided doses; INFANT 1 to 4 weeks, 1,20,000 units /kg daily in 3 divided doses; CHILD 1 month to 12 years, 1.5 lakh units /kg daily in 4 divided doses, with higher doses in severe infections (see also below).

Bacterial endocarditis, *by slow intravenous injection or by intravenous infusion*, ADULT up to 12 million daily in 6 divided doses.

Meningococcal meningitis, *by slow intravenous injection or by intravenous infusion*, ADULT up to 24 million units doses; PREMATURE INFANT and NEONATE 100 mg/kg daily in 2 divided doses; INFANT 150 mg/kg daily in 3 divided doses; CHILD 1 month to 12 years, 50,000 – 1 lakh units in divided doses.

Suspected meningococcal disease (before transfer to hospital), *by intramuscular injection or by slow intravenous injection*.

ADULT and CHILD over 10 years, 2 million units; CHILD 1 to 9 years, 1 million units; CHILD under 1 year, 5 lakh units.

Neurosyphilis, *by slow intravenous injection*, ADULT 1.8–2.4 g every 4 hours for 2 weeks.

Congenital syphilis, *by intramuscular injection or by slow intravenous injection*, CHILD up to 2 years, 30 mg/kg daily in 2 divided doses for 10 days; CHILD over 2 years, 120–180 mg/kg (to a maximum of 1.44 g) daily in divided doses for 14 days.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: hypersensitivity reactions including urticaria, fever, joint pains, rashes, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, interstitial nephritis (see also notes above); diarrhoea, antibioticassociated colitis; neutropenia, thrombocytopenia, coagulation disorders, central nervous system toxicity, including convulsions, coma, and encephalopathy (associated with high dosage, or severe renal failure); electrolyte disturbances; Jarisch-Herxheimer reaction (during treatment for syphilis and other spirochaete infections, probably due to release of endotoxins); inflammation, phlebitis or thrombophlebitis at injection sites.

Benzathine benzylpenicillin

Injection (Powder for solution for injection), benzathine benzyl penicillin, 1.8-g vial (equivalent to benzylpenicillin 1.44 g, 2.4 million units), \4 /6/8/12/20/24 lakh units vials.

Uses: streptococcal pharyngitis; diphtheria carrier state; syphilis and other treponemal infections (yaws, pinta, bejel); rheumatic fever prophylaxis.

Contraindications: penicillin hypersensitivity (see notes above); intravascular injection; neurosyphilis.

Precautions: history of allergy (see notes above); renal failure; pregnancy and breastfeeding (Appendices 2 and 3);

Interactions: Appendix 1

Dosage:

Streptococcal pharyngitis; primary prophylaxis of rheumatic

fever, *by deep intramuscular injection*, ADULT and CHILD over 30 kg body weight, 1.2 million as a single dose; CHILD under 30 kg body-weight, 0.6 to 0.9 million units as a single dose

Secondary prophylaxis of rheumatic fever, *by deep intramuscular injection*, ADULT and CHILD over 30 kg body-weight, 1.2 million once every 3–4 weeks; CHILD under 30 kg bodyweight, 0.6 million units once every 3–4 weeks.

Early syphilis, *by deep intramuscular injection*, ADULT 2.4 million units as a single dose, divided between 2 sites Late syphilis, *by deep intramuscular injection*, ADULT 2.4 million divided between two sites, once weekly for 3 consecutive weeks.

Congenital syphilis (where no evidence of CSF involvement), *by deep intramuscular injection*, CHILD up to 2 years, 50,000 units /kg as a single dose.

Yaws, pinta, and bejel, *by deep intramuscular injection*, ADULT 1.2 million units as a single dose; CHILD 0.6 million units as a single dose.

RECONSTITUTIONAND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: hypersensitivity reactions including urticaria, fever, joint pains, rashes, angioedema, anaphylaxis, serum sickness-like reaction, haemolytic anaemia, interstitial nephritis (see also notes above); neutropenia, thrombocytopenia, coagulation disorders and central nervous system toxicity (associated with high dosage or severe renal failure); Jarisch Herxheimer reaction (during treatment for syphilis and other spirochaete infections, probably due to release of endotoxins); rarely, non-allergic (embolic-toxic) reactions; pain and inflammation at injection site.

Phenoxymethylpenicillin

Tablets, phenoxymethylpenicillin (as potassium salt) 65 mg, 130 mg, 250 mg, 500 mg.

Oral suspension (Powder for oral suspension), phenoxy-methylpenicillin (as potassium salt) 125 mg/5 ml when reconstituted.

Uses: streptococcal pharyngitis; otitis media; erysipelas; mouth infections; secondary prophylaxis of rheumatic fever; postsplenectomy prophylaxis.

Contraindications: hypersensitivity to penicillins (see notes above); serious infections (see notes above).

Precautions: history of allergy (see notes above); pregnancy and breastfeeding (Appendices 2 and 3);

Interactions: Appendix 1

Dosage:

Infections due to sensitive organisms, *by mouth*, ADULT 500–750 mg every 6 hours; CHILD up to 1 year, 62.5 mg every 6 hours; CHILD 1–5 years, 125 mg every 6 hours; CHILD 6–

12 years, 250 mg every 6 hours.

Secondary prophylaxis of rheumatic fever, *by mouth*, ADULT 500 mg twice daily; CHILD 1–5 years, 125 mg twice daily; CHILD 6–12 years, 250 mg twice daily PATIENT ADVICE. Phenoxymethylpenicillin should be taken at least 30 minutes before or 2 hours after food.

Adverse effects: hypersensitivity reactions including urticaria, joint pain, rash, angioedema, anaphylaxis (see notes above); nausea and diarrhoea.

6.2.1.2 Cloxacillin, ampicillin, and amoxicillin.

Cloxacillin is used to treat infections due to penicillinase producing staphylococci which are resistant to benzyl-penicillin. It is acid-stable and may therefore be given by mouth as well as by injection.

Ampicillin is active against certain Gram-positive and Gram-negative organisms. It is used to treat a wide range of infections including otitis media, respiratory-tract and urinary-tract infections, and gonorrhoea due to susceptible bacteria. However, ampicillin is inactivated by penicillinases including those produced by *Staphylococcus aureus* and by common Gramnegative bacilli such as *Escherichia coli*; many strains of *Haemophilus influenzae*, *Moraxella catarrhalis*, *Neisseria gonorrhoea*, and *Salmonella* and *Shigella* spp. are resistant.

There are geographical variations in the incidence of resistance and an awareness of local patterns is important. In some areas, oral use should be restricted to treatment of *Shigella* infections; it is given in an oral dose of 1 g every 6 hours for 7–10 days.

Amoxicillin has a similar spectrum of activity to ampicillin, but is also inactivated by penicillinases. However, it is better absorbed after oral administration than ampicillin and higher plasma and tissue levels are achieved. Amoxicillin is preferred to ampicillin for the treatment of some infections including otitis media and respiratory-tract and urinary-tract infections.

Clavulanic acid is a beta-lactamase inhibitor. Available at higher referral centres, it has no significant antibacterial activity but in combination with.

Amoxicillin widens amoxicillin's spectrum of activity and allows its use against amoxicillin-resistant strains of bacteria. It is used in respiratory-tract, genito-urinary and abdominal infections, cellulitis, animal bites, and dental infections. These antibiotics may also be administered with an aminoglycoside to increase their spectrums of activity. The penicillin and aminoglycoside should not be mixed before or during administration, because loss of aminoglycoside activity can occur on mixing.

Amoxicillin

Amoxicillin is a representative broad-spectrum penicillin. Various drugs can serve as alternatives.

Capsules, amoxicillin 250 mg, 500 mg,

Tablet 125 mg (paediatric), 250 mg (DS) 750 mg (dispersible)

Oral suspension (Powder for oral suspension), amoxicillin 125 mg/5 ml

Uses: urinary-tract infections, upper respiratory-tract infections, bronchitis; pneumonia; otitis media; dental abscess; osteomyelitis; Lyme disease in children; endocarditis prophylaxis; post-splenectomy prophylaxis; gynaecological infections;gonorrhoea; *Helicobacter pylori* eradication (section 17.1)

Contraindications: hypersensitivity to penicillins (see notes above).

Precautions: history of allergy (see notes above); renal impairment ; erythematous rashes common in glandular fever, chronic lymphatic leukaemia, and possibly HIV infection; pregnancy and breastfeeding (Appendices 2 and 3);

Interactions: Appendix 1

Dosage:

Infections due to sensitive organisms, *by mouth*, ADULT and CHILD over 10 years, 250 mg every 8 hours, doubled in severe infections; CHILD up to 10 years, 125 mg every 8 hours, doubled in severe infections.

Severe or recurrent purulent respiratory-tract infections, *by mouth*, ADULT 3 g every 12 hours .

Dental abscess (short course), *by mouth*, ADULT 3 g repeated once after 8 hours.

Urinary-tract infections (short course), *by mouth*, ADULT 3 g repeated once after 10–12 hours.

Gonorrhoea (short course), *by mouth*, ADULT 3 g as a single dose .

Otitis media (short course), *by mouth*, CHILD aged 3–10 years, 750 mg twice daily for 2 days.

Adverse effects: nausea and vomiting, diarrhoea; rashes (hypersensitivity or toxic response; may be serious reaction—discontinue treatment); hypersensitivity reactions including urticaria, angioedema, anaphylaxis, serum sickness- like reactions, haemolytic anaemia, interstitial nephritis (see also notes above); rarely, antibiotic-associated colitis; neutropenia, thrombocytopenia, coagulation disorders; rarely, central nervous system disorders including convulsions—associated with high doses or impaired renal function.

Ampicillin

Injection (Powder for solution for injection), ampicillin (as sodium salt) 500-mg vial.

Uses: mastoiditis; gynaecological infections; septicaemia; peritonitis; endocarditis; meningitis; cholecystitis; osteomyelitis.

Contraindications: hypersensitivity to penicillins (see notes above).

Precautions: history of allergy (see notes above); renal impairment ; erythematous rashes common in glandular fever, chronic lymphatic leukaemia, and possibly HIV infection; pregnancy and breastfeeding (Appendices 2 and 3);

Interactions: Appendix 1

Dosage:

Severe infections due to sensitive organisms, *by intramuscular, by slow intravenous injection or by intravenous infusion*, ADULT 500 mg every 4–6 hours; CHILD under 10 years, half the adult dose.

Meningitis, *by slow intravenous injection*, ADULT 1–2 g every 3–6 hours (maximum 14 g daily); CHILD 150–200 mg/kg daily in divided doses.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: nausea and vomiting, diarrhoea; rashes (hypersensitivity or toxic response—may be serious reaction, discontinue treatment); hypersensitivity reactions including urticaria, angioedema, anaphylaxis, serum sickness-like reaction, haemolytic anaemia, interstitial nephritis (see also notes above); rarely, antibiotic-associ ated colitis; neutropenia, thrombocytopenia, coagulation disorders.

Cloxacillin

Cloxacillin is a representative penicillinase-resistant penicillin. Various drugs can serve as alternatives.

Capsules, cloxacillin (as sodium salt) 250 mg, 500 mg, *Syrup* 125 mg/ 5 ml.

Oral solution (Powder for oral solution), cloxacillin (as sodium salt) 125 mg/5 ml when reconstituted.

Injection (Powder for solution for injection), cloxacillin (as sodium salt) 500-mg vial

Uses: infections due to beta -lactamase produc ing staphylococci including impetigo, cellulitis and other soft-tissue infections; staphylococcal endocarditis, septicaemia, pneumonia and osteomyelitis.

Contraindications: hypersensitivity to penicillins (see notes above).

Precautions: history of allergy (see notes above); renal and hepatic impairment (Appendices 4 and 5); heart failure; pregnancy and breastfeeding (Appendices 2 and 3);

Interactions: Appendix 1

Dosage:

Infections due to susceptible beta - lactamase producing staphylococci, *by mouth*, ADULT 500 mg 4 times daily, doubled in severe infection; *by intramuscular injection*, 250 mg every 4–6 hours, doubled in severe infection; *by slow intravenous injection or intravenous infusion*, 1–2 g every 6 hours; CHILD up to 2 years, quarter adult dose; CHILD 2–10 years, half adult dose

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: nausea and vomiting, diarrhoea; hypersensitivity reactions including urticaria, fever, joint pain, rashes, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, interstitial nephritis (see also notes above); neutropenia, thrombocytopnia, coagulation disorders; antibiotic-associated colitis; hepatitis and cholestatic jaundice—may be delayed in onset; electrolyte disturbances; pain, inflammation, phlebitis or thrombophlebitis.

6.2.1.3 Cephalosporins and imipenem with cilastatin

Reserved for use in higher referral centres.

6.2.2 Other antibacterials

Chloramphenicol

Chloramphenicol is a potent broad-spectrum antibiotic. It is associated with serious haematological adverse effects and should be reserved for the treatment of severe infections, particularly those caused by *Haemophilus influenzae* and typhoid fever. The oily suspension shold be reserved for use in situations of catastrophic epidemics of meningococcal meningitis occurring mainly in sub-Saharan Africa, during which the medical services are overwhelmed by the epidemic and in which the overwhelming scale of the epidemic precludes any other form of antimicrobial therapy.

Chloramphenicol

Chloramphenicol is a representative broad-spectrum antibiotic. Various drugs can serve as alternatives.

Chloramphenicol (oily injection) is a complementary drug

Capsules, chloramphenicol 125 mg, 250 mg, 500 mg.

Tablets/dragees 250 mg.

Oral suspension, chloramphenicol (as palmitate) 125 mg/5 ml

Injection (Powder for solution for injection), chloramphenicol (as sodium succinate) 1-g vial

Oily injection (Suspension for injection), chloramphenicol (as sodium succinate) 500 mg/ml, 2-ml ampoule.

Uses: severe life-threatening infections, particularly those caused by *Haemophilus influenzae*, and typhoid fever; also, cerebral abscess; mastoiditis; relapsing fever; gangrene; granuloma inguinale; listeriosis; severe melioidosis; plague; psitticosis; tularaemia; Whipple disease; septicaemia; empirical treatment of meningitis.

Contraindications: pregnancy (Appendix 2); porphyria.

Precautions: avoid repeated courses and prolonged use; reduce dose in hepatic impairment and renal failure ; blood counts required before and during treatment; monitor plasma concentrations in neonates (see below); breastfeeding (Appendix 3);

Interactions: Appendix 1

Dosage:

Infections due to susceptible organisms (not susceptible to other antimicrobials), *by mouth or by intravenous injection or intravenous infusion*, ADULT and CHILD 50 mg/kg daily in 4 divided doses; up to 100 mg/kg daily in divided doses, in Severe infections such as meningitis, septicaemia, and haemophilus epiglottitis (reduce high doses as soon as clinically indicated); INFANTS under 2 weeks, 25 mg/kg daily in 4 divided doses, 2 weeks to 1 year, 50 mg/kg daily in 4 divided doses.

Epidemics of meningococcal meningitis, *by intramuscular injection* (of oily injection), ADULT 0.5–1 g daily; CHILD 25 mg/ kg daily.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions. The oily injection is for intramuscular use only (see notes above).

NOTE. Plasma concentration monitoring required in neonates and preferred in those under 4 years of age; recommended peak plasma concentration (measured approximately 1 hour after intravenous injection or infusion) 15–25 mg/litre; pre-dose 'trough' concentration should not exceed 15 mg/litre.

Adverse effects: bone marrow depression—reversible and irreversible aplastic anaemia (with reports of leukaemia), anaemia, leukopenia and thrombocytopenia; nocturnal haemoglobinuria; peripheral neuritis and optic neuritis; nausea, vomiting, diarrhoea, stomatitis, glossitis; hypersensitivity reactions including, rashes, fever, angioedema and rarely anaphylaxis; grey syndrome (vomiting, greenish diarrhoea, abdominal distension, hypothermia, pallid cyanosis, irregular respiration, circulatory collapse) may follow excessive doses in neonates with immature hepatic metabolism; also reported in infants born to mothers treated in late pregnancy.

6.2.2.2 Quinolones

Ciprofloxacin is active against both Gram-positive and Gram negative bacteria. It is particularly active against salmonella, shigella, campylobacter, neisseria and pseudomonas. It is also active against chlamydia and some mycobacteria. Most anaerobic organisms are not susceptible. Ciprofloxacin is used with doxycycline and metronidazole to treat pelvic inflammatory disease. **Nalidixic acid** is an older quinolone effective in uncomplicated urinary-tract infections and, in the treatment of shigella in areas where it remains susceptible. *Precautions.* Quinolones should be used with caution inpatients with a history of epilepsy or conditions predisposing to seizures; convulsions may be induced in patients with or without a history of convulsions; also, use with caution in G6PD deficiency, pregnancy (Appendix 2) or breastfeeding (Appendix 3); use in children or adolescents is generally not recommended (quinolones cause arthropathy in weight- bearing joints in young *animals*), although in some specific circumstances, short-term use may be justified. Exposure to sunlightshould be avoided (discontinue if photosensitivity occurs).*Adverse effects.* Adverse effects of quinolones include nausea,vomiting, dyspepsia, abdominal pain,diarrhoea, and rarely,antibiotic-associated colitis; headache, dizziness, sleep disorders,rash (rarely Stevens-Johnson syndrome and toxic epidermal necrolysis), and pruritus; less commonly, anorexia,transient disturbances in liver enzymes and bilirubin and increases in blood urea and creatinine;drowsiness, restlessness,depression, confusion, hallucinations, convulsions, paraesthesia; photosensitivity; hypersensitivity reactions including fever, urticaria, angioedema, arthralgia, myalgia, and anaphylaxis;blood disorders; disturbances in vision, taste, hearing, and smell; isolated reports of tendon inflammation and damage; ifpsychiatric, neurological, or hypersensitivity reactions occur—discontinue drug.

Ciprofloxacin

Ciprofloxacin is a representative quinolone antibacterial. Various drugs can serve as alternatives.

Tablets, ciprofloxacin (as hydrochloride) 100 mg, 250 mg, 500 mg, 750 mg

Capsules, 250 mg, 500 mg.

Infusion, 2mg/ ml in 100 ml infusion packs.

Uses: gastroenteritis—including cholera, shigellosis, travellers' diarrhoea, campylobacter and salmonella enteritis; typhoid;gonorrhoea; chancroid; legionnaires' disease; meningitis (including meningococcal meningitis prophylaxis); respiratory-tract infections including pseudomonal infections in cystic fibrosis, but not

pneumococcal pneumonia; urinary tract infections; bone and joint infections; septicaemia; skininfections; prophylaxis in surgery.

Precautions: see notes (above); hepatic impairment ; renal failure ; avoid excessive alkalinity of urine and ensure adequate fluid intake as risk of crystalluria;

Interactions: Appendix 1

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving.

Dosage :

Infections due to susceptible organisms, *by mouth*, ADULT 250–750 mg twice daily.

Acute uncomplicated cystitis, *by mouth*, ADULT 100 mg twice daily for 3 days.

Gonorrhoea, chancroid, shigellosis, or cholera, *by mouth*, 500 mg as a single dose.

Pseudomonal lower respiratory-tract infection in cystic fibrosis, *by mouth*, ADULT 750 mg twice daily; CHILD 5–17 years (see Precautions) up to 20 mg/kg twice daily (maximum 1.5 g daily).

Surgical prophylaxis, *by mouth*, ADULT 750 mg 60–90 minutes before procedure .

Prophylaxis of meningococcal meningitis, *by mouth*, ADULT 500 mg as a single dose.

Systemic infections may require infusion followed by oral 500 to 750 mg 12 hourly.

Adverse effects: see notes above; flatulence, dysphagia, tremor, altered prothrombin concentration, jaundice and hepatitis, renal failure, nephritis, vasculitis, erythema nodosum, petechiae, haemorrhagic bullae, tinnitus, tenosynovitis, and tachycardia, also reported .

Nalidixic acid

Tablets, nalidixic acid 125 mg, 150 mg. 300 mg, 500 mg .

Syrup 300 mg per 5 ml.

Uses: urinary-tract infections; shigellosis.

Precautions: see notes above; porphyria; hepatic impairment ; renal failure ; false positive urinary glucose (if tested for reducing substances); monitor blood counts, renal and liver function if treatment exceeds 2 weeks;

Interactions: Appendix 1

Dosage:

Urinary-tract infections, *by mouth*, ADULT 1 g every 6 hours for 7 days, reduced in chronic infections to 500 mg every 6 hours; CHILD over 3 months, maximum 50 mg/kg daily in divided doses, reduced in prolonged treatment to 30 mg/kg daily. Shigellosis, *by mouth*, ADULT 1 g every 6 hours for 5 days; CHILD over 3 months, 15 mg/kg every 6 hours for 5 days.

PATIENT ADVICE. Take on an empty stomach, preferably one hour before a meal.

Adverse effects: see notes above; toxic psychosis, weakness, increased intracranial pressure, cranial nerve palsy, cholestasis and metabolic acidosis also reported.

6.2.2.3 Tetracyclines

Doxycycline is a tetracycline and is a broad-spectrum antibiotic effective for conditions caused by chlamydia, rickettsia, brucella and the spirochaete, *Borrelia burgdorferi* (Lyme disease). It is the preferred tetracycline since it has a more favourable pharmacokinetic profile than tetracycline. It is deposited in growing bone and teeth causing staining and occasionally dental hypoplasia. It should not be given to children under 8 years or pregnant women; in some countries, use in children under 12 years is contraindicated.

Doxycycline

Doxycycline is a representative broad-spectrum antibiotic. Various drugs can serve as alternatives.

Capsules, doxycycline (as hydrochloride) 100 mg.

Uses: respiratory-tract infections, including pneumonia and chronic bronchitis; urinary-tract infections; syphilis; chlamydia, mycoplasma, and rickettsia; prostatitis; lymphogranuloma venereum; pelvic inflammatory disease (with metronidazole); Lyme disease; brucellosis (with rifampicin); leptospirosis, scrub typhus and travellers' diarrhoea; psittacosis; cholera; melioidosis; plague; anthrax; Q fever; malaria (section 6.4.3)

Contraindications: pregnancy (Appendix 2); children (see notes above); porphyria; systemic lupus eryt hematosus.

Precautions: avoid exposure to sunlight or sunlamps—photosensitivity reported; hepatic impairment ; breastfeeding (Appendix 3);

Interactions: Appendix 1

Dosage:

Infections due to susceptible organisms, *by mouth*, ADULT and CHILD over 8 years, 200 mg on first day then 100 mg daily.

In severe infections, 200 mg daily.

Syphilis, *by mouth*, 200–300 mg daily in 1–2 divided doses.

Uncomplicated genital chlamydia, non-gonococcal urethritis, *by mouth*, 100 mg twice daily.

Louse and tick-borne relapsing fevers, *by mouth*, 100 mg or 200 mg as a single dose.

Cholera, *by mouth*, ADULT 300 mg as a single dose; CHILD over 8 years, 100 mg as a single dose.

PATIENT ADVICE. Capsules should be swallowed whole with plenty of fluid while sitting or standing to prevent oesophageal irritation. May be given with milk or food to counter gastric irritation.

Adverse effects: gastrointestinal disturbances; erythema (discontinue treatment); photosensitivity; headache and visual disturbances; hepatotoxicity, pancreatitis, and antibiotic associated colitis reported; staining of growing teeth and occasional dental hypoplasia.

6.2.2.4 Macrolides

Erythromycin is a macrolide; it has an antibacterial spectrum that is similar but not identical to penicillin and is used as an alternative in penicillin-allergic patients. It is effective in respiratory infections, whooping cough, legionnaires' disease and campylobacter enteri.

Erythromycin

Erythromycin is a representative macrolide antibiotic. Various drugs can serve as alternatives.

Tablets, erythromycin (as estolate) 100 mg, 125 mg, 250 mg, 333 mg, 500 mg; erythromycin (as stearate) 250 mg, 400 mg, 500 mg; erythromycin (as ethyl succinate) 333 mg

Capsules, erythromycin 250 mg.

Oral suspension, syrup, erythromycin (as stearate) 100 mg/ 5 ml (dry) , 125 mg/5 ml; erythromycin (as ethyl succinate) 125 mg/5 ml.

Uses: alternative to penicillin in hypersensitive patients; pneumonia; legionnaires' disease; syphilis; chancroid; nongonococcal urethritis; prostatitis; lymphogranuloma venereum; campylobacter enteritis; relapsing fever; diphtheria and whooping cough prophylaxis.

Contraindications: hypersensitivity to erythromycin or other macrolides; porphyria

Precautions: hepatic impairment and renal failure; prolongation of the QT interval (tachycardia reported); pregnancy (not known to be harmful); breastfeeding (Appendix 3);

Interactions: Appendix 1

Dosage:

Infections due to sensitive organisms, *by mouth*, ADULT and CHILD over 8 years, 250–500 mg every 6 hours; up to 4 g daily in severe infections; CHILD up to 2 years, 125 mg every 6 hours, doubled in severe infections; CHILD 2–8 years, 250 mg every 6 hours, doubled in severe infections.

Early syphilis, *by mouth*, ADULT 500 mg 4 times daily for 14 days.

Non-gonococcal urethritis, *by mouth*, ADULT 500 mg 4 times daily for 7 days.

(*Severe infections, by intravenous infusion, ADULT and CHILD 50 mg/kg daily by continuous infusion or in divided doses every 6 hours if injections are available).*

PATIENT ADVICE. Gastro-resistant tablets and capsules should be swallowed whole.

Adverse effects: nausea, vomiting, abdominal discomfort,

diarrhoea (and antibiotic-associated colitis); urticaria, rashes, and other allergic reactions (rarely, anaphylaxis); reversible hearing loss after large doses; cholestatic jaundice and cardiac effects (including chest pain and arrhythmias).

6.2.2.5 Aminoglycosides

Aminoglycosides including **gentamicin** are bactericidal and active against some Gram-positive and many Gram-negative organisms including *Pseudomonas aeruginosa*. Aminoglycosides are not absorbed from the gut and must therefore be given by injection for systemic infections. Excretion is mainly by the kidney and accumulation occurs in renal impairment. Use of gentamicin should be restricted to trained health personnel and care must be taken to ensure correct dosage and duration of treatment are not exceeded, because most adverse effects are dose related. The most important adverse effects are ototoxicity and nephrotoxicity and they are most common in the elderly and in patients with renal impairment. These groups and, if possible, all patients should be monitored for ototoxicity by audiometry. If there is impairment of renal function the dose interval must be increased; in severe renal impairment, the dose should also be reduced. Plasma concentration monitoring avoids both excessive and subtherapeutic concentrations and can prevent toxicity and ensure efficacy. If possible plasma concentrations should be monitored in all patients, but **must** be measured in infants, the elderly, in obesity, in cystic fibrosis, in high-dosage regimens, in renal impairment, or if treatment lasts for longer than 7 days. For most infections, doses of up to 5 mg/kg daily in divided doses are used if renal function is normal; higher doses are used occasionally for serious infections. Loading and maintenance doses are based on the patient's weight and renal function (for example, using a nomogram) with adjustments based on plasma gentamicin concentration.

Gentamicin

Gentamicin is a representative aminoglycoside antibiotic. Various drugs can serve as alternatives

Injection, gentamicin (as sulfate) 10 mg/ml, 2-ml vial; 20 mg/ ml, 2- ml vial, 40 mg/ml, 2-ml vial, 80 mg/ ml, 2-ml vials.

Uses: pneumonia; cholecystitis; peritonitis; septicaemia; acute pyelonephritis; prostatitis; skin infections; pelvic inflammatory disease; endocarditis; meningitis; listeriosis; tularaemia; brucellosis; plague; surgical prophylaxis; eye (section 21.1).

Contraindications: myasthenia gravis

Precautions: renal impairment , infants and elderly (dosage adjustment and monitor renal, auditory, and vestibular

function, and plasma-gentamicin concentrations); avoid prolonged use; see notes above; pregnancy. (Appendix 2);

Interactions: Appendix 1

Dosage:

Infections due to susceptible organisms, *by intramuscular injection or by slow intravenous injection* (over at least 3 minutes) *or by intravenous infusion*, ADULT 2–5 mg/kg daily in divided doses every 8 hours; CHILD up to 2 weeks, 3 mg/kg every 12 hours; 2 weeks–12 years, 2 mg/kg every 8 hours

Streptococcal and enterococcal endocarditis (as part of combination therapy), *by intravenous injection* (over at least 3 minutes), ADULT 80 mg twice daily.

Surgical prophylaxis, *by intravenous injection*, ADULT 5 mg/kg as a single dose at induction (with clindamycin) .

NOTE:- One hour (peak) concentrations should not exceed 10 mg/litre; predose (trough) concentration should be less than 2 mg/litre

DILUTION AND ADMINISTRATION. According to manufacturer's directions .

Adverse effects: vestibular and auditory damage, nephrotoxicity; rarely, hypomagnesaemia on prolonged therapy; antibiotic-associated colitis; also, nausea, vomiting, rash.

6.2.2.6 Metronidazole

Metronidazole

Metronidazole is a representative antibacterial and antiprotozoal agent. Various drugs can serve as alternatives.

Tablets, metronidazole 200 mg, 400 mg.

Oral suspension, metronidazole (as benzoate) 100mg /5 ml, 200 mg/5 ml.

Intravenous infusion, metronidazole 5 mg/ml, 100-ml bag .

Suppositories, metronidazole 0.5 g, 1 g.

Uses: anaerobic bacterial infections, including gingivitis, pelvic inflammatory disease, tetanus, peritonitis, brain abscess, necrotizing pneumonia, antibiotic-associated colitis, leg ulcers and pressure sores and surgical prophylaxis; bacterial vaginosis; tissue nematode infections (6.1.1.3); trichomonal vaginitis, amoebiasis, and giardiasis (section 6.4.1); *Helicobacter pylori* eradication (section 17.1).

Contraindications: chronic alcohol dependence

Precautions: disulfiram-like reaction with alcohol; hepatic impairment and hepatic encephalopathy; pregnancy (Appendix 2); breastfeeding (Appendix 3); clinical and laboratory monitoring in courses lasting longer than 10 days;

Interactions: Appendix 1

Dosage:

Anaerobic infections (usually treated for 7 days), *by mouth*, ADULT 800 mg initially then 400 mg every 8 hours *or* 500 mg every 8 hours; CHILD 7.5 mg/kg every 8 hours; *by intravenous infusion*, ADULT 500 mg every 8 hours; CHILD 7.5 mg/kg every 8 hours.

Surgical prophylaxis, *by mouth*, ADULT 400 mg every 8 hours started 24 hours before surgery, then continued postoperatively, *by intravenous infusion* (see below) or *by rectum* (seebelow); CHILD 7.5 mg/kg every 8 hours.

Surgical prophylaxis, *by rectum*, ADULT 1 g 2 hours before surgery then 1 g every 8 hours; CHILD 5–10 years, 500 mg 2 hours before surgery then 500 mg every 8 hours Surgical prophylaxis *by intravenous infusion* (if rectal administration inappropriate), ADULT 500 mg shortly before surgery then every 8 hours until oral administration can be started;CHILD 7.5 mg/kg every 8 hours.

Bacterial vaginosis, *by mouth*, ADULT 2 g as a single dose *or* 400–500 mg twice daily for 5–7 days.

Leg ulcers and pressure sores, *by mouth*, ADULT 400 mg every 8 hours for 7 days.

Acute ulcerative gingivitis, *by mouth*, 200–250 mg every 8 hours for 3 days; CHILD 1–3 years, 50 mg every 8 hours for 3 days; 3–7 years, 100 mg every 12 hours for 3 days; 7–10 years, 100 mg every 8 hours for 3 days.

Acute dental infections, *by mouth*, ADULT 200 mg every 8 hours for 3–7 days.

Antibiotic-associated colitis, *by mouth*, 400 mg 3 times daily

PATIENT ADVICE. Metronidazole tablets should be swallowed whole with water, during or after a meal; metronidazole suspension should be taken one hour before a meal.

Adverse effects: nausea, vomiting, unpleasant metallic taste, furred tongue and gastrointestinal disturbances; rarely, headache, drowsiness, dizziness, ataxia, darkening of urine, erythema multiforme, pruritus, urticaria, angioedema, and anaphylaxis; abnormal liver function tests, hepatitis, jaundice, thrombocytopenia, aplastic anaemia, myalgia, arthralgia; peripheral neuropathy, epileptiform seizures, leukopenia, on prolonged or high dosage regimens.

6227 Nitrofurantoin

Nitrofurantoin is bactericidal *in vitro* to most Gram-positive and Gram-negative urinary-tract pathogens and it is used to treat acute and recurrent urinary-tract infections. It is also used prophylactically.

Nitrofurantoin

Tablets, nitrofurantoin 50 mg, 100 mg;

Suspension, 25 mg/5 ml.

Uses: urinary-tract infections

Contraindications: impaired renal function ; infants less than 3 months; G6PD-deficiency including breastfeeding of affected infants (Appendix 3); pregnancy, at term (Appendix 2); porphyria.

Precautions: pulmonary disorders or hepatic impairment ; monitor lung and liver function on long-term therapy

(discontinue if lung function deteriorates); neurological or allergic disorders; anaemia; diabetes mellitus; elderlyand debilitated; vitamin B and folate deficiency; false positive urinary glucose (if testing for reducing substances); urine maybe coloured yellow or brown.

Dosage:

Acute uncomplicated urinary-tract infections, *by mouth*, ADULT 100 mg every 12 hours *or* 50 mg every 6 hours with food for 7 days; CHILD over 3 months, 3 mg/kg daily in 4 divided doses.

Severe recurrent urinary-tract infection, *by mouth*, ADULT 100 mg every 6 hours with food for 7 days (dose reduced to 200 mg daily in divided doses, if severe nausea).

Prophylaxis of urinary-tract infections (see Precautions), *by mouth*, ADULT 50–100 mg at night; CHILD over 3 months, 1 mg/ kg at night.

Adverse effects: dose-related gastrointestinal disorders; nausea; hypersensitivity reactions including urticaria, rash, pruritus, angioedema; anaphylaxis reported; rarely, cholestatic jaundice, hepatitis, exfoliative dermatitis; erythema multiforme, pancreatitis, arthralgia; blood disorders; pulmonary reactions (discontinue treatment); peripheral neuropathy; benign intracranial hypertension; transient alope.

6.2.2.8 Spectinomycin
Reserved for use in higher referral centers

6.2.2.9 Sulfonamides and trimethoprim

The usefulness of sulfonamides is limited by an increasing incidence of bacterial resistance. For many indications they have been replaced by antibiotics that are more active and safer.

Sulfadiazine: is used in the prevention of rheumatic fever recurrence.

Sulfamethoxazole is used in combination with **trimethoprim** because of their synergistic activity. In some countries, indications for the use of this combination have been restricted. The treatment of *Pneumocystis carinii* infections must only be undertaken with specialist supervision where there are appropriate monitoring facilities (section 6.4.5).

Sulfadiazine

Sulfadiazine is a representative sulfonamide antibacterial. Various drugs can serve as alternatives .

Tablets, sulfadiazine 500 mg.

Uses: prevention of recurrences of rheumatic fever; toxoplasmosis (section 6.4.5)

Contraindications: hypersensitivity to sulfonamides; renal failure or liver failure; porphyria.

Precautions: hepatic and renal impairment; maintain adequate fluid intake (to avoid crystalluria); avoid in blood disorders (unless under specialist supervision); monitor blood counts and discontinue immediately if blood disorder develops; rashes—discontinue immediately; elderly; asthma; G6PD deficiency; pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid in infants under 6 weeks;

Interactions: Appendix 1

Dosage:

Prevention of recurrences of rheumatic fever, *by mouth*, ADULT 1 g daily; CHILD 500 mg daily.

Adverse effects: nausea, vomiting, diarrhoea, headache; hypersensitivity reactions including rashes, pruritus, photosensitivity reactions, exfoliative dermatitis, and erythema nodosum; rarely, erythema multiforme and toxic epidermal necrolysis; crystalluria—resulting in haematuria, oliguria, anuria; blood disorders including granulocytopenia, agranulocytosis, aplastic anaemia, purpura—discontinue immediately; also reported, liver damage, pancreatitis, antibiotic-associated colitis, eosinophilia, cough and shortness of breath, pulmonary infiltrates, aseptic meningitis, depression, convulsions, ataxia, tinnitus, and electrolyte disturbances .

Sulfamethoxazole with trimethoprim

Sulfamethoxazole with trimethoprim is a representative antibacterial drug combination. Various drugs can serve as alternatives.

Tablets,

Sulfamethoxazole 100 mg with trimethoprim 20 mg;.
Sulfamethoxazole 200 mg with trimethoprim 40 mg;.
Sulfamethoxazole 400 mg with trimethoprim 80 mg;.
Sulfamethoxazole 800 mg with trimethoprim 160 mg.

Oral suspension,

Sulfamethoxazole 200 mg with trimethoprim 40 mg/5 ml

Injection (Solution for dilution for infusion),

Sulfamethoxazole 800 mg with trimethoprim 160 mg/3 ml, 3-ml ampoules.

Uses: urinary-tract infections; respiratory-tract infections including bronchitis, pneumonia, infections in cystic fibrosis; melioidosis; listeriosis; brucellosis; granuloma inguinale; otitis media; skin infections; *Pneumocystis carinii* pneumonia (section 6.4.5).

Contraindications: hypersensitivity to sulfonamides or trimethoprim; severe renal and hepatic failure; porphyria.

Precautions: renal or hepatic impairment (Appendices 4 and 5); maintain adequate fluid intake (to avoid crystalluria); avoid in blood disorders (unless under specialist supervision); monitor blood counts and discontinue immediately if blood

disorder develops; rash—discontinue immediately; elderly; asthma; G6PD deficiency; folate deficiency; pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid in infants under 6 weeks;

Interactions: Appendix 1

Dosage:

Severe infections due to susceptible organisms, *by mouth or by intravenous infusion*, ADULT sulfamethoxazole 800 mg with trimethoprim 160 mg every 12 hours, increased to sulfamethoxazole 1.2 g with trimethoprim 240 mg, every 12 hours in more severe infections. *by mouth*, CHILD 6 weeks–5 months, sulfamethoxazole 100 mg with trimethoprim 20 mg every 12 hours; 6 months–5 years, sulfamethoxazole 200 mg with trimethoprim 40 mg every 12 hours; 6–12 years, sulfamethoxazole 400 mg with trimethoprim 80 mg every 12 hours; *by intravenous infusion*, CHILD sulfamethoxazole 30 mg/kg daily with trimethoprim 6 mg/kg daily in 2 divided doses

DILUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: nausea, vomiting, diarrhoea, headache; hypersensitivity reactions including rashes, pruritus, photosensitivity reactions, exfoliative dermatitis, and erythema nodosum; rarely, erythema multiforme and toxic epidermal necrolysis; crystalluria—resulting in haematuria, oliguria, anuria; blood disorders including granulocytopenia, agranulocytosis, aplastic anaemia, purpura—discontinue immediately; also reported, liver damage, pancreatitis, antibiotic-associated colitis, eosinophilia, cough and shortness of breath, pulmonary infiltrates, aseptic meningitis, depression, convulsions, ataxia, tinnitus, and electrolyte disturbances; megaloblasticanaemia due to trimethoprim.

6.2.2.10 Clindamycin : Reserved for use in higher referral centres

6.2.2.11 Vancomycin: Reserved for use in higher referral centres

6.2.3 Antileprosy drugs

Leprosy is a chronic mycobacterial infection due to *Mycobacterium leprae*, which is a slow-growing intracellular bacillus that infiltrates the skin, peripheral nerves, the nasal and other mucosa, and the eyes; it affects people of all ages and both sexes. The incubation period between infection and appearance of leprosy is normally between 2 to 10 years, but may be up to 20 years. It is transmitted from person -to-

person when bacilli are shed from the nose; most individuals have natural immunity and symptoms are suppressed. For treatment purposes patients may be classified as having paucibacillary (PB) or multibacillary (MB) leprosy. The 2 forms may be distinguished by skin smears, but facilities are not always available to process them and their reliability is often doubtful. In practice, most leprosy programmes classify and choose a regimen based on number of skin lesions; these are PB single-lesion leprosy (1 lesion), PB leprosy (2–5 skin lesions) and MB leprosy (more than 5 skin lesions).

Combination therapy has become essential to prevent the emergence of resistance. **Rifampicin** is now combined with **dapsone** to treat PB leprosy and **rifampicin** and **clofazimine** are now combined with **dapsone** to treat MB leprosy.

The WHO Action Programme for the Elimination of Leprosy currently provides oral multidrug therapy (MDT) in blister packs which ensure better patient adherence. More recently, a single dose of combination therapy has been recommended to cure patients with single-skin-lesion leprosy. Any patient with a positive skin smear should be treated with the MDT regimen for MB leprosy. The regimen for PB leprosy should never be given to a patient with MB leprosy. If diagnosis in a particular patient is not possible the MDT regimen for MB leprosy must be used.

Lepra reactions are episodes of sudden increase in the activity of leprosy and are often accompanied by neuritis; reactions must always be treated promptly to prevent permanent nerve damage and disability. Leprosy multidrug therapy should continue during a lepra reaction without interruption. This reduces the frequency and severity of lepra reactions.

Type I lepra reactions, or reversal reactions, are delayed hypersensitivity reactions and may occur in either PB or MB leprosy. If there is no nerve damage, type I reactions may be treated with analgesics such as acetylsalicylic acid or paracetamol.

If there is nerve involvement corticosteroids, such as oral prednisolone should be used in addition to analgesics. The type II lepra reaction, also known as erythema nodosum leprosum (ENL), is an antibody response to dead leprosy bacteria and occurs only in MB leprosy. Therapy for type II reactions may include analgesics, such as acetylsalicylic acid or paracetamol, and corticosteroids, such as oral prednisolone. In patients not responding to corticosteroids, clofazimine may be used. Thalidomide is rarely useful and in any case it should be avoided in women of childbearing age since it is a proven teratogen. If this is not possible, it is imperative that pregnancy is excluded before this treatment is initiated. Severe type II lepra reactions should be treated

under medical supervision in hospital.If a patient does not respond to lepra reaction treatment within 6 weeks or seems to become worse, the patient must be sent immediately to the nearest specialist centre. Neuritis may occur during or independently of lepra reactions. It can be successfully treated with a 12-week course of oral prednisolone; if patients do not respond, specialist centre treatment is required.

TREATMENT REGIMENS. Single doses of rifampicin 600 mg, ofloxacin 400 mg and minocycline 100 mg in combination are recommended for the treatment of single-lesion paucibacillary (PB) leprosy in adults. Children aged 5 to 14 years may be given half the adult single dose; appropriate dose adjustments are required for younger children. Although minocycline and ofloxacin are not recommended for use in children or ofloxacin for adolescents, field trials with single-dose regimens of these drugs for the treatment of single-lesion PB leprosy have not shown adverse effects.

The recommended regimen for paucibacillary leprosy in adults (50–70 kg) is rifampicin 600 mg once monthly under supervision and dapsone 100 mg daily, self-administered. Children aged 10–14 years may be given rifampicin 450 mg once monthly under supervision and dapsone 50 mg daily. Appropriate dose adjustments are required for younger children. For example, dapsone 25 mg daily and rifampicin 300 mg once a month under supervision. Treatment is continued for 6 months for PB leprosy.

The recommended regimen for multibacillary (MB) leprosy in adults (50–70 kg) is rifampicin 600 mg and clofazimine 300 mg, both given once a month under supervision together with clofazimine 50 mg and dapsone 100 mg, both daily. Children aged 10–14 years may be given rifampicin 450 mg and clofazimine 150 mg, both once a month under supervision together with clofazimine 50 mg every other day and dapsone 50 mg daily. Appropriate dosage adjustments are required for younger children.

For example, dapsone 25 mg daily, clofazimine 50 mg twice a week, and clofazimine 100 mg and rifampicin 300 mg once a month under supervision. Treatment is continued for 12 months for MB leprosy.

For patients who cannot take rifampicin because of allergy,other diseases, or rifampicin-resistant leprosy, and for patients who refuse to take clofazimine, there are alternative regimens which incorporate ofloxacin and minocycline.

Clofazimine

Capsules, clofazimine 50 mg, 100 mg

Uses: multibacillary (MB) leprosy; type II lepra reactions.

Precautions: pre-existing gastrointestinal symptoms (reduce dose, increase dose interval or discontinue if symptoms develop during treatment); liver and renal impairment; pregnancy and breastfeeding; may discolour soft contact lenses.

Dosage:

Multibacillary leprosy (in combination with dapsone and rifampicin, see notes above), *by mouth*, ADULT 50 mg once daily and 300 mg once a month, under supervision; CHILD 10–14 years 50 mg on alternate days and 150 mg once a month under supervision; CHILD under 10 years, see notes above; continue treatment for 12 months

Type II lepra reaction (erythema nodosum leprosum; see notes above), *by mouth*, ADULT and CHILD 200–300 mg daily in 2 or 3 divided doses; 4–6 weeks treatment may be required before effect is seen

Adverse effects: reversible discoloration of skin, hair, cornea, conjunctiva, tears, sweat, sputum, faeces, and urine; doserelated gastrointestinal symptoms including pain, nausea, vomiting and diarrhoea; severe mucosal and submucosal oedema, with prolonged treatment with high doses—may be severe enough to cause subacute small-bowel obstruction (see also Precautions)

Dapsone

Tablets, dapsone 25 mg, 50 mg, 100 mg

Uses: paucibacillary (PB) and multibacillary (MB) leprosy.

Contraindications: hypersensitivity to sulfones; severe anaemia.

Precautions: anaemia (treat severe anaemia before therapy, and monitor blood counts during treatment); G6PD deficiency (including breastfeeding affected infants); pregnancy (Appendix 2); breastfeeding (Appendix 3); porphyria;

Interactions: Appendix 1

BLOOD DISORDERS. On long-term treatment patients and their carers should be told how to recognize blood disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop.

Dosage:

Paucibacillary leprosy (in combination with rifampicin, see notes above), *by mouth*, ADULT 100 mg daily; CHILD 10–14 years 50 mg daily; CHILD under 10 years, see notes above; continue treatment for 6 months.

Multibacillary leprosy (in combination with rifampicin and clofazimine, see notes above), ADULT 100 mg daily; CHILD 10 - 14 years 50 mg daily; CHILD under 10 years, see notes above; continue treatment for 12 months.

Adverse effects: haemolysis and methaemoglobinaemia; allergic dermatitis (rarely including toxic epidermal necrolysis and

the Stevens-Johnson syndrome); rarely, hepatitis and agranulocytosis; 'dapsone syndrome' resembling mononucleosis—rare hypersensitivity reaction with symptoms including rash, fever, jaundice, and eosinophilia; gastrointestinal irritation; headache, nervousness, insomnia, blurred vision, paraesthesia, reversible peripheral neuropathy, and psychoses reported.

Rifampicin

Tablets, rifampicin 50 mg (kid), 150 mg, 300 mg, 450 mg, 600 mg.
Capsules, rifampicin 150 mg, 300 mg, 450 mg, 600 mg..
Supsension, 100 mg/ 5ml, 200 mg/ 5 ml.

Uses: paucibacillary leprosy; multibacillary leprosy; tuberculosis (section 6.2.4)

Contraindications: hypersensitivity to rifamycins; jaundice.

Precautions: reduce dose in hepatic impairment ; liver function tests and blood counts required in liver disorders, elderly, and on prolonged therapy; renal impairment (if dose above 600 mg daily); pregnancy (Appendix 2); breastfeeding (Appendix 3); porphyria; discolours soft contact lenses.

Important : advise patients on oral contraceptives to use additional means.

Interactions : Appendix 1

NOTE. Resumption of rifampicin treatment after a long interval may cause serious immunological reactions, resulting in renal impairment, haemolysis, or thrombocytopenia discontinue permanently if serious adverse effects occur.

LIVER DISORDERS. Patients or their carers should be told how to recognize signs of liver disorders and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

Dosage:

Single-lesion paucibacillary leprosy (in combination with ofloxacin and minocycline; see notes above), *by mouth*, ADULT 600 mg as a single dose; CHILD 5–14 years 300 mg as a single dose; CHILD under 5 years, see notes above

Paucibacillary leprosy (in combination with dapsone; see notes above), *by mouth*, ADULT 600 mg once a month under supervision; CHILD 10–14 years 450 mg once a month under supervision; CHILD under 10 years, see notes above; continuetreatment for 6 months.

Multibacillary leprosy (in combination with dapsone and clofazimine; see notes above), *by mouth*, ADULT 600 mg once a month under supervision; CHILD 10–14 years 450 mg once a month under supervision; CHILD under 10 years, see notes above; continue treatment for 12 months.

PATIENT ADVICE. Take dose at least 30 minutes before a meal, since absorption is reduced by food.

Adverse effects: severe gastrointestinal disturbances including anorexia, nausea, vomiting, and diarrhoea (antibiotic-

associated colitis reported); rashes, fever, influenza-like syndrome and respiratory symptoms, collapse, shock, haemolytic anaemia, acute renal failure, and thrombocytopenic purpura—more frequent with intermittent therapy; alterations of liver function—jaundice and potentially fatal hepatitis (dose-related; do not exceed maximum daily dose of 600 mg); urine, tears, saliva, and sputum coloured orange-red.

Minocycline

Tablets, minocycline (as hydrochloride) 50 mg, 100 mg.

Uses: single-lesion paucibacillary leprosy.

Contraindications: pregnancy (Appendix 2); systemic lupus erythematosus.

Precautions: hepatic impairment—monitor liver function before use ; avoid exposure to sunlight —photosensitivity reaction; children (see notes above); breastfeeding (Appendix 3);

Interactions: Appendix 1

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving.

Dosage:

Single-lesion paucibacillary leprosy (in combination with rifampicin and ofloxacin; see notes above), *by mouth*, ADULT 100 mg as a single dose; CHILD 5–14 years 50 mg as a single dose; CHILD under 5 years, see notes above.

Adverse effects: dizziness and vertigo (more common in women); nausea, vomiting, and diarrhoea; headache and visual disturbances may indicate intracranial hypertension; hepatotoxicity, pancreatitis, and antibiotic-associated colitis reported; severe exfoliative rashes; pigmentation (sometimes irreversible); discoloration of conjunctiva, tears, and sweat; systemic lupus erythematosus and liver damage reported.

Ofloxacin

Tablets, ofloxacin 100 mg, 200 mg, 400 mg

Uses: single-lesion paucibacillary leprosy.

Precautions: epilepsy or history of CNS disorders; renal impairment ; hepatic impairment ; avoid exposure to sunlight—pho tosensitivity reactions; pregnancy (Appendix 2); breastfeeding (Appendix 3); children and adolescents (arthropathy in weight-bearing joints in young *animals*; see also notes above).

Interactions: Appendix 1

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery or driving.

Dosage:

Single-lesion paucibacillary leprosy (in combination with rifampicin and minocycline; see notes above), *by mouth*,

ADULT 400 mg as a single dose; CHILD 5–14 years 200 mg as a single dose; CHILD under 5, see notes above.

Adverse effects: convulsions in patients with or without history of convulsions; nausea, vomiting, abdominal pain, diarrhoea; headache, visual disturbances, sleep disorders and other CNS disturbances; psychotic reactions—discontinue treatment; rashes (rarely Stevens-Johnson syndrome and toxic epidermal necrolysis), pruritus, and fever .

6.2.4 Antituberculosis drugs

Tuberculosis is a chronic infectious disease caused primarily by *Mycobacterium tuberculosis* or sometimes *M. bovis*. Infection is usually due to inhalation of infected droplet nuclei with the lung generally being the first organ affected, but the primary infection is usually asymptomatic. Infection and inflammatory responses resolve with the development of acquired immunity. Surviving bacteria may become dormant or in susceptible patients, progress to active primary disease; dormant organisms may produce disease and this often occurs if immune status is altered. Tuberculosis is the most prevalent infectious disease of adults and causes 26% of avoidable adult deaths in the developing world. More than 80% of tuberculosis cases are pulmonary (PTB). At least 30% of patients who are infected with HIV will also develop active tuberculosis. The increase in resistant strains and poor compliance which may contribute to resistance and treatment failure has led to the development of regimens with directly supervised treatment. Directly Observed Treatment, Short-course (DOTS) therapy which lasts for 6 or 8 months, given under direct observation is one of the most important components of the WHO and RNTCP strategy against tuberculosis. Simplified drug regimens and intermittent therapy have been introduced to improve compliance. WHO does not generally recommend twice weekly regimens. If a patient receiving a twice weekly regimen misses a dose of tablets, the missed dose represents a bigger fraction of the total number of treatment doses than if the patient was receiving a three times weekly or daily dose regimen. Therefore, there is a greater risk of treatment failure with twice weekly regimens. Fixed dose combination tablets incorporating 2 or more drugs are also used to improve compliance and decrease inadvertent medication errors. Modern short-course therapy is usually in 2 phases. The initial phase (2 months) involves the concurrent use of at least 3 drugs to reduce the bacterial population rapidly and prevent drug resistant bacteria emerging. The second continuation phase (4–6 months) involves fewer drugs and is used to eliminate any remaining bacteria and prevent recurrence. Direct observation of therapy is considered essential to ensure compliance in the initial phase and also

useful in the continuation phase if patients are receiving rifampicin. The six antituberculosis drugs, **isoniazid**, **rifampicin**, **pyrazinamide**, **streptomycin**, (which are bactericidal) **ethambutol** and **thioacetazone** (which are bacteriostatic) are used in various combinations as part of WHO recommended treatment regimens. In supervised regimens change of drug regimen should be considered only if the patient fails to respond after 5 months of DOTS.

Isoniazid, rifampicin, and pyrazinamide are components of all antituberculosis drug regimens currently recommended by WHO. Unsupervised and alternative regimens as set out in the following tables may be administered as specified. Additional reserve antituberculosis drugs for the treatment of drug- resistant tuberculosis should be used in specialized centres only with WHOrecommended TB control strategy, DOTS, and treatment programmes. Worldwide, an important predisposing cause of immunosuppression leading to tuberculosis is human immunodeficiency virus (HIV) infection; it increases susceptibility to primary infection and increases the reactivation rate of tuberculosis.

Preventative antituberculosis therapy of such persons is recommended. Chemoprophylaxis with isoniazid can prevent the development of clinically apparent disease in persons in close contact with infectious patients, and in other persons at high risk particularly those who are immunodeficient. Where the disease remains highly prevalent routine immunization of infants within the first year of age with BCG vaccine is cost-effective. However, there is no evidence that BCG will protect children older than 15 years of age. Infants born to HIVpositive mothers should be vaccinated during the first year of life, provided they have no clinical signs suggestive of HIV.

The **tuberculin test** has limited diagnostic value. A positive tuberculin test indicates previous exposure to mycobacterial antigens through infection with one of the tubercle bacilli, or BCG vaccination. The tuberculin test does not distinguish between tuberculosis and other mycobacterial infection, between active and quiescent disease, or between acquired infection and seroconversion induced by BCG vaccination.

Note: Check guidelines for Treatment as prescribed by RNTCP as applciable to Chhattisgarh

Ethambutol hydrochloride

Tablets, ethambutol hydrochloride 100 mg, 400 mg, 800 mg, 1200 mg.

Uses: tuberculosis, in combination with other drugs (see notes and tables above).

Contraindications: optic neuritis; children under 5 years—unable to report symptomatic visual disturbances; severe renal impairment.

Precautions: visual disturbances—ocular examination

recommended before and during treatment (see note below); reduce dose in renal impairment and monitor plasma concentration; elderly; pregnancy; breastfeeding (Appendix 3).

NOTE. Patients should report visual disturbances immediately and discontinue treatment; children who are incapable of reporting symptomatic visual changes accurately should be given alternative therapy, as should, if possible, any patient who cannot understand warnings about visual adverse effects.

Dosage:

Tuberculosis (initial phase of combination therapy; see notes above), *by mouth*, ADULT 15 mg/kg daily *or* 30 mg/ kg 3 times a week; CHILD 15 mg/kg daily.

Tuberculosis, continuation phase of combination therapy with isoniazid and riphampicin. *by mouth*, ADULT 15 mg/kg daily *or* 30 mg/ kg 3 times a week; CHILD 15 mg/kg daily.

Adverse effects: optic neuritis — reduced visual acuity and red/ green colour blindness (early changes usually reversible, prompt withdrawal may prevent blindness); peripheral neuritis — especially in legs; gout; rarely, rash, pruritus, urticaria, thrombocytopenia.

Isoniazid

Tablets, isoniazid 100 mg, 300 mg.
Injection (Solution for injection), isoniazid 25 mg/ml, 2-ml ampoule.

Uses: tuberculosis treatment, in combination with other drugs (see notes and tables above); tuberculosis prophylaxis.

Contraindications: drug-induced hepatic disease.

Precautions: hepatic impairment (monitor hepatic function; Appendix 5); malnutrition, chronic alcohol dependence, chronic renal failure, diabetes mellitus, and HIV infection — proph lactic pyridoxine 10 mg daily required because risk of peripheral neuritis; epilepsy; slow acetylator status (increased risk of adverse effects); history of psychosis; pregnancy; breastfeeding (Appendix 3); porphyria;

Interactions: Appendix 1

LIVER DISORDERS. Patients or their carers should be told how to recognize signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as nausea, vomiting, malaise or jaundice develop.

Dosage:

Tuberculosis, treatment (combination therapy; see also notes), *by mouth*, ADULT and CHILD 5 mg/kg (4–6 mg/kg) daily (maximum, 300 mg daily), *or* 10 mg/kg 3 times weekly.

Tuberculosis, treatment in critically ill patients unable to take oral therapy (combination therapy), *by intramuscular injection*, ADULT 200–300 mg as single daily dose; CHILD 10–20 mg/kg daily.

Tuberculosis, prophylaxis, *by mouth*, ADULT 300 mg daily for at least 6 months; CHILD 5 mg/kg daily for at least 6 months

PATIENT ADVICE. Isoniazid should be taken on an empty stomach; if taken with food to reduce gastrointestinal irritation, oral absorption and bioavailability may be impaired

Adverse effects: gastrointestinal disorders including nausea and vomiting, diarrhoea and pain; hypersensitivity reactions including fever, rashes, joint pain, erythema multiforme, purpura usually during first weeks of treatment; peripheral neuropathy; optic neuritis, toxic psychoses, and convulsions; hepatitis (especially over age of 35 years and regular users of alcohol) — withdraw treatment; also reported, systemic lupus ery thematosus-like syndrome, pellagra, hyperglycaemia andgynaecomastia.

Pyrazinamide

Tablets, pyrazinamide, 500 mg, 750 mg, 1000 mg, 1500 mg.

Uses: tuberculosis, in combination with other drugs (see notes and tables above)

Contraindications: severe hepatic impairment; porphyria.

Precautions: hepatic impairment (monitor hepatic function; Appendix 5); renal impairment; diabetes mellitus (monitor-blood glucose — may change suddenly); gout; breastfeeding (Appendix 3)

LIVER DISORDERS. Patients or their carers should be told how to recognize signs of liver disorder, and advised to is continue treatment and seek immediate medical attention if symptoms such as persistent nausea,vomiting, malaise or jaundice develop.

Dosage:

Tuberculosis (initial phase of combination therapy; see notes above), *by mouth*, ADULT and CHILD 25 mg/kg daily *or* 35 mg/kg 3 times weekly.

Adverse effects: hepatotoxicity including fever, anorexia, hepatomegaly, jaundice, liver failure; nausea, vomiting; arthralgia; gout; sideroblastic anaemia;urticaria; skin flushing 126 6.2.4: Antituberculosis drugs.

Rifampicin

Capsules, rifampicin 150 mg, 300 mg, 450 mg, 600 mg
Suspension, 100 mg/5 ml, 200 mg /5 ml

Uses: tuberculosis, in combination with other drugs (see notes and tables above); leprosy (section 6.2.3).

Contraindications: hypersensitivity to rifamycins; jaundice.

Precautions: reduce dose in hepatic impairment ; liver function tests and blood counts required in liver disorders, elderly, and on prolonged therapy; renal impairment (if dose above 600 mg daily); pregnancy (Appendix 2);breastfeeding (Appendix 3); porphyria; discolours soft contact lenses. **important:** advise patients on oral contraceptives to use additional means;

Interactions: Appendix 1

NOTE. Resumption of rifampicin treatment after a long interval may cause serious immunological reactions, resulting in renal impairment, haemolysis, or thrombocytopenia — discontinue permanently if serious adverseeffects occur.

LIVER DISORDERS. Patients or their carers should be told how to recognize signs of liver disorders and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea,vomiting, malaise or jaundice develop.

Dosage:

Tuberculosis (combination therapy; see notes above),*by mouth*, ADULT and CHILD 10 mg/kg daily *or* 3 times weekly (maximum dose, 600 mg daily).

PATIENT ADVICE. Take dose at least 30 minutes before a meal, as absorption is reduced when taken with food.

Adverse effects: severe gastrointestinal disturbances including anorexia, nausea, vomiting, and diarrhoea (antibiotic-associated colitis reported); rashes, fever, influenza-like syndrome and respiratory symptoms, collapse, shock, haemolytic anaemia, acute renal failure, and thrombocytopenic purpura — more frequent with intermittent therapy; alterations of liver function — jaundice and potentially fatal hepatitis (dose related; do not exceed maximum dose of 600 mg daily);urine, tears, saliva, and sputum coloured orange-red.

Streptomycin

Injection (Powder for solution for injection), streptomycin (as sulfate) 1 g vial .75 g vial.

Uses: tuberculosis, in combination with other drugs (see notes and tables above).

Contraindications: hearing disorders; myas thenia gravis; pregnancy (Appendix 2)

Precautions: children — painful injection, avoid use if possible; renal impairment , infants, and elderly (dosage adjustment and monitor renal, auditory, and vestibular function, and plasma streptomycin concentrations);

Interactions: Appendix 1

Dosage:

Tuberculosis (in itial phase of combination therapy;), *by deep intramuscular injection*, ADULT andCHILD 15 mg/kg daily *or* 3 times a week (patients over 60 years and those weighing less than 50 kg may not tolerate doses above 500–750 mg daily).

RECONSTITUTIONANDADMINISTRATION. According to manufacturer's directions.

NOTE. One hour (peak) concentration should be 15–40 mg/litre; pre-dose (trough) concentration should be less than 5 mg/litre (less than 1 mg/litre in renal impairment or those over 50 years).

Adverse effects: vestibular and auditory damage, nephrotoxicity; hypersensitivity reactions — withdraw

treatment; paraesthesia of mouth; rarely, hypomagnesaemia on prolongedtherapy; antibiotic-associated colitis; also, nausea, vomiting,rash; rarely, haemolytic anaemia,aplastic anaemia, agranulocytosis, thrombocytopenia; pain and abscess at injection site.

BCG vaccine

Injection (Powder for solution for injection), live bacteria of a strain derived from the bacillus of Calmette and Guerin.

Uses: for active immunization against tuberculosis; see also section 19.3.1.1

Contraindications: see section 19.3.1; generalized oedema; hypogammaglobulinaemia and immunodeficiency due to antimetabolites, irradiation, corticosteroids; HIV positive — except asymptomatic children in areas of high tuberculosis risk; malignant disease; antimycobacterial treatment.

Precautions: see section 19.3.1; pregnancy (Appendix 2); eczema, scabies — vaccine site must be lesion-free.

Interactions: Appendix 1

Dosage:

Immunization against tuberculosis, *by intradermal injection*, INFANTS up to 3 months, 0.05 ml; ADULT and CHILD over 3 months 0.1 ml.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: lymphadenitis and keloid formation; osteitis and localized necrotic ulceration; rarely, disseminated BCG infection in immunodeficient patients; rarely, anaphylaxis.

Tuberculin purified protein derivative (tuberculin PPD)

Injection, tuberculin purified protein derivative 10 units/ml, 100 units/ml.

Uses: test for hypersensitivity to tuberculoprotein.

Contraindications: should not be used within 3 weeks of receiving a live viral vaccine.

Precautions: elderly; malnutrition, viral or bacterial infections (including HIV and severe tuberculosis), malignant disease, corticosteroid or immunosuppressant therapy — diminished sensitivity to tuberculin; avoid contact with open cuts, abraded or diseased skin, eyes or mouth.

Dosage:

Test for hypersensitivity to tuberculoprotein, *by intradermal injection*, ADULT and CHILD 5 or 10 units (1 unit may be used in hypersensitive patients or if tuberculosis is suspected)

ADMINISTRATION. According to manufacturer's directions.

Adverse effects: occasionally nausea, headache, malaise, rash; immediate local reactions (more common in atopic patients);

rarely, vesicular or ulcerating local reactions, regional adenopathy and fever.

6.3 Antifungal drugs

Fungal infections can be superficial or systemic. Superficial infections affect only the skin, hair, nails or mucous membranes whereas systemic fungal infections affect the body as a whole.

Systemic fungal infections are sometimes caused by inhalation, ingestion or inoculation of primary pathogens, and sometimes by opportunistic invasion of commensals in patients with lowered host resistance. They are increasing in prevalence not only because of the pandemic of HIV infection, but also because of the rise in illicit intravenous drug use in many countries, and greater use of broad spectrum antibiotics and invasive medical procedures. In immunodeficient patients systemic fungal infections are often disseminated.

Amphotericin B is a lipophilic polyene antibiotic; it is fungistatic against a broad spectrum of pathogenic fungi, including *Candida* spp., *Aspergillus* spp., *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*, *Mucor*, *Absidia* and *Phicopes* spp.; it is active agains talgal *Prototheca* spp. and against the *Leishmania protozoa*. It is used inconjunction with flucytosine to treat cryptococcal meningitis and systemic candidosis .

Amphotericin B has to be administered parenterally as there is little or no absorption from the gastrointestinal tract; amphotericin B is liable to cause nephrotoxicity. Duration of therapy varies with the initial severity of the infection and the clinical response of the patient. In some infections a satisfactory response is only obtained after several months of continuous treatment. Intrathecal infusion has been used successfully in patients with meningeal coccidioidomycosis.

Fluconazole, an orally active synthetic imidazole derivative, possesses fungistatic activity against dermatophytes, yeasts and other pathogenic fungi. It is widely used in the treatment of serious gastrointestinal and systemic mycoses as well as in the management of superficial infections. Fluconazole is also used to prevent fungal infections in immunocompromised patients.

Nystatin, a polyene antifungal antibiotic derived from *Streptomyces noursei*, is effective against infections caused by a wide range of yeasts and yeast-like fungi. It is used for the prophylaxis and treatment of candidosis .

Amphotericin B

Injection (powder for solution for injection), Amphotericin B 50-mg vial.

Uses: life-threatening fungal infections including histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis, aspergillosis, cryptococcosis, mucormycosis, sporotrichosis, and candidosis; leishmaniasis

Precautions: close medical supervision throughout treatmentand initial test dose required (see note, below); renal impairment; hepatic and renal function tests;blood counts and plasma electrolyte monitoring; corticosteroids (avoid, except to control reactions); pregnancy(Appendix 2); breastfeeding (Appendix 3); avoid rapi dinfusion (risk of arrhythmias).

Interactions: Appendix 1

ANAPHYLAXIS. Anaphylaxis occurs rarely with intravenous amphotericin B and a test dose is advisable before the first infusion. The patient should be observed for about 30 minutes after the test dose.

Dosage:

Systemic fungal infections, *by intravenous infusion*, ADULT and CHILD initial test dose of 1 mg over 20–30 minutes, then 250 micrograms/kg daily, gradually increased up to 1 mg/kg daily or in severe infection, up to 1.5 mg/kg daily or on alternate days.

NOTE. Prolonged treatment usually necessary; if interrupted for longer than 7 days, recommence at 250 micrograms/kg daily and increase gradually.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions

Adverse effects: fever, headache, anorexia, weight loss, nausea and vomiting, malaise, diarrhoea, muscle and joint pain, dyspepsia, and epigastric pain; renal function disturbances including hypokalaemia, hypomagnesaemia and renal toxicity; blood disorders; cardiovascular toxicity (including arrhythmias); neurological disorders (including peripheral neuropathy); abnormal liver function (discontinue treatment); rash; anaphylactoid reactions (see above); pain and thrombophlebitisat injection site.

Fluconazole

Fluconazole is a representative azole antifungal. Various drugs can serve as alternatives .

Capsules, tablets, fluconazole 50 mg, 100 mg, 150 mg, 200 mg.

Oral suspension (Powder for oral suspension), fluconazole 50 mg/5 ml.

Infusion (Solution for infusion), fluconazole 2 mg/ml, 25-ml bottle, 100-ml bottle.

Uses: systemic mycoses including histoplasmosis, non-meningeal coccidioidomycosis, paracoccidioidomycosis and blastomycosis; treatment and, in AIDS and other immunosuppressed patients, prophylaxis of cryptococcal meningitis; oesophageal and oropharyngeal candidosis, vaginal candidosis and systemic candidosis.

Precautions: renal impairment ; pregnancy (Appendix 2); breastfeeding (Appendix 3); raised liver enzymes (review need for treatment; risk of hepatic necrosis; Appendix 5);
Interactions: Appendix 1
Dosage:
Systemic mycoses, *by mouth or by intravenous infusion*, ADULT 200 mg daily for at least 6 months; CHILD over 2 years 3–6 mg/ kg daily for at least 6 months.
Cryptococcal meningitis (following amphotericin B induction therapy), *by mouth or by intravenous infusion*, ADULT 800 mg daily for 2 days, then 400 mg daily for 8 weeks; CHILD 6–12 mg/kg daily (every 72 hours in NEONATES up to 2 weeks old, every 48 hours in NEONATES 2–4 weeks old).
Prevention of relapse of cryptococcal meningitis in AIDS patients after completion of primary therapy, *by mouth or by intravenous infusion*, ADULT 100–200 mg daily .
Systemic candidosis (in patients unable to tolerate amphotericin B), *by mouth or by intravenous infusion*, ADULT 400 mg as initial dose, then 200 mg daily for at least 4 weeks; CHILD 6–12 mg/ kg daily (every 72 hours in NEONATES up to 2 weeks old, and every 48 hours in NEONATES 2–4 weeks old).
Oesophageal and oropharyngeal candidosis, *by mouth or by intravenous infusion*, ADULT 200 mg as an initial dose, then 100 mg daily until symptoms resolved; up to 400 mg daily in very resistant infections; CHILD 3–6 mg/kg on the first day, then 3 mg/kg daily (every 72 hours in NEONATES up to 2 weeks old, every 48 hours in NEONATES 2–4 weeks old).
Vaginal candidosis, *by mouth*, ADULT 150 mg as a single dose.
Adverse effects: nausea, vomiting, abdominal distension and discomfort; headache; elevation of liver enzymes, infrequently (see Precautions above); rash (withdraw treatment); angioedema, anaphylaxis, bullous lesions, toxic epidermal necrolysis and Stevens Johnson syndrome reported (skin reactions more common in AIDS); rarely, thrombocyto penia.

Nystatin

Tablets, nystatin 500 000 units
Pessaries, nystatin 100 000 units
Uses: oral, oesophageal, intestinal, vaginal, and cutaneous candidosis
Precautions: pregnancy and breastfeeding (Appendices 2 and 3)
Dosage:
Oral candidosis, *by mouth*, ADULT and CHILD, 100 000 units after food 4 times daily
Intestinal and oesophageal candidosis, *by mouth*, ADULT 500 000 units 4 times daily; CHILD 100 000 units 4 times daily; continue for 48 hours after clinical cure

Vaginal candidosis, *vaginal administration*, ADULT insert 1–2 pessaries at night for at least 2 weeks.
Adverse effects: nausea, vomiting, diarrhoea at high doses; oral irritation and sensitization; rash and rarely, Stevens-Johnsonsyndrom.

6.4 Antiprotozoal drugs

6.4.1 Antiamoebic, antigiardial and antitrichomonal drugs

AMOEBIASIS. Amoebic dysentery is caused by *Entamoeba histolytica*. It is transmitted by the faeco-oral route and infection is usually caused by ingestion of cysts from contaminated food and drink. Asymptomatic carriers are common in endemic areas, but there is rare necessity to treat.
Symptomatic (invasive) amoebiasis may be classified as intestinal or extra-intestinal. Intestinal amoebiasis is either amoebic dysentery or non-dysenteric amoebic colitis. Extraintestinal amoebiasis most commonly involves the liver, but may involve the skin, genito-urinary tract, lung and brain. Invasive amoebiasis is more likely in malnutrition, immunosuppression and pregnancy. Amoebic dysentery may take a fulminating course in late pregnancy and the puerperium; treatment with **metronidazole** may be life saving. In less severe infection, metronidazole should, if possible, be avoided in the first trimester. All patients with invasive amoebiasis require treatment with a systemically active compound such as **metronidazole**, followed by a luminal amoebicide in order to eliminate any surviving organisms in the colon. Combined preparations are useful. In severe cases of amoebic dysentery, tetracycline given in combination with a systemic amoebicide lessens the risk of superinfection, intestinal perforation and peritonitis. Hepatic abscesses should be lanced by needle as piration.
GIARDIASIS. Giardiasis is caused by *Giardia intestinalis* and is acquired by oral ingestion of *Giardia* cysts. Giardiasis can be treated with **metronidazole**; it is highly effective and should be offered when practicable to all infected patients. Family and institutional contacts should also be treated. Larger epidemics are difficult to eradicate because of the high proportion of symptomless carriers and because excreted cysts can survive for long periods outside the human host.
TRICHOMONIASIS. Trichomoniasis is an infection of the genitourinary tract caused by *Trichomonas vaginalis* and transmission is usually sexual. In women it causes vaginitis although some are asymptomatic. It is usually asymptomatic

in men but may cause urethritis. Patients and their sexual partners should betreated with **metronidazole**.

Metronidazole

Metronidazole is a representative antibacterial and antiprotozoal agent. Various drugs can serve as alternatives.

Tablets, metronidazole 200 mg, 400 mg.

Oral suspension, metronidazole (as benzoate) 200 mg/5 ml.

Intravenous infusion, metronidazole 5 mg/ml, 100-ml bag .

Uses: invasive amoebiasis and giardiasis; trichomoniasis; tissue nematode infections (section 6.1.1.3); bacterial infections (section 6.2.2.6); *Heliobacter pylori* eradication (section 17.1).

Contraindications: chronic alcohol dependence

Precautions: disulfiram-like reaction with alcohol; hepatic impairment and hepatic encephalopathy; pregnancy (Appendix 2; see also notes above); breastfeeding (Appendix 3); clinical and laboratory monitoring in courses lasting longer than 10 days.

Interactions: Appendix 1

Dosage:

Invasive amoebiasis, *by mouth*, ADULT and CHILD 30 mg/kg daily in 3 divided doses for 8–10 days; subsequent course of luminal amoebicide (see notes above).

Invasive amoebiasis (if oral administration not possible), *by intravenous infusion*, ADULT and CHILD 30 mg/kg daily in 3 divided doses (until patient able to complete course with oral drugs); subsequent course of luminal amoebicide (see notes above).

Giardiasis, *by mouth*, ADULT 2 g once daily for 3 days; CHILD 15 mg/kg daily in divided doses for 5–10 days.

Urogenital trichomoniasis, *by mouth*, ADULT 2 g as a single dose; sexual partners should be treated concomitantly.

NOTE. In amoebiasis and giardiasis, various dosage regimens are used and definitive recommendations should be based on local experience.

PATIENT ADVICE. Metronidazole tablets should be swallowed whole with water, during or after a meal; metronidazole suspension should be taken one hour before a meal.

Adverse effects: nausea, vomiting, unpleasant metallic taste, furred tongue and gastrointestinal disturbances; rarely headache, drowsiness, dizziness, ataxia, darkening of urine, erythema multiforme, pruritus, urticaria, angioedema, and anaphylaxis; abnormal liver function tests, hepatitis, jaundice, thrombocytopenia, aplastic anaemia, myalgia, arthralgia; peripheral neuropathy, epileptiform seizures, leukopenia, on prolonged or high dosage regimens.

6.4.2 Antileishmanial drugs

Leishmaniasis is caused by the protozoa *Leishmania*. It can becategorized as visceral, cutaneous or mucocutaneous. It may bea self-limiting localized skin lesion but may range from this to disseminated progressive disease. In endemic areas there is usually a reservoir of disease in a mammalian host and the usual vectors are sandflies.

VISCERAL LEISHMANIASIS. It is caused by parasites of the *Leishmania donovani* complex, and is usually responsive initially to the **pentavalent antimony compounds**, **meglumine antimoniate**. Both dosage and duration of treatment need to be adjusted according to the clinical response. Patients are considered to be clinically cured when no parasites are detected in splenic or bone. marrow aspirates. However, biopsies should be repeated after 3 and 12 months since relapse is frequent. Antimonials combined with **allopurinol**, **pentamidine isetionate** and **amphotericin B** have been used with success in patients in relapse who have become unresponsive to antimonials alone.

All drugs given below are available only for areas that report Kala Azar.

Pentavalent antimony compounds

Meglumine antimoniate is a representative pentavalent antimony compound used to treat leishmaniasis; sodium stibogluconate can serve as an alternative

Injection (Solution for injection), pentavalent antimony (as meglumine antimoniate) 85 mg/ml, 5-ml ampoule; pentavalent antimony (as sodium stibogluconate) 100 mg/ml, 100-ml bottle .

Uses: leishmaniasis (see notes above)

Contraindications: severe kidney disorders; breastfeeding.

Precautions: provide protein-rich diet throughout treatment and, if possible, correct iron and other nutritional deficiencies; renal and hepatic impairment (Appendices 4 and 5); monitor cardiac, renal and hepatic function reduce dose or withdraw treatment if abnormalities occur; pregnancy — in potentially fatal visceral leishmaniasis, treat without delay; intravenous injections must be given slowly over 5 minutes (to reduce risk of local thrombosis) and stopped if coughing or substernal pain; mucocutaneous disease (see below); treat intercurrent infection (for example pneumonia)

MUCOCUTANEOUS DISEASE. Successful treatment of mucocutaneous leishmaniasis may induce severe inflammation around lesions (may be lifethreatening if pharyngeal or tracheal involvement) — may require corticosteroids.

Dosage:

NOTE. Doses are expressed in terms of pentavalent antimony

Visceral leishmaniasis, *by intramuscular injection*, ADULT and CHILD 20 mg/kg daily for a minimum of 20 days; if relapse, retreat immediately with same daily dosage .

ADMINISTRATION. Meglumine antimoniate may be given by deep intramuscular injection. Sodium stibogluconate may be given by intramuscular injection or by slow intravenous injection (over at least 5 minutes). Both may be administered intralesionally.

Adverse effects: anorexia, nausea, vomiting, abdominal pain, ECG changes (possibly requiring dose reduction or withdrawal), headache, lethargy, myalgia; raised liver enzymes; renal function impairment; coughing and substernal pain (seePrecautions); rarely anaphylaxis, fever, sweating, flushing,vertigo, bleeding from nose or gum, jaundice, rash; pain andthrombosis on intravenous administration; pain on intramuscularinjection.

Pentamidine isetionate

Injection (Powder for solution for injection), pentamidine isetionate 200-mg vial, 300-mg vial

Uses: leishmaniasis (see notes, above); African trypanosomiasis (section 6.4.4.1); *Pneumocystis carinii* pneumonia (section 6.4.5)

Contraindications: severe renal impairment

Precautions: risk of severe hypotension following administration (establish baseline blood pressure and administer with patient lying down); monitor blood pressure during administration and treatment period; hypo tension or hypertension; hypoglycaemia or hyperglycaemia; hepatic impairment; leukopenia, thrombocytopenia, anaemia; immunodeficiency — if acute deterioration in bone marrow, renal or pancreatic function, interrupt or discontinue treatment; renal impairment ; pregnancy — in potentially fatal visceral leishmaniasis, treat without delay (Appendix 2); breastfeeding (Appendix 3); carry out laboratory monitoring according to manufacturer's literature.

Dosage:

Visceral leishmaniasis (unresponsive to or intolerant of pentavalent antimony compounds), *by deep intramuscular injection or by intravenous infusion*, ADULT and CHILD 4 mg/kg 3 times a week for 5–25 weeks or longer, until two consecutive splenic aspirates taken 14 days apart are negative Cutaneous leishmaniasis (*L. aethiopica*, *L. guyanensis*), *by deep intramuscular injection or by intravenous infusion*, ADULT and CHILD 3–4 mg/kg once or twice a week until the lesion is no longer visible; relapse is unusual.

Diffuse cutaneous leishmaniasis (*L. aethiopica*), *by deep intramuscular injection or by intravenous infusion*, ADULT and CHILD 3–4 mg/kg once a week, continued for at least 4 months after parasites no longer detectable in slit-skin smears; relapse frequent during first few months until immunity established.

Mucocutaneous leishmanisais (*L. braziliensis*, *L. aethiopica*), *by deep intramuscular injection or by intravenous infusion*, ADULT and CHILD 4 mg/kg 3 times a week for 5–25 weeks or longer, until lesion no longer visible.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer'sdirections.

NOTE. Pentamidine isetionate is toxic; care required to protect personnel during handling and administration.

Deep intramuscular injection is the WHO preferred route of administration.

Adverse effects: nephrotoxicity; acute hypotension — with dizziness, headache, breathlessness, tachycardia and syncope following rapid intravenous injection; hypoglycaemia — may be followed by hyperglycaemia and type I diabetes mellitus; pancreatitis; also hypocalcaemia, gastrointestinal disturbances, confusion, hallucinations, arrhythmias; thrombocytopenia, leukopenia, abnormal liver function tests; anaemia; hyperkalaemia; rash, Stevens-Johnson syndrome, reported;pain, local induration, sterile abscess and muscle necrosis at injection site.

Amphotericin B

Amphotericin B is a complementary drug for the treatment of leishmaniasis

Injection (Powder for solution for injection), amphotericin B 50-mg vial.

Uses: visceral and mucocutaneous leis hmaniasis unresponsive to pentavalent antimony compounds; fungal infections (section 6.3).

Precautions: close medical supervision throughout treatment and initial test dose required (see note below); renal impairment ; hepatic and renal function tests; blood counts and plasma electrolyte monitoring; corticosteroids (avoid except to control reactions); pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid rapid infusion (risk of arrhythmias).

Interactions: Appendix 1

ANAPHYLAXIS. Anaphylaxis occurs rarely with intravenous amphotericin B and a test dose is advisable before the first infusion. The patient should be observed for about 30 minutes after the test dose.

Dosage:

Visceral and mucocutaneous leishmaniasis (unresponsive to pentavalent antimony compounds), *by intravenous infusion*, ADULT initial test dose of 1 mg over 20–30 minutes, then, 5– 10 mg, increased by 5–10 mg daily up to maximum of 0.5– 1 mg/kg, which is then administered on alternate days (total cumulative dose of 1–3 g usually required).

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions

Adverse effects: fever, headache, anorexia, weight loss, nausea

and vomiting, malaise, diarrhoea, muscle and joint pain, dyspepsia, and epigastric pain; renal function disturbances including hypokalaemia, hypomagnesaemia and renal toxicity; blood disorders; cardiovascular toxicity (including arrhythmias); neurological disorders (including peripheral neuropathy); abnormal liver function (discontinue treatment); rash; anaphylactoid reactions (see above); pain and thrombophlebitis at injection.

6.4.3 Antimalarial drugs

Human malaria, which is transmitted by anopheline mosquitoes (and rarely by congenital transmission, transfusion of infected blood or use of contaminated syringes among drug addicts), is caused by four species of plasmodial parasites. *Plasmodium vivax* is the most extensively distributed and causes much debilitating disease. *P. falciparum* is also widespread, and causes the most severe infections which are responsible for nearly all malaria-related deaths. *P. ovale* is mainly confined to Africa - not in India - and is less prevalent, while *P. malariae*, which causes the least severe but most persistent infections, also occurs widely. Certain tissue forms of *P. vivax* and *P. ovale* which persist in the liver for many months and even years are responsible for the relapses characteristic of malaria. Such latent forms are not generated by *P. falciparum* or *P. malariae.* Recrudescence of these infections reults from persistent blood forms in inadequately treated or untreated patients.

Treatment of malaria

Blood schizontocides are the mainstay of the treatment of acute malaria and some are used for prophylaxis. They include the 4-aminoquinolines (**chloroquine**), the related arylaminoalcohols (**mefloquine** and **quinine**), and **artemisinin** and its derivatives (**artemether** and **artesunate**). They suppress malaria by destroying the asexual blood forms of the parasites but, because they are not active against intrahepatic forms, they do not eliminate infections by *P. vivax* and *P. ovale*. Some antimetabolites act synergistically when given in combination. For example, **pyrimethamine** in combination with a sulfonamide or sulfone (**sulfadoxine**) and some antibiotics (particularly tetracyclines for example **doxycycline**) are blood schizontocides. Because they act more slowly, these substances are of little value when used alone. The tetracyclines are used primarily as adjuncts to quinine where multiple-drug resistant *P. falciparum* is prevalent.

Chloroquine, a rapidly acting schizontocide, is well tolerated, safe and inexpensive. It should be used to treat malaria

wherever the parasites remain susceptible. *P. malariae* and *P. ovale* remain fully sensitive to chloroquine. However, widespread chloroquine-resistant strains of *P. falciparum* have been reported in many parts of the Indian subcontinent, A 3-day course by mouth is sufficient to eliminate susceptible *P. falciparum* infections, since effective plasma concentrations are sustained for several weeks.

Parenteral administration may be used when there is no expectation of resistance in cases of severe and complicated malaria, when the patient is unable to take oral medication and when neither quinine nor quinidine are available. The intravenous route is preferred, but it is essential to administer by slow intravenous infusion. Rapid administration (or high dose) can result in cardiovascular toxicity and other potentially fatal symptoms of acute overdose. The intramus cular and subcutaneous routes may be used if facilities for administration by intravenous infusion are not available. If subsequent relapse occurs in *P. ovale* and *P. vivax* infections **primaquine** should be administered, after a second course of chloroquine, to eliminate the intrahepatic infection. The combination of **pyrimethamine with sulfadoxine** is recommended for therapeutic use only in areas of high chloroquine resistance. A single dose of pyrimethamine with sulfadoxine is usually sufficient to eliminate infection; quinine should also be given for 3 days in patients in whom quinine may accelerate reduction of parasitaemia and in those patients with risk of fulminating disease. However, resistance to these combinations is now widespread, particularly in south-east Asia. Because sulfonamides can induce hypersensitivity in pregnant women and possible kernicterus in the newborn, quinine should be used, whenever possible, to treat chloroquine-resis tant malaria during pregnancy (see note on quinine).

Mefloquine remains effective but is best left to be used in higher referral centres.

Quinine given orally, should be reserved for *P. falciparum* infections likely to be unresponsive to other drugs. Resistance to quinine was, until recently, rare, but the prevalence of resistant strains is now increasing in parts of south-east Asia and South America. Doxycycline, which is an effective oral schizontocide should be given in combination with quinine except in pregnant women and children under 8 years. In multi-drug resistant malaria, preparations of **artemisinin** or its derivatives (**artemether** or **artesunate**) offer the only prospect of cure. They should not be used in the first trimester of pregnancy. Nor is it expected that the drug should be made available for common use. Its use will remain restricted where well documented chloroquine resistance on a wide scale is present. For the

treatment of multiresistant falciparum malaria oral **artesunate** may be an effective antimalarial. It should always be given in combination with mefloquine. Parenteral artemether or artesunate, whose use is restricted, are effective alternatives to quinine for the treatment of severe falciparum malaria and are preferred in areas where decreased efficacy of quinine has been documented. To ensure radical cure following parenteral treatment with artemether or oral treatment with artesunate, a full therapeutic dose of mefloquine should be given. The combination is not for use in pregnancy or breastfeeding. Trials are ongoing to determine the safety and efficacy of artemisinin with other antimalarials.

Prophylaxis against malaria

No drug regimen gives assured protection to everybody, and indiscriminate use of existing antimalarials increases the risk of inducing resistance.

Chloroquine:- which is usually well tolerated at the required dosage, is preferred where *P. falciparum* remains fully sensitive. The recommended prophylactic regimen (see below) has been employed effectively even in areas of marginal resistance. However, it must be started 1 week before exposure, and be maintained in pregnant women until after delivery and for at least a week after the last risk of exposure in the case of non-immune individuals. This is sufficient to ensure elimination of *P. falciparum* and *P. malariae*, but not of *P. vivax* and *P. ovale*, whose residual hepatic forms survive.

Artemether

Artemether is a restricted drug used for the treatment of malaria.

Oily injection (Solution for injection) artemether 80 mg/ml, 1-ml ampoule;
Capsule, 40 mg .

Uses: treatment of severe *P. falciparum* malaria in areas where there is evidence that quinine is ineffective.

Contraindications: first trimester of pregnancy

Dosage:

Treatment of severe *P. falciparum* malaria (in areas of quinine resistance), *by intramuscular injection,* ADULT and CHILD over 6 months, loading dose of 3.2 mg/kg, then 1.6 mg/kg daily until patient can tolerate oral medication or to maximum of 7 days; this is followed by a single dose of mefloquine 15 mg/kg (or occasionally, if necessary 25 mg/kg) to effect a radical cure.

ADMINISTRATION. Since small volumes are required for children, a 1-ml syringe should be used to ensure correct dosage.

Adverse effects: headache, nausea, vomiting, abdominal pain, diarrhoea; dizziness, tinnitus, neutropenia, elevated liver

enzyme values; cardiotoxicity (after high doses); neurotoxicity—in *animal* studies.

Artesunate

Artesunate is a restricted drug used for the treatment of malaria.

Tablets, artesunate 50 mg,
Injection 60 mg vial.

Uses: treatment of uncomplicated *P. falciparum* malaria in areas of multiple-drug resistance.

Contraindications: first trimester of pregnancy

Precautions: risk of recurrence if used alone in non-immune patients.

Dosage:

Treatment of uncomplicated malaria (in areas of multiple-drug resistance), *by mouth,* ADULT and CHILD over 6 months, 4 mg/kg daily for 3 days; a single dose of mefloquine 15 mg/kg (or occasionally 25 mg/kg, if necessary) is given on day 2 or 3 to effect a radical cure; if artesunate used alone, treat for 7 days.

Adverse effects: headache, nausea, vomiting, abdominal pain, diarrhoea, dizziness, tinnitus, neutropenia, elevated liver enzyme values; ECG abnormalities, including prolongation of QT interval; temporary suppression of reticulocyte response and induction of blackwater fever, reported; neurotoxicity—in *animal* studies.

Chloroquine

Chloroquine is a representative antimalarial. Various drugs can serve as alternatives .

Tablets, chloroquine base (as phosphate or sulfate) 100 mg, 150 mg .
Oral syrup, chloroquine base (as phosphate or sulfate) 50 mg/5 ml.
Injection (Solution for injection), chloroquine base (as phosphate or sulfate) 40 mg/ml, 5-ml ampoule, 30 ml vial .

Uses: treatment of acute malaria caused by *P. malariae* and susceptible *P. falciparum*; *P. vivax* and *P. ovale* (followed by primaquine to eliminate intrahepatic forms); prophylaxis ofmalaria for pregnant women and non-immune individuals at risk; rheumatic disorders (section 2.4).

Precautions: if patient continues to deteriorate after chloroquine-suspect resistance and administer quinine intravenously as emergency measure; hepatic impairment; renal impairment ; pregnancy (but in malaria, benefit considered to outweigh risk; Appendix 2); breastfeeding (Appendix 3); may exacerbate psoriasis; neurological disorders (avoid for prophylaxis if history of epilepsy); may aggravate myasthenia gravis; severe gastrointestinal disorders; G6PD deficiency; avoid concurrent therapy with hepatotoxic drugs;

Interactions: Appendix 1

Dosage:

NOTE. All doses are in terms of the base .

Treatment of malaria, *by mouth*, ADULT and CHILD 10 mg/kg once daily for the first two days followed by 5 mg/kg on the third day; total dose, 25 mg/kg over 3 days (NAMP guidelines)

PATIENT ADVICE. Oral chloroquine should be taken after meals to minimize nausea and vomiting; if part or all a dose is vomited, the same amount must be immediately readministered

Treatment of malaria (in patients unable to take chloroquine by mouth), *by very slow intravenous infusion* (over at least 8 hours), ADULT and CHILD 10 mg/kg as an initial dose, then 2 further infusions of 5 mg/kg at 8-hour intervals (as soon as patient is able to take chloroquine by mouth, discontinue infusions and complete the course with oral preparations total dose, 25 mg/kg over 3 days); *by intramuscular or by subcutaneous injection* (when intravenous infusion facilities not available) ADULT and CHILD 2.5 mg/kg every 4 hours *or* 3.5 mg/kg every 6 hours (until total dose of 25 mg/kg administered) .

Prophylaxis of malaria, *by mouth*, ADULT 300 mg once a week; CHILD 5 mg/kg once a week

PATIENT ADVICE. Warn travellers about importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return .

DILUTION AND ADMINISTRATION. According to manufacturer's directions. Avoid rapid parenteral administration (risk of toxic plasma concentrations and fatal cardiovascular collapse).

Adverse effects: headache, gastrointestinal disturbances; also convulsions; visual disturbances (retinopathy associated with long-term, high dose therapy or inappropriate self-medication); depigmentation or loss of hair; rashes; pruritus—may become intolerable; bone-marrow suppression; atrioventricular block (may be result of inappropriate self-medication); porphyria and psoriasis in susceptible individuals.

Primaquine

Tablets, primaquine (as phosphate) 2.5 mg, 7.5 mg, 15 mg.

Uses: elimination of intrahepatic forms of *P. vivax* and *P. ovale* (after standard chloroquine therapy); elimination of gametocytes of *P. falciparum* (after routine therapy with a blood schizontocide).

Contraindications: pregnancy (treatment with primaquine should be delayed until after delivery; Appendix 2); breastfeeding (Appendix 3); conditions that predispose to granulocytopenia (including active rheumatoid arthritis and lupus erythematosus).

Precautions: monitor blood count; if methaemoglobinaemia

or haemolysis occurs, withdraw treatment and consult physician; G6PD deficiency (exclude before radical treatment for *P. vivax* and *P. ovale*, but not before single dose gametocytocidal treatment)

Dosage:

NOTE. All doses are in terms of the base

Radical treatment of *P. vivax* and *P. ovale* malaria (after standard chloroquine therapy), *by mouth*, ADULT 0.25 mg / kg daily (*or* 15 mg daily) for 5 days (NAMP); CHILD 0.25 mg /kg daily for 5 days (NAMP); in G6PD deficiency, ADULT 0.75 mg/kg once a week for 8 weeks; CHILD 0.5 – 0.75 micrograms/kg once a week for 8 weeks.

Gametocytocidal treatment of *P. falciparum* (after routine blood schizontocide therapy), *by mouth*, ADULT and CHILD 0.5-0.75 mg/kg as a single dose.

Adverse effects: anorexia, nausea and vomiting, abdominal pain; acute haemolytic anaemia (frequently in G6PD deficiency); rarely, methaemoglobinaemia, haemoglobinuria, agranulocytosis, granulocytopenia and leukopenia.

Pyrimethamine with sulfadoxine

Pyrimethamine with sulfadoxine is a representative antimalarial drug combination. Various drugs can serve as alternatives Pyrimethamine with sulfadoxine are complementary drugs for the treatment of malaria.

Tablets, pyrimethamine 25 mg with sulfadoxine 500 mg.

Uses: treatment of malaria due to susceptible *P. falciparum* in areas of high chloroquine resistance and in patients who have not responded to chloroquine; additionally quinine may be given for 3 days (see notes above).

Contraindications: hypersensitivity to sulfonamides or pyrimethamine; severe hepatic or renal impairment (except where no alternative treatment available).

Precautions: avoid in blood disorders—unless specialist supervision; discontinue immediately if blood disorder occurs; rash, sore throat, mouth ulcers, or shortness of breath—with draw treatment; G6PD deficiency; pregnancy (Appendix 2); breastfeeding (Appendix 3);

Interactions: Appendix 1

Dosage:

Treatment of malaria due to susceptible *P. falciparum* (see notes above), *by mouth*, ADULT pyrimethamine 75 mg with sulfadoxine 1.5 g (3 tablets) as a single dose for those above 40 kgs and 2 tablets for those below 40 kilos (NAMP); CHILD 5–10 kg, half tablet; 11–20 kg, 1 tablet; 21–30 kg, 1 and ½ tablets; 31–45 kg, 2 tablets, as a single dose.

Adverse effects: rashes, pruritus, slight hair loss; rarely Stevens-Johnson syndrome and toxic epidermal necrolysis; gastrointestinal disturbances including nausea, vomiting,

stomatitis; rarely, hepatitis, leukopenia, thrombocytopenia, megaloblastic anaemia and purpura – withdraw treatment;fatigue, headache, fever, polyneuritis, also reported; pulmonaryinfiltrates such as eosinophilic or allergic alveolitis – if symptoms of cough or shortness of breath – withdraw treatment.

Quinine

Quinine is a representative antimalarial. Various drugs can serve as Alternatives

Tablets, quinine sulfate 300 mg; 600 mg

Injection (Solution for dilution for infusion), quinine dihydrochloride 300 mg/ml, 2-ml ampoule.

Uses: multiple-drug resistant *P. falciparum* malaria; severe malaria.

Contraindications: haemoglobinuria; optic neuritis; tinnitus.

Precautions: atrial fibrillation, conduction defects, heart block; monitor for signs of cardiac toxicity and blood glucose levels (with intravenous use); pregnancy (but appropriate for treatment of malaria, Appendix 2); renal impairment ; G6PD deficiency; may aggravate myasthenia gravis;

Interactions: Appendix 1

Dosage:

NOTE. Quinine (anhydrous base) 100 mg = quinine bisulfate 169 mg =quinine dihydrochloride 122 mg = quinine sulfate 121 mg .

Quinine bisulfate 300 mg tablets provide *less* quinine than 300 mg of the sulfate or dihydrochloride .

Treatment of multiple-drug resistant *P. falciparum* malaria or continuation of treatment of severe malaria once patient is able swallow orally, *by mouth*, ADULT 600 mg (quinine sulfate) every 8 hours for 7 days; CHILD 10 mg/kg (quinine sulfate) every 8 hours for 7 days; susceptibility of *P. falciparum* and whether or not additional antimalarials also used .

PATIENT ADVICE. If all or part of a dose is vomited within one hour, the same amount must be readministered immediately

Treatment of multiple-drug resistant *P. falciparum* malaria (in patients unable to take quinine by mouth), *by slow intravenous infusion* (over 4 hours), ADULT 20 mg/kg (quininedihydrochloride) followed by 10 mg/kg (quinine dihydrochloride) every 8 hours; CHILD 20 mg/kg (quinine dihydrochloride) followed by 10 mg/kg (quinine dihydrochloride) every 12 hours; initial dose should be halved in patients who have received quinine, quinidine or mefloquine during the previous 12–24 hours. ***Switch to oral quinine as soon as patient is able to swllow..***

DILUTION AND ADMINISTRATION. According to manufacturer's directions; intravenous injection of quinine is so hazardous that it has been superceded by infusion; ***use 5 or 10 % dextrose for infusion to safeguard from hypoglycaemia of P. falciparum made worse by administration of Quinine;*** where facilities for intravenous infusion

are unavailable, an appropriate dilution may be administered by intramuscular injection.

Adverse effects: cinchonism (tinnitus, headache, blurred vision, altered auditory acuity, nausea, diarrhoea, hot and flushed skin, rashes, confusion); hypersen sitivity reactions including angioedema; rarely haemorrhage and asthma; hypoglycaemia (especially after parenteral administration); renal damage (culminating in acute renal failure and anuria); blood disorders; cardiovascular, gastrointe stinal and CNS effects; very toxic in overdosage – immediate medical attentionrequired.

6.4.4 Antitrypanosomal drugs

Note: Trypanosomial diseases are not found here and hence this group of drugs is not used.

6.5 Antiviral drugs

6.5.1 Herpes and cytomegalovirus infections

HERPES SIMPLEX VIRUS (HSV). **Aciclovir** is active against herpes viruses but does not eradicate them. It is only effective if started at onset of infection; it is also used for prevention of recurrence in the immunocompromised. Genital lesions, oesophagitis and proctitis may be treated with oral aciclovir. HSV encephalitis or pneumo nitis should be treated with intravenous aciclovir.

HERPES ZOSTER VIRUS. While most HIV positive patients with zoster experience only one self-limiting course, some will experience repeated episodes. Treatment should be reserved for debilitating disease and when there is high risk of serious complications, such as in advanced HIV disease. Aciclovir is the treatment of choice and it can be administered in high oral dose or in the case of lack of response to oral therapy or CNS involvement, it should be given intravenously. CYTOMEGALOVIRUS (CMV). Maintenance therapy with oral ganciclovir should be given to prevent relapse of retinitis.

Aciclovir

Tablets, aciclovir 200 mg, 400 mg, 800 mg

Oral suspension, aciclovir 200 mg/5 ml; aciclovir 400 mg / 5 ml *Infusion* (Powder for solution for infusion), aciclovir (as sodium salt) 250-mg vial.

Uses: treatment of primary genital herpes; disseminated varicella- zoster in immunocompromised patients; herpes simplex encephalitis.

Precautions: maintain adequate hydration; renal impairment ; pregnancy (Appendix 2); breastfeeding (Appendix 3)

Dosage:

Treatment of primary genital herpes, *by mouth*, ADULT 200–

400 mg 5 times daily for 5–7 days; occasionally up to 800 mg 5 times daily .

Prevention of recurrence of genital herpes, *by mouth*, ADULT 400 mg twice daily.

Disseminated varicella-zoster in immunocompromised patients, *by intravenous infusion*, ADULT 10 mg/kg 3 times daily for 7days Herpes simplex encephalitis, *by intravenous infusion*, ADULT 10 mg/kg 3 times daily for 10 days.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: rashes; nausea and vomiting, rises in bilirubin and liver enzymes, increases in blood urea and creatinine, decreases in haematological indices, headache, dizziness, fatigue; on intravenous infusion, local inflammation (rarely ulceration), confusion, hallucinations, agitation, tremors, somnolence, psychosis, convulsions and coma.

6.5.2 Antiretroviral drugs

These drugs are intended for use only by initia tion of a specialist at the medical college.

6.6 Insect repellents

Diethyltoluamide, an effective insect repellent, is used for the prevention of infections transmitted by insect bites, ticks, harvest mites and fleas. One application offers protection for 4 to 8 hours.

Diethyltoluamide

Cutaneous solution, diethyltoluamide 50%, 75%

Uses: insect repellent against mosquitoes, biting flies, ticks, harvest mites and fleas.

Precautions: avoid contact with eyes or mouth, mucous membranes, areas of flexures, wounds, broken or irritated skin.

Administration: Apply sparingly to exposed skin and when treatment no longer needed, wash skin thoroughly with soap and water.

Adverse effects: systemic toxicity — reported with application of large topical doses, especially in children; occasionally, hypersensitivity reactions.

Section 7: Antimigraine drugs

Chronic recurrent headache is associated with many disorders, both somatic and psychogenic. An accurate diagnosis must consequently be made before appropriate treatment can be initiated for migraine. Untreated, migraine attacks last for several hours and sometimes for as long as 3 days. Migraine headache is frequently accompanied by episodes of gastrointestinal disturbance including nausea and vomiting. The headache may be preceded or accompanied by aura (classical migraine) which is characterised by visual disturbances such as flickering lines and fragmented vision or sensory disturbances such as tingling or numbness; rarely, hemiparesis or impaired consciousness may occur. Migraine without aura (common migraine) is the more common form occurring in about 75% of patients who experience migraine. Emotional or physical stress, lack of or excess sleep, missed meals, menstruation, alcohol and specific foods including cheese and chocolate are often identified as precipitating factors; oral contraceptives may increase the frequency of attacks. Avoidance of such precipitating factors can be of great benefit in preventing or reducing the frequency of attacks and should be addressed in detail. Women taking combined oral contraceptives who experience an onset or increase in frequency of headaches should be advised of other contraceptive measures.The two principal strategies of migraine management are treatment of acute attacks and prophylactic treatment.

7.1 Acute migraine attack

Treatment of acute attacks may be non-specific using simple analgesics, or specific using ergotamine. If nausea and vomiting are features of the attack, an antiemetic drug may be given.Treatment is generally by mouth; some drugs are available as suppositories which may be administered if the oral route is not effective (poor oral bioavailability, or absorption from the gutimpaired by vomiting) or not practicable (patient unable to takedrugs orally). Simple analgesics including NSAIDs (nonsteroidal anti-inflammatory drugs) can be effective in mild to moderate forms of migraine if taken early in the attack; most migraine headaches respond to **paracetamol**, **acetylsalicylic acid** or an NSAID such as **ibuprofen**. Peristalsis is often reduced during migraine attacks and, if available, a dispersible or effervescent preparation of the drug is preferred because of enhanced absorption compared with a conventional tablet. The risk of Reye syndrome due to acetylsalicylic acid in children under the age of 12 years can be avoided by giving paracetamol instead.

Ergotamine: should be considered only when attacks are unresponsive to non-opioid analgesics. It is poorly absorbed

when taken orally or sublingually. Rectal suppositories may offer an advantage when other routes of administration are unsatisfactory. To be fully effective ergotamine must be taken in adequate amounts as early as possible during each attack. Adverse effects limit how much ergotamine can be used in a single attack and consequently the recommended dosage should never be exceeded, and at least four days should elapse between successive treatments. Even normal dosage can lead to dependence, tolerance to adverse effects and to a withdrawal syndrome on discontinuing the drug. Adverse effects include nausea, vomiting, diarrhoea and vertigo; chronic ergotism is characterized by severe peripheral vasoconstriction which can lead to gangrene in the extremeties. The severity of adverse effects prevents the use of ergotamine for migraine prophylaxis.

An antiemetic such as **metoclopramide**, given as a single dose orally or by intramuscular injection at the onset of a migraine attack, preferably 10–15 minutes before the analgesic or ergotamine, is useful not only in relieving nausea but also in restoring gastric motility, thus improving absorption of the antimigraine drug. Products which contain barbiturates or codeine are undesirable, particularly in combination with ergotamine, since they may cause physical dependence and withdrawal headaches.

Ergotamine tartrate

reserved for use by higher referral centres.

Acetylsalicylic acid

Tablets, acetylsalicylic acid 300 mg, 500 mg.
Dispersible tablets, acetylsalicylic acid 300 mg.
Suppositories, acetylsalicylic acid 300 mg.

Uses: acute migraine attacks; tension headache; also pyrexia, mild to moderate pain and inflammation (section 2.1.1); antiplatelet (section 12.5).

Contraindications: hypersensitivity (including asthma, angioedema, urticaria or rhinitis) to acetylsalicylic acid or any other NSAID; children under 12 years (Reye syndrome); gastrointestinal ulceration; haemophilia; gout.

Precautions: asthma, allergic disease; impaired renal or hepatic function (Appendices 4 and 5); pregnancy (Appendix 2); breastfeeding (Appendix 3); elderly; G6PD-deficiency; dehydration;

Interactions: see Appendix 1

Dosage:

Treatmetn of acute mingaine atack, by mouth preferable with or after food, ADULT 300-900 mg at first sign of attack, may be repeated every 4-6 hours if ecessary; maximum 4 g

daily; CHILD contraindicated under 12 years; by rectum, ADULT 600-900 mg inserted at first sign of attack, may be repeated every4 hours if necessary; maximum 3.6 daily; CHILD contraindicated under 12 years.

Adverse effects: generally mild and infrequent but high incidence of gastrointestinal irritation with slight asymptomatic blood loss, increased bleeding time; bronchospasm and skin reactions in hypersensitive patients; see also section 2.1.1.

Paracetamol

Tablets, paracetamol 125 mg, 250 mg, 500 mg, 650 mg
Syrup, paracetamol 125 mg / 5ml 50 ml, 400 ml, 1 litre and 4.5 litre packs
Drops *(paediatric)* 150 mg / ml.
Suppositories, paracetamol 250 mg, 500 mg

Uses: acute migraine attacks, tension headache; also mild to moderate pain, pyrexia (section 2.1.2).

Precautions: hepatic impairment ; renal impairment; alcohol dependence; pregnancy and breastfeeding (Appendices 2 and 3); **Overdosage:** see section 4.2.1;

Interactions: see Appendix 1

Dosage:

Treatment of acute migraine attack, *by mouth,* ADULT 0.5–1 g at first sign of attack, may be repeated every 4–6 hours if necessary, maximum 4 g daily; CHILD 6–12 years 250–500 mg at first sign of attack, may be repeated every 4–6 hours if necessary, maximum 4 doses in 24 hours; *by rectum*, ADULT and CHILD over 12 years 0.5–1 g at first sign of attack, may be repeated every 4–6 hours if necessary, maximum 4 doses in 24 hours; CHILD 6–12 years 250–500 mg at first sign of attack, may be repeated every 4–6 hours if necessary, maximum 4 doses in 24 hours.

Adverse effects: rare, but rashes, blood disorders; acute pancreatitis reported after prolonged use; **important:** liver damage (and less frequently renal damage) following overdosage.

Ibuprofen

An example of a nonsteroidal anti-infla mmatory drug. Various drugs can serve as alternatives

Tablets, ibuprofen 200 mg, 400 mg, 600 mg.

Uses: acute migraine attacks, tension headache; also mild to moderate pain and inflammation, pyrexia (section 2.1.3).

Contraindications: hypersensitivity (including asthma, angioedema, urticaria or rhinitis) to acetylsalicylic acid or any other NSAID; active peptic ulceration.

Precautions: hepatic or renal impairment (Appendices 4 and 5); cardiac disease; elderly; pregnancy and breastfeeding (Appendices 2 and 3); coagulation defects; allergic disorders;

Interactions: see Appendix 1

Dosage:

Treatment of acute migraine attack, *by mouth* preferably with or after food, ADULT 400–600 mg at first sign of attack, may be repeated every 6–8 hours if necessary, maximum 2.4 g daily; CHILD 8–12 years 200 mg at first sign of attack, may be repeated every 6–8 hours if necessary.

Adverse effects: gastrointestinal disturbances including nausea, diarrhoea, dyspepsia, gastric ulceration; hypersensitivity reactions including rash, bronchospasm; headache, dizziness, tinnitus, renal failure; rarely hepatic damage; very rarely exfoliative dermatitis, purpura; prolonged administration, see section 2.1.3

Metoclopramide hydrochloride

Tablets, metoclopramide hydrochloride 5 mg, 10 mg
Syrup, 5mg/5ml
Injection, metoclopramide hydrochloride 5 mg/ml, 2-ml ampoule; 10 mg/ml.

Uses: nausea and vomiting associated with migraine; also nausea and vomiting in gastrointestinal disorders and cytotoxic therapy (section 17.2).

Contraindications: gastrointestinal obstruction, haemorrhage or perforation; epilepsy; phaeochromocytoma.

Precautions: hepatic or renal impairment (Appendices 4 and 5); elderly; children and young adults; pregnancy and breastfeeding (Appendices 2 and 3); porphyria;

Interactions: see Appendix 1

Dosage:

Nausea and vomiting of migraine, *by mouth or by intramuscular injection*, ADULT single dose of 10–20 mg at first sign of attack preferably10–15 minutes before antimigraine drug; ADOLESCENT single dose of 5–10 mg (5 mg if body weight less than 60 kg).

Adverse effects: drowsiness, restlessness, diarrhoea; prolonged administration, see section 17.2

7.2 Migraine prophylaxis

Prophylactic treatment should be considered for patients in whom treatment of acute migraine attacks with analgesics or ergotamine is ineffective, or in whom attacks occur more than once a month, or for those with less frequent but severe or prolonged attacks. Prophylaxis can reduce the severity and frequency of attacks but does not eliminate them completely; additional symptomatic treatment is still needed. However, long-term prophylaxis is undesirable and treatment should be reviewed at 6-monthly intervals. Of the many drugs that have been advocated beta-adrenoceptor

antagonists (beta-blockers) are most frequently used. **Atenolol,** a betablocker and other related compounds with similar profile are generally preferred. The potential for betablockers to interact with ergotamine should be borne in mind. Tricyclic antidepressants, such as **imipramine** (section 24.2.1) or calcium-channel blocking drugs such as **verapamil** (section 12.1) may be of value.

Atenolol

An example of a b_1-selective adrenergic antagonist. Various drugs can serve as alternatives

Tablets, Atenolol 25 mg, 50 mg, 100 mg .

Uses: prophylaxis of migraine

Contraindications: asthma or history of obstructive airways disease, uncontrolled heart failure, Prinzmetal angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third-degree atrioventricular block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease; haeochromocytoma.

Precautions: first-degree atrioventricular block; renal impairment ; liver disease ; pregnancy and breastfeeding (Appendices 2 and 3); portal hypertension; diabetes mellitus; myasthenia gravis; history of hypersensitivity (increased reaction to allergens, also reduced response to epinephrine);

Interactions: see Appendix 1

Dosage:

Prophylaxis of migraine, *by mouth* ADULT initially 25 to 50 mg per day gradually increased by same amount at weekly intervals if necessary; usual range 50 –150 mg daily; CHILD under 12 years, 1-1.3 mg / kg per day in 2 – 3 divided.

Adverse effects: bradycardia, heart failure, hypotension, conduction disorders, bronchospasm, peripheral vasoconstriction, exacerbation of intermittent claudication and Raynaud phenomenon, gastrointestinal disturbances, fatigue, sleep disturbances including nightmares; rarely, rash, dry eyes (reversible), exacerbation of psoriasis.

Section 8: Antineoplastic and immunosuppressive and drugs used in palliative care

8.1 Immunosuppressive drugs,
8.2 Cytotoxic (antineoplastic) drugs,
8.3 Hormones and antihormones,
8.4 Drugs used in palliative care,

Drugs in this section are left to the use of higher referral centres where there is expertise and infrastructure to handle these drugs.

Section : 9 Antiparkinson drugs

9.1 Drugs used in parkinsonism

The use of pharmacotherapy will depend upon the degree of incapacity of the patient and is generally not justified until symptoms compromise working ability and social relationships; although levodopa is used in the early stages in some patients.Close supervision is then needed to ensure that treatment regimens are tolerated and that appropriate changes are made to the regimen as the disease progresses.

The most effective form of therapy is a combination of **levodopa** and a peripheral dopa-decarboxylase inhibitor, such as **carbidopa**. The response to levodopa with carbidopa is a compromise between increased mobility and adverse effects. Dyskinesias may be dose limiting and increasingly frequent with increased duration of treatment. Many factors including tolerance and progression of the disease may result in complications after 2 to 5 years of treatment. 'End-of-dose' deterioration occurs when there is a reduced duration of benefit from a dose, resulting in disability and dystonias. The 'on-off' phenomenon is characterized by sudden swings from mobility to episodes of akinesia, tremor and rigidity lasting from a few minutes to several hours. Amelioration of these effects can sometimes be achieved by administering levodopa in a sustained-release preparation or in a greater number of fractionated doses throughout the day. Supplementary use of amantadine, bromocriptine or selegiline can be of value either to enhance the effect of levodopa or to reduce 'end-of-dose' fluctuations and 'on-off' effects. Psychiatric symptoms inducing disruption of sleep, vivid dreams and hallucinations are characteristic adverse effects that may occur at any time, especially in the elderly, and may require dose reduction or withdrawal of levodopa. Anticholinergic (more correctly termed antimuscarinic) drugs such as **biperiden** are usually sufficient in drug-induced pseudo-parkinsonism. They are also used as adjunctive therapy in other forms of parkinsonism where the primary need is to stimulate dopaminergic activity in the striatal system.

Levodopa with carbidopa

Carbidopa is a representative peripheral dopa decarboxylase inhibitor. Various drugs can serve as alternatives

Tablets, levodopa 100 mg with carbidopa 10 mg, levodopa 100 mg with carbidopa 25 mg levodopa 250 mg with carbidopa 25 mg.

Uses: all forms of parkinsonism other than drug-induced.

Contraindications: concurrent use of monoamine oxidase inhibitors; angle-closure glaucoma; confirmed or suspected malignant melanoma.

Precautions: pulmonary disease, peptic ulceration,

cardiovascular disease (including previous myocardial infarction); diabetes mellitus, osteomalacia, open-angle glaucoma, psychiatric illness (avoid if severe); close supervision of patients is necessary with monitoring of hepatic, haematological, cardiovascular and renal function in long-term therapy; elderly: avoid rapid dose increases; avoid abrupt withdrawals; pregnancy (toxicity in *animals*) (Appendix 2), breastfeeding (Appendix3);

Interactions: Appendix 1

Dosage:

Parkinsonism, *by mouth*, ADULT expressed in terms of levodopa, initially 100 mg (with carbidopa 10 mg) twice daily, increased by 100 mg (with carbidopa 10 mg) every few days as necessary, to a maximum of levodopa 1.5 g

ADMINISTRATION. Optimum daily dose must be determined for each patient by careful monitoring and be taken after meals.

Adverse effects: nausea, anorexia and vomiting, particularly at the start of treatment; postural hypotension at the start of treatment, particularly in elderly and those receiving antihypertensives; confusion, vivid dreams, dizziness, tachycardia, arrhythmias; reddish discoloration of body fluids; drowsiness, headache, flushing, gastrointestinal bleeding, peripheral neuropathy; taste disturbances, pruritis, rash, liver enzyme changes; psychiatric symptoms including psychosis, depression, hallucinations, delusions and neurological disturbances including dyskinesias may be dose-limiting; painful dystonic spasms ('end-of-dose' effects) and ('on-off' effects) after prolonged treatment (see notes above); neuroleptic malignant syndrome, on sudden withdrawal.

Trihexy phenidyl hydrochloride

Trihexy phenidyl hydrochloride is a central anticholinergic drug. Various drugs can serve as alternatives

Tablets trihexy phenidyl hydrochloride 2 mg, 2.5 mg, 5 mg

Injection, 5mg/ml in 1 ml vial.

Uses: drug-induced extrapyramidal symptoms (but not tardive dyskinesias) and adjunctive treatment of parkinsonism.

Contraindications: acute narrow angle glaucoma; obstructive uropathy; myasthenia gravis; gastrointestinal obstruction.

Precautions: elderly; cardiovascular disease, hepatic or renal impairment; avoid abrupt withdrawal;

Interactions: Appendix 1

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving.

Dosage:

Drug induced extrapyramidal symptoms,parkinsonism, *by mouth*, ADULT, initially 1 mg twice daily, increased to 2 mg 3 times daily, gradually increased according to response and tolerance to maximum 6-10 mg daily. To be given with meals

and at bedtime; post-encephalitic patients may need higher doses.

Adverse effects: drowsiness, dry mouth, constipation, blurred vision; hesitancy of micturition, dizziness, tachycardia, arrhythmias, confusion and psychiatric disturbances with high dosage, especially in the elderly, may require withdrawal of treatment.

9.2 Drugs used in essential tremor and related disorders

ESSENTIAL TREMOR. It can be treated with beta-blockers such as **atenolol** (100 mg daily) (section 7.2) which may be of value if the tremor results in physical or social disability.

DYSTONIAS. If no identifiable cause is found and the patient does not go into spontaneous remission, a trial of **levodopa** should be given to determine whether the patient has dopamineresponsive dystonia. If there is no response within three months, the drug should be withdrawn and small doses of an anticholinergic drug such as trihexy phenidyl should be given. The dosage may be increased gradually and up to 16 mg daily may be tolerated. In patients who fail to respond to either levodopa or an anticholinergic, other drugs including diazepam, baclofen, carbamazepine or phenothiazines may be of value. Psychological treatments have also been used successfully in the management of dyskinesias.

CHOREA. Choreiform movements can be induced by certain drugs including levodopa, phenytoin and antipsychotic drugs. Huntington disease is the most common of the hereditary choreas. Drug treatment is symptomatic and does not alter the progression of the disease. The aim of therapy is to reduce dopaminergic transmission which results from excessive or enhanced cholinergic activity. Antipsychotic drugs antagonize dopamine and usually lessen the chorea temporarily. Tetrabenazine, the dopamine-depleting drug is currently under investigation. TICS. Tics which resemble choreiform movements are commonly associated with anxiety. However, in the more complex multiple tic disorder, Tourette syndrome, treatment with antipsychotic drugs may be required.

TARDIVE DYSKINESIA. It is associated with chronic administration of antipsychotic drugs. It is characterized by involuntary, repetitive, choreiform movement of the cheek, mouth and fingers. The first step of treatment should always be discontinuation of the antipsychotic drug or dosage reduction if the underlying psychotic disorder permits. In some cases this disorder may be irreversible and if the symptoms are very disabling small dosages of reserpine may be tried.

Section 10 : Drugs affecting the blood

10.1 Antianaemia drugs

IRON-DEFICIENCY ANAEMIA. Anaemia has many different aetiologies. It occurs when the haemoglobin concentration falls below the normal range for the age and sex of the individual. It is essential that a correct diagnosis is made before initiating therapy.Any serious underlying cause of iron-deficiency anaemia, including gastric erosion and colonic carcinoma, should be excluded before giving iron replacement. Prophylaxis with iron salts in pregnancy should be given to women who have additional factors for iron-deficiency; low-dose iron and folic acid preparations are used for the prophylaxis of megaloblastic anaemia in pregnancy.

Ferrous salts should be given orally wherever possible. They differ only marginally in efficiency of absorption and thus the choice of preparation is usually decided by incidence of adverse effects and cost. The oral dose of elemental iron for treatment of iron-deficiency anaemia in adults should be 100–200 mg daily with meals. The approximate elemental iron content of various ferrous salts is ferrous fumarate 200 mg (65 mg iron), ferrous gluconate 300 mg (35 mg iron), ferrous succinate 100 mg (35 mg iron), ferrous sulfate 300 mg (60 mg iron), and dried ferrous sulfate 200 mg (65 mg iron). *Iron intake in the evening has been reported to improve its absorption.* Iron intake with meals may reduce bioavailability but improve tolerability and adherence. If adverse effects arise with one salt, dosage can be reduced or a change made to an alternative iron salt. The haemoglobin concentration should rise by about 100–200 mg/100 ml per day or 2 g/100 ml over 3–4 weeks. ***After the haemoglobin has risen to normal, treatment should be continued for a further three months in an attempt to replenish the iron stores.*** Gastrointestinal irritation may occur. Nausea and epigastric pain are do se-related. Oral iron may exacerbate diarrhoea in patients with inflammatory bowel disease but care is also needed in patients with intestinal strictures and diverticulae. Iron as **iron dextran** should be given parenterally only if the patient has severe gastrointestinal adverse effects with oral preparations, continuing severe blood loss or malabsorption. Parenteral iron may cause more harm than benefit. Provided that the oral iron preparation is taken reliably and is absorbed, then the haemoglobin response is not significantly faster with the parenteral route than the oral route.

MEGALOBLASTIC ANAEMIAS. These are due to the lack of either vitamin B12 (hydroxocobalamin) or folate or both. The clinical features of folate-deficient megaloblastic anaemia are similar to those of vitamin B12 deficiency except that the accompanying severe neuropathy does not occur;

it is essential to determine which deficiency is present and the underlying cause is established in every case. **Hydroxocobalamin** is the form of vitamin B12 used for treatment of vitamin B12 deficiency whether due to dietary deficiency or malabsorption including pernicious anaemia (due to a lack of intrinsic factor essential for B12 absorption). Folate deficiency due to poor nutrition, pregnancy, antiepileptics or malabsorption is treated with **folic acid** but this should never be administered without vitamin B12 in undiagnosed megaloblastic anaemia because of the risk of precipitating neurological changes due to vitamin B12 deficiency. Preparations containing a **ferrous salt and folic acid** are used for the prevention of megaloblastic anaemia in pregnancy. The low doses of folic acid in these preparations are inadequate for the treatment of megaloblastic anaemias.

PREVENTION OF NEURAL TUBE DEFECTS. **Folic acid** 5 mg is given to prevent the recurrence of neural tube defect in women who wish to become pregnant (or are at risk of becoming pregnant). To prevent first occurrence of neural tube defect women of childbearing age should be advised to take folic acid as a medicinal or food supplement at a dose of 400 mcg daily before conception and continue until the twelfth week of pregnancy.

Ferrous salts

Tablets, dried
ferrous sulfate 200 mg (65 mg iron), 300 mg (100 mg iron);
ferrous sulfate 300 mg (60 mg iron);
ferrous fumarate 210 mg (68 mg iron), 350 mg (100 mg iron);
ferrous gluconate 300 mg (35 mg iron)

Syrups in different strengths.

Uses: iron-deficiency anaemia

Contraindications: haemosiderosis, haemochromatosis; any form of anaemia not caused by iron deficiency; patients receiving repeated blood transfusions; parenteral iron therapy.

Precautions: should not be administered for longer than 6 months; pregnancy; peptic ulcer, regional enteritis, ulcerative colitis, intestinal strictures, diverticulae; **overdosage:** see section 4.2.4; **interactions:** Appendix 1

Dosage:

Iron-deficiency anaemia, *by mouth*, ADULT elemental iron 100–200 mg daily in divided doses.

Adverse effects: constipation, diarrhoea, dark stools, nausea, epigastric pain, gastrointestinal irritation; long-term or excessive administration may cause haemosiderosis.

Iron dextran reserved for higher referral centres

Folic acid

Tablets, folic acid 5 mg.

Uses: treatment of folate-deficiency megaloblastic anaemia; prevention of neural tube defect in pregnancy.

Contraindications: should never be given without vitamin B12 in undiagnosed megaloblastic anaemia or other vitamin B12 deficiency states because risk of precipitating subacute combined degeneration of the spinal cord; folate-dependent malignant disease.

Precautions: women receiving antiepileptic therapy need counselling before starting folic acid;

Interactions: Appendix 1

Dosage:

Treatment of folate-deficiency, megaloblastic anaemia, *by mouth*, ADULT 5 mg daily for 4 months; up to 15 mg daily may be necessary in malabsorption states

Prevention of first occurrence of neural tube defect, *by mouth*, ADULT 0.5 mg daily before conception and during the first twelve weeks of pregnancy

Prevention of recurrence of neural tube defect, *by mouth*, ADULT 5 mg daily (reduced to 4 mg daily, if suitable preparation available) from at least 4 weeks before conception until twelfth week of pregnancy.

NOTE. Patients unable to take folic acid *by mouth*, may be given the same dose as sodium salt where available *by deep intramuscular injection.*

Ferrous salt with folic acid

Tablets, dried ferrous sulfate with folic acid in different strengths.
ferrous sulfate 200 mg (65 mg iron), folic acid 1 mg;
ferrous sulfate 325 mg (105 mg iron), folic acid 350 mcg;
ferrous sulfate 160 mg (50 mg iron), folic acid 400 mcg;
ferrous fumarate 322 mg (105 mg iron), folic acid 350 mg.

Uses: prevention of iron and folic acid deficiencies in pregnancy.

Precautions: low doses of folic acid in the combination preparations above are inadequate for treatment of megaloblastic anaemia. **Overdosage:** see section 4.2.4;

Interactions: Appendix 1

Dosage:

Prevention of iron and folic acid deficiencies in pregnancy, *by mouth* ADULT the equivalent of about 100 mg elemental iron with 350–400 mcg folic acid daily throughout pregnancy.

Adverse effects: see Ferrous salts

Hydroxocobalamin

Injection (Solution for injection), hydroxocobalamin 500 mcg/ml and 1000 mcg (1 mg) per ml, 5-ml ampoule.

Uses: megaloblastic anaemia due to vitamin B12 deficiency.

Precautions: except in emergencies, should not be given before

diagnosis confirmed; monitor serum potassium levels — arrhythmias secondary to hypokalaemia in early therapy.

Dosage:

Megaloblastic anaemia without neurological involvement, *by intramuscular injection*, ADULT and CHILD initially 0.25–1 mg on alternate days for 1–2 weeks, then 250 mcg weekly until blood count is within normal range, thereafter 1 mg every 2–3 months

Megaloblastic anaemia with neurological involvement, *by intramuscular injection*, ADULT and CHILD initially 1 mg on alternate days until no further improvement occurs, then 1 mg every 2 months

Prophylaxis of macrocytic anaemias, *by intramuscular injection*, ADULT and CHILD 1 mg every 2–3 months

Tobacco amblyopia and Leber optic atrophy, *by intramuscular injection*, ADULT and CHILD 1 mg daily for 2 weeks, then 1 mg twice weekly until no further improvement, then 1 mg every 1–3 months.

Adverse effects: itching, exanthema, fever, chills, hot flushes, nausea, dizziness; rarely acneiform and bullous eruptions, anaphylaxis.

10.2 Drugs affecting coagulation

Anticoagulants are used to prevent thrombus formation or extension of an existing thrombus in the slower-moving venous side of the circulation, where the thrombus consists of a fibrin web enmeshed with platelets and red cells. They are therefore used widely in the prevention and treatment of deep-vein thrombosis in the legs, prophylaxis of embolization in rheumatic heart disease and atrial fibrillation and to prevent thrombi forming on prosthetic heart valves.

Heparin is a parenteral anticoagulant that initiates anticoagulation rapidly but has a short duration of action. The low molecular weight heparins have a longer duration of action.For the treatment of deep venous thrombosis and pulmonary embolism heparin is given as an intravenous loading dose followed by continuous intravenous infusion (using an infusion pump) or by intermittent subcutaneous injection. An oral anticoagulant is started at the same time as heparin. The heparin needs to be continued for at least 3 days, until the oral anticoagulant has taken effect. Laboratory monitoring is essential, on a daily basis. Heparin is also used in regimens for the management of myocardial infarction, the management of unstable angina, acute peripheral arterial occlusion and in dialysis.In patients undergoing general surgery, low-dose heparin by subcutaneous injection is used to prevent postoperative deepvein thrombosis and pulmonary embolism in high risk patients (those with obesity, malignant disease, history of deep-vein thrombosis or

pulmonary embolism, patients over 40 years, those with an established thrombophilic disorder or those undergoing large or complicated surgery). It is also of value in high-risk medical patients, for example obesity, heart failure, when confined to bed.If haemorrhage occurs it is usually sufficient to withdraw heparin, but if rapid reversal of the effects of heparin is required, **protamine sulfate** is a specific antidote. Oral anticoagulants take at least 48 to 72 hours for the anticoagulant effect to develop fully; if an immediate effect is needed, heparin must be given concomitantly. **Warfarin** is indicated in deep-vein thrombosis, pulmonary embolism and patients with atrial fibrillation who are at risk of embolization; oral anticoagulants should not be used in cerebral thrombosis or peripheral arterial occlusion as first-line therapy. The main adverse effect of oral anticoagulants is haemorrhage. Prothrombin time should be checked on a daily basis initially then at longer intervals depending on response.If severe haemorrhage occurs, stop warfarin and give **phytomenadione** (vitamin K) by slow intravenous injection.

ANTICOAGULANTS IN PREGNANCY. Oral anticoagulants are teratogenic and should not be given in the first trimester of pregnancy. Women at risk of pregnancy should be warned of this danger since stopping warfarin before the sixth week of gestation may largely avoid the risk of fetal abnormality. Oral anticoagulants cross the placenta with the risk of placental or fetal haemorrhage, especially during the last few weeks of pregnancy and at delivery. Therefore, if at all possible, oral anticoagulants should be avoided in pregnancy, especially in the first and third trimester. Difficult decisions may have to be made, particularly in women with prosthetic heart valves or with a history of recurrent venous thrombosis or pulmonary embolism. HAEMOPHILIA. For the use of factor VIII and factor IX in haemophilia, see section 11.2.

Heparin sodium

Injection (Solution for injection), heparin sodium 1000 units/ml, 1-ml ampoule; 5000 units/ml, 0.5 ml, 1 ml and 5 ml ampoule; 20,000 units per ml, 25 000 units/ml, 1-ml ampoule.

Uses: treatment and prophylaxis of deep-vein thrombosis and pulmonary embolism.

Contraindications: hypersensitivity to heparin; haemophilia and other haemorrhagic disorders, thrombocytopenia, peptic ulcer, recent cerebral haemorrhage, severe hypertension, severe liver or renal disease, after major trauma or recent surgery (especially to eye or nervous system).

Precautions: hepatic impairment and renal failure ; hypersensitivity to low molecular weight heparins; spinal or epidural anaesthesia — risk of spinal haematoma; pregnancy (Appendix 2); diabetes mellitus, acidosis, concomitant potassium-sparing drugs — increased risk of hyperkalaemia.

Interactions: Appendix 1

Dosage:

Treatment of deep-vein thrombosis and pulmonary embolism: *by intravenous injection*, ADULT loading dose of 5000 units (10 000 units in severe pulmonary embolism) followed *by continuous intravenous infusion* of 15–25 units/kg/hour *or by subcutaneous injection* of 15 000 units every 12 hours; laboratory monitoring is essential, preferably on a daily basis and dose adjusted accordingly; *by intravenous injection,* SMALL ADULT and CHILD, lower loading dose, then *by continuous intravenous infusion,* 15–25 units/kg/hour *or by subcutaneous injection*, 250 units/kg every 12 hours

Prophylaxis in general surgery, *by subcutaneous injection*, ADULT 5000 units 2 hours before surgery, then every 8–12 hours for 7 days or until patient is ambulant (monitoring not needed); during pregnancy (with monitoring) 5000–10 000 units every 12 hours (**important:** not intended to cover prosthetic heart valve management in pregnancy, which requires specialist management).

Adverse effects: immune-mediated thrombocytopenia usually developing 6 to 10 days after commencement of therapy (requires immediate withdrawal of heparin); haemorrhage, skin necrosis, hypersensitivity reactions including urticaria, angioedema and anaphylaxis, osteoporosis after prolonged use and rarely alopecia.

Warfarin sodium

Warfarin is a representative oral anticoagulant. Various drugs can serve as alternatives

Tablets, warfarin sodium 1 mg, 2 mg, 5 mg.

Uses: prophylaxis of embolization in rheumatic heart disease and atrial fibrillation; prophylaxis after insertion of prosthetic heart valve; prophylaxis and treatment of venous thrombosis and pulmonary embolism; transient ischaemic attacks.

Contraindications: pregnancy (see notes above and Appendix 2); peptic ulcer, severe hypertension, bacterial endocarditis.

Precautions: hepatic impairment or renal failure, recent surgery, breastfeeding (Appendix 3);

Interactions: Appendix 1

Dosage:

NOTE. Wherever possible, the base-line prothrombin time should be determined before the initial dose is given

Prophylaxis and treatment of thromboembolic disorders, *by mouth*, ADULT usual induction dose is 10 mg daily for 2 days, according to the individual patient; the subsequent dose depends upon the prothrombin time; the usual daily maintenance dose is 3 to 9 mg taken at the same time each day.

Adverse effects: haemorrhage; hypersensitivity, rash, alopecia,

diarrhoea, unexplained drop in haematocrit, 'purple toes', skin necrosis, jaundice, hepatic dysfunction, nausea, vomiting and pancreatitis.

Reversal of anticoagulation
Protamine sulfate

Injection (Solution for injection), protamine sulfate 10 mg/ml, 5-ml ampoule.

Uses: antidote to overdosage with heparin.

Precautions: if used in excess protamine has an anticoagulant effect; allergic reactions increased in persons at risk including previous treatment with protamine or protamine insulin, fish allergies, men who are infertile or who have had a vasectomy.

Dosage:

Heparin overdose, *by intravenous injection* over approximately 10 minutes, 1 mg neutralizes 80–100 units heparin when given within 15 minutes; if longer time, less protamine needed as heparin is rapidly excreted.

Adverse effects: nausea, vomiting, lassitude, flushing, hypotension, bradycardia, dyspnoea, allergic reactions.

Phytomenadione

This is a Vitamin K analogue like

Tablets, phytomenadione 10 mg

Injection (Solution for injection), phytomenadione 10 mg/ml, 5-ml ampoule.

Uses: antagonist to warfarin; prophylaxis against haemorrhagic disease of the newborn.

Precautions: reduce dose in elderly; hepatic impairment; not an antidote to heparin; pregnancy (Appendix 2).

Interactions: Appendix 1

Dosage:

Warfarin-induced hypoprothrombinaemia; no bleeding or minor bleeding, *by slow intravenous injection*, ADULT 500 mcg *or by mouth*, ADULT 5 mg; less severe haemorrhage, *by mouth or by intramuscular injection*, ADULT 10–20 mg; severe haemorrhage, ADULT, *by slow intravenous injection*, 2.5–25 mg, very rarely up to 50 mg

Haemorrhagic disease of the newborn, treatment, *by intravenous or intramuscular injection*, NEONATE 1 mg with further doses if necessary at 8-hour intervals; prophylaxis, *by intramuscular injection*, NEONATE 0.5–1 mg as single dose *or by mouth*, 2 mg followed by a second dose after 4–7 days and for breast-fed babies a third dose after 1 month.

Adverse effects: hypersensitivity reactions including flushing, dyspnoea, bronchospasm, dizziness, hypotension and respiratory or circulatory collapse which may be due to polyethoxylated castor oil surfactant in some injection formulations rather than due to phytomenadione.

Section 11: Blood products and plasma substitutes

11.1 Plasma substitutes

Dextran 70 is a macromolecular substance which is slowly metabolized; it may be used to expand and maintain blood volume in shock arising from conditions such as burns or septicaemia. It is rarely needed when shock is due to sodium and water depletion as, in these circumstances, the shock responds to water and electrolyte repletion. *Plasma substitutes should not be used to maintain plasma volume in conditions such as burns or peritonitis where there is loss of plasma protein, water and electrolytes over periods of several days.* In these situations, plasma or plasma protein fractions containing large amounts of albumin should be given. Plasma substitutes may be used as an immediate short-term measure to treat massive haemorrhage until blood is available. Dextran may interfere with blood group cross-matching or biochemical measurements and these should be carried out before the infusion is begun.

Dextran 70

Dextran is a representative plasma substitute. Various preparations can serve as alternatives.

Infusion (Solution for infusion), dextran –70 as 6% in glucose intravenous infusion 5% or sodium chloride intravenous infusion 0.9%.

Uses: short-term blood volume expansion

Contraindications: severe congestive heart failure, renal failure; bleeding disorders such as thrombocytopenia and hypofibrinogenaemia.

Precautions: cardiac disease or renal impairment; monitor urine output; avoid haematocrit falling below 25–30%; can interfere with blood group cross-matching and biochemical tests — take samples before start of infusion; monitor for hypersensitivity reactions

Dosage:

Short-term blood volume expansion, *by rapid intravenous infusion*, 500–1000 ml initially, followed by 500 ml if necessary; total dosage should not exceed 20 ml/kg during the initial 24 hours.

Adverse effects: urticarial and other hypersensitivity reactions — rarely severe anaphylactoid reactions

11.2 Plasma fractions for specific use

Reserved for use in higher referral centres.

Section 12: Cardiovascular drugs

12.1 Antianginal drugs

The three main types of angina are: *stable angina* (angina of effort), where atherosclerosis restricts blood flow in the coronary vessels; attacks are usually caused by exertion and relieved by rest. *unstable angina* (acute coronary insufficiency), which is considered to be an intermediate stage between stable angina and myocardial infarction. *Prinzmetal angina* (variant angina), caused by coronary vasospasm, in which attacks occur at rest. Management depends on the type of angina and may include drug treatment, coronary artery bypass surgery, or percutaneous transluminal coronary angioplasty.

Stable angina

Drugs are used both for the relief of acute pain and for prophylaxis to reduce further attacks; they include organic nitrates, beta-adrenoceptor antagonists (beta-blockers), and calcium-channel blockers.

NITRATES. Organic nitrates have a vasodilating effect; they are sometimes used alone, especially in elderly patients with infrequent symptoms. Tolerance leading to reduced antianginal effect is often seen in patients taking prolonged-action nitrate formulations. Evidence suggests that patients should have a 'nitrate-free' interval to prevent the development of tolerance. Adverse effects such as flushing, headache, and postural hypotension may limit nitrate therapy but tolerance to these effects also soon develops. A sublingual tablet of **isosorbide dinitrate** is more stable in storage than glyceryl trinitrate and is useful in patients who require nitrates infrequently; it has a slower onset of action, but effects persist for several hours.

CALCIUM-CHANNEL BLOCKERS.

A calcium-channel blocker, such as **verapamil,** is used as an alternative to a beta-blocker to treat stable angina. Calcium-channel blockers interfere with the inward movement of calcium ions through the slow channels in heart and vascular smooth muscle cell membranes, leading to relaxation of vascular smooth muscle. Myocardial contractility may be reduced, the formation and propagation of electrical impulses within the heart may be depressed and coronary or systemic vascular tone may be diminished. Calcium-channel blockers are used to improve exercise tolerance in patients with chronic stable angina due to coronary atherosclerosis or with abnormally small coronary arteries and limited vasodilator reserve. Calcium-channel blockers can also be used in patients with unstable angina with a vasospastic origin, such as Prinzmetal angina, and in patients in whom alterations in cardiac tone may influence the angina threshold.

Unstable angina

Unstable angina requires prompt aggressive treatment to prevent progression to myocardial infarction. Initial treatment is with acetylsalicylic acid to inhibit platelet aggregation, followed by heparin. Nitrates and beta-blockers are given to relieve ischaemia; if beta-blockers are contraindicated, verapamil is an alternative, provided left ventricular function is adequate.

Prinzmetal angina

Treatment is similar to that for unstable angina, except that a calcium-channel blocker is used instead of a beta-blocker.

Isosorbide dinitrate

Isosorbide dinitrate is a representative nitrate vasodilator. Various drugs can serve as alternatives .

Sublingual tablets, isosorbide dinitrate 5 mg, 10 mg, 20 mg, 40 mg .

Sustained-release *(prolonged-release) tablets or capsules,* isosorbide dinitrate 20 mg, 40 mg .

Spray 200 metred doses.

Uses: prophylaxis and treatment of angina; heart failure (section 12.4).

Contraindications: hypersensitivity to nitrates; hypotension; hypovolaemia; hypertrophic obstructive cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis; marked anaemia; head trauma; cerebral haemorrhage; angle-closure glaucoma.

Precautions: severe hepatic or renal impairment; hypothyroidism; malnutrition; hypothermia; recent history of myocardial infarction.

Interactions: Appendix 1

TOLERANCE. Patients taking isosorbide dinitrate for the long-term management of angina may often develop tolerance to the antianginal effect; this can be avoided by giving the second of 2 daily doses of longer-acting oral presentations after an 8-hour rather than a 12-hour interval, thus ensuring a nitrate-free interval each day.

Dosage:

Angina (acute attack), *sublingually,* ADULT 5–10 mg, repeated as required.

Angina prophylaxis, *by mouth,* ADULT 30–120 mg daily in divided doses (see advice on Tolerance above).

Adverse effects: throbbing headache; flushing; dizziness, postural hypotension; tachycardia (paradoxical bradycardia also reported).

Verapamil hydrochloride

Verapamil is a representative calcium-channel blocker. Various drugs can serve as alternatives .

Tablets, verapamil hydrochloride 40 mg, 80 mg

NOTE. Sustained-release (prolonged-release) tablets are available. A proposal to include such a product in a national list of essential drugs should be supported by adequate documentation

Uses: angina, including stable, unstable, and Prinzmetal; arrhythmias (section 12.2).

Contraindications: hypotension, bradycardia, second- and third-degree atrioventricular block, sinoatrial block, sick sinus syndrome; cardiogenic shock; history of heart failure or significantly impaired left ventricular function (even if controlled by therapy); atrial flutter or fibrillation complicating Wolff-Parkinson-White syndrome; porphyria.

Precautions: first-degree atrioventricular block; acute phase of myocardial infarction (avoid if bradycardia, hypotension, left ventricular failure); hepatic impairment ; children (specialist advice only); pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid grapefruit juice.

Interactions: Appendix 1

Dosage:

Angina, *by mouth,* ADULT 80–120 mg 3 times daily (120 mg 3 times daily usually required in Prinzmetal angina).

Adverse effects: constipation; less commonly nausea, vomiting, flushing, headache, dizziness, fatigue, ankle oedema; reversible impairment of liver function; allergic reactions (erythema, pruritus, urticaria, angioedema, Stevens-Johnson syndrome); myalgia, arthralgia, paraesthesia, erythromelalgia; increased prolactin concentration; gynaecomastia and gingival hyperplasia on long-term treatment; with high doses, hypotension, heart failure, bradycardia, heart block, and asystole (due to negative inotropic effect).

12.2 Antiarrhythmic drugs

Treatment of arrhythmias requires precise diagnosis of the type of arrhythmia. Antiarrhythmic drugs must be used cautiously since they have a narrow therapeutic index; ECG monitoring is often advised. When two or more antiarrhythmic drugs are used together, their negative inotropic effects tend to be additive, particularly if myocardial function is impaired. Also, most drugs that are effective in treating arrhythmias can provoke them in some circumstances; this arrhythmogenic effect is often enhanced by hypokalaemia.

Atrial fibrillation

Oral administration of **digoxin** is usually effective in slowing the increased ventricular rate in atrial fibrillation. Intravenous digoxin is occasionally required if the ventricular rate needs rapid control. If adequate control at rest or during exercise cannot be achieved readily with digoxin, a **beta-adrenoceptor antagonist** (beta-blocker) like **atenolol** or

verapamil may be added; both should be used with caution if ventricular function is impaired. Anticoagulants are indicated especially in valvular or myocardial disease, and in the elderly. **Warfarin** is preferred to acetylsalicylic acid in preventing emboli. If atrial fibrillation began within the past 48 hours it is better to refer to a higher referral centre.

Atrial flutter

Digoxin will slow the ventricular rate. Reversion to sinus rhythm is best achieved by direct current electrical shock. If the arrhythmia is long-standing, treatment with anticoagulants should be considered before cardioversion to prevent emboli. Intravenous **verapamil** reduces ventricular fibrillation during paroxysmal (sudden onset and intermittent) attacks of atrial flutter. An initial intravenous dose may be followed by oral treatment; hypotension may occur with high doses. It should not be used for tachyarrhythmias where the QRS complex is wide unless a supraventricular origin has been established beyond doubt.

Paroxysmal supraventricular tachycardia

In most patients this remits spontaneously or can revert to sinus rhythm by reflex vagal stimulation. Failing this, intravenous injection of a beta-adrenoceptor antagonist (beta-blocker) or verapamil may be effective. These drugs should **never** be administered concomitantly because of the risk of hypotension and asystole.

Ventricular tachycardia

Very rapid ventricular fibrillation causes profound circulatory collapse and must be treated immediately with direct current shock. After sinus rhythm is restored, drug therapy to prevent recurrence of ventricular tachycardia should be considered; a beta-adrenoceptor antagonist (betablocker) or verapamil may be effective. *Torsades de pointes* is a special form of ventricular tachycardia associated with prolongation of the QT interval. Initial treatment with intravenous infusion of magnesium sulfate is usually effective, followed by temporary pacing; alternatively, isoprenaline infusion may be given with extreme caution until pacing can be instituted. Isoprenaline is an inotropic sympathomimetic; it increases the heart rate and therefore shortens the QT interval, but given alone may induce arrhythmias.

Bradyarrhythmias

Sinus bradycardia (less than 50 beats/minute) associated with acute myocardial infarction may be treated with atropine.

Temporary pacing may be required in unresponsive patients. Drugs are of limited value for increasing the sinus rate long term in the presence of intrinsic sinus node disease and permanent pacing is usually required.

Cardiac arrest

In cardiac arrest, **epinephrine** (adrenaline) is given by intravenous injection in a dose of 1 mg (10 ml of 1 in 10 000 solution) as part of the procedure for cardiopulmonary resuscitation.

Atenolol

Atenolol is a representative beta-adrenoceptor antagonist. Various drugs can serve as alternatives

Tablets, atenolol 50 mg, 100 mg.

Uses: arrhythmias; angina; hypertension (section 12.3); migraine prophylaxis (section 7.2).

Contraindications: asthma or history of obstructive airways disease (unless no alternative, then with extreme caution and under specialist supervision); uncontrolled heart failure, Prinzmetal angina, marked bradycardia, hypotension, sick sinus syndrome, second- and third-degree atrioventricular block, cardiogenic shock; metabolic acidosis; severe peripheral arterial disease; phaeochromocytoma (unless used with alpha-blocker).

Precautions: avoid abrupt withdrawal in angina; may precipitate or worsen heart failure; pregnancy (Appendix 2); breastfeeding (Appendix 3); first-degree atrioventricular block; liver function deteriorates in portal hypertension; reduce dose in renal impairment ; diabetes mellitus (small decrease in glucose tolerance, masking of symptoms of hypoglycaemia); history of hypersensitivity (increased reaction to allergens, also reduced response to epinephrine); myasthenia gravis.

Interactions: Appendix 1

Dosage:

Arrhythmias, *by mouth,* ADULT 50 mg once daily, increased if necessary to 50 mg twice daily *or* 100 mg once daily.

Adverse effects: gastrointestinal disturbances (nausea, vomiting, diarrhoea, constipation, abdominal cramp); fatigue; cold hands and feet; exacerbation of intermittent claudication and Raynaud phenomenon; bronchospasm; bradycardia, heart failure, conduction disorders, hypotension; sleep disturbances, including nightmares; depression, confusion, convulsions; hypo- or hyperglycaemia; exacerbation of psoriasis; rare reports of rashes and dry eyes (oculomucocutaneous syndrome—reversible on withdrawal)

Digoxin

Tablets, digoxin 62.5 mcg,250 mcg (0.25 mg)
Paediatric elixir solution, digoxin 0.05 mg (50 mcg)/ ml.
Injection (Solution for injection), digoxin 250 mcg (0.25 mg)/ ml, 2-ml ampoule.

Uses: supraventricular arrhythmias, particularly atrial fibrillation; heart failure (section 12.4).

Contraindications: hypertrophic obstructive cardiomyopathy (unless also severe heart failure); Wolff-Parkinson-White syndrome or other accessory pathway, particularly if accompanied by atrial fibrillation; intermittent complete heart block; second-degree atrioventricular block.

Precautions: recent myocardial infarction; sick sinus syndrome; severe pulmonary disease; thyroid disease; elderly (reduce dose); renal impairment ; avoid hypokalaemia; avoid rapid intravenous administration (nausea and risk of arrhythmias); pregnancy (Appendix 2); breastfeeding (Appendix 3).

Interactions: Appendix 1

Dosage:

Atrial fibrillation, *by mouth,* ADULT 1–1.5 mg in divided doses over 24 hours for rapid digitalization *or* 250 mcg 1–2 times daily if digitalization less urgent; maintenance 62.5– 500 mcg daily (higher dose may be divided), according to renal function and heart rate response; usual range 125– 250 mcg daily (lower dose more appropriate in elderly).

Emergency control of atrial fibrillation, *by intravenous infusion,* ADULT 250–500 mcg over 10–20 minutes, repeated at intervals of 4–8 hours according to response to total loading dose of 0.5–1 mg.

NOTE. Infusion dose may need to be reduced if digoxin or other cardiac glycoside given in previous 2 weeks.

Adverse effects: usually associated with excessive dosage and include anorexia, nausea, vomiting, diarrhoea, abdominal pain; visual disturbances, headache, fatigue, drowsiness, confusion, delirium, hallucinations, depression; arrhythmias, heart block; rarely rash, intestinal ischaemia; gynaecomastia on long-term use; thrombocytopenia reported.

Lidocaine hydrochloride

Injection, lidocaine hydrochloride 20 mg/ ml (2%), 5-ml ampoule, 50 ml vial.

Uses: ventricular arrhythmias (especially after myocardial infarction); local anaesthesia (section 1.2).

Contraindications: sino-atrial disorder, any grade of atrioventricular block or any other type of conduction disturbances, severe myocardial depression, acute porphyria or hypovolaemia.

Precautions: lower dosage in congestive heart failure,

bradycardia, hepatic impairment, marked hypoxia, severe respiratory depression, following cardiac surgery and in elderly;

Interactions: Appendix 1

Dosage:

Ventricular arrhythmias, *by intravenous injection,* ADULT, loading dose of 50–100 mg (*or* 1–1.5 mg/kg) at a rate of 25–50 mg/minute, followed immediately by *intravenous infusion* of 1–4 mg/minute, with ECG monitoring of all patients (reduce infusion dose if required for longer than 24 hours).

Adverse effects: dizziness, paraesthesia, drowsiness, confusion, apnoea, respiratory depression, coma, seizures, and convulsions, hypotension, arrhythmias, heart block, cardiovascular collapse and bradycardia (may lead to cardiac arrest); nystagmus often an early sign of lidocaine overdosage.

Verapamil hydrochloride

Tablets, verapamil hydrochloride 40 mg, 80 mg, 120 mg Sustained-release (prolonged-release) tablets are available in 120 and 240 mg strength. A proposal to include such a product in a national list of essential drugs should be supported by adequate documentation.
Injection (Solution for injection), verapamil hydrochloride 2.5 mg/ ml, 2-ml ampoule.

Uses: supraventricular arrhythmias; angina (section 12.1).

Contraindications: hypotension, bradycardia, second- and third-degree atrioventricular block, sinoatrial block, sick sinus syndrome; cardiogenic shock; history of heart failure or significantly impaired left ventricular function (even if controlled by therapy); atrial flutter or fibrillation complicating Wolff-Parkinson-White syndrome; porphyria.

Precautions: first-degree atrioventricular block; acute phase of myocardial infarction (avoid if bradycardia, hypotension, left ventricular failure); hepatic impairment; children (specialist advice only); pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid grapefruit juice;

Interactions: Appendix 1

VERAPAMIL AND BETA-BLOCKERS. Both verapamil and beta-blockers have cardiodepressant activity, and their use together may lead to bradycardia, heart block and left ventricular failure, particularly in patients with myocardial insufficiency. Treatment with beta-blockers should be discontinued at least 24 hours before intravenous administration of verapamil; they should only be given together by mouth if myocardial function is well preserved.

Dosage:

Supraventricular arrhythmias, *by mouth,* ADULT 40–120 mg 3 times daily.

Supraventricular arrhythmias, *by intravenous injection,* ADULT

5–10 mg over 2 minutes (preferably with ECG monitoring); ELDERLY 5–10 mg over 3 minutes; in paroxysmal tachyarrhythmias, further 5 mg may be given after 5–10 minutes if required.

Adverse effects: constipation; less commonly nausea, vomiting, flushing, headache, dizziness, fatigue, ankle oedema; reversible impairment of liver function; allergic reactions (erythema, pruritus, urticaria, angioedema, Stevens-Johnson syndrome); myalgia, arthralgia, paraesthesia, erythromelalgia; increased prolactin concentration; gynaecomastia and gingival hyperplasia on long-term treatment; with high doses, hypotension, heart failure, bradycardia, heart block, and asystole (due to negative inotropic effect).

12.3 Antihypertensive drugs

Management of hypertension

Since treatment for hypertension is often life-long, it is important to integrate the treatment of hypertension into an overall programme of management of associated risk factors and conditions, particularly in elderly patients who often have multiple associated disorders. Mild hypertension is defined as 140–159mmHg systolic blood pressure and 90–99mmHg diastolic blood pressure, moderate hypertension 160– 180 mmHg systolic and 100–109mmHg diastolic and severe hypertension more than 180mmHg systolic and more than 110 mmHg diastolic. The goal of treatment is to obtain the maximum tolerated reduction in blood pressure.

Lifestyle changes should be introduced for all patients; they include weight reduction, reduction in alcohol intake, reduction of dietary sodium, stopping tobacco smoking, and reduction in saturated fat intake. The patient should eat a healthy nutritious diet including adequate fruit and vegetables and should exercise regularly. These measures alone may be sufficient in mild hypertension, but patients with moderate to severe hypertension will also require specific antihypertensive therapy.

Drug treatment of hypertension

Five classes of drug are used for first-line treatment of hypertension: diuretics, beta-adrenoceptor antagonists (betablockers), angiotensin-converting enzyme (ACE) inhibitors, calcium-channel blockers and alpha-adrenoceptor blocking drugs (alpha-blockers). All five classes are effective in reducing blood pressure; thiazide diuretics and beta-blockers have been shown to reduce mortality due to cardiovascular complications of hypertension. Other classes of drugs may be used in certain

situations. Thiazide diuretics, such as **hydrochlorothiazide** (see also section 16.1), have been used as first-line antihypertensive therapy, and are particularly indicated in the elderly. They have few adverse effects in low doses, but in large doses they may cause a variety of unwanted metabolic effects (principally potassium depletion), reduced glucose tolerance, ventricular ectopic beats and impotence; they should be avoided in gout. These effects can be reduced by keeping the dose as low as possible; higher doses do not produce an increased reduction in blood pressure. Thiazides are inexpensive and, when used in combination, can enhance the effectiveness of many other classes of antihypertensive drug. Beta-adrenoceptor antagonists (beta-blockers) such as **atenolol** are effective in all grades of hypertension, and are particularly useful in angina and following myocardial infarction; they should be avoided in asthma, chronic obstructive pulmonary disease, and heart block. Angiotensin-converting enzyme inhibitors (ACE inhibitors) such as **enalapril** are effective and well tolerated by most patients. They can be used in heart failure, left ventricular dysfunction and diabetic nephropathy, but should be avoided in renovascular disease and in pregnancy. The most common adverse affect is a dry persistent cough. Calcium-channel blockers such as **amlodipine** are effective antihypertensives, particularly for isolated systolic hypertension, and in the elderly when thiazides cannot be used. Short-acting formulations of nifedipine should be avoided as they may evoke reflex tachycardia and cause large variations in blood pressure. Drugs acting on the central nervous system are also effective anti-hypertensive drugs. In particular methlydopa is effective in the treatment of hypertension in pregnancy and may also be used in asthma and in heart failure. Combining antihypertensive drugs often produces and beneficial additive effect.

Hypertension in pregnancy

This is defined as a sustained diastolic blood pressure of 90mmHg or more. Drug therapy for chronic hypertension during pregnancy remains controversial. If diastolic blood pressure is greater than 95 mmHg, **methyldopa** is the safest drug. Beta-blockers should be used with caution in early pregnancy, since they may retard fetal growth; they are effective and safe in the third trimester. ACE inhibitors are contraindicated in pregnancy since they may damage fetal and neonatal blood pressure control and renal function. Women who are taking these drugs and become pregnant should have their antihypertensive therapy changed immediately. *Pre-eclampsia and eclampsia*. If pre-eclampsia

or severe hypertension occurs beyond the 36th week of pregnancy, delivery is the treatment of choice. For acute severe hypertension in pre-eclampsia or eclampsia, intravenous **hydralazine** can be used. **Magnesium sulfate** (section 22.1) is the treatment of choice to prevent eclamptic convulsions.

Hypertensive emergencies

In situations where immediate reduction of blood pressure is essential and treatment by mouth is not possible, intravenous infusion of **sodium nitroprusside** is effective. However, over-rapid reduction in blood pressure is hazardous and can lead to reduced organ perfusion and cerebral infarction and **hence the drug is reserved for higher referral centres only.**

Atenolol

Atenolol is a representative beta-adrenoceptor antagonist. Various drugs can serve as alternatives.

Tablets, atenolol 50 mg, 100 mg.

Uses: hypertension; angina (section 12.1); arrhythmias (section 12.2); migraine prophylaxis (section 7.2).

Contraindications: asthma or history of obstructive airways disease (unless no alternative, then with extreme caution and under specialist supervision); uncontrolled heart failure, Prinzmetal angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third-degree atrioventricular block, cardiogenic shock; metabolic acidosis; severe peripheral arterial disease; phaeochromocytoma (unless used with alpha-blocker).

Precautions: avoid abrupt withdrawal in angina; may precipitate or worsen heart failure; pregnancy (Appendix 2); breastfeeding (Appendix 3); first-degree atrioventricular block; liver function deteriorates in portal hypertension; reduce dose in renal impairment ; diabetes mellitus (small decrease in glucose tolerance, masking of symptoms of hypoglycaemia); history of hypersensitivity (increased reaction to allergens, also reduced response to epinephrine); myasthenia gravis.

Interactions: Appendix 1

Dosage:

Hypertension, *by mouth*, ADULT 50 mg once daily (higher doses rarely necessary).

Adverse effects: gastrointestinal disturbances (nausea, vomiting, diarrhoea, constipation, abdominal cramp); fatigue; cold hands and feet; exacerbation of intermittent claudication and Raynaud phenomenon; bronchospasm; bradycardia, heart failure, conduction disorders, hypotension; sleep disturbances, including nightmares;

depression, confusion, convulsions; hypo- or hyperglycaemia; exacerbation of psoriasis; rare reports of rashes and dry eyes (oculomucocutaneous syndrome—reversible on withdrawal).

Enalapril

An ACE inhibitor for reducing hypertension.

Tablets of 2.5 mg, 5 mg, 10 and 20 mg Enalapril maleate.

Uses: all grades of essential hypertension; renal/surgically correctable hypertension, as adjunct in congestive cardiac failure.

Contraindications: 2nd and 3rd trimester of pregnancy, patients on immunosuppression, shock, anuria, cirrhosis, aortic stenosis, hypersensitivity.

Precautions: repeated blood counts are important, 1st trimester of pregnancy, careful in congestive heart failure and in hyperkalaemia, may drop glucose levels in diabetics on treatment.

USE WITH DIURETICS. Risk of very rapid falls in blood pressure in volume depleted patients; diuretic should be discontinued, or dose significantly reduced, 2–3 days before starting enalapril (may not be possible in heart failurerisk of pulmonary oedema); if diuretic cannot be stopped, medical supervision advised for first 2 hours after administration or until blood pressure has stabilized.

ANAPHYLACTOID REACTIONS. Avoid enalapril during dialysis with high-flux polyacrilonitrile membranes and during low-density lipoprotein apheresis with dextran sulfate; also withhold before desensitization with wasp or bee venom.

Dosage:

Adults: 5 mg orally once daily increased gradually upto 10 to 40 mg per day until maximum of 40 mg per day. Start with 2.5 mg if diuretic also given or in the eldrely.

Children: not recommended .

Adverse effects: profound hypotension, renal impairment; angioedema (onset may be delayed), rash (possibly associated with pruritus and urticaria); persistent dry cough and upper respiratory-tract symptoms such as sinusitis, rhinitis, sore throat; pancreatitis, gastrointestinal disturbances including nausea, vomiting, dyspepsia, diarrhoea and constipation; altered liver function tests, cholestatic jaundice, hepatitis; blood disorders including thrombocytopenia, leukopenia, neutropenia, and haemolytic anaemia reported; also headache, dizziness, fatigue, malaise, taste disturbance, paraesthesia, bronchospasm, fever, serositis, vasculitis, myalgia, arthralgia, positive antinuclear antibody, raised erythrocyte sedimentation rate, eosinophilia, leukocytosis, and photosensitivity.

Hydrochlorothiazide

Hydrochlorothiazide is a representative thiazide diuretic. Various drugs can serve as alternatives

Tablets, hydrochlorothiazide 25 mg.

Uses: alone in mild hypertension, and in combination with other drugs in moderate to severe hypertension; heart failure (section 12.4); oedema (section 16.1).

Contraindications: severe kidney or severe hepatic impairment; hyponatraemia, hypercalcaemia, refractory hypokalaemia, symptomatic hyperuricaemia; Addison disease.

Precautions: renal and hepatic impairment (Appendices 4 and 5); pregnancy and breastfeeding (Appendices 2 and 3); elderly (reduce dose); may cause hypokalaemia; may aggravate diabetes mellitus and gout; may exacerbate systemic lupus erythematosus; porphyria;

Interactions: Appendix 1

Dosage:

Hypertension, *by mouth*, ADULT 12.5–25 mg daily; ELDERLY initially 12.5 mg daily.

Adverse effects: fluid and electrolyte imbalance leading to dry mouth, thirst, gastrointestinal disturbances (including nausea, vomiting), weakness, lethargy, drowsiness, seizures, headache, muscle pains or cramps, hypotension (including postural hypotension), oliguria, arrhythmias; hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraemic alkalosis, hypercalcaemia; hyperglycaemia, hyperuricaemia, gout; rashes, photosensitivity; altered plasma lipid concentration; rarely impotence (reversible); blood disorders (including neutropenia, thrombocytopenia); pancreatitis, intrahepatic cholestasis; acute renal failure; hypersensitivity reactions (pneumonitis, pulmonary oedema, severe skin reactions).

Methyldopa

Tablets, methyldopa 250 mg.

Uses: hypertension, including hypertension in pregnancy.

Contraindications: depression; active liver disease; phaeochromocytoma, porphyria.

Precautions: history of hepatic impairment ; renal impairment; blood counts and liver-function tests advised; history of depression; positive direct Coomb test in up to 20% of patients (affects blood cross-matching); interference with laboratory tests; pregnancy and breastfeeding (Appendices 2 and 3);

Interactions: Appendix 1

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving.

Dosage:

Hypertension, *by mouth*, ADULT initially 250 mg 2–3 times daily; if necessary, gradually increased at intervals of 2 or more days; maximum 3 g daily.

ELDERLY initially 125 mg twice daily, gradually increased to maximum 2 g daily.

Adverse effects: tend to be transient and reversible, including sedation, dizziness, lightheadedness, postural hypotension, weakness, fatigue, headache, fluid retention and oedema, sexual dysfunction; impaired concentration and memory, depression, mild psychosis, disturbed sleep and nightmares; drug fever, influenza-like syndrome; nausea, vomiting, constipation, diarrhoea, dry mouth, stomatitis, sialadenitis; liver function impairment, hepatitis, jaundice, rarely fatal hepatic necrosis; bone-marrow depression, haemolytic anaemia, leukopenia, thrombocytopenia, eosinophilia; Parkinsonism; rash (including toxic epidermal necrolysis); nasal congestion; black or sore tongue; bradycardia, exacerbation of angina; myalgia, arthralgia, paraesthesia, Bell palsy; pancreatitis; hypersensitivity reactions including lupus erythematosus-like syndrome, myocarditis, pericarditis; gynaecomastia, hyperprolactinaemia, amenorrhoea; urine darkens on standing.

Amlodipine

Amlodipine is dihydropyridine calcium-channel blocker. Various drugs can serve as alternatives

Tablets, amlodipine 2.5 mg, 5 mg, 7.5 mg,10mg

Uses: hypertension

Contraindications: cardiogenic shock; advanced aortic stenosis; within 1 month of myocardial infarction; unstable or acute attacks of angina; porphyria.

Precautions: stop if ischaemic pain occurs or existing pain worsens shortly after starting treatment; poor cardiac reserve; heart failure or significantly impaired left ventricular function; reduce dose in hepatic impairment ; diabetes mellitus; may inhibit labour; pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid grapefruit juice (may affect metabolism);

Interactions: Appendix 1

Dosage:

Hypertension, *by mouth* ADULT usual range 5 to 10 mg once daily, and should be titrated over a period of 7 to 14 days. Initial dose may be reduced to 2.5 mg in the elderly and in those with liver disorders.

NOTE: Maximal hypotensive effect of amlodipine may take seveeral weeks to fully manifest.

Adverse effects: headache, flushing, dizziness, lethargy; tachycardia, palpitations; gravitational oedema (only partly responsive to diuretics); rash (erythema multiforme reported), pruritus, urticaria; nausea, constipation or diarrhoea; increased frequency of micturition; eye pain, visual disturbances; gum hyperplasia; paraesthesia, myalgia, tremor; impotence, gynaecomastia; depression; telangiectasis; cholestasis, jaundice.

12.4 Drugs used in heart failure

Treatment of heart failure aims to relieve symptoms, improve exercise tolerance, reduce incidence of acute exacerbations, and reduce mortality. Drugs used to treat heart failure due to left ventricular systolic dysfunction include ACE inhibitors, diuretics, cardiac glycosides and vasodilators. In addition, measures such as weight reduction, moderate salt restriction, and appropriate exercise should be introduced.

The primary treatment of heart failure is with angiotensin converting enzyme inhibitors (ACE inhibitors) such as **enalapril** which can be used in all stages of chronic heart failure to prevent further deterioration and progression of heart disease. A thiazide diuretic such as **hydrochlorothiazide** is used in the management of mild to moderate heart failure when the patient has mild fluid retention and severe pulmonary oedema is not present; however thiazides are ineffective if renal function is poor. In these patients, and in more severe fluid retention, a loop diuretic such as **Frusemide** (section 16.2) is required. In severe fluid retention, intravenous Frusemide produces relief of breathlessness and reduces preload sooner than would be expected from the time of onset of diuresis. Hypokalaemia may develop, but is less likely with the shorter-acting loop diuretics than with the thiazides; care is needed to avoid hypotension. A combination of a thiazide and a loop diuretic may be required to treat refractory oedema. The combination often produces a synergistic effect on solute and water excretion, which relieves symptoms in the diuretic-resistant heart failure patient. However, the combination may produce excessive intravascular volume depletion and electrolyte disturbances including potentially life-threatening hypokalaemia.

Digoxin, a cardiac glycoside, increases the strength of cardiac muscle contractions and increases cardiac output. In mild heart failure, digoxin inhibits the sympathetic nervous system and produces arterial asodilation. It produces symptomatic improvement, increases exercise tolerance, and reduces the risk of clinical deterioration. It is considered for patients with atrial fibrillation and those who do not respond to ACE inhibitors.

Vasodilators are used in heart failure to reduce systemic vascular resistance.

Isosorbide dinitrate (section 12.1) produces mainly venous dilatation, which reduces left ventricular preload, leading to a reduction in pulmonary congestion and dyspnoea.

Dopamine, an inotropic sympathomimetic, may be given for short periods in the treatment of severe heart failure. Dosage

is critical; at low doses it stimulates myocardial contractility and increases cardiac output and renal perfusion, however higher doses (more than 5 mcg/kg per minute) cause vasoconstriction, with a worsening of heart failure.

Enalapril

Enalapril is an angiotensin-converting enzyme inhibitor. Various drugs can serve as alternatives

Tablets, enalapril 2.5 mg, 5 mg, 10 mg, 20 mg.

Uses: heart failure (with a diuretic); prophylaxis after myocardial infarction; hypertension (section 12.3).

Contraindications: hypersensitivity to ACE inhibitors (including angioedema); known or suspected renovascular disease; aortic stenosis, outflow tract obstruction; pregnancy (Appendix 2); porphyria.

Precautions: use with diuretics; hypotension with first doses, especially in patients on diuretics, on a low-sodium diet, on dialysis, if dehydrated, or with heart failure; peripheral vascular disease or generalized atherosclerosis (risk of clinically silent renovascular disease); monitor renal function before and during treatment; renal impairment (reduce dose, see also); possibly increased risk of agranulocytosis in collagen vascular disease; history of idiopathic or hereditary angioedema (use with care or avoid); breastfeeding (Appendix 3);

Interactions: Appendix 1

USE WITH DIURETICS. Risk of very rapid falls in blood pressure in volume depleted patients; diuretic should be discontinued, or dose significantly reduced, 2–3 days before starting enalapril (may not be possible in heart failure — risk of pulmonary oedema); if diuretic cannot be stopped, medical supervision dvised for first 2 hours after administration or until blood pressure has stabilized

APHYLACTOID REACTIONS. Avoid enalapril during dialysis with high-flux polyacrilonitrile membranes and during low-density lipoprotein apheresis with dextran sulfate; also withhold before desensitization with wasp or bee venom.

Dosage:

Heart failure (adjunct), *by mouth,* ADULT, initially 5 mg once daily under close medical supervision; increased gradually as necessary, usual maintenance dose 10 to 40 mg in single dose or two divided doses; usual maximum 40 mg daily.

Prophylaxis after myocardial infarction (in clinically stable patients), *by mouth*, ADULT initially 2.5 mg, gradually increased over several weeks to 40 mg daily in divided doses.

Adverse effects: profound hypotension, renal impairment; angioedema (onset may be delayed), rash (possibly associated with pruritus and urticaria); persistent dry cough and upper respiratory-tract symptoms such as sinusitis, rhinitis, sore throat; pancreatitis, gastrointestinal disturbances including nausea, vomiting, dyspepsia, diarrhoea and constipation; altered liver

function tests, cholestatic jaundice, hepatitis; blood disorders including thrombocytopenia, leukopenia, neutropenia, and haemolytic anaemia reported; also headache, dizziness, fatigue, malaise, taste disturbance, paraesthesia, bronchospasm, fever, serositis, asculitis, myalgia, arthralgia, positive antinuclear antibody, raised erythrocyte sedimentation rate, eosinophilia, leukocytosis, and photosensitivity.

Digoxin

Tablets, digoxin 250 mcg (0.25 mg).
Peadiatric elixir, digoxin 0.05 mg (50 mcg)/ml
Injection (Solution for injection), digoxin 0.25 mg (250 mcg)/ml, 2-ml ampoule.

Uses: heart failure; arrhythmias (section 12.2)

Contraindications: hypertrophic obstructive cardiomyopathy (unless also severe heart failure); Wolff-Parkinson-White syndrome or other accessory pathway, particularly if accompanied by atrial ibrillation; intermittent complete heart block; second-degree atrioventricular block.

Precautions: recent myocardial infarction; sick sinus syndrome; severe pulmonary disease; thyroid disease; elderly (reduce dose); renal impairment ; avoid hypokalaemia; avoid rapid intravenous administration (nausea and risk of arrhythmias); pregnancy (Appendix 2); breastfeeding (Appendix 3);

Interactions: Appendix 1

Dosage:

Heart failure, *by mouth*, ADULT 1–1.5 mg in divided doses over 24 hours for rapid digitalization *or* 0.25 mg 1–2 times daily if digitalization less urgent; maintenance 0.125–0.5 mg daily (higher dose may be divided), according to renal function and heart rate response.

Emergency loading dose, *by intravenous infusion*, ADULT 0.25–0.5 mg over 10–20 minutes, repeated at intervals of 4–8 hours according to response to total loading dose of 0.5– 1 mg

NOTE. Infusion dose may need to be reduced if digoxin or other cardiac glycoside given in previous 2 weeks .

Adverse effects: usually associated with excessive dosage and include anorexia, nausea, vomiting, diarrhoea, abdominal pain; visual disturbances, headache, fatigue, drowsiness, confusion, delirium, hallucinations, depression; arrhythmias, heart block; rarely rash, intestinal ischaemia; gynaecomastia on long-term use; thrombocytopenia reported.

Dopamine hydrochloride

It is a naturally occurring organic amine.

Concentrate for infusion (Concentrate for solution for infusion), dopamine hydrochloride 40 mg/ml, 5-ml ampoule.

Uses: cardiogenic shock in myocardial infarction or cardiac surgery.

Contraindications: tachyarrhythmia, ventricular fibrillation; ischaemic heart disease; phaeochromocytoma; hyperthyroidism.

Precautions: correct hypovolaemia before, and maintain blood volume during treatment; correct hypoxia, hypercapnia, and metabolic acidosis before or at same time as starting treatment; low dose in shock due to myocardial infarction; history of peripheral vascular disease (increased risk of ischaemia of extremities); elderly;

Interactions: Appendix 1

Dosage:

Cardiogenic shock, *by intravenous infusion* into large vein, ADULT initially 2–5 mcg/kg/minute; gradually increased by 5–10 mcg/kg/minute according to blood pressure, cardiac output and urine output; seriously ill patients up to 20–50 mcg/kg/minute.

DILUTION AND ADMINISTRATION. According to manufacturer's directions .

Adverse effects: nausea and vomiting; peripheral vasoconstriction; hypotension with dizziness, fainting, flushing; tachycardia, ectopic beats, palpitations, anginal pain; headache, dyspnoea; hypertension particularly in overdosage.

Hydrochlorothiazide

Hydrochlorothiazide is a representative thiazide diuretic. Various drugs can serve as alternatives

Tablets, hydrochlorothiazide 25 mg, 50 mg.

Uses: heart failure; hypertension (section 12.3); oedema (section 16.1).

Contraindications: severe kidney or severe hepatic impairment; hyponatraemia, hypercalcaemia, refractory hypokalaemia, symptomatic hyperuricaemia; Addison disease .

Precautions: renal and hepatic impairment (Appendices 4 and 5); pregnancy and breastfeeding (Appendices 2 and 3); elderly (reduce dose); may cause hypokalaemia; may aggravate diabetes mellitus and gout; may exacerbate systemic lupus erythematosus; porphyria.

Interactions: Appendix 1

Dosage:

Heart failure, *by mouth*, ADULT initially 25 mg daily on rising, increasing to 50 mg daily if necessary; ELDERLY initially 12.5 mg daily.

Adverse effects: fluid and electrolyte imbalance leading to dry mouth, thirst, gastrointestinal disturbances (including nausea, vomiting), weakness, lethargy, drowsiness, seizures, headache, muscle pains or cramps, hypotension (including postural hypotension), oliguria, arrhythmias; hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraemic

alkalosis, hypercalcaemia; hyperglycaemia, hyperuricaemia, gout; rashes, photosensitivity; altered plasma lipid concentration; rarely impotence (reversible); blood disorders (including neutropenia, thrombocytopenia); pancreatitis, intrahepatic cholestasis; acute renal failure; hypersensitivity reactions (pneumonitis, pulmonary oedema, severe skin reactions).

2.5 Antithrombotic drugs and myocardial infarction

Anticoagulants prevent thrombus formation or the extension of an existing thrombus. For further details see section 10.2 (drugs affecting coagulation). Antiplatelet drugs also help to inhibit thrombus formation by decreasing platelet aggregation. Thrombolytics (fibrinolytics) such as **streptokinase** are used to break up thrombi; they are used to treat acute myocardial infarction, extensive deep vein thrombosis, major pulmonary embolism and acute arterial occlusion. **The expertise to use them is likely to be present only in higher referral centres and is reserved for such centres.**

Myocardial infarction

Management of myocardial infarction includes two phases: initial management of the acute attack. long-term management, including prevention of further attacks .

Initial management

Oxygen (section 1.1.3) should be given to all patients, except those with severe chronic obstructive airways disease. Pain and anxiety are relieved by slow intravenous injection of an opioid analgesic such as **morphine** (section 2.2).

Metoclopramide (section 17.2) may also be given by intramuscular injection to prevent and treat nausea and vomiting caused by morphine.

Acetylsalicylic acid 150–300 mg by mouth (preferably chewed or dispersed in water) is given immediately for its antiplatelet effect.

ACE inhibitors (section 12.4) have also been shown to be beneficial in initial management (unless patient has contraindications) when given within 24 hours, and if possible continued for 5–6 weeks. If arrhythmias occur, they should be treated aggressively, but the likelihood decreases rapidly over the first 24 hours after infarction. Ventricular fibrillation should be treated immediately with a defibrillator; if this is ineffective alone, the antiarrhythmic drug **lidocaine** (section 12.2) should be given.

Long-term management

Acetylsalicylic acid should be given to all patients in a dose of 75–150 mg daily by mouth, unless it is contraindicated. The prolonged antiplatelet effect has been shown to reduce the rate of reinfarction. Treatment with **beta-blockers** should

be continued for at least 1 year, and possibly for up to 3 years. ACE inhibitors such as **enalapril** (section 12.4) should also be used since they reduce mortality, particularly in patients with left ventricular dysfunction.

Nitrates (section 12.1) may be required for patients with angina.

Stroke

Stroke (cerebrovascular accident) may be ischaemic or haemorrhagic; precise diagnosis is essential, as management for the two types of stroke is quite different. Primary prevention of both types of stroke includes reduction of high blood pressure, stopping smoking, weight reduction, and cholesterol reduction. Atrial fibrillation, acute myocardial infarction, and valvular disease may produce embolism and ischaemic stroke. Prophylaxis in these patients includes oral anticoagulants such as warfarin (section 10.2) and antiplatelet drugs such as acetylsalicylic acid. Treatment of acute ischaemic stroke includes use of **acetylsalicylic acid.** There is a role of anticoagulants such as heparin, and of thrombolytics, such as streptokinase, but may be given only in higher referral centres. Long-term therapy with acetylsalicylic acid reduces the risk of having another stroke. Antiplatelet and thrombolytic drugs are not used in the management of haemorrhagic stroke, as they may exacerbate bleeding. The main treatment is to normalize blood pressure. Acetylsalicylic acid is normally given for at least one year after coronary artery bypass surgery. It is also given to patients with prosthetic heart valves who have had cerebral embolism despite warfarin treatment.

Acetylsalicylic acid

Tablets, acetylsalicylic acid 100 mg.

Uses: prophylaxis of cerebrovascular disease or myocardial infarction; pyrexia, pain, inflammation (section 2.1.1); migraine (section 7.1).

Contraindications: hypersensitivity (including asthma, angioedema, urticaria or rhinitis) to acetylsalicylic acid or any other NSAID; children under 12 years (risk of Reye syndrome); active peptic ulceration; haemophilia and other bleeding disorders .

Precautions: asthma; uncontrolled hypertension; pregnancy (Appendix 2); breastfeeding (Appendix 3); see also section 2.1.1;

Interactions: Appendix 1

Dosage:

Prophylaxis of cerebrovascular disease or myocardial infarction, *by mouth*, ADULT 75–300 mg daily.

Adverse effects: bronchospasm; gastrointestinal haemorrhage (rarely major), also other haemorrhage (for example subconjunctival); see also section 2.1.1

12.6 Lipid-regulating drugs: use reserved to higher referral centres.

Section 13: Dermatological Drugs (topical)

13.1 Antifungal drugs, p.

RINGWORM. **Benzoic acid** and **methylrosanilinium chloride** (gentian violet) solution are inexpensive and effective fungistatic compounds for the treatment of dermatophyte infections such as ringworm. Minor skin lesions due to ringworm can be cleared with repeated applications of **compound benzoic acid** ointment (Whitfield ointment), which combines the fungistatic action of benzoic acid with the keratolytic action of salicylic acid. However, the most effective topical treatment for dermatophyte infections is a cream containing an imidazole such as **miconazole**, which is effective for long-established lesions but is more expensive than compound benzoic acid ointment. Extensive and generalized infections of the skin, nails and scalp should be treated systemically for several weeks with **fluconazole** (see section 6.3). Scalp ringworm (tinea capitis) typically appears as a patch of scaling alopecia, or a swollen inflammatory area (tinea kerion). Mild forms may remit spontaneously at puberty. Inflamed lesions should be treated systemically with **fluconazole**. Application of **miconazole** cream may accelerate healing of scaly lesions. Ringworm on the body (tinea corporis) can also be cleared with a topical imidazole such as **miconazole**. In resistant cases a longer course of oral **fluconazole** is required. Foot ringworm (tinea pedis or athlete's foot) is usually treated topically. **Miconazole** ointment should be applied twice daily to all infected areas and all toe clefts for at least 4 weeks. Systemic therapy with **fluconazole** may be required if the foot is extensively infected. Tinea pedis commonly recurs and may be treated with miconazole cream. Severe weeping lesions respond to frequent soaking in solutions of **potassium permanganate (1:10,000)**, and systemic antifungals may also be needed. Nail infections (onychomycosis, tinea unguium) are difficult to treat; fingernails may require 6 months treatment with repeated oral **fluconazole** and toenails may require 12 months or more of this treatment. Approximately 60% of nail infections either do not respond or relapse after treatment with **fluconazole**. Ringworm of the groin (tinea cruris) is usually limited to the skin of the inner thigh in contact with the scrotum. Flexural eczema, often superinfected with candida or bacteria, occurs in the same site. The latter is frequently treated with combined antifungal/corticosteroid preparations, but must not be treated with a corticosteroid alone, which will worsen the condition. An imidazole cream such as **miconazole** applied daily for 2 weeks is usually effective. Lesions unresponsive to topical preparations can usually be cleared with a 4-week course of **fluconazole**.

CANDIDOSIS. Candida can infect the oral cavity, the vagina or the skin. Cutaneous lesions tend to occur in patients with diabetes mellitus and some chronic debilitating conditions, including hypoparathyroidism and various congenital disorders of the immune system. The most severe infections of candida are now seen in patients with HIV infection. Cutaneous candidosis usually responds to **miconazole** cream as a twice daily application. Chronic candida paronychia, which can result ultimately in nail dystrophy, is more difficult to cure. Treatment should be based on determination of the underlying cause and its reduction or elimination; hands and folds of the nail must be kept dry and daily application of an imidazole cream for several months may be required, ensuring penetration of the cleft between the nail plate and the swollen skin around the nail.

PITYRIASIS VERSICOLOR. Pityriasis (tinea) versicolor is caused by a commensal yeast. Application of **sodium thiosulfate** twice daily for 4 weeks is usually curative although areas of depigmentation on darker skins remain after completion of treatment. Relapses can be frequent, however, probably because much of the infected area may appear normal and be left untreated. Better results have been reported with topical applications of **miconazole.**

Miconazole nitrate

Miconazole is a representative topical antifungal. Various drugs can serve as alternatives

Cream, gel, miconazole nitrate 2%.

Uses: superficial fungal infections due to dermatophytes and yeasts, and secondary infections caused by Gram-positive cocci, including ringworm, intertrigo, candida napkin rash, paronychia, and pityriasis versicolor.

Administration: Apply twice daily to clean dry lesions, continuing for at least 10 days after the condition has cleared.

Adverse effects: occasional local irritation and burning, also contact dermatitis; discontinue if sensitization occurs.

Sodium thiosulfate

Cutaneous solution, sodium thiosulfate 15%

Uses: pityriasis versicolor; cyanide poisoning (section 4.2.7).

Administration: Apply twice daily for 4 weeks

13.2 Anti-infective (antibacterial) drugs

Staphylococcal infections of the skin such as impetigo, folliculitis, and furunculi and streptococcal infections such as cellulitis and erysipelas are very common where the climate is hot and humid, where standards of hygiene are

compromised, and in immunodeficient patients. In all skin infections, an important part of treatment is cleansing and thorough drying. Washing with soap and water will often help to prevent infection. Superficial crusts should be gently washed with soap and water or a 0.01% solution of **potassium permanganate**. Infected burns should be treated with **silver sulfadiazine**, which is bactericidal against both Gram-positive and Gram-negative organisms. An ointment containing 2% mupirocin, which is active against Gram-positive bacteria, is of value, particularly in impetigo. To prevent the development of resistance, mupirocin should not be used for more than 10 days. Topical preparations containing **neomycin** and **bacitracin** are also widely used but these carry a risk of sensitization particularly with continued or repeated use.***Topical use of preparations containing antimicrobials which are widely used systemically should be avoided. These include penicillins, sulfonamides, streptomycin and gentamicin, which should be reserved for the systemic treatment of infections because of the possibility of inducing sensitivity and favouring the emergence of resistant organisms.*** Only widespread superficial or deep-seated infections associated with fever require treatment with a systemic antibiotic (sections 6.2.1 and 6.2.2). Whenever possible, the choice of an antimicrobial should be based on the results of sensitivity tests.

Methylrosanilinium chloride Gentian violet; Crystal violet

Methylrosanilinium chloride is a representative topical anti-infective drug. Various drugs can serve as alternatives.

Cutaneous solution, methylrosanilinium chloride 0.5%

Uses: superficial fungal and bacterial infections.

Contraindications: excoriated or ulcerated lesions, broken skin, mucous membranes.

Administration: Apply 2 or 3 times daily for 2–3 days.

Adverse effects: severe irritation (discontinue treatment); temporary staining of skin, permanent staining of fabrics; *animal* carcinogenicity (restricted use in some countries)

Potassium permanganate

Cutaneous solution, potassium permanganate 1:10000 (0.01% solution)

NOTE. Potassium permanganate is sometimes supplied as an aqueous stock solution of 1 in 1000 (0.1%) for dilution before use.

Uses: wet dressings to assist healing of suppurating superficial wounds, tropical ulcers, tinea pedis, pemphigus, impetigo.

Contraindications: avoid occlusive dressings.

Precautions: irritant to mucous membranes.

Administration: Suppurating superficial wounds and tropical ulcers, wet dressings of 1:10,000 (0.01%) solution, changed 2 or 3 times daily;

tropical ulcers also require treatment for 2–4 weeks with procaine benzylpenicillin (section 6.2.1.1).

Tinea pedis, soak severe weeping lesions in 1:10 000 (0.01%) solution every 8 hours.

Pemphigus, soak compresses in 1:10,000 (0.01%) solution and apply every 4 hours. Impetigo, superficial crusts should be gently separated with a 1:10,000 (0.01%) solution.

Adverse effects: local irritation; skin and fabrics stained brown.

Neomycin with bacitracin

Bacitracin is a representative topical antibacterial. Various drugs can serve as alternatives.

Ointment, neomycin sulfate 5 mg, bacitracin zinc 500 units/g.

Uses: superficial bacterial infections of the skin due to staphylococci and streptococci.

Precautions: avoid application to substantial areas of skin or to broken skin (risk of significant systemic absorption); overgrowth of resistant organisms on prolonged use.

Administration: Apply thin layer 3 times daily.

Adverse effects: sensitization, especially to neomycin, causing reddening and scaling; anaphylaxis reported rarely; systemic absorption leading to irreversible ototoxicity, particularly in renal impairment.

Silver sulfadiazine

Cream, silver sulfadiazine 1%.

Uses: prophylaxis and treatment of infection in burns.

Contraindications: hypersensitivity to sulfonamides; pregnancy (Appendix 2); neonates.

Precautions: renal or hepatic impairment; G6PD deficiency; breastfeeding (Appendix 3).

Administration: Apply using aseptic technique daily (more frequently if volume of exudate is large) whilst there is a possibility of infection, or until healing is complete.

Adverse effects: allergic reactions include rashes, burning and itching; argyria and sulfonamide-induced systemic toxicity, including blood disorders following application to large areas or prolonged use; transient leukopenia reported .

13.3 Anti-inflammatory and antipruritic drugs

CONTACT DERMATITIS. Contact dermatitis can result from an allergic or irritant skin reaction. Removal of the substance provoking the reaction is the first step in treating this condition. Mild cases of contact dermatitis can be treated with topical **hydrocortisone** which suppresses inflammation. A short course of oral prednisolone or a topical corticosteroid such as **betamethasone** should be considered for more severe cases and for suppression of severe acute reactions

associated with blistering, exudation and oedema. Soaking in clean water or mild saline solution is recommended in the acute stages of severe dermatitis.PRURITUS. Pruritus or itching is a common symptom of many skin diseases. However, contact with certain substances, conditions that dry the skin, stress, and extremes of temperature may also be a cause. Thus, an important part of treatment is to eliminate or minimize the reason for the irritation. Corticosteroids, such as hydrocortisone or betamethasone applied topically, can give relief. Soothing baths, or the application of calamine lotion or an emollient cream may also be helpful. Systemic antihistamines, such as oral chlorphenamine (section 3.1), may relieve generalized pruritus.

ATOPIC DERMATITIS. Atopic dermatitis (or eczema) is a common skin disorder, which mainly occurs in infants and children; it is associated with intense itching, with areas of red skin. Topical **hydrocortisone** should be applied in short courses of 1–2 weeks to treat even mild areas of involvement. The use of **betamethasone** should be considered in the treatment of persistent localized dermatitis in adults. Topical antihistamines are not effective and should be avoided because of the risk of sensitization. However, a sedative antihistamine can be given at night to calm pruritus and facilitate sleep (see section 3.1). A secondary infection, often involving *Staphylococcus aureus*, may be responsible for exacerbations; in such cases, an oral antibiotic such as erythromycin can be given for 7–10 days (section 6.2.2.4).

ICHTHYOSIS. In ichthyosis, emollients such as aqueous creams and emulsifying creams should be applied daily (or more frequently in severe cases) to affected skin. The addition of a keratolytic, such as **salicylic acid** 5% can be helpful.LICHEN PLANUS. Lichen planus is a chronic, papular, pruritic skin eruption that occurs typically in middle age and later life; the condition is often mild and may need no treatment. In more severe cases, when the underlying cause cannot be identified, a topical corticosteroid offers the only prospect of remission.

CORTICOSTEROIDS

Betamethasone

Betamethasone is a representative potent topical corticosteroid. Various drugs can serve as alternatives

Cream, betamethasone (as valerate) 0.1% *Ointment*, betamethasone (as valerate) 0.1%

Scalp lotion 0.12%.

Uses: severe inflammatory skin conditions inluding contact dermatitis, atopic dermatitis (eczema), seborrhoeic dermatitis, lichen planus, psoriasis and intractable pruritus.

Contraindications: untreated skin infections or broken skin, rosacea, acne, perioral dermatitis.

Precautions: children (avoid prolonged use); adrenal suppression if used on a large area of the body or for a long time, particularly with an occlusive dressing or on broken skin; avoid use on the face for more than 7 days; secondary infection requires treatment with an appropriate antimicrobial.

Administration: ADULTS and CHILDREN over 2 years of age, apply small quantity to the affected area 1–2 times daily until improvement occur, then less frequently.

Adverse effects: exacerbation of local infection; local atrophic changes particularly on the face and in skinfolds, characterized by thinning of the dermis, depigmentation, dilatation of superficial blood vessels and formation of striae; perioral dermatitis; acne at site of application; suppression of the hypothalamic-pituitary-adrenal axis with prolonged or widespread use (particularly under occlusion).

Hydrocortisone acetate

Hydrocortisone acetate is a representative mild topical corticosteroid. Various drugs can serve as alternatives

***Cream*,** hydrocortisone acetate 0.25%, 0.5%, 1%

***Ointment*,** hydrocortisone acetate 0.5%, 1%

Uses: contact dermatitis, atopic dermatitis (eczema), lichen planus; intractable pruritus and phototoxic reactions, including polymorphic light eruptions and actinic prurigo; shortterm treatment of psoriasis of the face, scalp, palms and soles.

Contraindications: untreated skin infections or broken skin; rosacea, acne, perioral dermatitis.

Precautions: children (avoid prolonged use); occlusive dressings increase penetration into keratinized lesions (use occlusive dressings only at night and for no longer than 2 days; avoid use on weeping lesions); secondary infection requires treatment with an appropriate antimicrobial.

Administration: Apply a small quantity to the affected area 1–2 times daily until improvement occurs, then less frequently.

Adverse effects: exacerbation of local infection; atrophic changes (see under Betamethasone) less likely with mild corticosteroids, but infants and children particularly susceptible.

13.4 Astringents

Potassium permanganate (section13.2) may be is a topical astringent used as an antiseptic for various skin conditions including suppurating superficial wounds and tropical ulcers, and the lesions produced by pemphigus and impetigo. used in the same way.

13.5 Drugs affecting skin differentiation and proliferation

ACNE VULGARIS. Acne is a disorder of the pilosebaceous follicles and typically first appears during puberty when androgenic stimulation triggers excessive production of sebum. *Mild acne* is characterized by comedones and a few pustules which heal without scarring, and usually responds to topical therapy alone. In *moderate acne*, where there are more extensive pustules causing mild scarring, oral antibiotics such as a tetracycline or erythromycin (section 6.2.2.4) are commonly used. In *severe acne*, widespread pustules are accompanied by nodular abscesses and cysts, requiring treatment with estrogens, antiandrogens, or retinoids. Since scarring of the skin resulting from severe nodular acne causes major distress, acne should always be treated as soon as possible. Exposure to substances suspected of causing or aggravating the condition should be avoided. Systemic treatment must be continued for several months before a response can be anticipated. During this time, topical preparations should be applied to the affected areas to prevent the development of new lesions.

Benzoyl peroxide is a keratolytic drug with bacteriostatic activity against *Propionibacterium acnes*; treatment is usually started at a lower strength and increased as tolerance develops to the initial irritant reaction. Preparations with **salicylic acid** may be used as a keratolytic agent. **Topical antibiotics** such as clindamycin are widely used in inflammatory acne. However, treatment must be maintained for 2 to 3 months before any benefit is seen and this prolonged course carries the risk of selection and spread of antibiotic resistant organisms.

Benzoyl peroxide

***Gel*,** 2.5% w/w, 5 % w/w

***Cream*,** benzoyl peroxide 10%

Lotion (cutaneous suspension), benzoyl peroxide 5%

Uses: mild to moderate acne and as an adjunct to oral therapy in more severe cases.

Precautions: avoid contact with eyes, mouth, and mucous membranes; avoid use of occlusive dressings

Administration: Initially apply to clean skin on alternate days, increasing frequency to 1–2 times daily as tolerance to irritant effect develops .

Adverse effects: initial irritation common but subsides with continued use; rarely, contact sensitivity occurs, occasionally even 1 application can cause severe irritation; may bleach fabrics, hair and skin PSORIASIS. Psoriasis, which affects people of all ages in all countries, is one of the most common chronic dermatoses in industrialized regions, and is

characterized by epidermal thickening and scaling. It needs specialisation to treat and the drugs for it are reserved for higher referral centres.

HYPERKERATOSES

A cream containing **urea** 10%, which has moisturizing, keratolytic and antimitotic properties, may prove effective.

Urea

Cream, urea 10%.

Uses: corns, warts, chronic dermatitis,

Precautions: avoid application to face or broken skin; avoid contact with eyes.

Administration: Apply twice daily, preferably to damp skin .

Adverse effects: transient stinging and local irritation WARTS. Warts most commonly affect the hands, feet (plantar warts, verrucas), and anogenital region (condylomata acuminata); all are caused by the human papilloma virus. They may regress spontaneously at any time within months or years of their first appearance; however, particularly in immunosuppressed patients, they may spread and be difficult to cure. Many common, plane and plantar warts can reasonably be left untreated, but painful or unsightly lesions generally respond to application of preparations containing **salicylic acid.** Where available, cryotherapy using liquid nitrogen applied with a cotton-tip or a spray is highly effective; however, freezing the skin can produce temporary or permanent depigmentation (particularly on dark skin), and should be used with caution.*Anogenital warts* are usually transmitted by sexual contact; they should always be treated, although they frequently recur, because of the increased risk of cervical cancer. **Podophyllum resin,** a caustic antimitotic agent, may be applied to small external lesions. The risk of extensive local necrosis and of systemic toxicity exclude the use of podophyllum resin on larger surfaces. When available podophyllotoxin is a less toxicalternative. Where podophyllum is contraindicated or ineffective surgical removal, electrocautery, cryosurgery and laser therapy are possible options.

Podophyllum resin

An example of an application to treat warts. Various drugs can serve as alternatives

Solution (cutaneous solution), podophyllum resin 10–25%.

Uses: external anogenital warts; plantar warts.

Contraindications: pregnancy (Appendix 2); breastfeeding; children.

Precautions: avoid use on large areas, mucous membranes; irritant to eyes; avoid contact with normal skin.

Administration: Medical supervision required; apply carefully to warts, avoiding contact with normal tissue; rinse off after 1–4 hours; may be repeated at weekly intervals but no more than 4 times in all; only few warts to be treated at any one time.

Adverse effects: systemic effects resulting from cutaneous absorption include nausea, vomiting, abdominal pain and diarrhoea; also transient leukopenia and thrombocytopenia; delayed neurotoxicity including visual and auditory hallucinations, delusions, disorientation, confusion and delirium following excessive application

Salicylic acid

Topical solution (cutaneous solution), salicylic acid 5% *Ointment,* salicylic acid 1–6%.

Uses: hyperkeratotic conditions.

Contraindications: broken or inflamed skin; children under 2 years.

Precautions: avoid contact with eyes, mouth, and mucous membranes; avoid application to large areas.

Administration: Apply once daily, starting with lower strength preparations; gradually increase strength until satisfactory response obtained.

Adverse effects: local irritation, dermatitis; salicylism on excessive application or treatment of large areas, particularly in children .

13.6 Scabicides and pediculicides

SCABIES. Scabies is caused by a mite, *Sarcoptes scabiei,* that burrows into the skin. It is readily transmitted from person to person, therefore the entire household must be treated at the same time to prevent reinfection. It is not necessary to take a bath before treatment with an acaricide, but all clothing and bedding should be washed to prevent reinfection.

Benzyl Benzoate and Gamma benzene hexachloride are inexpensive scabicides. It must be applied toll skin surfaces, from the scalp to the soles of the feet, avoiding contact with the eyes; it is too irritant for use on children. PEDICULOSIS. Pediculosis of the head and body is caused by *Pediculus humanus capitis* and *ediculus humanus corporis* respectively; pubic lice (crab lice) infestations are caused by *Pthirus pubis*, which may also affect the eye lashes and brows. All are transmitted by person to person contact, and may also contaminate clothing and bedding. All members of the affected household (and sexual contacts) must be treated

at the same time, and clothing and bedding should be washed or exposed to the air; in head lice infestations, hair brushes and combs should also be disinfected. Head, body and pubic lice are readily treated with **GAMMA BENZENE HEXACHLORIDE.**

Uses: scabies, pediculosis

Contraindications: none

Precautions: do not apply to face and neck; avoid contact with eyes; do not use oil massage before application to avoid faster absorption into blood. Breastfeeding and pregnant women (see Appendix)

Dosage: (1% lotion) ***Adults:*** scabies – apply to entire body except face and neck after a bath and drying; scrub bath is taken 12 to 24 hours after. All clothes and linen to be sun / iron dried.

Pediculosis – apply to scalp and hair (taking care not to enter eyes) and is left for 24 hours (a polythene cover may be used for long hair) and then washed.

***Children*:** use with caution; may be diluted with equal amount of water for children under 5 years of age.

Adverse Effects may irritate the skin; systemic toxicity may occur leading to CNS stimulation, vertigo, convulsions, and cardiac arrhythmias.

Section 14: Diagnostics

14.1 Ophthalmic drugs

For general information on the use of eye drops, see section 21.

Fluorescein sodium is used in ocular diagnostic procedures and for locating damaged areas of the cornea due to injury or disease.

Tropicamide is a short-acting relatively weak mydriatic that dilates the pupil and paralyses the ciliary Muscles. It facilitates the examination of the fundus of the eye.

Fluorescein sodium

Eye drops, solution, fluorescein sodium 1%

Uses: detection of lesions and foreign bodies in the eye.

Contraindications: avoid use with soft contact lenses.

Precautions:

SKILLED TASKS. Transient blurring of vision—advise patient not to operate machinery or drive until vision is clear.

Dosage:

Detection of lesions and foreign bodies in eye, *by ocular instillation*, ADULT and CHILD instil sufficient solution dropwise to stain damaged area.

Tropicamide

Tropicamide is a representative mydriatic. Various drugs can serve as alternatives

Eye drops, solution, tropicamide 0.5%.

Uses: dilatation of the pupil to examine the fundus.

Precautions: patients aged over 60 years and hypermetropic (long-sighted)—may precipitate acute angle-closure glaucoma; darkly pigmented iris, more resistant to pupillary dilatation—exercise caution to avoid overdosage

SKILLED TASKS. Avoid operating machinery or driving for 1–2 hours after mydriasis.

Dosage:

Dilatation of pupil to examine the fundus, *by ocular instillation*, ADULT and CHILD 1 or 2 drops, 15–20 minutes before examination of eye

Adverse effects: transient stinging and raised intraocular pressure; onprolonged administration—local irritation, hyperaemia, oedema and conjunctivitis.

14.2 Radiocontrast media

Radiographic contrast media are needed for delineating soft tissue structures such as blood vessels, stomach, bowel loops and body cavities not otherwise visualized by standard X-ray examination. The contrast media in this group containing heavy atoms (metal or iodine) absorb a significantly different amount of X-rays than the surrounding

soft tissue, thereby making the examined structures visible on radiographs. **Barium sulfate** is a metal salt which is used to delineate the gastrointestinal tract. It is not absorbed by the body and does not interfere with stomach or bowel secretion or produce misleading radiographic artefacts. Barium sulfate may be used in either single or double contrast techniques or computer-assisted axial tomography. For double contrast examination gas can be introduced into the gastrointestinal tract by using suspensions of barium sulfate containing carbon dioxide or by using separate gas producing preparations. Air administered by a gastrointestinal tube can be used as an alternative to carbon dioxide to achieve a double contrast effect. **Diatrizoates** (meglumine diatrizoate and sodium diatrizoate) are iodinated ionic monomeric organic compounds. Both salts have been used alone in diagnostic radiography but a mixture of both is often preferred to minimize adverse effects and to improve the quality of the examination. Diatrizoates are mainly used for urography and for computer-assisted axial tomography examinations. Owing to their high osmolality and the resulting hypertonic solutions, they are associated with a high incidence of adverse effects. adiodensity depends on iodine concentration, and osmolality depends on number of particles in a given weight of solvent. The osmolality for a given radiodensity can be reduced by using an ionic dimeric medium such as **meglumine iotroxate** which contains twice the number of iodine atoms in a molecule or by using a non-ionic medium such as **iohexol** that does not dissociate into cation and anion. Low osmolality media such as iohexol are associated with a reduction in some adverse effects (see below), but they are generally more expensive. **Iopanoic acid** is an oral iodinated ionic monomeric organic compound. It is absorbed from the gastrointestinal tract, excreted into the bile and concentrated in the gallbladder thus making it ideal for cholecystography.

Propyliodone is an iodinated organic compound which is used for the examination of the bronchial tract. **Meglumine iotroxate** is excreted into the bile after intravenous administration and used for cholangiography. HYPERSENSITIVITY. Anaphylactoid reactions to iodinated radiocontrast media are more common with high osmolality compounds. Patients with a history of asthma or allergy, drug hypersensitivity, adrenal suppression, heart disease, previous reaction to contrast media, and those receiving beta-adrenoceptor antagonists (beta-blockers) or interleukin-2 are at increased risk. Non-ionic media are preferred for these patients and beta-blockers should be discontinued if possible.

Barium sulfate

Oral suspension *(or Rectal suspension)*, barium sulfate 30 to 200% w/v.

Uses: radiographic examination of the gastrointestinal tract (see notes above)

Contraindications: intestinal obstruction or conditions predisposing to obstruction such as pyloric stenosis; intestinal perforation or conditions with risk of perforation, such as acute ulcerative colitis, diverticulitis, or after rectal or colonic biopsy, sigmoidoscopy or radiotherapy

Precautions: adequate hydration after procedure to prevent severe constipation.

Dosage:

Radiographic examination of gastrointestinal tract, ADULT and CHILD, route and dosage depend on procedure and preparation used (consult manufacturer's literature)

ADMINISTRATION. Only by specialist radiographers, according to manufacturer's directions

Adverse effects: constipation or diarrhoea, abdominal cramps and bleeding; perforation of bowel resulting in peritonitis, adhesions, granulomas and high mortality rate; electrocardiographical changes — may occur with rectal administration; pneumonitis or granuloma formation — following accidental aspiration into lungs.

Diatrizoates

Diatrizoates are representative iodinated ionic monomeric contrast media. Various media can serve as alternatives

Injection (Solution for injection), iodine (as sodium and/or meglumine diatrizoate)40–420 mg/ml, 20-ml ampoules.

Uses: urography, venography, operative cholangiography, splenoportography, arthrography, diskography.

Contraindications: hypersensitivity to iodine-containing compounds.

Precautions: history of allergy, atopy or asthma; severe hepatic impairment; renal impairment ; dehydration — correct fluid and electrolyte balance before administration; multiple myeloma (risk if dehydrated, may precipitate fatal renal failure); cardiac disease, hypertension, phaeochromocytoma, sickle-cell disease, hyperthyroidism, elderly, debilitated or children — increased risk of adverse effects; pregnancy; breastfeeding; may interfere with thyroid-function tests; biguanides (withdraw 48 hours before administration; restart when renal function stabilized); **important:** because of risk of hypersensitivity reactions, adequate resuscitation facilities must be immediately available when radiographic procedures are carried out.

Dosage:

Diagnostic radiography, ADULT and CHILD, route and dosage depend on procedure and preparation used (consult manufacturer's literature).

ADMINISTRATION. Only by specialist radiographers, according to manufacturer's directions

Adverse effects: nausea, vomiting, metallic taste, flushing, sensations of heat, weakness, dizziness, headache, coughing, rhinitis, sweating, sneezing, lacrimation, visual disturbances, pruritus, salivary gland enlargement, pallor, cardiac disorders, haemodynamic disturbances and hypotension; rarely, convulsions, paralysis, coma, rigors, arrhythmias, pulmonary oedema, circulatory failure and cardiac arrest; occasionally anaphylactoid or hypersensitivity reactions; hyperthyroidism; pain on injection; extravasation may result in tissue damage, thrombophlebitis, thrombosis, venospasm and embolism.

Iohexol

Iohexol is a representative iodinated non-ionic contrast medium. Various media can serve as alternatives

Injection (Solution for injection), iodine (as iohexol) 140–350 mg/ml, 5-ml, 10-ml, and 20-ml ampoules .

Uses: urography, venography, angiography, ventriculography, operative cholangiography, plenoportography, arthrography, diskography; computer-assisted axial tomography.

Contraindications: hypersensitivity to iodine-containing compounds .

Precautions: history of allergy, atopy or asthma; severe hepatic impairment; renal impairment ; dehydration — correct fluid and electrolyte balance before administration; multiple myeloma (risk if dehydrated, may precipitate fatal renal failure); cardiac disease, hypertension, phaeochromocytoma, sickle-cell disease, hyperthyroidism, elderly, debilitated or children — increased risk of adverse effects; pregnancy; breastfeeding; may interfere with thyroid-function tests; biguanides (withdraw 48 hours before administration; restart when renal function stabilized); **important:** because of risk of hypersensitivity reactions, adequate resuscitation facilities must be immediately available when radiographic procedures are carried out .

Dosage:

Diagnostic radiography, ADULT and CHILD, route and dosage depend on procedure and preparation used (consult manufacturer's literature).

ADMINISTRATION. Only by specialist radiographers, according to manufacturer's directions.

Adverse effects: (see also notes above); nausea, vomiting, metallic taste, flushing, sensations of heat, weakness, dizziness, headache, coughing, rhinitis, sweating, sneezing, lacrimation, visual disturbances, pruritus, salivary gland enlargement, pallor, cardiac disorders, haemodynamic disturbances and hypotension; rarely, convulsions, paralysis, coma, rigors, arrhythmias, pulmonary oedema, circulatory

failure and cardiac arrest; occasionally anaphylactoid or hypersensitivity reactions; hyperthyroidism; pain on injection; extravasation may result in tissue damage, thrombophlebitis, thrombosis, venospasm and embolism.

Iopanoic acid

Iopanoic acid is a representative iodinated ionic monomeric contrast medium. Various media can serve as alternatives.

Tablets, iopanoic acid 500 mg

Uses: examination of the gallbladder and biliary tract.

Contraindications: severe renal disease and hepatic disease ; jaundice caused by biliary-tract obstruction; impaired absorption due to acute gastrointestinal disorders.

Precautions: hypersensitivity to iodine-containing compounds or other contrast media; severe hyperthyroidism, hyperuricaemia or cholangitis; may interfere with thyroid-function tests; **important:** because of risk of hypersensitivity reactions, adequate resuscitation facilities must be immediately available when radiographic procedures are carried out .

Dosage:

Examination of gallbladder and biliary tract, *by mouth*, ADULT 3 g with plenty of water 10–14 hours before examination; if examination needs to be repeated, a further 3 g on the same day; alternatively, repeat examination carried out after 5–7 days with single 6-g dose (maximum dose; 6 g over 24 hours; avoid doses over 3 g in renal impairment)

ADMINISTRATION. Only by specialist radiographers, according to manufacturer's directions.

Adverse effects: nausea and vomiting, abdominal pain and diarrhoea; mild stinging on micturition, rashes and flushing; acute renal failure, thrombocytopenia and hypersensitivity reactions reported; also uricosuric and anticholinesterase effects.

Meglumine iotroxate

Meglumine iotroxate is a representative iodinated ionic dimeric contrast medium. Various media can serve as alternatives. It is a complementary drug

Injection (Solution for injection), iodine 50 mg/ml (as meglumine iotroxate 105 mg/ml), 100-ml bottle.

Uses: examination of the gallbladder and biliary tract.

Contraindications: hypersensitivity to iodine-containing compounds.

Precautions: history of allergy, atopy or asthma; severe hepatic impairment; renal impairment ; dehydration — correct fluid and electrolyte balance before administration; multiple myeloma (risk if dehydrated, may precipitate fatal renal failure); cardiac disease, hypertension, phaeochromocytoma,

sickle-cell disease, hyperthyroidism, elderly, debilitated or children — increased risk of adverse effects; pregnancy; breastfeeding; may interfere with thyroid-function tests; biguanides (withdraw 48 hours before administration; restart when renal function stabilized); **important:** because of risk of hypersensitivity reactions, adequate resuscitation facilities must be immediately available when radiographic procedures are carried out.

Dosage:

Examination of gallbladder and biliary tract, *by intravenous injection*, ADULT 100 ml of meglumine iotroxate 10.5% solution over at least 15 minutes (consult manufacturer's literature)

ADMINISTRATION. Only by specialist radiographers, according to manufacturer's directions.

Adverse effects: nausea, vomiting, metallic taste, flushing, sensations of heat, weakness, dizziness, headache, cough, rhinitis, sweating, sneezing, lacrimation, visual disturbances, pruritus, salivary gland enlargement, pallor, cardiac disorders, haemodynamic disturbances and hypotension; rarely, convulsions, paralysis, coma, rigors, arrhythmias, pulmonary oedema, circulatory failure and cardiac arrest; occasionally anaphylactoid or hypersensitivity reactions; hyperthyroidism; pain on injection; extravasation may result in tissue damage, thrombophlebitis, thrombosis, venospasm and embolism

Propyliodone

Propyliodone is a representative iodinated organic contrast medium. Various drugs can serve as alternatives

Oily suspension, propyliodone 600 mg/ml, 20-ml ampoule.

Uses: examination of the bronchial tree (use only if no other alternative available).

Contraindications: hypersensitivity to iodine-containing compounds; severe heart disease.

Precautions: asthma, bronchiectasis, pulmonary emphysema or reduced pulmonary function; use of excessive volume or too rapid administration may result in lobar collapse; may interfere with thyroid-function tests; **important:** because of risk of hypersensitivity reactions, adequate resuscitation facilities must be immediately available when radiographic procedures are carried out .

Dosage:

Examination of bronchial tree, *by instillation into the lungs*, ADULT dose (consult manufacturer's literature)

ADMINISTRATION. Only by specialist radiographers, according to manufacturer's directions.

Adverse effects: pyrexia, malaise, arthralgia, cough; occasionally, dyspnoea, atelectasis, pneumonia; rarely, hypersensitivity reactions.

Section 15: Disinfectants and Antiseptics

15.1 Disinfectants and antiseptics

ANTISEPTICS. An antiseptic is a type of disinfectant, which destroys or inhibits growth of micro-organisms on living tissues without causing injurious effects when applied to surfaces of the body or to exposed tissues. Some antiseptics are applied to the unbroken skin or mucous membranes, to burns and to open wounds to prevent sepsis by removing or excluding microbes from these areas. Iodine has been modified for use as an antiseptic. The iodophore, **polyvidone-iodine**, is effective against bacteria, fungi, viruses, protozoa, cysts and spores and significantly reduces surgical wound infections. The solution of polyvidone-iodine releases iodine on contact with the skin.

Chlorhexidine has a wide spectrum of bactericidal and bacteriostatic activity and is effective against both Grampositive and Gram-negative bacteria although it is less effective against some species of *Pseudomonas* and *Proteus* and relatively inactive against mycobacteria. It is not active against bacterial spores. Chlorhexidine is incompatible with soaps and other anionic materials, such as bicarbonates, chlorides, and phosphates, forming salts of low solubility which may precipitate out of solution.

Ethanol has bactericidal activity and is used to disinfect skin prior to injection, venepuncture or surgical procedures.

DISINFECTANTS. A disinfectant is a chemical agent, which destroys or inhibits growth of pathogenic micro-organisms in the non-sporing or vegetative state. Disinfectants do not necessarily kill all organisms but reduce them to a level, which does not harm health or the quality of perishable goods. Disinfectants are applied to inanimate objects and materials such as instruments and surfaces to control and prevent infection. They may also be used to disinfect skin and other tissues prior to surgery (see also Antiseptics, above). Disinfection of water for purposes other than drinking can be either physical or chemical. Physical methods include boiling, filtration and ultraviolet irradiation. Chemical methods include the addition of **chlorine releasing compounds**, such as sodium hypochlorite solution. Chlorine is a hazardous substance. It is highly corrosive in concentrated solution and splashes can cause burns and damage the eyes. Appropriate precautions must be taken when concentrated chlorine solutions or powders are handled. The aldehyde bactericidal disinfectant, **glutaral**, is strongly active against both Gram-positive and Gram-negative bacteria. It is active against the tuberculosis bacillus, fungi, such as *Candida albicans*, and viruses, such as HIV and hepatitis B. A 2% w/v aqueous alkaline (buffered to pH 8) glutaral solution can be used to sterilize heat-sensitive pre-cleansed instruments and other equipment.

Chlorhexidine gluconate

Chlorhexidine gluconate is a representative disinfectant and antiseptic. Various agents can serve as alternatives

Solution (Concentrate for solution), chlorhexidine gluconate 5%.

Uses: antiseptic; disinfection of clean instruments .

Precautions: instruments with cemented glass components (avoid preparations containing surface active agents); avoid contact with middle ear, eyes, brain and meninges; not for use in body cavities; alcoholic solutions not suitable before diathermy; syringes and needles treated with chlorhexidine (rinse thoroughly with sterile water or saline before use); inactivated by cork (use glass, plastic or rubber closures); alcohol based solutions are flammable.

Administration: Antiseptic (pre-operative skin disinfection and hand washing), *use* 0.5% solution in alcohol (70%).

Antiseptic (wounds, burns and other skin damage), *apply* 0.05% aqueous solution.

Disinfection of clean instruments, *immerse* for at least 30 minutes in 0.05% solution containing sodium nitrite 0.1% (to inhibit metal corrosion).

Emergency disinfection of clean instruments, *immerse* for 2 minutes in 0.5% solution in alcohol (70%).

Adverse effects: occasional skin sensitivity and irritation.

Chlorine releasing compounds

Chlorine releasing compounds are representative disinfectants. Various agents can serve as alternatives

Powder *for solution*, chlorine releasing compound, 1 g available chlorine/litre (1000 parts per million; 0.1%)

Uses: disinfection of surfaces, equipment, water

Contraindications: avoid exposure of product to flame; activity diminished in presence of organic material and increasing pH (can cause release of toxic chlorine gas) .

Administration: Surface disinfection (minor contamination), *apply* solutions containing 1000 parts per million.

Instrument disinfection, *soak* in solution containing 1000 parts per million for a minimum of 15 minutes; to avoid corrosion do not soak for more than 30 minutes; rinse with sterile water.

Adverse effects: irritation and burning sensation on skin.

Ethanol

Ethanol is a representative disinfectant. Various agents can serve as alternatives.

Cutaneous solution, ethanol 70%

Uses: disinfection of skin prior to injection, venepuncture or surgical procedures.

Precautions: flammable; avoid broken skin; patients have suffered severe burns when diathermy has been preceded by application of alcoholic skin disinfectants.

Administration:

Disinfection of skin, *apply* undiluted solution.

Adverse effects: skin dryness and irritation with frequent application..

Glutaral

Solution, glutaral 2% aqueous alkaline (pH 8) solution.

Uses: disinfection and sterilization of instruments and surfaces.

Precautions: minimize occupational exposure by adequate skin protection and measures to avoid inhalation of vapour.

Administration:

Disinfection of clean instruments, *immerse* in undiluted solution for 10–20 minutes; up to 2 hours may be required for certain instruments (for example bronchoscopes with possible mycobacterial contamination); rinse with sterile water or alcohol after disinfection.

Sterilization of clean instruments, *immerse* in undiluted solution for up to 10 hours; rinse with sterile water or alcohol after disinfection.

Adverse effects: (occupational exposure) nausea, headache, airway obstruction, asthma, rhinitis, eye irritation and dermatitis and skin discoloration .

Polyvidone-iodine

Polyvidone-iodine is a representative antiseptic. Various agents can serve as alternatives.

Cutaneous solution, polyvidone-iodine 10%

Uses: antiseptic; skin disinfection.

Contraindications: avoid regular or prolonged use in patients with thyroid disorders or those taking lithium; avoid regular use in neonates; avoid in very low birthweight infants.

Precautions: pregnancy (Appendix 2); breastfeeding (Appendix 3); renal impairment LARGE OPEN WOUNDS. The application of polyvidone-iodine to large wounds or severe burns may produce systemic adverse effects such as metabolic acidosis, hypernatraemia, and impairment of renal function.

Administration:

Pre- and post-operative skin disinfection, ADULT and CHILD *apply* undiluted (see also Contraindi-cations above).

Antiseptic (minor wounds and burns), ADULT and CHILD *apply* twice daily (see also Contraindications above).

Adverse effects: irritation of skin and mucous membranes; may interfere with thyroid function tests; systemic effects (see under Precautions).

Section 16: Diuretics

Section 16: Diuretics

Diuretics increase urinary excretion of water and electrolytes and are used to relieve oedema associated with heart failure, nephrotic syndrome or hepatic cirrhosis. Some diuretics are used at lower doses to reduce raised blood pressure. Osmotic diuretics are mainly used to treat cerebral oedema, and also to lower raised intraocular pressure. Most diuretics increase urine volume by inhibiting the reabsorption of sodium and chloride ions in the renal tubule; they also modify renal handling of potassium, calcium, magnesium and urate. Osmotic diuretics act differently; they cause an increase in urine volume by an osmotic effect. Although **loop diuretics** are the most potent their duration of action is relatively short, whilst **thiazide diuretics** are moderately potent but produce diuresis for a longer period. **Potassium-sparing diuretics** are relatively weak. Carbonic anhydrase inhibitors are weak diuretics which are rarely used for their diuretic effect and are principally used to lower intraocular pressure in glaucoma (section 21.4.4).

ELECTROLYTE IMBALANCE. The adverse effects of diuretic therapy are mainly due to the fluid and electrolyte imbalance induced by the drugs. *Hyponatraemia* is an adverse effect of all diuretics. The risk of *hypokalaemia*, which may occur with both thiazide and loop diuretics, depends more on the duration of action than on potency and is thus greater with thiazides than with loop diuretics (when given in equipotent doses). Potassium-sparing diuretics can cause *hyperkalaemia*. Other electrolyte disturbances include *hypercalcaemia* (thiazides), *hypocalcaemia* (loop diuretics) and *hypomagnesaemia* (thiazide and loop diuretics). Symptoms of fluid and electrolyte imbalance include dry mouth, thirst, gastrointestinal disturbances (including nausea, vomiting), weakness, lethargy, drowsiness, restlessness, seizures, confusion, headache, muscle pains or cramps, hypotension (including postural hypotension), oliguria, arrhythmias.

ELDERLY. The elderly are more susceptible to electrolyte imbalance than younger patients. Treatment should begin with a lower initial dose of the diuretic (commonly about 50% of the adult dose) and then adjusted carefully according to renal function, plasma electrolytes and diuretic response.

16.1 Thiazide diuretics

Thiazide diuretics, such as **hydrochlorothiazide**, are moderately potent and act by inhibiting sodium and chloride reabsorption at the beginning of the distal convoluted tubule. They produce diuresis within 1–2 hours of oral administration and most have a duration of action of 12–24 hours. Thiazide diuretics are used in the management of

oedema associated with mild to moderate congestive heart failure, renal dysfunction or hepatic disease; however, thiazides are not effective in patients with poor renal function (creatinine clearance of less than 30 ml per minute). In severe fluid retention a loop diuretic may be necessary. In hypertension, a thiazide diuretic is used at a low dose to produce a maximal or near maximal blood-pressure lowering effect with very little biochemical disturbance; the maximum therapeutic effect may not be seen for several weeks. Higher doses should not be used because they do not necessarily increase the hypotensive response but may cause marked changes in plasma potassium, magnesium, uric acid, glucose and lipids. A thiazide diuretic may also be used in combination with another antihypertensive such as a beta-blocker (section12.3). Urinary excretion of calcium is reduced by thiazide diuretics and this property is occasionally utilized in the treatment of idiopathic hypercalciuria in patients with calcium-containing calculi. Paradoxically, thiazide diuretics are used in the treatment of diabetes insipidus, since in this disease they reduce urine volume. Thiazide diuretics, especially in high doses, produce a marked increase in potassium excretion which may cause hypokalaemia; this is dangerous in patients with severe coronary artery disease and those being treated with cardiac glycosides. In hepatic failure hypokalaemia can precipitate encephalopathy, particularly in alcoholic cirrhosis. Potassium-sparing diuretics are used as a more effective alternative to potassium supplements for prevention of hypokalaemia induced by thiazide diuretics; however supplementation with potassium in any form is seldom necessary with the smaller doses of diuretics used to treat hypertension.

Hydrochlorothiazide

An example of a thiazide diuretic. Various drugs can serve as alternatives.

Tablets, hydrochlorothiazide, 50 mg.

Uses: oedema; diabetes insipidus; hypertension (see also section 12.3); heart failure (section 12.4).

Contraindications: severe kidney or severe hepatic impairment; hyponatraemia, hypercalcaemia, refractory hypokalaemia, symptomatic hyperuricaemia; Addison disease.

Precautions: renal and hepatic impairment (Appendices 4 and 5); pregnancy and breastfeeding (Appendices 2 and 3); elderly (reduce dose); may cause hypokalaemia; may aggravate diabetes mellitus and gout; may exacerbate systemic lupus erythematosus; porphyria.

Interactions: see Appendix 1.

Dosage:

Hypertension, *by mouth,* ADULT 12.5–25 mg daily; ELDERLY initially 12.5 mg daily .

Oedema, *by mouth,* ADULT initially 25 mg daily on rising, increasing to 50 mg daily if necessary; ELDERLY initially 12.5 mg daily.

Severe oedema in patients unable to tolerate loop diuretics, *by mouth,* ADULT up to 100 mg *either* daily *or* on alternate days (maximum 100 mg daily). Nephrogenic diabetes insipidus, *by mouth,* ADULT initially up to 100 mg daily.

Adverse effects: hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraemic alkalosis (for symptoms of fluid and electrolyte imbalance see introductory notes); hypercalcaemia; hyperglycaemia; hyperuricaemia, gout; rash, photosensitivity; altered plasma lipid concentration; rarely impotence (reversible), blood disorders (including neutropenia, thrombocytopenia); pancreatitis, intrahepatic cholestasis and hypersensitivity reactions (including pneumonitis, pulmonary oedema, severe skin reactions) also seported; acute renal failure.

16.2 Loop diuretics

Loop diuretics, or high-ceiling diuretics, such as **Frusemide**, are the most potent and rapidly produce an intense dosedependent diuresis of relatively short duration. Oral Frusemide produces diuresis within 30–60 minutes of administration, with the maximum diuretic effect in 1–2 hours. The diuretic action lasts for 4–6 hours. Intravenous Frusemide produces diuresis within 5 minutes, with the maximum diuretic effect in 20–60 minutes and diuresis complete within 2 hours. Loop diuretics inhibit reabsorption from the ascending loop of Henle´ in the renal tubule and are useful, particularly in situations where rapid and effective diuresis is needed such as reduction of acute pulmonary oedema due to left ventricular failure. They are also used to treat oedema associated with renal and hepatic disorders and are used in high doses in the management of oliguria due to chronic renal insufficiency. Loop diuretics may be effective in patients unresponsive to thiazide diuretics. Because of their shorter duration of action, the risk of hypokalaemia may be less with loop diuretics than with thiazide diuretics; if required, potassium-sparing diuretics may be used for prevention of hypokalaemia. Loop diuretics may cause hypovolaemia and excessive use can produce severe dehydration with the possibility of circulatory collapse. Frusemide may cause hyperuricaemia and precipitate attacks of gout. Rapid high-dose injection or infusion of Frusemide may cause tinnitus and even permanent deafness.

Frusemide

An example of a loop diuretic. Various drugs can serve as alternatives.

Tablets, Frusemide 40 mg.
Injection, Frusemide 10 mg/ml, 2-ml ampoule.
Uses: oedema; oliguria due to renal failure.
Contraindications: renal failure with anuria; precomatose states associated with liver cirrhosis.
Precautions: monitor electrolytes particularly potassium and sodium; elderly (reduce dose); pregnancy and breastfeeding (Appendices 2 and 3); correct hypovolaemia before using in oliguria; aggravates diabetes mellitus and gout; renal and hepatic impairment ; prostatic enlargement; porphyria.
Interactions: see Appendix 1.
Dosage:
Oedema, *by mouth,* ADULT initially 40 mg daily on rising; maintenance, 20 mg daily or 40 mg on alternate days; may be increased to 80 mg daily in resistant oedema; CHILD 1–3 mg/kg body weight daily (maximum 40 mg daily)
Acute pulmonary oedema, *by slow intravenous injection,* ADULT 20–50 mg, if necessary increase by 20-mg steps every 2 hours; if effective single dose is more than 50 mg, consider using *slow intravenous infusion* at a rate not exceeding 4 mg/ minute; CHILD 0.5–1.5 mg/kg body weight daily (maximum 20 mg daily)
Oliguria (glomerular filtration rate less than 20 ml/minute), *by slow intravenous infusion* at a rate not exceeding 4 mg/minute, ADULT initially 250 mg over 1 hour; if urine output not satisfactory during hour after first dose, infuse 500 mg over 2 hours then, if no satisfactory response during hour after second dose, infuse 1 g over 4 hours; if no response after third dose, dialysis probably necessary
NOTE. Dose to be diluted in suitable amount of infusion fluid, depending on hydration of patient .
Adverse effects: hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraemic alkalosis (for symptoms of fluid and electrolyte imbalance, see introductory notes), increased calcium excretion, hypovolaemia, hyperglycaemia (but less often than with thiazide diuretics); temporary increase in plasma cholesterol and triglyceride concentration; less commonly hyperuricaemia and gout; rarely rash, photosensitivity, bone marrow depression (withdraw treatment), pancreatitis (with large parenteral doses), tinnitus and deafness (with rapid administration of large parenteral doses and in renal impairment; deafness may be permanent if other ototoxic drugs taken).

16.3 Potassium-sparing diuretics

Potassium-sparing diuretics include **spironolactone**; which is a weak diuretic and reduces potassium excretion and increases sodium excretion in the distal tubule. Spironolactone, which acts by antagonising aldosterone, has a relatively slow onset

of action requiring 2–3 days to achieve maximum diuretic effect, and a similar period of 2–3 days for diuresis to cease after discontinuation of treatment. Spironolactone is used in the treatment of refractory oedema due to heart failure, hepatic cirrhosis (with or without ascites), nephrotic syndrome and ascites associated with malignancy. It is frequently given with a thiazide or a loop diuretic, helping to conserve potassium in those at risk from hypokalaemia. A low dose of spironolactone is beneficial in severe heart failure in patients who are already taking an ACE inhibitor and a diuretic. Spironolactone is used in the diagnosis and treatment of primary hyperaldosteronism; presumptive evidence for diagnosis is provided by correction of hypokalaemia and of hypertension. The most dangerous adverse effect of a potassium-sparing diuretics such as spironolactone is hyperkalaemia, which can be life-threatening. Such a diuretic is best avoided or used very carefully in patients who have or may develop hyperkalaemia, such as those with renal failure, patients receiving other potassium-sparing diuretics and patients taking ACE inhibitors or potassium supplements.

Spironolactone

Tablets, spironolactone, 25 mg.
Uses: refractory oedema in congestive heart failure; adjunct to ACE inhibitor and diuretic in severe congestive heart failure; nephrotic syndrome; hepatic cirrhosis with ascites and oedema; ascites associated with malignancy; primary hyperaldosteronism.
Contraindications: pregnancy (Appendix 2); breastfeeding; hyperkalaemia; hyponatraemia; severe renal impairment; Addison disease.
Precautions: monitor blood urea nitrogen and plasma electrolytes (discontinue if hyperkalaemic); elderly (reduce dose); diabetes mellitus; renal impairment ; hepatic impairment; porphyria; high doses carcinogenic in *rodents*.
Interactions: see Appendix 1.
Dosage:
Oedema, *by mouth,* ADULT 100–200 mg daily, increased if necessary to 400 mg daily in resistant oedema; usual maintenance dose 75–200 mg daily; CHILD initially 3 mg/kg body weight daily in divided doses.
Primary hyperaldosteronism, *by mouth,* ADULT, diagnosis, 400 mg daily for 3–4 weeks (see notes above); preoperative management, 100–400 mg daily; if not suitable for surgery, lowest effective dose for long-term maintenance.
Adjunct in severe heart failure, *by mouth,* ADULT usually 25 mg daily .

Adverse effects: hyperkalaemia, hyponatraemia, hyperchloraemic acidosis, dehydration (for symptoms of fluid and electrolyte imbalance see introductory notes); transient increase in blood urea nitrogen; diarrhoea; gynaecomastia, menstrual irregularities; impotence, hirsutism, deepening of voice; rash, ataxia, fever, hepatotoxicity.

16.4 Osmotic diuretics

Reserved for use in higher referral centres

Section 17 Gastrointestinal drugs

17.1 Antacids and other antiulcer drugs

PEPTIC ULCER. Ulcer disease is caused by peptic ulceration that involves the stomach, duodenum, and lower oesophagus. General and inexpensive measures like introducing healthy life-style, stopping smoking and taking antacids should be promoted. The possibilitiy of malignant disease should be considered in all patients over the age of 40 years who are suspected of having an ulcer. Gastric and duodenal ulcers are healed by 4–6 weeks treatment with H2-receptor antagonists but there is a high rate of relapse (greater than 70% over 2 years). Prevention of relapse has been revolutionized by an understanding of the role of *Helicobacter pylori* which is causally associated with most peptic ulcers (except those related to NSAID use). Eradication of *H. pylori* reduces the relapse rate to about 10–15%. This is undoubtedly cost-effective compared to the alternatives of long-term maintenance therapy with low dose H2-receptor antagonists or repeated treatment of recurrent ulcers. Verification of *H. pylori* is recommended, particularly with gastric ulcers, but not necessary before eradication treatment. Eradication regimens are based on a combination of acid-inhibiting drug and antibiotic. The best eradication regimen has not been established. Two eradication regimens are suggested based on their efficacy, simplicity and availability (only adult doses are described). Both regimens are associated with an 80–85% clearance rate. However, poor hygiene conditions allow a very high reinfection rate, thus limiting the role of eradication of H. pylori as it is not a cost – effective regimen in treating ulcers in our region.

TREATMENT:

Regimen A:
bismuth subsalicylate 107.7 mg orally 6 hourly for 2 weeks
plus
metronidazole 200 mg orally 8 hourly + 400 mg at night for 2 weeks
plus either
tetracycline 500 mg orally 6 hourly for 2 weeks
or
amoxicillin 500 mg orally 6 hourly for 2 weeks

Regimen B:
omeprazole 40 mg orally 24 hourly for 1 week
plus
metronidazole 400 mg orally 8 hourly for 1 week
plus
amoxicillin 500 mg orally 8 hourly for 1 week

NSAID-ASSOCIATED ULCERS. astrointestinal bleeding and ulceration may occur with NSAID use. To avoid this,

emphasis should be on stopping NSAID use but this is not always possible. NSAID-induced ulcers can be healed by H2-receptor antagonists although a treatment period of up to 8 weeks may be necessary. In patients who must continue NSAID therapy, prophylaxis by concomitant use of high dose H2-receptor antagonists is more cost effective if targeted to those at higher risk such as patients with a previous history of peptic ulceration. Omeprazole has been shown to be effective but is more expensive and misoprostol is also effective but is associated with more adverse effects and is expensive.

DYSPEPSIA AND GASTRO-OESOPHAGEAL REFLUX. Dyspepsia, typically as heartburn or food-related discomfort (indigestion) occurs with gastro-oesophageal reflux, gastric and duodenal ulceration and gastric cancer. In most patients dyspepsia is of uncertain origin and there is no identifiable systemic disease. A stepped care approach to treatment is appropriate, with attention first paid to life-style measures such as weight reduction, avoidance of alcohol, cessation of smoking, avoidance of aggravating food, such as fats and elevating the bed head. Antacids are useful and cheap in providing symptom relief in ulcer dyspepsia and gastro-oesophageal reflux and may be of benefit in non-ulcer dyspepsia. The next step is to use H2- receptor antagonists for more severe symptoms and oesophageal ulceration not responding to the above measures. The extent of oesophageal healing depends on severity of disease and duration of therapy. Effective treatment is important in the presence of severe oesophageal ulceration to prevent longer term outcomes such as oesophageal stricture and carcinoma. Proton pump inhibitors are most effective in erosive ulcerative or stricturing disease.

ZOLLINGER-ELLISON SYNDROME. Management of Zollinger- Ellison syndrome requires high dose H2-receptor antagonist treatment. The proton pump inhibitors are more effective particularly for cases resistant to other treatment but they are more expensive.

Aluminium hydroxide

Tablets, aluminium hydroxide 500 mg.
Oral suspension, aluminium hydroxide 320 mg/5 ml.

Uses: ulcer and non-ulcer dyspepsia; gastro-oesophageal reflux; hyperphosphataemia.

Contraindications: hypophosphataemia; undiagnosed gastrointestinal or rectal bleeding; appendicitis; porphyria.

Precautions: impaired renal function and renal dialysis ; hepatic impairment ; constipation; dehydration; fluid restriction; gastrointestinal disorders associated with decreased bowel motility or obstruction.

Interactions: Appendix 1.

Dosage:

Dyspepsia, gastro-oesophageal reflux, *by mouth*, ADULT 1–2 tablets chewed 4 times daily and at bedtime *or* 5–10 ml suspension 4 times daily between meals and at bedtime; CHILD 6–12 years 5 ml up to three times daily

Hyperphosphataemia, *by mouth*, ADULT 2–10 g daily in divided doses with meals

PATIENT ADVICE. Do not take other medicines within 2–4 hours of aluminium hydroxide preparations. May be taken with water to reduce constipating adverse effects.

Adverse effects: constipation; intestinal obstruction (large doses); hypophosphataemia with increased bone resorption, hypercalciuria and risk of osteomalacia (patients on low phosphate diet or prolonged therapy); hyperaluminaemia — resulting in osteomalacia, encephalopathy, dementia, microcytic anaemia (in chronic renal failure treated with aluminium hydroxide as phosphate-binding agent).

Ranitidine

Ranitidine is a H2 receptor antagonist and has lesser drug interactions and easier administration than Cimetidine.

Tablet Ranitidine hydrochloride 150 mg, 300 mg;
Injection 50 mg / 2 ml.

Uses duodenal ulcer, oesophagitis, gastric ulcer, gastro-esophageal reflux disease (GERD), multiple endocrine adenoma syndrome, systemic mastocystosis, Zollinger Ellison syndrome.

Contraindications: acute porphyria, hypersensitivity to drug earlier.

Precautions: reduce dosage in those with creatinine clearance less than 50 ml / min; cautiously give in hepatic diseases; excreted in breast milk, hence care in breastfeeding mothers is necessary; gastric malignancy may get masked by ranitidine.

Dosage:

Duodenal ulcer & Gastric ulcer *Adults:* 150 mg twice daily or 300 mg once daily at bedtime; later 150 mg as once daily bedtime maintenance dose. Inj 50mg IV or IM intermittent infusion every 6-8 hours; later 6.25 mg per hour via continuous infusion for maintenance.

GERD & Erosive gastritis *Adults:* 150 mg twice daily

Zollinger Ellison Syndrome would need 600 to 900 mg of Ranitidine in two divided doses – as much as 6000 mg may be needed orally *Children*: safety and efficacy have not been established; 2mg per kg every 8 hours in neonates and 4 mg /kg twice daily may be given.

Adverse effects: diarrhoea, constipation, nausea/vomiting, abdominal pain, hepatitis, pancreatitis; blood dyscrasias

neutropenia, thrombocytopenia; agitation, delirium, hallucinations, etc. are reversible gynaecomastia, decreased libido, impotence, maculopapular rash, Steven Johnsons syndrome, alopecia.

17.2 Antiemetic drugs

Metoclopramide has antiemetic properties and also stimulates upper gastrointestinal motility. Metoclopramide is effective against nausea and vomiting following surgery and chemotherapy and is also effective against radiation-induced nausea and vomiting. Combining metoclopramide with corticosteroids (such as dexamethasone) can improve its antiemetic effect in chemotherapy-induced nausea and vomiting. Metoclopramide may be useful in the management of gastro-oesophageal reflux and gastroparesis, as well as preoperatively in the prevention of aspiration syndromes. It is also used to facilitate intubation of the small bowel during radiographic examinations. Metoclopramide is **not** effective in the prevention or treatment of motion sickness. Metoclopramide may cause acute dystonic reactions with facial and skeletal muscle spasms and oculogyric crises. These reactions are most common in the young (especially girls and young women) and the elderly; they occur shortly after the start of treatment and subside within 24 hours of drug withdrawl.

Promethazine is a phenothiazine that in addition to D2 dopaminergic blockade has pronounced histamine H1 and muscarinic receptor blocking properties. It is effective in the prevention and treatment of vertigo and motion sickness. Promethazine may be useful in the prevention and treatment of postoperative and drug-induced nausea and vomiting. It has limited effect on chemotherapy-induced mild to moderate emesis.

Metoclopramide hydrochloride

Tablets, metoclopramide hydrochloride 10 mg
Injection (Solution for injection), metoclopramide hydrochloride 5 mg/ml, 2- ml ampoule *Liquid,* 5 mg / 5 ml.

Uses: nausea and vomiting in gastrointestinal disorders and treatment with cytotoxics or radiotherapy; gastro-oesophageal reflux; gastroparesis; premedication and postoperatively; aid to gastrointestinal intubation; nausea and vomiting in migraine (section 7.1) NOTE. In children (and in some countries, patients under 20 years) use restricted to severe intractable vomiting of known cause, vomiting of radiotherapy and chemotherapy, aid to gastrointestinal intubation, premedication.

Contraindications: gastrointestinal obstruction, haemorrhage or perforation; convulsive disorders; phaeochromocytoma .

Precautions: elderly, children and young adults; hepatic impairment ; renal impairment ; may mask underlying disorders such as cerebral irritation; avoid for 3–4 days after gastrointestinal surgery; pregnancy (Appendix 2); breastfeeding (Appendix 3); Parkinson disease; depression; porphyria.

Interactions: Appendix 1

Dosage:

Nausea and vomiting, gastro-oesophageal reflux, gastroparesis, *by mouth or by intramuscular injection or by slow intravenous injection*, ADULT 10 mg 3 times daily; YOUNG ADULT 15– 19 years (under 60 kg) 5 mg 3 times daily; CHILD up to 1 year (up to 10 kg) 1 mg twice daily, 1–3 years (10–14 kg) 1 mg 2–3 times daily, 3–5 years (15–19 kg) 2 mg 2–3 times daily, 5–9 years (20–29 kg) 2.5 mg 3 times daily, 9–14 years (30 kg and over) 5 mg 3 times daily (usual maximum 500 mcg/kg daily, particularly for children and young adults)

Premedication, *by slow intravenous injection*, ADULT 10 mg as a single dose Aid to gastrointestinal intubation, *by mouth or by intramuscular injection or by slow intravenous injection*, ADULT 10–20 mg as a single dose 5–10 minutes before examination; YOUNG ADULT (15–19 years), 10 mg; CHILD under 3 years 1 mg, 3–5 years 2 mg, 5–9 years 2.5 mg, 9–14 years 5 mg.

NOTE. High dose metoclopramide with cytotoxic chemotherapy, see section 8.2

Adverse effects: extrapyramidal symptoms (especially in children and young adults; see notes above); tardive dyskinesias on prolonged use; hyperprolactinaemia; drowsiness, restlessness, dizziness, headache, diarrhoea, depression, hypotension and hypertension reported; rarely, neuroleptic malignant syndrome; cardiac conduction abnormalities following intravenous administration.

Promethazine hydrochloride

Promethazine is a representative phenothiazine antiemetic. Various drugs can serve as alternatives.

Tablets, promethazine hydrochloride 10 mg, 25 mg *Elixir* (Oral solution), promethazine hydrochloride 5 mg/5 ml.

Injection (Solution for injection), promethazine hydrochloride 25 mg/ml, 2- ml ampoule .

Uses: nausea, vomiting, labyrinthine disorders, motion sickness; premedication (section 1.3). **Contraindications:** porphyria; children under 2 years .

Precautions: prostatic hypertrophy; urinary retention; glaucoma; hepatic disease ; epilepsy; elderly and children (more susceptible to adverse effects); pregnancy (Appendix 2); breastfeeding (Appendix 3).

Interactions: Appendix 1.

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving.

Dosage:

Nausea and vomiting (including postoperative), *by mouth or by intramuscular injection or by slow intravenous injection*, ADULT 12.5 to 25 mg, repeated at intervals of not less than 4 hours (usual maximum, 100 mg in 24 hours).

Motion sickness, prevention, *by mouth*, ADULT 20–25 mg at bedtime on night before travelling, repeated on following morning if necessary; CHILD 2–5 years, 5 mg at night and following morning, if necessary; 5–10 years, 10 mg at night and following morning, if necessary

DILUTION AND ADMINISTRATION. Intravenous injection, according to manfacturer's directions.

Adverse effects: drowsiness, dizziness, sedation (but paradoxical stimulation may occur, especially with high doses or in children and elderly); headache, psychomotor impairment; urinary retention, dry mouth, lurred vision, gastrointestinal disturbances; hypersensitivity reactions; rashes, photosensitivity reactions; jaundice; blood disorders; cardiovascular adverse effects — after injection; venous thrombosis at site of intravenous injection; pain on intramuscular injection.

17.3 Antihaemorrhoidal drugs

Haemorrhoids are enlarged or varicose veins of the tissues at the anus or rectal outlet. They are the most frequent cause of rectal bleeding. Anal and perianal pruritus, soreness and excoriation occur commonly in patients suffering from haemorrhoids, fistulas and proctitis. Careful local toilet with attention to any minor faecal soiling, adjustment of the diet to avoid hard stools, the use of bulk-forming materials such as bran and a high residue diet are helpful. Soothing preparations containing mild astringents such as bismuth subgallate, zinc oxide and hamamelis with lubricants, vasoconstrictors or mild antiseptics, in the form of topical ointments, creams and suppositories, are used to provide symptomatic relief. Local anaesthetics are included in some preparations. Corticosteroids may be combined in such preparations (but should only be used after exclusion of infection).

Anti-hemorrhoidal ointments :Local anaesthetic, astringent and anti-inflammatory drug

Ointment or suppository

Uses: short-term symptomatic treatment of hemorrhoids.

17.4 Anti-inflammatory drugs

Ulcerative colitis and Crohn disease are inflammatory diseases of the intestinal tract. ULCERATIVE COLITIS. Acute attacks of ulcerative colitis require treatment with local corticosteroids such as **hydrocortisone** in the form of suppositories or retention enemas. Because of the risk of intestinal perforation, rectal administration of hydrocortisone must be used with extreme caution in patients with severe ulcerative disease and should not be given to such patients without conducting a thorough roctological examination. More extensive disease requires oral corticosteroid treatment and severe extensive or fulminant disease needs hospital admission and intravenous corticosteroid administration. The minosalicylate **sulfasalazine** is useful in the treatment of symptomatic disease. It also has value in the maintenance of remission in ulcerative colitis for which corticosteroid treatment is unsuitable because of adverse effects. The most common adverse effects of sulfasalazine are nausea and vomiting, abdominal discomfort, headache, fever, loss of appetite, and rashes. In resistant cases azathioprine 2 mg/kg daily (section 8.1) given under close supervision may be helpful. Laxatives are required to facilitate bowel movement when proctitis is present but a high-fibre diet and bulk-forming drugs are more useful in adjusting faecal consistency. General nutritional care and appropriate supplements are essential. CROHN DISEASE. Treatment of Crohn disease of the colon is similar to that of ulcerative colitis. In small bowel disease **sulfasalazine** may have marginal benefit. Symptoms and inflammation associated with disease exacerbation are suppressed by oral corticosteroids such as prednisolone. **Metronidazole** may be beneficial possibly through its antibacterial activity. Other antibacterials should be given if specifically indicated and for managing bacterial overgrowth in the small bowel. General nutritional care and appropriate supplements are essential.

Hydrocortisone

Hydrocortisone retention enema is a representative rectal corticosteroid preparation (other than suppository). Various formulations can serve as alternatives.

Suppositories, hydrocortisone acetate 25 mg *Retention enema* (Rectal solution), hydrocortisone 100 mg, 60-ml bottle.

Uses: ulcerative colitis, proctitis, proctosigmoiditis; anaphylaxis (section 3.1); skin (section 13.3); drenocortical insufficiency (section 18.1).

Contraindications: bowel obstruction, bowel perforation, or extensive fistulas; untreated infections

Precautions: proctological examination required before treatment; systemic absorption may occur (see section 18.1); prolonged use should be avoided; pregnancy (Appendix 2); breastfeeding (Appendix 3);

Interactions: Appendix 1.

Dosage:

Ulcerative colitis, proctitis, *by rectum* (suppositories), ADULT 25 mg twice daily for 2 weeks; may be increased to 25 mg 3 times daily *or* 50 mg twice daily in severe cases; In factitial proctitis treatment may be required for 6–8 weeks

Ulcerative colitis, ulcerative proctitis, ulcerative proctosigmoiditis, *by rectum* (retention enema), ADULT 100 mg at night for 21 days or until clinical and proctological remission; if no clinical and proctological improvement after 21 days, discontinue; treatment for 2–3 months may be required for proctological remission; when used for more than 21 days, discontinue gradually using 100 mg every other night for 2–3 weeks.

Adverse effects: local pain or burning sensation; rectal bleeding (reported with use of enema); exacerbation of untreated infections; suppositories may stain fabrics; systemic adverse effects (section 18.1).

Sulfasalazine

Sulfasalazine is a representative aminosalicylate. Various drugs can serve as alternatives.

Tablets, sulfasalazine 500 mg *Suppositories,* sulfasalazine 500 mg

Retention enema (Rectal solution), sulfasalazine 3 g, 100-ml bottle.

Uses: ulcerative colitis; Crohn disease; severe rheumatoid arthritis (section 2.4).

Contraindications: hypersensitivity to salicylates or sulfonamides; child under 2 years; porphyria; intestinal or urinary obstruction; severe renal impairment.

Precautions: renal impairment ; hepatic impairment; G6PD deficiency; slow acetylator status; monitor blood counts and liver function initially and at monthly intervals for first 3 months; monitor kidney function initially and at intervals during treatment; history of allergy; pregnancy and breastfeeding (Appendices 2 and 3);

Interactions: Appendix 1.

BLOOD DISORDERS. Patients should be advised to report any unexplained bleeding, bruising, purpura, sore throat, fever or malaise occurring during treatment; blood count should be performed and sulfasalazine stopped immediately if there is suspicion or evidence of blood disorder.

Dosage:

Ulcerative colitis, *by mouth*, ADULT 1–2 g 4 times daily in acute attack until remission, reducing to maintenance dose of 500 mg 4 times daily; CHILD over 2 years, 40–60 mg/kg daily in

acute attack, reducing to maintenance dose of 20–30 mg/kg daily.

Active Crohn disease, *by mouth*, ADULT 1–2 g 4 times daily in acute attack until remission occurs; CHILD over 2 years, 40–60 mg/kg daily in acute attack

Ulcerative colitis, Crohn colitis; *by rectum* (suppositories, used alone or in conjunction with oral therapy), ADULT 0.5–1 g morning and evening after a bowel movement; *by rectum* (retention enema), ADULT 3 g at night retained for at least an hour; CHILD not a suitable formulation.

Adverse effects: nausea, exacerbation of colitis; diarrhoea, loss of appetite, fever, blood disorders (including Heinz body anaemia, megaloblastic anaemia, leukopenia, neutropenia, thrombocytopenia); hypersensitivity reactions (including rash, urticaria, Stevens-Johnson syndrome (erythema multiforme), exfoliative dermatitis, epidermal necrolysis, pruritus, photosensitization, anaphylaxis, serum sickness, interstitial nephritis, lupus erythematosus-like syndrome); lung complications (including eosinophilia, fibrosing alveolitis); ocular complications (including periorbital oedema); stomatitis, parotitis; ataxia, aseptic meningitis, vertigo, tinnitus, alopecia, peripheral neuropathy, insomnia, depression, headache, hallucinations; kidney reactions (including proteinuria, crystalluria, haematuria); oligospermia; rarely acute pancreatitis, hepatitis; urine may be coloured orange; some soft contact lenses may be stained.

17.5 Antispasmodic drugs

The smooth muscle relaxant properties of anticholinergic (more correctly, antimuscarinic) and other antispasmodic drugs may be useful as adjunctive treatment in non-ulcer dyspepsia, in irritable bowel syndrome, and in diverticular disease. The gastric antisecretory effects of conventional anticholinergic drugs are of little practical significance since dosage is limited by atropine-like adverse effects. Moreover they have been superseded by more powerful and specific antisecretory drugs, including the histamine H2-receptor antagonists and the selective anticholinergic drugs. Anticholinergics that are used for gastrointestinal smooth muscle spasm include dicyclomine.

Dicyclomine

An antimuscarinic, anticholinergic agent that can be used as an antispasmodic.

Tablet 10mg, 20 mg of Dicyclomine hydrochloride.

Injection 10 mg/ml of Dicyclomine hydrochloride.

Uses: gastrointestinal spasm; irritable bowel syndrome; functional diarrhoea.

Contraindications: breastfeeding, ileus, acute abdomen, infants below 6 months.

Precautions: may precipitate glaucoma attack unless care is taken; may aggravate coronary artery disease; may exacerbate myasthenia gravis; hyperthyroidism, peripheral neuropathy, UTI; great caution in hot weather as it may reduce sweating; may blur the vision and hence may require low doses.

Dosage:

Adults: start 20 mg orally, later upto 40 mg in four doses. *Children above 6 years:* 10 mg tds/qid. *Children 6 months – 6 years:* 2.5 -10 mg orally tds- qid. *Below 6 months children:* not recommended *Injection:* 20 mg IM every 4-6 hours for 1-2 days and replace with oral treatment as early as possible.

Adverse Reaction: dryness of mouth/skin,**;** blurred vision, cycloplegia, mydriasis, photophobia, urinary retention, palpitations, constipation, increased eye tension, dysphagia, headache, drowsiness, impotence, flushing, insomnia, nausea, vomiting, urticaria, anaphylaxis.

17.6 Laxatives

A balanced diet, including adequate fluid intake and fibre is of value in preventing constipation. Before prescribing laxatives, it is important to be sure that the patient is constipated and that the constipation is not secondary to an underlying undiagnosed complaint. It is also important that the patient understands that bowel habit can vary considerably in frequency without doing harm. For example some people consider themselves constipated if they do not have a bowel movement each day. A useful definition of constipation is the passage of hard stools less frequently than the patient's own normal pattern and this should be explained to the patient since misconceptions about bowel habits have led to excessive laxative use which in turn has led to hypokalaemia and an atonic non-functioning colon. Laxatives should generally be avoided except where straining will exacerbate a condition such as angina or increase the risk of rectal bleeding as in haemorrhoids. Laxatives are of value in drug-induced constipation, for the expulsion of parasites after anthelminthic treatment and to clear the alimentary tract before surgery and radiological procedures. Prolonged treatment of constipation is rarely necessary except occasionally in the elderly. There are many different laxatives. These include **bulkforming laxatives** which relieve constipation by increasing faecal mass and stimulating peristalsis, **stimulant laxatives** which increase intestinal motility and often cause abdominal cramp, **faecal softeners** which lubricate and soften impacted faeces and **osmotic**

laxatives which act by retaining fluid in the bowel by osmosis. **Bowel cleansing solutions** are used before colonic surgery, colonoscopy or radiological examination to ensure that the bowel is free of solid contents; they are **not** a treatment for constipation.

Bisacodyl

Bisacodyl is a stimulant laxative
Tablets, 5 mg;
Suppository 10 mg .
Uses: constipation, bowel preparation for surgery/radiography.
Contraindications: acute abdomen, faecal impaction, ulcerative colitis.
Precautions: dependence may occur on laxatives hence patients must be weaned off early. Pregnancy precautions as Appendix; prolonged use may deplete potassium; not to take antacids or milk within 2 hours of Bisacodyl dose; should not be crushed or chewed.
Dosage:
Oral: *Adults:* 10 to 15 mg given in the evening or before breakfast; upto 30 mg maybe used for thorough preparation for radiology or surgery. *Children more than 6 years of age*: 5 mg orally once daily
Per rectal : *Adults:* 10 mg suppository (maybe cooled in refrigerator/cold water if too soft) to be wetted and inserted half to one hour before expected result. *Children above 3 years:* ½ to 1 suppository (5 mg) *Children under 3 years:* ½ a suppository (5 mg).
Adverse Reaction: abdominal pain, cramps, faintness, nausea, vomiting, GI irritation, hypokalaemia on prolonged use, constipation when stopped, dependence is used more than a week or two, anal burning, mild proctitis, (suppository).

17.7 Drugs used in diarrhoea

Acute diarrhoeal diseases are a leading cause of childhood morbidity and mortality. In adults acute diarrhoea is the most frequent health problem of travellers to developing countries and is increasingly common among HIV-infected persons. Assessment and correction of dehydration and electrolyte disturbance is the priority in all cases of acute diarrhoea. Symptomatic relief in adults may be warranted in some cases but antidiarrhoeals should never be used in children since they do not reduce fluid and electrolyte loss and may cause adverse effects. Diarrhoea persisting for longer than a month is known as chronic diarrhoea. A mild malabsorption syndrome, tropical enteropathy, is apparent in most healthy indigenous populations of tropical countries. However the majority of cases of chronic diarrhoea have

non-infectious causes including gluten-sensitivity, inherited metabolic disorders or inflammatory bowel disease. Bloody diarrhoea is usually a sign of invasive enteric infection and should be treated with an appropriate anti-infective agent.

17.7.1 Oral rehydration

Acute diarrhoea in children should always be treated with oral rehydration solution according to plan A, B or C as shown. Severely dehydrated patients must be treated initially with intravenous fluids until they are able take fluids by mouth. For oral rehydration it is important to administer the solution in small amounts at regular intervals as indicated below.

Treatment of dehydration: WHO recommendations

According to the degree of dehydration, health professionals are advised to follow one of 3 management plans.
Plan A: no dehydration. Nutritional advice and increased fluid intake are sufficient (soup, rice, water and yoghurt, or even water). For infants aged under 6 months who have not yet started taking solids, oral rehydration solution must be presented before offering milk. Mother's milk or dried cow's milk must be given without any particular restrictions. In the case of mixed breast-milk/formula feeding, the contribution of breastfeeding must be increased.
Plan B: moderate dehydration. Whatever the child's age, a 4-hour treatment plan is applied to avoid short-term problems. Feeding should not therefore be envisaged initially. It is recommended that parents are shown how to give approximately 75 ml/kg of oral rehydration solution with a spoon over a 4-hour period, and it is suggested that parents should be watched to see how they cope at the beginning of the treatment. A larger amount of solution can be given if the child continues to have frequent stools. In case of vomiting, rehydration must be discontinued for 10 minutes and then resumed at a slower rate (about one teaspoonful every 2 minutes). The child's status must be re-assessed after 4 hours to decide on the most appropriate subsequent treatment. Oral rehydration solution should continue to be offered once dehydration has been controlled, for as long as the child continues to have diarrhoea.
Plan C: severe dehydration. Hospitalization is necessary, but the most urgent priority is to start rehydration. In hospital (or elsewhere), if the child can drink, oral rehydration solution must be given pending, and even during, intravenous infusion (20 ml/kg every hour by mouth before infusion, then 5 ml/kg every hour by mouth during intravenous rehydration). For intravenous supplementation,

it is recommended that compound solution of sodium lactate (see section 26.2) is administered at a rate adapted to the child's age (infant under 12 months: 30 ml/kg over 1 hour then 70 ml/kg over 5 hours; child over 12 months: the same amounts over 30 minutes and 2.5 hours respectively). If the intravenous route is unavailable, a nasogastric tube is also suitable for administering oral rehydration solution, at a rate of 20 ml/kg every hour. If the child vomits, the rate of administration of the oral solution should be reduced.

Oral rehydration salts

Glucose salt solution

sodium chloride	3.5 g/litre of clean water
trisodium citrate	2.9 g/litre of clean water
potassium chloride	1.5 g/litre of clean water
glucose (anhydrous)	20.00 g/litre of clean water

When glucose and trisodium citrate are not available, they may be replaced by

sucrose (common sugar)	40.00 g/litre of clean water
sodium bicarbonate	2.5 g/litre of clean water

NOTE. The solution may be prepared either from prepackaged sugar/salt mixtures or from bulk substances and water. Solutions must be freshly prepared, preferably with recently boiled and cooled water. Accurate weighing and thorough mixing and dissolution of ingredients in the correct volume of clean water is important. Administration of more concentrated solutions can result in hypernatraemia.

Uses: dehydration from acute diarrhoea.

Precautions: renal impairment.

Dosage:

Fluid and electrolyte loss in acute diarrhoea, *by mouth*, ADULT 200–400 ml solution after every loose motion; INFANT and CHILD according to Plan A, B or C (see notes above).

Adverse effects: vomiting—may indicate too rapid administration; hypernatraemia and hyperkalaemia may result from overdose in renal impairment or administration of too concentrated a solution.

17.7.2 Antimotility drugs

Opioids such as codeine are used in the symptomatic relief of acute diarrhoea in adults. They act on opioid receptors in the gut wall and decrease bowel motility. However, they are open to abuse and **are being reserved for higher referral centres.**

Section 18 Hormones and other endocrine drugs and contraceptives

18.1 Adrenal hormones and synthetic substances

Corticosteroids are hormones secreted by the adrenal cortex or are synthetic analogues of these hormones. The adrenal cortex normally secretes **hydrocortisone** which has glucocorticoid activity and weak mineralocorticoid activity. It also secretes the mineralocorticoid aldosterone. Synthetic glucocorticoids include beclomethasone, **dexamethasone** and **prednisolone**. Fludrocortisone also has glucocorticoid properties but has potent mineralocorticoid properties and is used for its mineralocorticoid effects. Pharmacology of the corticosteroids is complex and their actions are wide-ranging. In physiologic (low) doses, they are administered to replace deficient endogenous hormones. In pharmacological (high) doses, glucocorticoids decrease inflammation, suppress the immune response, stimulate erythroid cells of the bone marrow, promote protein catabolism, reduce intestinal absorption, increase blood glucose, and elevate blood pressure, increase renal excretion of calcium and promote redistribution of fat and development of cushingoid features. In therapeutic doses glucocorticoids suppress release of corticotrophin (ACTH) from the pituitary thus the adrenal cortex ceases secretion of endogenous corticosteroids. If suppressive doses are given for prolonged periods, the adrenal cortex may atrophy and this leads to a deficiency on sudden withdrawal or dosage reduction or situations such as stress or trauma where corticosteroid requirements are increased. After high dosage or prolonged therapy, withdrawal should be gradual, the rate depending on various factors including patient response, corticosteroid dose, duration of treatment and disease state. The suppressive action of a corticosteroid on cortisol secretion is least when given in the morning. Corticosteroids should normally be given in a single morning dose to attempt to minimize pituitary-adrenal suppression. Because the therapeutic effects of corticosteroids are of longer duration than the metabolic effects, intermittent therapy may allow the body's normal metabolic rhythm and the therapeutic effects to be maintained. Alternate day dosing is, however, suitable only in certain disease states and with corticosteroids with small mineralocorticoid effects and a relatively short duration of action.

Hydrocortisone is used in adrenal replacement therapy and on a short-term basis by intravenous injection for the emergency management of some conditions. Its mineralocorticoid activity is too high for it to be used on a long-term basis for disease suppression.

Prednisolone has predominantly glucocorticoid activity and is the corticosteroid most commonly administered for long-term disease suppression. It is the active metabolite of prednisone, conversion of which is variable and prednisone should not be used interchangeably with prednisolone.

Dexamethasone has very high glucocorticoid activity in conjunction with insignificant mineralocorticoid activity making it particularly suitable for high-dose therapy in conditions where water retention would be a disadvantage such as cerebral oedema. It also has a long duration of action and this, together with its lack of mineralocorticoid activity makes it particularly suitable for conditions requiring suppression of corticotrophin secretion such as congenital adrenal hyperplasia.

DISADVANTAGES OF CORTICOSTEROIDS. Overdosage or prolonged use may exaggerate some of the normal physiological actions of corticosteroids leading to mineralocorticoid and glucocorticoid adverse effects.

Mineralocorticoid adverse effects include hypertension, sodium and water retention and potassium loss. These effects are most marked with fludrocortisone but are significant with hydrocortisone, occur slightly with prednisolone and are negligible with dexamethasone. Glucocorticoid adverse effects include diabetes mellitus and osteoporosis which is of particular importance in the elderly since it may result in osteoporotic fractures of the hip or vertebrae. High doses may also be associated with avascular necrosis of the femoral neck. Muscle wasting may also occur and there is a weak link with peptic ulceration. Mental disturbances can occur, including serious paranoid state or depression with risk of suicide, particularly in patients with a history of mental disorders; euphoria is also common. High doses may cause Cushing syndrome (typical moon face, striae and acne), which is usually reversible on withdrawal of treatment, but this should always be tapered gradually to avoid symptoms of acute adrenal insufficiency (see also Withdrawal). In children, corticosteroids may result in suppression of growth and corticosteroids administered during pregnancy can affect adrenal development in the fetus. Any adrenal suppression in the neonate following prenatal exposure usually resolves spontaneously after birth and is rarely clinically important. Healing of wounds may be impaired and infections and thinning of the skin may occur; spread of infections may result from modification of tissue reactions. Adrenal atrophy can persist for years after stopping prolonged therapy; therefore any illness or surgical emergency may require temporary reintroduction of corticosteroid therapy in order to compensate for lack of sufficient adrenocortical response. It is important for anaesthetists to know whether a patient

is taking or has been taking corticosteroids in order to avoid a precipitous fall in blood pressure during anaesthesia or in the immediate postoperative period.

DOSAGE AND ADMINISTRATION. Adverse effects of systemic glucocorticoids, including suppression of the HPA (hypothalamo- pituitary adrenal) axis, are dose and duration dependent; thus patients should be given treatment for the shortest length of time at the lowest dose that is clinically necessary. Patient response is variable and doses should therefore be individualized. In life-threatening diseases, high doses may need to be given because the complications of therapy are likely to be less serious than the disease. In long-term therapy in relatively benign chronic conditions such as rheumatoid arthritis, adverse effects often outweigh the advantages. In order to minimize the adverse effects, the maintenance dose should be kept as low as possible and if possible, single morning doses or alternate day therapy should be used. Glucocorticoids can improve the prognosis of serious conditions such as systemic lupus erythematosus, temporal arteritis and polyarteritis nodosa; in such disorders the effects of the disease process may be suppressed and symptoms relieved but the underlying condition is not cured.

Glucocorticoids are used both topically and systemically. In emergency situations, hydrocortisone may be given intravenously; in the treatment of asthma, inhalation therapy with beclometasone may be used (section 25.1). Whenever possible, local treatment with creams, intra-articular injections, inhalations, eye-drops or enemas should be used in preference to systemic therapy.

WITHDRAWAL OF SYSTEMIC CORTICOSTEROIDS. The rate of withdrawal of systemic glucocorticoids is dependent upon several factors including size of dose, duration of treatment, individual patient's response and the likelihood of relapse of the underlying disease. If there is uncertainty about suppression of the HPA axis, withdrawal should be gradual to enable the adrenal gland to recover. Patients should be advised not to stop taking glucocorticoids abruptly unless permitted by their doctor.

Gradual withdrawal should be considered in those whose disease is unlikely to relapse and who have:

+ recently received repeated courses (particularly if taken for longer than 3 weeks).
+ taken a short course within 1 year of stopping long-term therapy.
+ other possible causes of adrenal suppression
+ received more than 40 mg daily prednisolone (or equivalent).
+ been given repeat doses in the evening.
+ received more than 3 weeks' treatment

Abrupt withdrawal may be considered in those whose disease is

unlikely to relapse *and* who have received treatment for 3 weeks or less *and* are not included in the patient groups described above. During corticosteroid withdrawal the dose may be reduced rapidly down to the physiological dosage (equivalent to 7.5 mg prednisolone daily) and then reduced more slowly. Assessment of the disease may be needed during withdrawal to ensure that relapse does not occur.

CORTICOSTEROID COVER DURING STRESS. The response of the HPA axis to stress is reduced during long-term therapy and for an extended period after withdrawal of the corticosteroid. If stress (infection, trauma, surgery) occurs during adrenal suppression, corticosteroid cover should be given. Cover should also be given to patients who suffer stress within 1 week of finishing a course of systemic corticosteroids lasting less than three weeks. Patients who are unable to take the dose by mouth should receive parenteral corticosteroid cover.

For patients requiring surgery, parenteral hydrocortisone should be administered as follows:

+ 200 mg hydrocortisone *intramuscularly* with premedication
+ 100 mg ydrocortisone by *intravenous infusion* in 500 ml 0.9% sodium chloride during surgery
+ 100 mg hydrocortisone *intramuscularly* every 6 hours for 72 hours after surgery

For patients requiring minor surgical procedures:

+ 100 mg hydrocortisone *intramuscularly* shortly before and after intervention.

Dexamethasone

Dexamethasone is a representative corticosteroid. Various drugs can serve as alternatives.

Tablets, dexamethasone 500 mcg (0.5 mg), 1 mg.

Injection (Solution for injection), dexamethasone phosphate (as dexamethasone sodium phosphate) 4 mg/ml, 1-ml ampoule.

Uses: suppression of inflammatory and allergic disorders (see also allergy and allergic disorders, section 3.1); diagnosis of Cushing syndrome; congenital adrenal hyperplasia; cerebral oedema.

Contraindications: see notes above; systemic infection (unless life-threatening or specific antimicrobial therapy given); avoid live virus vaccines in those receiving immuno-suppressive doses (serum antibody response diminished).

Precautions: adrenal suppression during prolonged treatment which persists for years after stopping treatment (see notes above); ensure patients understand importance of compliance with dosage and have guidance on precautions to reduce risks; monitor weight, blood pressure, fluid and electrolyte balance and blood glucose levels throughout prolonged treatment; infections (greater susceptibility,

symptoms may be masked until advanced stage; clinical presentation may be atypical; risks of chickenpox and measles increased—passive immunization recommended for non-immune patients in contact with either infection; specialist care required); quiescent tuberculosis—chemoprophylactic therapy during prolonged corticosteroid treatment; elderly; children and adolescents (growth retardation possibly irreversible); hypertension, recent myocardial infarction (rupture reported), congestive heart failure, liver failure, renal impairment, diabetes mellitus including family history, osteoporosis (may be manifested as back pain, postmenopausal women at special risk), glaucoma including family history, severe affective disorder (particularly if history of steroid-induced psychosis), epilepsy, psoriasis, peptic ulcer, hypothyroidism, history of steroid myopathy; pregnancy (Appendix 2); breastfeeding (Appendix 3).

Interactions: Appendix 1.

Dosage:

Suppression of inflammatory and allergic disorders, *by mouth*, ADULT usual range 0.5–10 mg daily; *by intramuscular injection or slow intravenous injection or intravenous infusion* (as dexamethasone phosphate), ADULT initially 0.5–20 mg daily; CHILD 200–500 mcg/kg daily

Cerebral oedema, *by intravenous injection* (as dexamethasone phosphate), ADULT 10 mg initially, then 4 mg *by intramuscular injection* (as dexamethasone phosphate) every 6 hours, as required for 2–10 days

Diagnosis of Cushing syndrome, see manufacturer's literature.

NOTE. Dexamethasone 1 mg = dexamethasone phosphate 1.2 mg = dexamethasone sodium phosphate 1.3 mg.

Adverse effects: gastrointestinal effects including dyspepsia, peptic ulceration (with perforation), abdominal distension, acute pancreatitis, oesophageal ulceration and candidosis; musculoskeletal effects including proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture; endocrine effects including adrenal suppression, menstrual irregularities and amenorrhoea, Cushing syndrome (with high doses, usually reversible on withdrawal), hirsutism, weight gain, negative nitrogen and calcium balance, increased appetite, increased susceptibility to and severity of infection; neuropsychiatric effects including euphoria, psychological dependence, depression, insomnia, increased intracranial pressure with papilloedema in children (usually after withdrawal), psychosis and aggravation of schizophrenia, aggravation of epilepsy; ophthalmic effects including glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning and exacerbation of ophthalmic viral or

fungal disease; also impaired healing, skin atrophy, bruising, striae, telangiectasia, acne, myocardial rupture following recent myocardial infarction, fluid and electrolyte disturbances, leukocytosis, hypersensitivity reactions (including anaphylaxis), thromboembolism, nausea, malaise and hiccups; perineal irritation may follow intravenous administration of phosphate ester .

Hydrocortisone

Tablets, hydrocortisone 10 mg

Injection (Powder for solution for injection), hydrocortisone (as sodium succinate) 100-mg vial.

Uses: adrenocortical insufficiency; hypersensitivity reactions including anaphylactic shock (section 3.1); inflammatory bowel disease (section 17.4); skin (section 13.3).

Contraindications: see notes above; systemic infection (unless life-threatening or specific antimicrobial therapy given); avoid live virus vaccines in those receiving immunosuppressive doses (serum antibody response diminished).

Precautions: adrenal suppression during prolonged treatment which persists for years after stopping treatment (see notes above); ensure patients understand importance of compliance with dosage and have guidance on precautions to reduce risks; monitor weight, blood pressure, fluid and electrolyte balance and blood glucose levels throughout prolonged treatment; infections (greater susceptibility, symptoms may be masked until advanced stage; clinical presentation may be atypical; risks of chickenpox and measles increased—passive immunization recommended for non-immune patients in contact with either infection; specialist care required); quiescent tuberculosis—chemoprophylactic therapy during prolonged corticosteroid treatment; elderly; children and adolescents (growth retardation possibly irreversible); hypertension, recent myocardial infarction (rupture reported), congestive heart failure, liver failure, renal impairment, diabetes mellitus including family history, osteoporosis (may be manifested as back pain, postmenopausal women at special risk), glaucoma including family history, severe affective disorder (particularly if history of steroid-induced psychosis), epilepsy, psoriasis, peptic ulcer, hypothyroidism, history of steroid myopathy; pregnancy (Appendix 2); breastfeeding (Appendix 3);

Interactions: Appendix 1.

Dosage:

Replacement therapy in adrenocortical insufficiency, *by mouth*, ADULT 20–30 mg daily in divided doses (usually 20 mg in the morning and 10 mg in early evening); CHILD 10–30 mg

Acute adrenocortical insufficiency, *by slow intravenous injection*

or by intravenous infusion, ADULT 100–500 mg, 3–4 times in 24 hours or as required; *by slow intravenous injection*, CHILD up to 1 year 25 mg, 1–5 years 50 mg, 6–12 years 100 mg

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: gastrointestinal effects including dyspepsia, peptic ulceration (with perforation), abdominal distension, acute pancreatitis, oesophageal ulceration and candidosis; musculoskeletal effects including proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture; endocrine effects including adrenal suppression, menstrual irregularities and amenorrhoea, Cushing syndrome (with high doses, usually reversible on withdrawal), hirsutism, weight gain, negative nitrogen and calcium balance, increased appetite, increased susceptibility to and severity of infection; neuropsychiatric effects including euphoria, psychological dependence, depression, insomnia, increased intracranial pressure with papilloedema in children (usually after withdrawal), psychosis and aggravation of schizophrenia, aggravation of epilepsy; ophthalmic effects including glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning and exacerbation of ophthalmic viral or fungal disease; also impaired healing, skin atrophy, bruising, striae, telangiectasia, acne, myocardial rupture following recent myocardial infarction, fluid and electrolyte disturbances, leukocytosis, hypersensitivity reactions (including anaphylaxis), thromboembolism, nausea, malaise and hiccups.

Prednisolone

Prednisolone is a representative corticosteroid. Various drugs can serve as alternatives

Tablets, prednisolone 5 mg, 10 mg, 20 mg, 30 mg, 40 mg

Syrup, 5 mg/5ml, 15 mg/5 ml.

Uses: suppression of inflammatory and allergic reactions (see also section 3.1); with antineoplastic drugs for acute leukaemias and lymphomas (section 8.3); eye (section 21.2).

Contraindications: see notes above; systemic infection (unless life-threatening or specific antimicrobial therapy given); avoid live virus vaccines in those receiving immunosuppressive doses (serum antibody response diminished).

Precautions: adrenal suppression during prolonged treatment which persists for years after stopping treatment (see notes above); ensure patients understand importance of compliance with dosage and have guidance on precautions to reduce risks; monitor weight, blood pressure, fluid and electrolyte balance and blood glucose levels throughout

prolonged treatment; infections (greater susceptibility, symptoms may be masked until advanced stage; clinical presentation may be atypical; risks of chickenpox and measles increased—passive immunization recommended for non-immune patients in contact with either infection; specialist care required); quiescent tuberculosis—chemoprophylactic therapy during prolonged corticosteroid treatment; elderly; children and adolescents (growth retardation possibly irreversible); hypertension, recent myocardial infarction (rupture reported), congestive heart failure, renal impairment, hepatic impairment; diabetes mellitus including family history, osteoporosis (may be manifested as back pain, postmenopausal women at special risk), glaucoma including family history, severe affective disorder (particularly if history of steroidinduced psychosis), epilepsy, psoriasis, peptic ulcer, hypothyroidism, history of steroid myopathy; pregnancy (Appendix 2); breastfeeding (Appendix 3);

Interactions: Appendix 1.

Dosage:

Suppression of inflammatory and allergic disorders, *by mouth*, ADULT initially up to 10–20 mg daily (severe disease, up to 60 mg daily), preferably taken in the morning after breakfast; dose can often be reduced within a few days, but may need to be continued for several weeks or months; maintenance, 2.5–15 mg daily or higher; cushingoid features are increasingly likely with doses above 7.5 mg daily; CHILD fractions of adult dose may be used (for example, at 1 year 25% of adult dose, at 7 years 50%, and at 12 years 75%) but clinical factors must be given due weight.

Adverse effects: gastrointestinal effects including dyspepsia, peptic ulceration (with perforation), abdominal distension, acute pancreatitis, oesophageal ulceration and candidosis; musculoskeletal effects including proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture; endocrine effects including adrenal suppression, menstrual irregularities and amenorrhoea, Cushing syndrome (with high doses, usually reversible on withdrawal), hirsutism, weight gain, negative nitrogen and calcium balance, increased appetite, increased susceptibility to and severity of infection; neuropsychiatric effects including euphoria, psychological dependence, depression, insomnia, increased intracranial pressure with papilloedema in children (usually after withdrawal), psychosis and aggravation of schizophrenia, aggravation of epilepsy; ophthalmic effects including glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning and exacerbation of ophthalmic viral or fungal disease; also impaired healing, skin atrophy, bruising,

striae, telangiectasia, acne, myocardial rupture following recent myocardial infarction, fluid and electrolyte disturbances, leukocytosis, hypersensitivity reactions (including anaphylaxis), thromboembolism, nausea, malaise and hiccups.

18.2 Androgens

Reserved for use in higher referral centres

18.3 Contraceptives

18.3.1 Hormonal contraceptives

Hormonal contraception is one of the most effective methods of reversible fertility control, but has unwanted major and minor adverse effects, especially for certain groups of women. Estrogen plus progestogen combinations are the most widely used. They produce a contraceptive effect mainly by suppressing the hypothalamic-pituitary system resulting in prevention of ovulation. In addition, changes in the endometrium make it unreceptive to implantation and changes in the cervical mucus may prevent sperm penetration.

Endometrial proliferation is usually followed by thinning or regression of the endometrium resulting in reduced menstrual flow. Ovulation usually resumes within three menstrual cycles after oral contraception has been discontinued in women who have previously had a baby; but anovulation and amenorrhoea may persist for six months or longer in some women including those who are nulliparous.

Potential non-contraceptive benefits of combined oral contraceptives include improved regularity of the menstrual cycle, decreased blood loss, less iron-deficiency anaemia and significant decrease in dysmenorrhoea. Long-term use is associated with reduced risk of endometrial and ovarian cancer and of some pelvic infections.

An association between the amount of estrogen and progestogen in oral contraceptives and an increased risk of adverse cardiovascular effects has been observed.

The risk of hypertension increases with increasing duration of oral contraceptive use and they should be discontinued if the woman becomes hypertensive during use. Combined oral contraceptives are associated with an increased risk of thromboembolic and thrombotic disorders and an increase in risk of cerebrovascular disorders including stroke and subarachnoid haemorrhage. The use of oral contraceptive combinations containing the progestogens, desogestrel or

gestodene are associated with a slightly increased risk of venous thromboembolism compared with oral contraceptives containing the progestogens, levonorgestrel or norethisterone.

RISK FACTORS FOR VENOUS THROMBOEMBOLISM OR ARTERIAL DISEASE. Risk factors for *venous thromboembolism* include family history of venous thromboembolism in first-degree relative aged under 45 years, obesity, long-term immobilization and varicose veins.

Risk factors for *arterial disease* include family history of arterial disease in first-degree relative aged under 45 years, diabetes mellitus, hypertension, smoking, age over 35 years (avoid if over 50 years), obesity and migraine.

If any one of the factors is present, combined oral contraceptives should be used with caution; if 2 or more factors for either venous thromboembolism or arterial disease are present, combined oral contraceptives should be avoided. Combined oral contraceptives are contraindicated if there is severe or focal migraine.

Estrogen-containing oral contraceptives should be discontinued four weeks prior to major elective surgery and all surgery to the legs. When discontinuation is not possible, consideration should be given to the prophylactic use of subcutaneous heparin.

REASONS TO STOP COMBINED ORAL CONTRACEPTIVES IMMEDIATELY. Combined estrogen-containing oral contraceptives should be stopped immediately if any of the following symptoms occur:

+ Sudden severe chest pain (even if not radiating to left arm);
+ Sudden breathlessness (or cough with blood-stained sputum);
+ Severe pain in calf of one leg;
+ Severe stomach pain;
+ Serious neurological effects including unusual, severe, prolonged headache especially if first time or getting progressively worse *or* sudden partial or complete loss of vision *or* sudden disturbance of hearing or other perceptual disorders *or* dysphagia *or* bad fainting attack or collapse *or* first unexplained epileptic seizure *or* weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body;
+ Hepatitis, jaundice, liver enlargement;
+ Severe depression;
+ Blood pressure above systolic 160 mmHg and diastolic100 mmHg;
+ Detection of a risk factor, see Precautions and Contraindications under Combined Oral Contraceptives.

Combined oral contraceptives

Ethinylestradiol with levonorgestrel is the representative combined oral contraceptive preparation. Various combinations can serve as alternatives.

Tablets,

Ethinylestradiol 30 mcg (0.03 mg), levonorgestrel 300 mcg (0.30 mg)

blister packs of 21 white tablets with clear daymarking followed by 7 tablets of red coloured Ferrous fumarate 60 mg as dummy for oestrogen withdrawal to initiate monthly bleeding.

Uses: contraception; menstrual symptoms; endometriosis (see also progestogens, section 18.5).

Contraindications: pregnancy; twenty-one days post partum; breastfeeding until weaning or for first 6 months post partum (Appendix 3); personal history of venous or arterial thrombosis; heart disease associated with pulmonary hypertension or risk of embolism; migraine (see below); history of sub-acute bacterial endocarditis; ischaemic cerebrovascular disease; liver disease, including disorders of hepatic secretion such as Dubin-Johnson or Rotor syndromes, infectious hepatitis (until liver function normal); porphyria; systemic lupus erythematosus; liver adenoma; history of cholestasis; gallstones; estrogen-dependent neoplasms; neoplasms of breast or genital tract; undiagnosed vaginal bleeding; history during pregnancy of pruritus, chorea, herpes, deteriorating otosclerosis, cholestatic jaundice; pemphigoid gestationis; diabetes mellitus (if either retinopathy, neuropathy or if more than 20 years duration); after evacuation of hydatidiform mole (until return to normal of urine and plasma gonadotrophin values).

Precautions: risk factors for venous thromboembolism and arterial disease (see notes above); migraine (see below); hyperprolactinaemia (seek specialist advice); some types of hyperlipidaemia; gallbladder disease; depression; long-term immobilization; sickle-cell disease; inflammatory bowel disease including Crohn disease.

Interactions: Appendix 1.

Contraindications: migraine with typical focal aura; severe migraine of more than 72 hours duration despite treatment; migraine treated with ergot derivatives;

Precautions: migraine without focal aura or controlled with 5HT1 agonist.

MIGRAINE. Patients should report any increase in headache frequency or onset of focal symptoms (discontinue immediately and refer urgently to neurology expert if focal neurological symptoms not typical of aura persist for more than one hour);

Dosage:

Contraception (21-day combined preparations), *by mouth*, ADULT (female), 1 white tablet ('pill') daily for 21 days starting on 5th day after beginning of menstrual cycle, followed by one red 'dummy' pill for seven days (during which withdrawal bleeding occurs); follow with one white 'pill' from next month's pack and continue subsequent courses.

ADMINISTRATION. Each tablet ('pill') should be taken at approximately the same time each day; if delayed by longer than 24 hours contraceptive protection may be lost. It is important to bear in mind that the critical time for loss of protection is when a pill is

omitted at the beginning or end of a cycle (which lengthens the pill-free interval).

The following advice is recommended:

If you forget a pill, take it as soon as you remember, and the next one at the normal time. If you are 12 or more hours late, the pill may not work; as soon as you remember, continue normal pill-taking, but for 7 days an additional method of contraception such as the sheath will be required. If the 7 days run beyond the end of your packet, start the next packet when you have finished the present one—do not have a gap between packets.

Emergency contraception: 2 tablets of the combination 'pills' at the earliest; repeat 2 'pills' after 12 hours. Menstrual irregularity: administer the 'pills' in the same manner as for contraception for three cycles at least. Many women with irregular mestrual cycles after three months of combination 'pills' are seen to return to regular normal menstrual cycles.

Adverse effects: nausea, vomiting, headache, breast tenderness, increase in body weight, thrombosis, changes in libido, depression, chorea, skin reactions, chloasma, hypertension, impairment of liver function, 'spotting' in early cycles, absence of withdrawal bleeding, irritation of contact lenses; rarely, photosensitivity and hepatic tumours; breast cancer (small increase in risk of breast cancer during use which reduces during the 10 years after stopping; risk factor seems related to age at which contraceptive is stopped rather than total duration of use; small increase in risk of breast cancer should be weighed against the protective effect against cancers of the ovary and endometrium).

Levonorgestrel

Levonorgestrel 30 mcg is a complementary drug

Tablets, levonorgestrel 30 mcg

Tablets, levonorgestrel 750 mcg, 2-tablet pack.

Uses: contraception (particularly when estrogens are contraindicated); emergency hormonal contraception.

Contraindications: *progestogen-only oral contraceptives:* pregnancy (Appendix 2); undiagnosed vaginal bleeding; severe arterial disease; liver tumours; breast cancer; thromboembolic disorders; sickle-cell anaemia; porphyria; after evacuation of hydatidiform mole (until return to normal of urine and plasma gonadotrophin values); *progestogen-only emergency hormonal contraceptives:* pregnancy (see Administration, below); severe liver disease; porphyria.

Precautions: cardiac disease; sex-steroid dependent cancer; past ectopic pregnancy; malabsorption syndrome; ovarian cysts; active liver disease, recurrent cholestatic jaundice, history of jaundice in pregnancy ; increase in frequency of headache (discontinue pending investigation); breastfeeding (Appendix 3).

Interactions: Appendix 1.

Dosage:

Contraception, *by mouth*, ADULT (female), 1 tablet ('pill')(30 mcg) daily, starting on the first day of the cycle and then continuously.

ADMINISTRATION. Each tablet ('pill') should be taken at approximately the same time each day. If delayed for longer than 3 hours contraceptive protection may be lost.

The following advice is recommended:

If you forget a pill, take it as soon as you remember, and the next one at the normal time. If you are more than 3 hours late, the pill may not work; as soon as you remember, continue normal pill-taking, but for 2 days an additional method of contraception such as the sheath will be required.

Emergency (post-coital) contraception, *by mouth*, ADULT (female), 1 tablet (750 mcg) followed by a second tablet 12 hours later .

ADMINISTRATION. Effective if first dose is taken within 72 hours (3 days) of unprotected intercourse; taking the first dose as soon as possible increases efficacy; should not be administered if menstrual bleeding overdue .

Adverse effects: menstrual irregularities but tend to resolve on long-term treatment (including oligomenorrhoea and menorrhagia); nausea, vomiting, headache, dizziness, breast discomfort, depression, skin disorders, disturbances of appetite, weight increase, change in libido.

18.3.2 Intrauterine contraceptive devices

Intrauterine devices consist of a plastic carrier wound with copper wire or fitted with copper bands; some also have a central core of silver to prevent fragmentation of copper. Smaller devices have been introduced to minimize adverse effects and the replacement time for these devices is 5 years. The intrauterine device is suitable for older parous women; they should be used with caution in young nulliparous women because of the increased risk of pelvic inflammatory disease. Insertion of a copper intrauterine contraceptive device is also an effective method of emergency contraception. The timing and technique of fitting an intrauterine device play a critical part in its subsequent performance and call for proper training and experience. Patients should receive full counselling backed by the manufacturer's approved leaflet. For routine contraception the optimal time for insertion is the three to four day period after the end of menstruation; for emergency contraception the device can be inserted at any time in the menstrual cycle. There is an increased risk of infection for 20 days after insertion and this may be related to existing lower genital tract infection. Pre-screening (at least for chlamydia)

should if possible be performed. If sustained pelvic or lower abdominal pain occur during the following 20 days after insertion of the device, the woman should be treated as having acute pelvic inflammatory disease. An intrauterine device should not be removed in mid-cycle unless an additional contraceptive was used for the previous 7 days. If removal is essential (for example to treat severe pelvic infection) postcoital contraception should be considered. If the woman becomes pregnant, the device should be removed in the first trimester.

Copper-containing IUD

Uses: contraception; emergency contraception.

Contraindications: pregnancy; severe anaemia; 48 hours–4 weeks post partum; puerperal sepsis; Post septic abortion; cervical or endometrial cancer; pelvic inflammatory disease; recent sexually transmitted disease (if not fully investigated and treated); pelvic tuberculosis; unexplained uterine bleeding; malignant gestational trophoblastic disease; distorted or small uterine cavity; copper allergy; Wilson disease; medical diathermy.

Precautions: anaemia; heavy menstrual bleeding, endometriosis, severe primary dysmenorrhoea, history of pelvic inflammatory disease, history of ectopic pregnancy or tubal surgery, diabetes mellitus, fertility problems, nulliparity and young age, severely scarred uterus or severe cervical stenosis, valvular heart disease (requires antibiotic cover) — avoid if prosthetic valve or history of endocarditis; HIV infection or immunosuppressive therapy; joint and other prostheses; epilepsy; increased risk of expulsion if inserted before uterine involution; gynaecological examination before insertion, 6–8 weeks after then annually, but counsel women to see doctor if significant symptoms such as pain; anticoagulant therapy; remove if pregnancy occurs (if pregnancy, increased likelihood of ectopic pregnancy).

Administration: Contraception, the device is best fitted after the end of menstrual bleeding and before the calculated timed of implantation; it should not be fitted during the heavy days of the period

Emergency contraception, the device may be inserted up to 120 hours (5 days) after unprotected intercourse, at any time in the menstrual cycle; if intercourse has occurred more than 5 days previously, the device can still be inserted up to 5 days after the earliest likely calculated ovulation. The device can be removed at the beginning of menstruation if the woman does not wish to continue using it .

Adverse effects: uterine or cervical perforation, displacement, expulsion; pelvic infection may be exacerbated; heavy

menstrual bleeding; dysmenorrhoea; pain and bleeding and occasionally epileptic seizure, or vasovagal attack on insertion.

18.3.3 Barrier and spermicidal methods

NOTE. Barrier methods are not as effective in preventing conception as hormonal contraception and copper intrauterine devices. Spermicidal methods when used alone are generally considered relatively ineffective and such use is not recommended

Barriers, male latex condoms, male non-latex condoms or female non-latex condoms

***Spermicidals*:** film, vaginal tablets, foam, gel or cream containing nonoxinol (various concentrations)

Barriers and spermicidals, diaphragm or cervical caps for use in conjunction with spermicide.

Uses:contraception; to decrease risk of transmission of AIDS and other sexually transmitted diseases.

Precautions:oil-based products including baby oil, massage oil, lipstick, petroleum jelly, sun-tan oil can damage latex condoms and render them less effective as barrier method of contraception and as a protection from sexually transmitted diseases (including AIDS); if a lubricant required, use one that is water-based; male condom must be put on before the penis touches the vaginal area and the penis must not touch the vaginal area after the condom has been taken off .

Adverse effects:vaginal irritation and allergic vaginitis, toxic shock syndrome, increased risk of urinary-tract infection (due to nonoxinol).

18.4 Estrogens

Estrogens are necessary for the development of female secondary sexual characteristics; they also stimulate myometrial hypertrophy with endometrial hyperplasia. They affect bone by increasing calcium deposition and have a favourable effect on blood cholesterol and phospholipid concentrations. They are secreted at varying rates during the menstrual cycle throughout the period of activity of the ovaries. During pregnancy, the placenta becomes the main source of estrogens. At the menopause, ovarian secretion declines at varying rates.

Estrogen therapy is given cyclically or continuously for a number of gynaecological conditions principally contraception and the alleviation of menopausal symptoms.If long-term therapy is required for menopausal hormone therapy a progestogen should be added to prevent cystic hyperplasia of the endometrium and possible transformation to cancer. The addition of a progestogen is not necessary if the patient has had a hysterectomy.

The palliative care of advanced inoperable, metastatic carcinoma of the breast in both men and postmenopausal women is another indication for estrogen therapy.

HORMONE REPLACEMENT THERAPY (HRT). Estrogens are used for replacement therapy in perimenopausal and menopausal women for the treatment of vasomotor instability, vulvar and vaginal atrophy associated with the menopause and for the prevention of osteoporosis and may reduce mortality from ischaemic heart disease. Hormone replacement therapy is indicated for menopausal women whose lives are inconvenienced by vaginal atrophy or vasomotor instability. Vaginal atrophy may respond to a short course of a vaginal estrogen preparation. Systemic treatment is needed for vasomotor symptoms and should be given for at least a year; in women with a uterus, a progestogen should be added to reduce the risk of endometrial cancer.

HRT for 5–10 years is indicated for women with early natural or surgical menopause (before age of 45) since they have a high risk of osteoporosis. Long-term HRT is favourable in risk:benefit terms for women without a uterus, because additional progestogen is not required, but the possible increased risk of breast cancer needs to be taken into account. In women with a uterus, the need for additional progestogen (for example norethisterone 1 mg on days 15–26 of each 28-day estrogen HRT cycle) may blunt the protective effect of low dose estrogen against myocardial infarction and stroke. In these cases, the risk factors for osteoporosis (recent corticosteroid therapy, family history, thinness, lack of exercise, alcoholism or smoking, fractures to the hip or forearm before age 65 years) should be taken into account in deciding risk:benefit before HRT use; women of Afro-Caribbean origin appear to be less susceptible than those who are white or of Asian origin.

Most of the severe adverse effects rarely associated with estrogen/progestogen contraception are not associated with hormonal replacement therapy. There is an increased risk of deep-vein thrombosis and of pulmonary embolism in women taking HRT but the overall balance of benefits outweighs the risk in most women. In women who have predisposing factors such as a personal or family history of deep venous thrombosis or pulmonary embolism, severe varicose veins, obesity, surgery, trauma or prolonged bed-rest, the overall risk may outweigh the benefit.

HRT does not provide contraception. If a potentially fertile woman needs to use HRT, non-hormonal contraceptive measures are necessary.

Ethinylestradiol

Ethinylestradiol is a representative estrogen. Various drugs can serve as alternatives

Tablets, ethinylestradiol 10 mcg (0.01 mg), 50 mcg (0.05 mg), 0.1 mg.

Uses: hormone replacement for menopausal symptoms; osteoporosis prophylaxis; palliation in breast cancer in men and postmenopausal women; contraception in combination with a progestogen (section 18.3.1).

Contraindications: pregnancy; estrog dependent cancer; active thrombophlebitis or thromboembolic disorders; undiagnosed vaginal bleeding; breastfeeding (Appendix 3); liver disease (where liver function tests have failed to return to normal), Dubin-Johnson and Rotor syndromes (or monitor closely).

Precautions: progestogen may need to be added to regimen to reduce risk of endometrial cancer due to unopposed estrogen (see notes above); migraine; history of breast nodules of fibrocystic disease; pre-existing uterine fibroids may increase in size; symptoms of endometriosis may be exacerbated; increased risk of gallbladder disease; porphyria;

Interactions: Appendix 1.

Dosage:

Hormone replacement, *by mouth*, ADULT (female) 10–20 mcg daily

Palliation in breast cancer in postmenopausal women, *by mouth*, ADULT 0.1–1 mg 3 times daily.

Adverse effects: nausea and vomiting, abdominal cramps and bloating, weight increase; breast enlargement and tenderness; premenstrual-like syndrome; sodium and fluid retention; changes in liver function; cholestatic jaundice; rashes and chloasma; changes in libido; depression, headache, migraine, dizziness, leg cramps (rule out venous thrombosis); contact lenses may irritate.

18.5 Progestogens

Progesterone is a hormone secreted by the corpus luteum whose actions include induction of secretory changes in the endometrium, relaxation of uterine smooth muscle and production of changes in the vaginal epithelium. Progesterone is relatively inactive following oral administration and produces local reactions at site of injection. This has led to the development of synthetic progestogens including **levonorgestrel, orethisterone** and **medroxyprogesterone**. Where endometriosis requires drug treatment, it may respond to synthetic progestogens on a continuous basis. They may also be used for the treatment of severe dysmenorrhoea. In postmenopausal women receiving long-term estrogen therapy for hormone replacement therapy, a progestogen needs to be added for

women with an intact uterus to prevent hyperplasia of the endometrium (section 18.4).

Progestogens are also used in combined oral contraceptives and progestogen-only oral contraceptives (section 18.3.1.).

Norethisterone

Tablets, norethisterone 5 mg.

Uses: endometriosis; menorrhagia; severe dysmenorrhoea; contraception (section 18.3.1); HRT (section 18.4).

Contraindications: pregnancy (Appendix 2); undiagnosed vaginal bleeding; hepatic impairment or active liver disease; severe arterial disease; breast or genital tract cancer; porphyria; history in pregnancy of idiopathic jaundice, severe pruritus or pemphigoid gestationis.

Precautions: epilepsy; migraine; diabetes mellitus; hypertension; cardiac or renal disease; breastfeeding (Appendix 3);

Interactions: Appendix 1.

Dosage:

Endometriosis, *by mouth*, ADULT (female) 10 mg daily starting on fifth day of cycle (increased if spotting occurs to 20–25 mg daily, reduced once bleeding has stopped)

Menorrhagia, *by mouth*, ADULT (female) 5 mg three times daily for 10 days to stop bleeding; to prevent bleeding 5 mg twice daily from day 19 to 26 of cycle.

Dysmenorrhoea, *by mouth*, ADULT (female) 5 mg 2–3 times daily from day 5 to 24 for 3 to 4 cycles.

Adverse effects: acne, urticaria, fluid retention, weight increase, gastrointestinal disturbances, changes in libido, breast discomfort, premenstrual symptoms, irregular menstrual cycles, depression, insomnia, somnolence, alopecia, hirsutism, anaphylactoid-like reactions; exacerbation of epilepsy and migraine; rarely jaundice.

18.6 Ovulation inducers

Reserved for higher referral centres

18.7 Insulins and other antidiabetic drugs

Diabetes mellitus is characterized by hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism. There are 2 principal types of diabetes.

Type 1 diabetes or insulin-dependent diabetes mellitus is due to a defiency of insulin caused by autoimmune destruction of pancreatic beta cells. Patients require administration of insulin.

Type 2 diabetes or non-insulin dependent diabetes mellitus is due to reduced secretion of insulin or to peripheral resistance

to the action of insulin. Patients may be controlled by diet alone, but often require administration of oral antidiabetic drugs or insulin. The energy and carbohydrate intake must be adequate but obesity should be avoided. In type 2 diabetes, obesity is one of the factors associated with insulin resistance. Diets high in complex carbohydrate and fibre and low in fat are beneficial. Emphasis should be placed on exercise and increased activity.

The aim of treatment is to achieve the best possible control of plasma glucose concentration and prevent or minimize complications including microvascular complications (retinopathy, albuminuria, neuropathy). Diabetes mellitus is a strong risk factor for cardiovascular disease. Other risk factors such as smoking, hypertension, obesity and hyperlipidaemia should also be addressed.

Insulin

For those who require administration of insulin, appropriate combinations of insulin therapy will have to be worked out for the individual patient. Insulin requirements may be affected by variations in lifestyle (diet and exercise) and use of drugs such as corticosteroids, infections, stress, accidental or surgical trauma, puberty and pregnancy (second and third trimesters) may increase insulin requirements; renal or hepatic impairment and some endocrine disorders (for example Addison disease, hypopituitarism) or coelic disease may reduce requirements. In pregnancy insulin requirements should be monitored frequently. Those patients who , should monitor their own blood glucose concentrations using blood glucose strips. Since blood glucose levels vary throughout the day, it is best to recommend that patients should maintain blood glucose concentrations of between 4 and 10 mmol/litre for most of the day while accepting that on occasions levels will be higher; strenuous efforts should be made to prevent blood glucose concentrations falling below 4 mmol/litre. Patients should be advised to look for troughs and peaks of blood glucose and to adjust their insulin dosage only once or twice a week. Insulin doses are determined on an individual basis, by gradually increasing the dose but avoiding hypoglycaemic reactions.

In the absence of blood glucose monitoring strips, urine glucose can be tested to ensure glucose levels are not too high. It is the method of personal choice for many patients with Type 2 diabetes mellitus. It is less reliable than blood glucose but is easier and costs much less. All patients should monitor either blood or urine glucose levels daily.

Hypoglycaemia is a potential complication in all patients with diabetes mellitus whether they are treated with insulin or

oral hypoglycaemic agents. The serious consequences of hypoglycaemia relate to its effects on the brain, including loss of cognitive function, seizures, coma and cerebral infarction.

The risk of hypoglycaemia is particularly high when meticulous glycaemic control is sought in patients receiving insulin. Very tight control lowers the blood glucose concentration needed to trigger hypoglycaemic symptoms; increase in the frequency of hypoglycaemic episodes reduces the warning symptoms experienced by patients. Some patients report loss of hypoglycaemic warning after transfer to human insulin. To restore warning signs, episodes of hypoglycaemia must be reduced to a minimum; this involves an appropriate adjustment of insulin type, dose and frequency and suitable timing and quantity of meals and snacks. Car drivers need to be particularly careful to avoid hypoglycaemia. They should check their blood glucose concentrations before driving and, on long journeys, at intervals of approximately two hours; they should ensure that a supply of sugar is always readily available. If hypoglycaemia occurs the driver should switch off the ignition until recovery is complete (may be 15 minutes or longer). Driving is not permitted when hypoglycaemic awareness has been lost. For sporadic physical activity departing from the patient's usual daily routine extra carbohydrate may need to be taken to avert hypoglycaemia. Blood glucose should be monitored before, during and after exercise. Hypoglycaemia can develop in patients taking oral antidiabetics, notably the sulfonylureas, although this is uncommon and usually indicates excessive dosage. Sulphonylurea-induced hypoglycaemia may persist for several hours and must be treated in hospital.

Diabetic ketoacidosis is a potentially lethal condition caused by an absolute or relative lack of insulin and commonly occurs after failure to adjust insulin dosage in the presence of factors which increase insulin requirements such a severe infection or major intercurrent illness. Diabetes ketoacidosis occurs mostly in patients with Type 1 diabetes mellitus. It also occurs in diabetics who are not insulin-dependent but in whom the need for insulin may be temporarily created. It is characterized by hyperglycaemia, hyperketonaemia and acidaemia with dehydration and electrolyte disturbances. It is essential that insulin (and intravenous fluids) should be readily available for its treatment.

Infections are more likely to develop in patients with poorly controlled diabetes mellitus. These should be treated promptly and effectively to avoid diabetic ketoacidosis.

Surgery. Particular attention should be given to the insulin requirements when an insulin-dependent diabetic patient

undergoes surgery that is likely to need an intravenous infusion of insulin for longer than 12 hours. Soluble insulin should be given together with glucose and potassium chloride (provided the patient is not hyperkalaemic) intravenously and adjusted to provide a blood glucose concentration of between 7 and 12 mmol/litre. The duration of action of intravenous insulin is only a few minutes therefore the infusion must not be stopped unless the patient becomes frankly hypoglycaemic. For non-insulin dependent diabetics, insulin treatment is almost always required during surgery (oral antidiabetic drugs having been omitted).

Insulin must be given by injection as it is inactivated by gastrointestinal enzymes. Following subcutaneous or intramuscular injection, it is absorbed directly into the blood. Subcutaneous injection into the upper arms, thighs, buttocks, or abdomen is the route most commonly used. There may be increased absorption from a limb site, if the limb is used in strenuous exercise following the injection. It is essential to use only syringes calibrated for the particular concentration of insulin administered.

There are three main types of insulin preparations, classified according to duration of action after subcutaneous injection:

+ those of short duration which have a relatively rapid onset of action, namely soluble or regular insulin;
+ those with an intermediate action for example isophane insulin and insulin zinc suspension;
+ those with a relatively slow onset and long duration of action for example crystalline insulin zinc suspension.

Soluble insulin is a short-acting form of insulin. When injected subcutaneously, it has a rapid onset of action (after 30– 60 minutes), a peak action between 2 and 4 hours, and a duration of action up to 8 hours. When injected intravenously, soluble insulin has a very short half-life of only about 5 minutes.

When administered subcutaneously, **intermediate-acting insulins** have an onset of action of approximately 1–2 hours, a maximal effect at 4–12 hours and a duration of action of 16–24 hours. They can be given twice daily together with short-acting insulin or once daily, particularly in elderly patients. They can be mixed with soluble insulin in the syringe, essentially retaining properties of each component.

The duration of action of different insulin preparations varies considerably from one patient to another and this needs to be assessed for every individual. The type of insulin used and its dose and frequency of administration depend on the needs of each patient. For patients with acute onset diabetes mellitus, treatment should be started with soluble insulin given 3 times daily with medium acting insulin at bedtime.

For those less seriously ill, treatment is usually started with a mixture of premixed short and medium acting insulins given twice daily. The proportions of soluble insulin can be increased in patients with excessive post-prandial hyperglycaemia. Patients should remain on the same insulin throughout treatment.

Regimens should be developed by each country.

Soluble insulin

Injection (Solution for injection), soluble insulin 40 units/ml, 10-ml vial; 100 units/ml, 10-ml vial.

Uses: diabetes mellitus; diabetic emergencies and at surgery; diabetic ketoacidosis or coma.

Precautions: see notes above; reduce dose in renal impairment; occasionally insulin resistance necessitating large doses; pregnancy and breastfeeding (Appendices 2 and 3).

Interactions: Appendix 1.

Dosage:

Diabetes mellitus, *by subcutaneous injection, by intramuscular injection, by intravenous injection or by intravenous infusion*, ADULT and CHILD according to individual requirements.

Adverse effects: hypoglycaemia in overdose; localized and rarely, generalized, allergic reactions; lipoatrophy at injection site; insulin resistance.

Isophane insulin

Injection (Suspension for injection), isophane insulin 40 units/ml, 10-ml vial; 100 units/ml, 10-ml vial.

Uses: diabetes mellitus.

Contraindications: intravenous administration.

Precautions: see notes above; reduce dose in renal impairment; occasionally insulin resistance necessitating large doses; pregnancy and breastfeeding (Appendices 2 and 3);

Interactions: Appendix 1.

Dosage:

Diabetes mellitus, *by subcutaneous injection*, ADULT and CHILD according to individual requirements.

IMPORTANT. Intravenous injection contraindicated.

Adverse effects: hypoglycaemia in overdose; localized and rarely generalized, allergic reactions; lipoatrophy at injection site; insulin resistance.

Oral antidiabetic drugs

Oral antidiabetic drugs are used for non-insulin dependent diabetes mellitus in patients who do not respond to dietary adjustment and an increase in physical exercise. They are used to supplement the effect of diet and exercise. There are various types of oral antidiabetic agents. The most

commonly used are the **sulfonylureas** and the **biguanide**, metformin.

Sulfonylureas act mainly by augmenting insulin secretion and are therefore only effective if there is some residual pancreatic beta-cell activity. They may occasionally lead to hypoglycaemia 4 hours or more after food. This may be dose-related and usually indicates excessive dose and it occurs more frequently with long-acting sulfonylureas such as **glibenclamide** and occurs particularly in the elderly. The sulfonylureas have the disadvantage that they may encourage weight gain. They should not be used during breastfeeding and caution is required in the elderly and those with renal or hepatic insufficiency because of the risk of hypoglycaemia. Insulin therapy is generally required during intercurrent illness, during surgery and also during pregnancy.

Metformin exerts its effect by decreasing gluconeogenesis and by increasing peripheral utilization of glucose. Metformin can only act in the presence of endogenous insulin therefore is effective only in diabetics with some residual functioning pancreatic islet cells. It is used as a first-line treatment in overweight non-insulin-dependent diabetic patients and in others when strict dieting and sulfonylureas have failed to control the disease. Gastrointestinal adverse effects are common on initial treatment and may persist, particularly when very high doses are given. Metformin should be avoided in situations which might predispose to lactic acidosis including renal or hepatic impairment and severe dehydration. One major advantage of metformin is that it does not usually cause hypoglycaemia. It may be used together with insulin (but weight gain and hypoglycaemia can be problems) or sulfonylureas (but may be increased hazard with such combinations). During medical and surgical emergencies insulin treatment is almost always required; insulin should be substituted for metformin before elective surgery.

Glibenclamide

Glibenclamide is a representative long-acting sulfonylurea. Various drugs can act as alternatives.

Tablets, glibenclamide 1.25 mg, 2.5 mg, 5 mg.

Uses: diabetes mellitus.

Contraindications: ketoacidosis; porphyria; pregnancy (Appendix 2); breastfeeding (Appendix 3)

Precautions: renal impairment ; hepatic impairment ; elderly; substitute insulin during severe infection, trauma, surgery (see notes above);

Interactions: Appendix 1.

Dosage:

Diabetes mellitus, *by mouth*, ADULT initially 5 mg once daily

with breakfast (ELDERLY 2.5 mg, but avoid — see notes above), adjusted according to response (maximum 15 mg daily)

Adverse effects: mild and infrequent, including gastrointestinal disturbances and headache; hypersensitivity reactions; hypoglycaemia, particularly in the elderly18.7: Insulins and other antidiabetic drugs WHO Model Formulary 2002.

Metformin hydrochloride

Tablets, metformin hydrochloride 250 mg, 500 mg, 850 mg.

Uses: diabetes mellitus (see notes above).

Contraindications: renal impairment (withdraw if renal impairment suspected;); hepatic impairment ; predisposition to lactic acidosis (see notes above); heart failure; severe infections or trauma; dehydration; alcohol dependence; pregnancy (Appendix 2).

Precautions: substitute insulin during severe infection, trauma, surgery (see notes above); breastfeeding (Appendix 3).

Interactions: Appendix 1.

Dosage:

Diabetes mellitus, *by mouth*, ADULT 500 mg. every 8 hours *or* 850 mg every 12 hours with or after food (maximum 2 g daily in divided doses)

Adverse effects: anorexia, nausea and vomiting, diarrhoea (usually transient); lactic acidosis most likely in patients with renal failure (discontinue); decreased vitamin B12 absorption.

18.8 Thyroid hormones and antithyroid drugs

Thyroid agents are natural or synthetic containing **levothyroxine** (thyroxine). The principal effect is to increase the metabolic rate. They also exert a cardiostimulatory effect which may be the result of a direct action on the heart.

Thyroid hormones are used in hypothyroidism (myxoedema) and also in diffuse non-toxic goitre, Hashimoto thyroiditis (lymphadenoid goitre) and thyroid carcinoma. Neonatal hypothyroidism requires prompt treatment for normal development.

Levothyroxine sodium (thyroxine sodium) is the treatment of choice for maintenance therapy. It is almost completely absorbed from the gastrointestinal tract but the full effects are not seen for up to 1 to 3 weeks after beginning therapy; there is a slow response to dose change and effects may persist for several weeks after withdrawal. Dosage of levothyroxine in infants and children for congenital hypothyroidism and juvenile myxoedema should be titrated according to clinical response, growth assessment and measurement of plasma thyroxine and thyroid-stimulating hormone.

Antithyroid drugs such as **propylthiouracil** and carbimazole are used in the management of thyrotoxicosis. They are also used to prepare the patient for thyroidectomy. They are usually well-tolerated, with mild leukopenia or rashes developing in a few percent of cases, usually during the first 6–8 weeks of therapy. During this time the blood count should be checked every 2 weeks or if a sore throat or other signs of infection develop. The drugs are generally given in a high dose in the first instance until the patient becomes euthyroid, the dose may then be gradually reduced to a maintenance dose which is continued for 12–18 months, followed by monitoring to identify relapse. There is a lag time of some 2 weeks between the achievement of biochemical euthyroidism and clinical euthyroidism. Beta adrenoceptor antagonists (beta-blockers) (usually propranolol) may be used as a short-term adjunct to antithyroid drugs to control symptoms but their use in heart failure associated with thyrotoxicosis is controversial.

Treatment can be given, if necessary, in pregnancy but antithyroid drugs cross the placenta and in high doses may cause fetal goitre and hypothyroidism. The lowest dose that will control the hyperthyroid state should be used (requirements in Graves disease tend to fall during pregnancy). Propylthiouracil appears in breast milk but does not preclude breastfeeding as long as neonatal development is closely monitored and the lowest effective dose is used.

If surgery (partial thyroidectomy) is contemplated, it may be necessary to give **iodine** for 10 to 14 days in addition to antithyroid drugs to assist control and reduce vascularity of the thyroid. Iodine should not be used for l ong-term treatment since its antithyroid action tends to diminish. In patients in whom drug therapy fails to achieve long-term remissions definitive treatment with surgery or (increasingly) radioactive iodine is preferable.

Levothyroxine sodium

Tablets, levothyroxine sodium 25 mcg (0.025 mg), 50 mcg (0.05 mg), 100 mcg (0.1 mg).

Uses: hypothyroidism.

Contraindications: thyrotoxicosis.

Precautions: cardiovascular disorders (myocardial insufficiency or ECG evidence of myocardial infarction); hypopituitarism or predisposition to adrenal insufficiency (must be corrected by corticosteroid prior to initial levothyroxine); elderly; long-standing hypothyroidism, diabetes insipidus, diabetes mellitus (may need to increase dose of insulin or oral antidiabetic drug); pregnancy (Appendix 2), breastfeeding (Appendix3).

Interactions: Appendix 1.

Dosage:

Hypothyroidism, *by mouth*, ADULT initially 50–100 mcg daily (25–50 mcg for those over 50 years) before breakfast, increased by 25–50 mcg every 3–4 weeks until normal metabolism maintained (usual maintenance dose, 100–200 mcg daily); Where there is cardiac disease, initially 25 mcg daily *or* 50 mcg on alternate days, adjusted in steps of 25 mcg every 4 weeks.

Congenital hypothyroidism and juvenile myxoedema (see notes above), *by mouth*, CHILD up to 1 month, initially 5–10 mcg/ kg daily, CHILD over 1 month, initally 5 mcg/ kg daily, adjusted in steps of 25 mcg every 2–4 weeks, until mild toxic symptoms appear, then reduce dose slightly.

Adverse effects: (usually with excessive dose) anginal pain, arrhythmias, palpitations, tachycardia, skeletal muscle cramps, diarrhoea, vomiting, tremors, restlessness, excitability, insomnia, headache, flushing, sweating, excessive loss of weight and muscular weakness

Propylthiouracil

Propylthiouracil is a representative antithyroid drug. Various drugs can serve as alternatives

Tablets, propylthiouracil 50 mg, 100 mg.

Uses: hyperthyroidism .

Precautions: large goitre; pregnancy and breastfeeding (see also notes; Appendices 2 and 3); hepatic impairment — withdraw treatment if hepatic function deteriorates (fatal reactions reported); renal impairment — reduce dosage.

Dosage:

Hyperthyroidism, *by mouth*, ADULT 300–600 mg daily until patient becomes euthyroid; dose may then be gradually reduced to a maintenance dose of 50–150 mg daily.

PATIENT ADVICE. Warn patient to tell doctor immediately if sore throat, mouth ulcers, bruising, fever, malaise, or non-specific illness occurs.

Adverse effects: nausea, rashes, pruritus, arthralgia, headache; rarely, alopecia, cutaneous vasculitis, thrombocytopenia, aplastic anaemia, lupus erythematosus-like syndrome, jaundice, hepatitis.

Potassium iodide

Tablets, potassium iodide 60 mg.

Uses: thyrotoxicosis (pre-operative treatment); sporotrichosis, subcutaneous phycomycosis (section 6.3).

Contraindications: breastfeeding (Appendix 3); long-term treatment.

Precautions: pregnancy (Appendix 2), children.

Dosage:

Pre-operative management of thyrotoxicosis, *by mouth*, ADULT 60–180 mg daily.

Adverse effects: hypersensitivity reactions including coryza like symptoms, headache, lacrimation, conjunctivitis, pain in salivary glands, laryngitis, bronchitis, rashes; on prolonged treatment, depression, insomnia, impotence, goitre in infants of mothers taking iodides.

Section 19 Immunologicals

Active immunity

Active immunity may be induced by the administration of micro-organisms or their products which act as antigens to induce antibodies to confer a protective immune response in the host. Vaccination may consist of (a) a **live attenuated** form of a virus or bacteria, (b) **inactivated** preparations of the virus or bacteria, or (c) **extracts of** or **detoxified exotoxins**. Live attenuated vaccines usually confer immunity with a single dose which is of long duration. Inactivated vaccines may require a series of injections in the first instance to produce an adequate antibody response and in most cases, require reinforcing (booster) doses. The duration of immunity varies from months to many years. Extracts of or detoxified exotoxins require a primary series of injections followed by reinforcing doses.

Passive immunity

Passive immunity is conferred by injecting preparations made from the plasma of immune individuals with adequate levels of antibody to the disease for which protection is sought. Treatment has to be given soon after exposure to be effective. This immunity lasts only a few weeks but passive immunization can be repeated where necessary.

19.1 Diagnostic agents

The **tuberculin test** has limited diagnostic value. A positive tuberculin test indicates previous exposure to mycobacterial antigens through infection with one of the tubercle bacilli, or BCG vaccination. The tuberculin test does not distinguish between tuberculosis and other mycobacterial infection, between active and quiescent disease, or between acquired infection and seroconversion induced by BCG vaccination.

Tuberculin purified protein derivative (tuberculin PPD)

All tuberculins should comply with the requirements for tuberculins (revised 1985). Who technical report series, no.745, 1987, annex 1.

Injection, tuberculin purified protein derivative 100 units/ml, 10 units/ml.

Uses: test for hypersensitivity to tuberculoprotein.

Contraindications: should not be used within 3 weeks of receiving a live viral vaccine.

Precautions: elderly; malnutrition; viral or bacterial infections (including HIV and severe tuberculosis), malignant disease, corticosteroid or immunosuppressant therapy—diminished sensitivity to tuberculin; avoid contact with open cuts, abraded or diseased skin, eyes or mouth.

Dosage:

NOTE. National recommendations may vary

Test for hypersensitivity to tuberculoprotein, *by intradermal injection*, ADULT and CHILD 5 or 10 units (1 unit may be used in hypersensitive patients or if tuberculosis is suspected).

ADMINISTRATION. According to manufacturer's directions.

Adverse effects: occasionally nausea, headache, malaise, rash; immediate local reactions (more common in atopic patients); rarely, vesicular or ulcerating local reactions, regional adenopathy and fever.

19.2 Sera and immunoglobulins

Antibodies of human origin are usually termed **immunoglobulins**. Material prepared from animals is called **antiserum**. Because of serum sickness and other allergic-type reactions that may follow injections of antisera, this therapy has been replaced wherever possible by the use of immunoglobulins. All immunoglobulins and antisera should comply with WHO requirements for blood and plasma products.

CONTRAINDICATIONS AND PRECAUTIONS. Anaphylaxis, although rare, can occur and epinephrine must always be immediately available during immunization.

The IgA content of normal immunoglobulins can result in the development of IgE and IgG anti-IgA antibodies in immunodeficient patients with IgA deficiency. Normal immunoglobulin should not be used in patients with known class specific antibody to immunoglobulin A (IgA).

Immunoglobulins may interfere with the immune response to live virus vaccines which should normally be given *either at least 3 weeks before or at least 3 months after* the administration of the immunoglobulin.

ADVERSE REACTIONS. *Intramuscular injection.* Local reactions including pain and tenderness may occur at the injection site. Hypersensitivity reactions may occur including, rarely, anaphylaxis.

Intravenous injection. Systemic reactions including fever, chills, facial flushing, headache and nausea may occur, particularly following high rates of infusion. Hypersensitivity reactions may ccur including, rarely, anaphylaxis.

19.2.1 Anti-D immunoglobulin (human)

Anti-D immunoglobulin is prepared from plasma with a high titre of anti-D antibody. It is available to prevent a rhesusnegative mother from forming antibodies to fetal rhesus positive cells which may pass into the maternal circulation. The aim is to protect any subsequent child from the hazard of haemolytic disease of the newborn. It should

be administered following any sensitizing episode (for example abortion, miscarriage, still-birth) immediately or within 72 hours of the episode but even if a longer period has elapsed it may still give protection and should be used. The dose of anti-D immunoglobulin given depends on the level of exposure to rhesuspositive blood. The injection of anti-D immunoglobulin is not effective once the mother has formed anti-D antibodies. It is also given following RhO (D) incompatible blood.

Anti-D immunoglobulin (human)

Injection, anti-D immunoglobulin 50 mcg/ml, 100 mcg, 300 mcg, 350 mcg-vial.

Uses: prevention of formation of antibodies to rhesus-positive blood cells in rhesus-negative patients (see notes above).

Contraindications: see introductory notes; known hypersensitivity.

Precautions: see introductory notes; caution in rhesus-positive patients for treatment of blood disorders; caution in rhesu snegative patients with anti-D antibodies in their serum.

Interactions: Appendix 1.

Rubella Vaccine. Rubella vaccine may be administered in the postpartum period at the same time as anti-D immunoglobulin injection, but only using separate syringes and separate contralateral sites.

MMR Vaccine. MMR vaccine should only be given either at least 3 weeks before or at least 3 months after an injection of anti-D immunoglobulin.

Dosage:

NOTE. National recommendations may vary Following birth of a rhesus-positive infant in rhesus-negative mother, *by intramuscular injection*, ADULT 250 mcg immediately or within 72 hours (see also notes above)

Following any potentially sensitizing episode (for example amniocentesis, still-birth), *by intramuscular injection*, ADULT up to 20 weeks' gestation, 250 mcg per episode (after 20 weeks, 500 mcg) immediately or within 72 hours (see notes above)

Following Rh O(D) incompatible blood transfusion, *by intramuscular injection*, ADULT 10–20 mcg per ml transfused rhesus-positive blood.

Adverse effects: see introductory notes.

19.2.2 Antitetanus immunoglobulin (human)

Antitetanus immunoglobulin of human origin is a preparation containing immunoglobulins derived from the plasma of adults immunized with tetanus toxoid. It is used for the management of tetanus-prone wounds in addition to wound toilet and if appropriate antibacterial prophylaxis and adsorbed tetanus vaccine (see section 19.3.1.2).

Antitetanus immunoglobulin (human)

Injection, antitetanus immunoglobulin 500 units/vial.

Uses: passive immunization against tetanus as part of the management of tetanus-prone wounds.

Contraindications: see introductory notes.

Precautions: see introductory notes

TETANUS VACCINE. If schedule requires tetanus vaccine and antitetanus immunoglobulin to be administered at the same time, they should be administered using separate syringes and separate sites.

Dosage:

NOTE. Management of tetanus-prone wounds, *by intramuscular injection*, ADULT and CHILD 250 units, increased to 500 units if wound older than 12 hours or there is risk of heavy contamination or if patient weighs more than 90 kg; second dose of 250 units given after 3–4 weeks if patient immunosuppressed or if active immunization with tetanus vaccine contraindicated (see also section 19.3.1.2)

Adverse effects: see introductory notes.

19.2.3 Diphtheria antitoxin

Diphtheria antitoxin is prepared from the plasma or serum of healthy horses immunized against diphtheria toxin or diphtheria toxoid. It is used for passive immunization in suspected cases of diphtheria without waiting for bacterial confirmation of the infection. A test dose should be given initially to exclude hypersensitivity. Diphtheria antitoxin is not used for prophylaxis of diphtheria because of the risk of hypersensitivity.

Diphtheria antitoxin

Injection, diphtheria antitoxin 10,000 units, 20,000 units/ vial.

Uses: passive immunization in suspected cases of diphtheria.

Precautions: initial test dose to exclude hypersensitivity; observation required after full dose (epinephrine and resuscitation facilities should be available).

Dosage:

NOTE. National recommendations may vary Passive immunization in suspected diphtheria, *by intramuscular injection*, ADULT and CHILD 10,000–30,000 units in mild to moderate cases; 40,000–100,000 units in severe cases (for doses of more than 40 000 units, a portion should be given *by intramuscular injection* followed by the bulk of the dose *intravenously* after an interval of 0.5–2 hours).

Adverse effects: anaphylaxis with urticaria, hypotension, dyspnoea and shock; serum sickness up to 12 days after injection

19.2.5 Rabies immunoglobulin (human)

Rabies immunoglobulin is a preparation containing immunoglobulins derived from the plasma of adults immunized with rabies vaccine. It is used as part of the management of potential rabies following exposure of an unimmunized

individual to an animal in or from a high-risk country. It should be administered as soon as possible after exposure without waiting for confirmation that the animal is rabid. The rabies immunoglobulin should be infiltrated round the site of the bite and also given intramuscularly. In addition rabies vaccine (see section 19.3.2.3) should be administered at a different site.

Rabies immunoglobulin (human)

Injection, rabies immunoglobulin 300-units vial, 1500-unit vial.

Uses: passive immunization either post-exposure or in suspected exposure to rabies in high-risk countries in unimmunized individuals (in conjunction with rabies vaccine).

Contraindications: see introductory notes; avoid repeat doses after vaccine treatment initiated; intravenous administration.

Precautions: see introductory notes.

Rabies Vaccine. If schedule requires rabies vaccine and rabies immunoglobulin to be administered at the same time, they should be administered using seperate syringes and seperate sites.

Dosage:

NOTE. National recommendations may vary Immunization against rabies: post-exposure (or suspected exposure) treatment, *by intramuscular injection* and *wound infiltration*, ADULT and CHILD 20 units/kg (half by intramuscular injection and half by wound infiltration).

Adverse effects: see introductory notes.

19.2.6 Antivenom sera

Acute envenoming from snakes or spiders is common in many parts of the world. The bite may cause local and systemic effects.

Local effects include pain, swelling, bruising and tender enlargement of regional lymph nodes. Wounds should be cleaned and pain may be relieved by analgesics.

If significant amounts of toxin are absorbed after a snake bite, this may result in early anaphylactoid symptoms such as transient hypotension, angioedema, abdominal colic, diarrhoea and vomiting, followed by persistent or recurrent hypotension and ECG abnormalities. Spontaneous systemic bleeding, coagulopathy, adult respiratory distress syndrome and acute renal failure may occur. Early anaphylactoid symptoms may be treated with epinephrine. **Snake antivenom sera** are the only specific treatment available but they can produce severe adverse reactions. They are generally only used if there is a clear indication of systemic involvement or severe local involvement or if supplies are not limited in patients at high risk of systemic or severe local involvement.

Spider bites may cause either necrotic or neurotoxic syndromes

depending on the species involved. Supportive and symptomatic treatment is required and in the case of necrotic syndrome, surgical repair may be necessary.

Antivenom sera

Injection, snake antivenom serum.

NOTE. There are many antivenom sera each containing specific venom neutralizing globulins. It is important that the specific antivenom serum suitable for the species causing the envenomation is administered.

Uses: treatment of snake bites and spider bites.

Precautions: resuscitation facilities should be immediately available.

Dosage:

Depends on the specific antivenom used; consult manufacturer's literature.

Adverse effects: serum sickness; anaphylaxis with hypotension, dyspnoea, urticaria and shock.

19.3 Vaccines

CONTRAINDICATIONS AND PRECAUTIONS. Recipients of any vaccine should be observed for an adverse reaction. Anaphylaxis though rare, can occur and epinephrine must always be immediately available whenever immunization is given. If a serious adverse event (including anaphylaxis, collapse, shock, encephalitis, encephalopathy, or non-febrile convulsion) occurs following a dose of any vaccine, a subsequent dose should not be given. In the case of a severe reaction to Diphtheria, Pertussis, and Tetanus vaccine, the pertussis component should be omitted and the vaccination completed with Diphtheria and Tetanus vaccine.

Immunization should be postponed in acute illness which may limit the response to immunization, but minor infections without fever or systemic upset are not contraindications. A definite reaction to a preceding dose is a definite contraindication.

If alcohol or other disinfecting agent is used to wipe the injection site it must be allowed to evaporate, otherwise inactivation of a live vaccine may occur.

The intramuscular route must not be used in patients with bleeding disorders such as haemophilia or thrombocytopenia.

When two live virus vaccines are required (and are not available as a combined preparation) they should be given *either* simultaneously at different sites using separate syringes *or* with an interval of at least 3 weeks. Live virus vaccines should normally be given *either at least 3 weeks before or at least 3 months after* the administration of immunoglobulin.

Live vaccines should not be routinely administered to pregnant women because of the possible harm to the fetus but where there is significant risk of exposure, the need for immunization may outweigh any possible risk to the fetus.

Live vaccines should not be given to anyone with malignant disease such as leukaemia or lymphomas or other tumours of the reticulo-endothelial system. Live vaccines should not be given to individuals with an impaired immune response caused by disease, radiotherapy or drug treatment (for example, high doses of corticosteroids).

However, the WHO recommends that immunocompromized individuals who are HIV-positive should, under certain circumstances, be given some live vaccines. *Asymptomatic* and *symptomatic* HIV-positive children and women of childbearing age should receive diphtheria, pertussis, tetanus, hepatitis B and oral poliomyelitis vaccines (included in the Expanded Programme on Immunization (EPI)). Because of the risk of early and severe measles infection, infants should receive an extra dose of measles vaccine at 6 months of age with the EPI dose as soon after 9 months of age as possible. Individuals with *symptomatic* HIV infection must **not** be given either BCG or yellow fever vaccines. Individuals with *asymptomatic* HIV infection should only be given BCG or yellow fever vaccines where the prevalence of tuberculosis or yellow fever, respectively, is high. National policies on immunization of HIV-positive individuals may vary.

ADVERSE REACTIONS. Local reactions including inflammation and lymphangitis may occur. Sterile abscess may develop at the injection site; fever, headache, malaise starting a few hours after injection and lasting for 1–2 days may occur. Hypersensitivity reactions can occur including rarely, anaphylaxis.

19.3.1 Vaccines for universal immunization

The WHO Expanded Programme on Immunization (EPI) currently recommends that all countries immunize against diphtheria, hepatitis B, measles, poliomyelitis, pertussis, tetanus and that countries with a high incidence of tuberculosis infections should immunize against tuberculosis. Immunization against yellow fever is recommended in endemic countries. Routine vaccination against *Haemophilus influenzae* type b infection is also recommended in some countries. In geographical regions where the burden of disease is unclear, efforts should be made to evaluate the magnitude of the problem.

IMMUNIZATION SCHEDULE RECOMMENDED BY THE GOVERNMENT

Scheme

Age	Vaccines
Birth	BCG; Poliomyelitis, oral (1st);
6 weeks	Diphtheria, pertussis, tetanus (1st); Poliomyelitis, oral (2nd);
10 weeks	Diphtheria, pertussis, tetanus (2nd); Poliomyelitis, oral (3rd)
14 weeks	Diphtheria, pertussis, tetanus (3rd); Poliomyelitis, oral (4th);
9 months	Measles.

19.3.1.1 BCG vaccine (dried)

Where tuberculosis remains highly prevalent, routine immunization of infants within the first year of life with BCG vaccine, derived from bacillus Calmette-Gue´rin (an attenuated strain of *Mycobacterium bovis*), is highly cost-effective. This has been estimated, in several settings, to reduce the incidence of meningeal and miliary tuberculosis in early childhood by 50 to 90%. However, estimates of its effectiveness in older children have differed greatly from region to region and because efficacy against pulmonary tuberculosis is doubtful, the mainstay of the tuberculosis control programme is case-finding and treatment.

BCG vaccine

Injection (Powder for solution for injection), live bacteria of a strain derived from the bacillus of Calmette and Gue´rin.

Uses: active immunization against tuberculosis; see also section. 6.2.4

Contraindications: see introductory notes; generalized oedema; antimycobacterial treatment.

Precautions: pregnancy (Appendix 2); eczema, scabies — vaccine site must be lesion-free; **Interactions:** Appendix 1.

Dosage:

NOTE. National immunization schedules may vary

Immunization against tuberculosis, *by intradermal injection*, INFANTS up to 3 months, 0.05 ml; ADULT and CHILD over 3 months 0.1 ml.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's direction.

Adverse effects: see introductory notes; lymphadenitis and keloid formation; osteitis and localized necrotic ulceration; rarely, disseminated BCG infection in immunodeficient patients.

19.3.1.2 Diphtheria, pertussis and tetanus (DPT or Triple) vaccines

DIPHTHERIA. Diphtheria is a bacterial infection caused by *Corynebacterium diphtheriae*, transmitted person to person through close physical and respiratory contact. Diphtheria vaccine is a formaldehyde-inactivated preparation of diphtheria toxin, adsorbed onto a mineral carrier to increase its antigenicity and reduce adverse reactions. Immunized individuals can be infected by toxin-producing strains of diphtheria but systemic manifestations of the disease do not occur.

When administered for primary immunization in infants, diphtheria vaccine is almost always given together with pertussis and tetanus vaccines as part of a *three-component* preparation (DPT).

A *two-component* diphtheria vaccine with tetanus but without pertussis exists in two forms, DT and Td. Diphtheria-tetanus vaccine for children (DT) is used for primary immunization in infants who have contraindications to pertussis vaccine; it is also used in children under the age of 10 years for reinforcing immunization against diphtheria and tetanus in those countries which recommend it. Tetanus-diphtheria vaccine for adults, adolescents and children over 10 years of age (Td), which has a reduced amount of diphtheria toxoid to reduce the risk of hypersensitivity reactions, is used for primary immunization in persons over the age of 10 years; it is also used for reinforcing immunization in persons over the age of 10 years in those countries that recommend it.

PERTUSSIS. Pertussis (whooping cough) is a bacterial respiratory infection caused by *Bordetella pertussis*. Many of the symptoms are thought to be caused by toxins released by *B. pertussis*. Whole cell vaccine composed of whole pertussis bacteria killed by chemicals or heat is effective in preventing serious illness. It causes frequent local reactions and fever and rarely it may cause neurological reactions. Neurological complications after pertussis infection are considerably more common than after the vaccine. It is combined with diphtheria tetanus vaccine for primary immunization unless immunization against pertussis is contra-indicated. Single component pertussis vaccines are available in some countries for use when the pertussis component has been omitted from all or part of the primary immunization schedule. An acellular form of the vaccine is also available.

In some countries it is recommended that children with a personal or family history of febrile convulsions or a family history of idiopathic epilepsy should be immunized. It is also

recommended that children with well-controlled epilepsy are immunized. Advice on prevention of fever should be given at the time of immunization. In children with evolving neurological problems, immunization with pertussis should be deferred until the condition is stable; in such children diphtheria and tetanus vaccine should be offered for primary immunization, and there may be an opportunity at a later date to complete immunization with a single-component pertussis vaccine. Where there is doubt advice should be sought from a paediatrician.

TETANUS. Tetanus is caused by the action of a neurotoxin of *Clostridium tetani* in necrosed tissues such as occur in dirty wounds. Tetanus vaccine is available as a single component vaccine for primary immunization in adults who have not received childhood immunization against tetanus and for reinforcing immunization. The vaccine is also used in the prevention of neonatal tetanus and in the management of clean wounds and tetanus-prone wounds. Some countries recommend a maximum of 5 doses of tetanus vaccine in a life-time; for the fully immunized patient reinforcing doses at the time of a tetanus-prone injury should only be required if more than 10 years have elapsed since the last dose.

Neonatal tetanus due to infection of the baby's umbilical stump during unclean delivery is the cause of many deaths of newborn infants. Control of neonatal tetanus may be achieved by ensuring adequate hygiene during delivery and by ensuring protective immunity of mothers in late pregnancy. Tetanus vaccine is highly effective and the efficacy of two doses during pregnancy in preventing neonatal tetanus ranges from 80–100%. Women of child-bearing age may be immunized by a course of 5 doses (3 primary and 2 reinforcing) of tetanus vaccine.

Wounds are considered to be tetanus-prone if they are sustained *either* more than 6 hours before surgical treatment of the wound *or* at any interval after injury and show one or more of the following: a puncture-type wound, a significant degree of devitalized tissue, clinical evidence of sepsis, contamination with soil/manure likely to contain tetanus organisms. All wounds should receive thorough surgical toilet. Antibacterial prophylaxis may also be required for tetanus prone wounds.

Diphtheria, pertussis, and tetanus vaccine (DPT)

Injection, diphtheria and tetanus toxoids and pertussis vaccine adsorbed onto a mineral carrier.

Uses: active immunization against diphtheria, tetanus and pertussis.

Contraindications: see introductory notes and notes above.

Precautions: see introductory notes and notes above; in cases

of severe reaction, the pertussis component should be omitted and the primary course of immunization completed with diphtheria and tetanus vaccine.

Dosage:

Primary immunization of children against diphtheria, pertussis and tetanus, *by intramuscular or deep subcutaneous injection*, INFANT 0.5 ml at 6, 10 and 14 weeks (see section 19.3.1).

Adverse effects: see introductory notes; tetanus component rarely associated with peripheral neuropathy; pertussis component rarely associated with convulsions and encephalopathy.

Diphtheria and tetanus vaccine (DT) (For children under 10 years)

Injection, diphtheria and tetanus toxoids adsorbed onto a mineral carrier.

Uses: active immunization of children under 10 years against diphtheria and tetanus (see notes above).

Contraindications: see introductory notes; adults and children over 10 years of age (see notes above).

Precautions: see introductory notes.

Dosage:

Primary immunization of children against diphtheria and tetanus when pertussis immunization is contraindicated, *by intramuscular or deep subcutaneous injection*, CHILD under 10 years 3 doses each of 0.5 ml with an interval of not less than 4 weeks between each dose (see also WHO schedule, section 19.3.1)

Reinforcing immunization of children against diphtheria and tetanus, *by intramuscular or deep subcutaneous injection*, CHILD under 10 years of age, 0.5 ml at least 3 years after completion of primary course of DPT or DT immunization.

Adverse effects: see introductory notes; tetanus component rarely associated with peripheral neuropathy.

Tetanus vaccine

Injection, tetanus toxoid adsorbed onto a mineral carrier.

Uses: active immunization against tetanus and neonatal tetanus; wound management (tetanus-prone wounds and clean wounds).

Contraindications: see introductory notes and notes above.

Precautions: see introductory notes and notes above.

ANTITETANUS IMMUNOGLOBULIN. If schedule requires tetanus vaccine and antitetanus immunoglobulin to be administered at the same time, they should be administered using separate syringes and separate sites.

Dosage:

NOTE. National immunization schedules may vary; some countries recommend a **maximum** of 5 doses of tetanus vaccine in a life-time

Primary immunization of unimmunized adults against tetanus, *by intramuscular or deep subcutaneous injection*, ADULT 3 doses each of 0.5 ml with an interval of 4 weeks between each dose

Reinforcing immunization of adults against tetanus, *by intramuscular or deep subcutaneous injection*, ADULT 2 doses each of 0.5 ml, the first 10 years after completion of primary course, and the second dose 10 years later

Immunization of women of child-bearing age against tetanus, *by intramuscular or deep subcutaneous injection*, WOMAN OF CHILD-BEARING AGE, 3 primary doses each of 0.5 ml with an interval of not less than 4 weeks between the first and second doses and 6 months between the second and third doses; 2 reinforcing doses each of 0.5 ml, the first 1 year after completion of the primary course and the second dose 1 year later; UNIMMUNIZED PREGNANTWOMAN 2 doses of 0.5 ml with an interval of 4 weeks between each dose, with the second dose at least 2 weeks before delivery

Management of tetanus-prone wounds and clean wounds, *by intramuscular or deep subcutaneous injection*, ADULT 0.5 ml, the dose schedule being dependent upon the immune status of the patient and the level of contamination of the wound (see also notes above and under Antitetanus Immunoglobulin, section 19.2.2).

Adverse effects: see introductory notes; tetanus component rarely associated with peripheral neuropathy.

19.3.1.3 Hepatitis B vaccine

Vaccine for restricted use as it is not cost effective. Hepatitis B is caused by hepatitis B virus. It is transmitted in blood and blood products, by sexual contact and by contact with infectious body fluids. Persons at increased risk of infection because of their life-style, occupation or other factors include parenteral drug abusers, individuals who change sexual partners frequently, health care workers who are at risk of injury from blood-stained sharp instruments and haemophiliacs. Also at risk are babies born to mothers who are HbsAg (hepatitis B virus surface antigen)-positive and individuals who might acquire the infection as the result of medical or dental procedures in countries of high prevalence. The main public health consequences are chronic liver disease and liver cancer rather than acute infection. Routine immunization is recommended and has been implemented in some countries. Plasma-derived hepatitis B vaccine is highly efficacious. Over 90% of susceptible children develop a protective antibody response. A recombinant DNA vaccine is also available.

Hepatitis B vaccine

Injection, inactivated hepatitis B surface antigen adsorbed onto a mineral carrier.

Uses: active immunization against hepatitis B.

Contraindications: see introductory notes.

Precautions: see introductory notes.

Dosage:

NOTE. National immunization schedules may vary

Immunization of children against hepatitis B, *by intramuscular injection*, INFANT 0.5 ml *either Scheme A* at birth and at 6 and 14 weeks of age, *or Scheme B* at 6, 10 and 14 weeks of age (see section 19.3.1)

Immunization of unimmunized high risk persons against hepatitis B, *by intramuscular injection*, ADULT and CHILD over 15 years of age 3 doses of 1 ml, with an interval of 1 month between the first and second dose and 5 months between the second and third doses; CHILD under 15 years, 0.5 ml

ADMINISTRATION. The vaccine should be given in the deltoid region in adults; anterolateral thigh is the preferred site in infants and children; it should not be injected into the buttock (vaccine efficacy reduced); subcutaneous route used for patients with haemophilia.

Adverse effects: see introductory notes; abdominal pain and gastrointestinal disturbances; muscle and joint pain, dizziness and sleep disturbance; occasionally cardiovascular effects.

19314 Measles vaccines

Measles is an acute viral infection transmitted by close respiratory contact. In some countries routine immunization of children against measles is given as one dose of a single component vaccine; in other areas, a two-dose schedule has been found to be more applicable. In developing countries, clinical efficacy is usually greater than 85%. Convulsions and encephalitis are rare complications. Single-component vaccines may be used in the control of outbreaks of measles and should be offered to susceptible children within 3 days of exposure.

Measles vaccine

Injection (Powder for solution for injection), live, attenuated measles virus.

Uses: active immunization against measles.

Contraindications: see introductory notes; hypersensitivity to any antibiotic present in vaccine; hypersensitivity to egg.

Precautions: see introductory notes; pregnancy (Appendix 2);

Interactions: Appendix 1.

Dosage:

Immunization of children against measles, *by intramuscular or deep subcutaneous injection*, INFANT at 9 months of age, 0.5 ml (see section 19.3.1)

Prophylaxis in susceptible children after exposure to measles, *by intramuscular or deep subcutaneous injection* within 72 hours of contact, CHILD over 9 months of age 0.5 ml

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: see introductory notes; rashes sometimes accompanied by convulsions; rarely, encephalitis and thrombocytopenia.

19315 Poliomyelitis vaccines

Poliomyelitis is an acute viral infection spread by the faecal-oral route which can cause paralysis of varying degree. There are two types of vaccine against poliomyelitis: oral and injectable. Oral poliomyelitis vaccine (OPV) is composed of three types of live attenuated poliomyelitis viruses. The efficacy of OPV in preventing paralytic polio in developing countries ranges from 72% to 98% and is the vaccine of choice in eradication of the disease. Oral poliomyelitis vaccine should not be given to patients with diarrhoea or vomiting and those with immunodeficiency disorders (or household contacts of patients with immunodeficiency disorders). The need for strict personal hygiene must be stressed as the vaccine virus is excreted in the faeces. The contacts of a recently vaccinated baby should be advised particularly of the need to wash their hands after changing the baby's nappies. After primary immunization reinforcing doses may be given.

Poliomyelitis vaccine (OPV) (live attenuated)

Oral suspension, live, attenuated poliomyelitis virus, types 1, 2, and 3.

Uses: active immunization against poliomyelitis.

Contraindications: see introductory notes; avoid in patients with diarrhoea or vomiting (vaccine virus excreted in faeces — strict personal hygiene required; see notes above); not to be taken with food which contains a preservative; hypersensitivity to any antibiotic present in vaccine — consult manufacturer's literature.

Precautions: see introductory notes; pregnancy (Appendix 2);

Interactions: Appendix 1.

Dosage:

Primary immunization of children against poliomyelitis, *by mouth*, CHILD 3 drops at birth and at 6, 10 and at 14 weeks of age (see section 19.3.1)

Reinforcing immunization of children against poliomyelitis, *by mouth*, CHILD 3 drops at least 3 years after completion of primary course and a further 3 drops at 15–19 years of age .

Adverse effects: rarely, vaccine-associated poliomyelitis in recipients of vaccine and contacts of recipients.

19.3.2 Vaccines for specific groups of individuals

19323 Rabies vaccine (inactivated)

Rabies vaccine is used as part of the *post-exposure treatment* to prevent rabies in patients who have been bitten by rabid animals or animals suspected of being rabid. Treatment is dependent upon the individual's immune status and upon the level of risk of rabies in the country concerned (consult national immunization schedule); in certain circumstances *passive immunization* with rabies immunoglobulin may be indicated (see Rabies Immunoglobulin, section 19.2.5). Treatment should also include thorough wound cleansing.

The vaccine is also used for *pre-exposure prophylaxis* against rabies in those at high risk such as laboratory workers, veterinary surgeons, animal handlers and health workers who are likely to come into close contact with patients with rabies. Pre-exposure prophylaxis is also recommended for those living or travelling in enzootic areas who may be exposed to unusual risk.

Rabies vaccine (inactivated) (prepared in cell culture)

Injection, inactivated rabies virus prepared in cell culture.

Uses: active immunization against rabies; pre-exposure prophylaxis, post-exposure treatment (see notes above).

Contraindications: see introductory notes

Precautions: see introductory notes;

Interactions: Appendix 1

Rabies Immunoglobulin. If schedule requires rabies vaccine and rabies immunoglobulin to be administered at the same time, they should be administered using separate syringes and separate sites.

Dosage:

Immunization against rabies: pre-exposure prophylaxis, *by deep subcutaneous or by intramuscular injection*, ADULT and CHILD 1 ml on days 0, 7 and 28, with reinforcing doses every 2–3 years for those at continued risk

Immunization against rabies: post-exposure treatment, *by deep subcutaneous or by intramuscular injection*, ADULT and CHILD 2–5 doses of 1 ml (see notes above).

Adverse effects: see introductory notes; pain, erythema and induration at injection site; nausea, myalgia; hypersensitivity — less likely with vaccines from human sources.

Section 20: Muscle relaxants (peripherally acting) and cholinesterase inhibitors

Muscle relaxants used in surgery include **suxamethonium**, **alcuronium,**and **vecuronium**.

20.1 Cholinesterase inhibitors

MYASTHENIA GRAVIS. Cholinesterase inhibitors, such as **neostigmine** and **pyridostigmine**, are used to treat myasthenia gravis. They act by inhibiting anticholinesterase, thereby prolonging the action of acetylcholine, and thus enhancing neuromuscular transmission; this produces at least a partial improvement in most myasthenic patients but complete restoration of muscle strength is rare. Unless the patient has difficulty in swallowing, cholinesterase inhibitors are given by mouth. Pyridostigmine has a slower onset (usually within 30–60 minutes), but a longer duration of effect than neostigmine; it also tends to cause fewer muscarinic effects such as diarrhoea, abdominal cramps, and excess salivation, so is usually preferred. Doses should be carefully adjusted to avoid precipitating a *cholinergic crisis* due to overdosage; this must be differentiated from a *myasthenic crisis* due to disease progression, and consequent underdosage; the principal effect in both cases is increased muscle weakness.

In myasthenic crisis, if the patient has difficulty in breathing and in swallowing, the cholinesterase inhibitor must be given parenterally; neostigmine is usually used, as intravenous injection of pyridostigmine is hazardous; to reduce muscarinic effects, atropine (section 1.3) should also be given.

For the use of neostigmine in surgery, see section 1.4.

Neostigmine

Neostigmine is a representative cholinesterase inhibitor. Various drugs can serve as alternatives

Tablets, neostigmine bromide 15 mg

Injection, neostigmine metilsulfate 500 mcg (0.5 mg)/ml, 1-ml ampoule; 2.5 mg/5ml - ampoule.

Uses: myasthenia gravis; reversal of non-depolarizing block, postoperative urinary retention (section 1.4).

Contraindications: recent intestinal or bladder surgery; mechanical intestinal or urinary tract obstruction; after suxamethonium; pneumonia; peritonitis.

Precautions: asthma; urinary tract infections; cardiovascular disease including arrhythmias (especially bradycardia or atrioventricular block); hypotension; peptic ulcer; epilepsy; parkinsonism; renal impairment ; pregnancy and breastfeeding (Appendices 2 and 3).

Interactions: Appendix 1.

Dosage:

Myasthenia gravis, *by mouth* as neostigmine bromide, ADULT initially 15 mg 3 times daily, gradually increased until desired response obtained; total daily dose within range 75–300 mg, taken at appropriate intervals when maximum strength required, but doses above 180 mg daily not usually tolerated; CHILD up to 6 years, initially 7.5 mg, 6–12 years, initially 15 mg; total daily dose usually 15–90 mg in divided doses at appropriate intervals

By subcutaneous or intramuscular injection as neostigmine metilsulfate, ADULT 0.5–2.5 mg as required, total daily dose 5–20 mg; NEONATE 50–250 mcg before feeds (not usually required beyond 8 weeks of age); CHILD 200–500 mcg as required.

NOTE. To reduce muscarinic effects, atropine sulfate *by intravenous injection* (ADULT 0.6–1.2 mg, CHILD 20 mcg/kg) with or before neostigmine injection.

Adverse effects: increased salivation and bronchial secretions, sweating, nausea and vomiting, abdominal cramps, diarrhoea, miosis, muscle spasm, bradycardia, bronchospasm, allergic reactions; hypotension; cholinergic crisis on overdosage; thrombophlebitis reported; rash associated with bromide salt.

Section 21 Ophthalmological preparations

Administration of eye preparations

Preparations for the eye should be sterile when issued. Use of single-application containers is preferable; multiple-application preparations include antimicrobial preservatives and when used particular care should be taken to prevent contamination of the contents, including the avoidance of contact between the applicator and the eye or other surfaces.Eye drops are generally instilled into the lower conjunctivital sac which is accessed by gently pulling down the lower eyelid to form a pocket into which one drop is instilled. The eye should be kept closed for as long as possible after application, preferably 1–2 minutes. A small amount of eye ointment is applied similarly; the ointment melts rapidly and blinking helps to spread it.When two different eye drops are required at the same time, dilution and overflow may occur when one immediately follows the other; an interval of 5 minutes should be allowed between the two applications.Systemic absorption, which may occur after topical application of eye drops, can be minimized by using the finger to compress the lacrimal sac at the medial canthus for at least one minute after instillation of the drops. This helps block the passage of the drops through the naso-lacrimal duct.

PERFORMANCE OF SKILLED TASKS. Application of eye preparations may cause blurring of vision which is generally transient; patients should be advised not to carry out skilled tasks such as operating machinery or driving until their vision has cleared.

21.1 Anti-infective drugs

Blepharitis, conjunctivitis, keratitis and endophthalmitis are common acute infections of the eye and can be treated topically. However, in some cases, for example, in gonococcal conjunctivitis, both topical and systemic anti-infective treatment may be necessary. Blepharitis and conjunctivitis are often caused by staphylococcus, while keratitis and endophthalmitis may be bacterial, viral or fungal. Bacterial blepharitis is treated with an antibacterial eye ointment or drops. Although most cases of acute bacterial conjunctivitis may resolve spontaneously, anti-infective treatment shortens the infectious process and prevents complications. Acute infective conjunctivitis is treated with antibacterial eye drops by day and eye ointment applied at night. A poor response may indicate viral or allergic conjunctivitis. Keratitis requires immediate specialist treatment.

Gentamicin is a broad spectrum bactericidal antibiotic with particular activity against *Pseudomonas aeruginosa*, *Neisseria gonorrhoea* and other bacteria that may be implicated in blepharitis or conjunctivitis. Topical application may lead to systemic absorption and possible adverse effects.

Silver nitrate is a topical anti-infective. Its antibacterial activity is attributed to precipitation of bacterial proteins by silver ions. It is available in 1% ophthalmic solutions and is used for prophylaxis of gonococcal ophthalmia neonatorum.

Tetracycline is a broad spectrum antibiotic with activity against many Gram-positive and Gram-negative bacteria including *N. gonorrhoea*, and most chlamydia, rickettsia, mycoplasma and spirochetes. Ophthalmic tetracycline is used in blepharitis, conjunctivitis, and keratitis produced by susceptible bacteria. Tetracycline is also used in the treatment of trachoma caused by *Chlamydia trachomatis* and in the prophylaxis of neonatal conjunctivitis (ophthalmia neonatorum) caused by *N. gonorrhoea* and *C. trachomatis*.

Gentamicin

An example of an antibacterial. Various drugs can serve as alternatives
Eye drops, solution, gentamicin (as sulfate) 0.3%.

Uses: blepharitis; bacterial conjunctivitis; systemic infections (section 6.2.2.5).

Contraindications: hypersensitivity to aminoglycoside group of antibiotics.

Precautions: prolonged use may lead to skin sensitization and emergence of resistant organisms including fungi; discontinue if purulent discharge, inflammation or exacerbation of pain.

Administration:

Mild to moderate infection, *by instillation into the eye,* ADULT and CHILD 1 drop every 2 hours, reducing frequency as infection is controlled, then continue for 48 hours after healing is complete

Severe infection, *by instillation into the eye,* ADULT and CHILD 1 drop every hour, reducing frequency as infection is controlled, then continue for 48 hours after healing is complete.

Adverse effects: burning, stinging, itching, dermatitis.

Silver nitrate

Eye drops, solution, silver nitrate 1%.

Uses: prophylaxis of neonatal conjunctivitis (ophthalmia neonatorum) due to *Neisseria gonorrhoea*, if tetracycline not available.

Precautions: avoid use of old, concentrated drops; wipe excess drops from skin near the eye to prevent staining.

Administration:

Prophylaxis of neonatal conjunctivitis, *by instillation into the eye,* NEWBORN at birth after cleansing eyes with sterile gauze, 2 drops into each eye.

Adverse effects: skin and mucous membrane irritation; mild

conjunctivitis; repeated use may cause skin discoloration, corneal cauterization and blindness.

Tetracycline hydrochloride

An example of an antibacterial. Various drugs can serve as alternatives
Eye ointment, tetracycline hydrochloride 1%.

Uses: superficial bacterial infection of the eye; mass treatment of trachoma in endemic areas; prophylaxis of neonatal conjunctivitis (ophthalmia neonatorum) due to *Neisseria gonorrhoea* or *Chlamydia trachomatis*.

Contraindications: hypersensitivity to tetracycline group of antibiotics.

Precautions: prolonged use may lead to overgrowth of nonsusceptible organisms.

Administration:

Superficial bacterial infection, *by application to the eye,* ADULT and CHILD aged over 8 years 1 application of ointment 3–4 times daily

Prophylaxis of neonatal conjunctivitis, *by application to the eye*, NEWBORN at birth after cleansing eyes with sterile gauze, 1 application of ointment into each eye; close eyelids and massage gently to aid spread of ointment

Trachoma, intermittent treatment, *by application to the eye,* ADULT and CHILD 1 application of ointment into each eye *either* twice daily for 5 days *or* once daily for 10 days, every month for 6 consecutive months each year, repeated as necessary

Trachoma, continuous intensive treatment, *by application to the eye,* ADULT and CHILD 1 application of ointment into each eye twice daily for at least 6 weeks.

Adverse effects: rash; rarely stinging, burning.

Ciprofloxacin Eye Drops

Ciprofloxacin is a quinolone antibacterial drug that is used against a wide range of Gram positive and negative bacteria including Pseudomonas.

Solution, *0.3% w/v sterile aqueous, of Ciprofloxacin lactate or hydrochloride (usually with 0.01 or 0.02% Benzalkonium).*

Uses: acute & subacute superficial eye infections like blepharitis, conjunctivitis, corneal ulcer. Also may be used for ear infections like otitis externa, acute otitis media & prophylaxis during surgeries.

Contraindications: hypersensitivity, burning sensation in the eye.

Precautions: may not be of much use in chronic suppurative otitis media – systemic antibiotics are more useful, if found necssary.

Dosage:

superficial infections like conjunctivitis *Adults: and children:*: 1-2 drops every two hours when awake for 2 days and every four hours for next five days.

Infections associated with corneal ulcer.

Adults: and children: 2 drops in affected eye every 15 minutes for 6 hours and then every 30 minutes for the rest of the day. For 2nd day, 2 drops every 2 hours. 3rd to 14 days, 2 drops every four hours.

Adverse Reactions: local burning or discomfort, corneal deposits in corneal ulcer patients, lid margin custing, crystals, scales, foreign body sensation, pruritus, conjunctival hyperaemia and a bad taste following administration as it trickles down into the throat and tongue.

21.2 Anti-inflammatory drugs

Ophthalmic corticosteroids should only be used under supervision of an ophthalmologist as inappropriate use is potentially blinding. Dangers include the development of open-angle glaucoma (chronic simple glaucoma) and cataracts, and the aggravation of a simple herpes simplex epithelial lesion into an extensive amoeboid ulcer and subsequent permanent corneal scarring.

Corticosteroids such as **prednisolone** are useful in the treatment of inflammatory conditions including uveitis and scleritis. They are also used for reducing postoperative ocular inflammation. Before administration of an ophthalmic corticosteroid, the possibility of bacterial, viral or fungal infection should be excluded. Treatment should be the lowest effective dose for the shortest possible time; if long-term therapy (more than 6 weeks) is unavoidable, withdrawal of an ophthalmic corticosteroid should be gradual to avoid relapse.

Prednisolone sodium phosphate

An example of a corticosteroid. Various drugs can serve as alternatives

Eye drops, solution, prednisolone sodium phosphate 0.5%.

Uses: short-term local treatment of inflammation of the eye; malignant disease (section 8.3); inflammatory and allergic reactions (section 18.1, also section 3.1).

Contraindications: undiagnosed 'red eye' caused by herpetic keratitis; glaucoma.

Precautions: cataract; corneal thinning, corneal or conjunctival infection; discontinue treatment if no improvement within 7 days; risk of adrenal suppression after prolonged use in infants.

Administration:

Use only under the supervision of an ophthalmologist Inflammation of the eye, *by instillation into the eye*, ADULT and CHILD 1 drop every 1–2 hours, reducing frequency as inflammation is controlled.

Adverse effects: secondary ocular infection; impaired corneal

healing (due to corneal thinning), optic nerve damage, cataract; glaucoma, mydriasis, ptosis, epithelial punctate keratitis, delayed hypersensitivity reactions including burning, stinging.

21.3 Local anaesthetics

Topical local anaesthetics are employed for simple ophthalmological procedures and for short operative procedures involving the cornea and conjunctiva. **Tetracaine**, available in 0.5% ophthalmic solution, provides a rapid local anaesthesia which lasts for 15 minutes or more. Prolonged or unsupervized use of tetracaine is not recommended.

Tetracaine hydrochloride
Amethocaine

An example of a local anaesthetic. Various drugs can serve as alternatives

Eye drops, solution, tetracaine hydrochloride 0.5%.

Uses: short-acting local anaesthesia of cornea and conjunctiva.

Contraindications: hypersensitivity to ester-type local anaesthetics; eye inflammation or infection.

Precautions: avoid prolonged use (cause of severe keratitis, permanent corneal opacification, scarring, delayed corneal healing); protect eye from dust and bacterial contamination until sensation fully restored.

Administration:

Local anaesthesia, *by instillation into the eye*, ADULT and CHILD 1 drop.

Adverse effects: burning, stinging, redness; rarely, allergic reactions may occur.

21.4 Antiglaucoma drugs

Glaucoma is normally associated with raised intra-ocular pressure and eventual damage to the optic nerve which may result in blindness. The rise in pressure is almost always due to reduced outflow of aqueous humour, the inflow remaining constant. The most common condition is chronic open-angle glaucoma (chronic simple glaucoma) in which the intra-ocular pressure increases gradually and the condition is usually asymptomatic until well advanced. In contrast, angle-closure glaucoma (closed-angle glaucoma) usually occurs as an acute emergency resulting from a rapid rise in intra-ocular pressure; if treatment is delayed, chronic angle-closure glaucoma may develop. Ocular hypertension is a condition in which intraocular pressure is raised without signs of optic nerve damage.

Drugs used in the treatment of glaucoma lower the intra-ocular

pressure by a variety of mechanisms including reduction in secretion of aqueous humour by the ciliary body, or increasing the outflow of the aqueous humour by opening of the trabecular network. Antiglaucoma drugs used include topical application of a beta-blocker (beta-adrenoceptor antagonist), a miotic, or a sympathomimetic such as epinephrine; systemic administration of a carbonic anhydrase inhibitor may be used as an adjunct.

Timolol is a non-selective beta-blocker which acts by reducing the secretion of aqueous humour. A beta-blocker is usually the drug of choice for initial and maintenance treatment of chronic open-angle glaucoma. If further reduction in intra-ocular pressure is required a miotic, epinephrine or a systemic carbonic anhydrase inhibitor may be used with timolol. If it is used to reduce elevated intra-ocular pressure in angle-closure glaucoma, timolol should be used with a miotic and not alone. Since systemic absorption can occur, an ophthalmic beta-blocker should be used with caution in certain individuals.

A miotic such as **pilocarpine**, through its parasympathomimetic action, contracts the iris sphincter muscle and the ciliary muscle, and opens the trabecular network. It is used in chronic open-angle glaucoma either alone or, if required, as an adjunct with a beta-blocker, epinephrine or a systemic carbonic anhydrase inhibitor. Pilocarpine is used with systemic acetazolamide in an acute attack of angle-closure glaucoma prior to surgery; however, it is not advisable to use pilocarpine after surgery because of a risk of posterior synechiae forming. Systemic absorption of topically applied pilocarpine can occur producing muscarinic-like adverse effects.

Acetazolamide, by reducing carbonic anhydrase in the eye, reduces the production of aqueous humour and so reduces intraocular pressure. It is used systemically as an adjunct in chronic open-angle glaucoma unresponsive to treatment with topically applied antiglaucoma drugs. Prolonged therapy with acetazolamide is not normally recommended, but if treatment is unavoidable blood count and plasma electrolyte concentration should be monitored. Acetazolamide is also used as part of emergency treatment for an acute attack of angle-closure glaucoma; however it should not be used in chronic angleclosure glaucoma as it may mask deterioration of the condition.

21.4.1 Miotics

Pilocarpine

An example of a miotic. Various drugs can serve as alternatives

Eye drops, solution, pilocarpine hydrochloride 2%, 4%; pilocarpine nitrate 2%, 4%.

Uses: chronic open-angle glaucoma, ocular hypertension; emergency treatment of acute angle-closure glaucoma; to antagonize effects of mydriasis and cycloplegia following surgery or ophthalmoscopic examination.

Contraindications: acute iritis, acute uveitis, anterior uveitis, some forms of secondary glaucoma; acute inflammation of anterior segment; not advisable after angle-closure surgery (risk of posterior synechiae).

Precautions: retinal disease, conjunctival or corneal damage; monitor intra-ocular pressure in chronic open-angle glaucoma and in long-term treatment; cardiac disease, hypertension, asthma, peptic ulceration, urinary-tract obstruction, Parkinson disease; stop treatment if symptoms of systemic toxicity develop

SKILLED TASKS. Causes difficulty with dark adaptation; may cause accommodation spasm. Do not carry out skilled tasks, for example operating machinery or driving until vision is clear.

Administration:

Chronic open-angle glaucoma, *by instillation into the eye*, ADULT 1 drop (2% or 4%) up to 4 times daily

Acute angle-closure glaucoma before surgery, *by instillation into the eye*, ADULT 1 drop (2%) every 10 minutes for 30–60 minutes, then 1 drop every 1–3 hours until intra-ocular pressure subsides.

Adverse effects: eye pain, blurred vision, ciliary spasm, lacrimation, myopia, browache; conjunctival vascular congestion, superficial keratitis, vitreous haemorrhage and increased pupillary block have been reported; lens opacities have occurred following prolonged use; rarely systemic effects including hypertension, tachycardia, bronchial spasm, pulmonary oedema, salivation, sweating, nausea, vomiting, diarrhoea

21.4.2 Beta-blockers

Timolol

An example of a beta-blocker. Various drugs can serve as alternatives

Eye drops, solution, timolol (as maleate) 0.25%, 0.5%.

Uses: ocular hypertension; chronic open-angle glaucoma, aphakic glaucoma, some secondary glaucomas.

Contraindications: uncontrolled heart failure, bradycardia, heart block; asthma, obstructive airways disease.

Precautions: older people (risk of keratitis); if used in angleclosure glaucoma, use with a miotic, and not alone.

Interactions: see Appendix 1.

Administration:

Ocular hypertension, chronic open-angle glaucoma, aphakic glaucoma, some secondary glaucomas, *by instillation into the eye*, ADULT 1 drop (0.25% or 0.5%) twice daily

Adverse effects: stinging, burning, pain, itching, erythema, transient dryness, allergic blepharitis, transient conjunctivitis, keratitis, decreased corneal sensitivity, diplopia, ptosis; systemic effects, particularly on the pulmonary, cardiovascular and central nervous systems, may follow absorption.

21.4.3 Sympathomimetics

Epinephrine (Adrenaline)

Reserved for use in higher referral centres

21.4.4 Carbonic anhydrase inhibitors

Acetazolamide

Tablets, acetazolamide 250 mg.

Uses: as an adjunct in the treatment of chronic open-angle glaucoma; secondary glaucoma; as part of pre-operative treatment of acute angle-closure glaucoma.

Contraindications: hypersensitivity to sulfonamides; chronic angle-closure glaucoma (may mask deterioration); hypokalaemia, hyponatraemia, hyperchloraemic acidosis; renal impairment , severe hepatic impairment.

Precautions: elderly; pregnancy (Appendix 2); breastfeeding (Appendix 3); diabetes; pulmonary obstruction; monitor blood count and electrolytes if used for long periods;

Interactions: see Appendix 1.

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving.

Dosage:

Chronic open-angle glaucoma, secondary glaucoma, *by mouth*, ADULT 0.25–1 g daily in divided doses.

Adverse effects: nausea, vomiting, diarrhoea, taste disturbance; loss of appetite, paraesthesia, flushing, headache, dizziness, fatigue, irritability, depression; thirst, polyuria; reduced libido; metabolic acidosis and electrolyte disturbances on long-term therapy; occasionally drowsiness, confusion, hearing disturbances, urticaria, melaena, glycosuria, haematuria, abnormal liver function, renal calculi, blood disorders including agranulocytosis and thrombocytopenia, rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis; transient myopia reported.

21.5 Mydriatics and cycloplegics

Antimuscarinics, by blocking the cholinergic effects of acetylcholine, paralyse the pupillary constrictor muscles causing dilation of the pupil (mydriasis) and paralyse the ciliary muscles resulting in paralysis of accommodation (cycloplegia). Mydriasis may precipitate acute angle-closure

glaucoma particularly in elderly or long-sighted patients. In patients with dark iridic pigmentation, higher concentrations of mydriatic drugs are usually required and care should be taken to avoid overdosing.

Atropine is a long-acting antimuscarinic used for cycloplegic refraction procedures, particularly in children. It is also used to immobilize the ciliary muscle and iris and to prevent formation of posterior synechiae in the treatment of inflammatory eye disorders such as iritis and uveitis.

Atropine sulfate

Eye drops, solution, atropine sulfate 0.1%, 0.5%, 1%.

Uses: iritis, uveitis; cycloplegic refraction procedures; premedication (section 1.3); organophosphate poisoning (section 4.2.3); antispasmodic (section 17.5).

Contraindications: angle-closure glaucoma

Precautions: may precipitate acute attack of angle-closure glaucoma, particularly in the elderly or long-sighted; risk of systemic effects with eye drops in infants under 3 months — eye ointment preferred

SKILLED TASKS. May cause sensitivity to light and blurred vision. Do not carry out skilled tasks, for example operating machinery or driving, until vision is clear.

Administration:

Cycloplegic refraction, *by instillation into the eye*, ADULT 1 drop (1%) twice daily for 1–2 days before procedure *or* a single application of 1 drop (1%) 1 hour before procedure; CHILD over 5 years (0.5–1%), 1–5 years (0.1– 0.5%), under 1 year (0.1%), 1 drop twice daily for 1–3 days before procedure with a further dose given 1 hour before procedure (child under 3 months, see Precautions)

Iritis, uveitis, *by instillation into the eye*, ADULT 1–2 drops (0.5% or 1%) up to 4 times daily; CHILD 1–2 drops (0.5%) or 1 drop (1%) up to 3 times daily.

Adverse effects: transient stinging and raised intra-ocular pressure; on prolonged administration, local irritation, hyperaemia, oedema and conjunctivitis may occur; contact dermatitis; systemic toxicity may occur in the very young and the elderly.

Section 22: Drugs used in Obstetrics

22.1 Drugs used in obstetrics,

Drugs may be used to modify uterine contractions. These include oxytocic drugs used to stimulate uterine contractions both in induction of labour and to control postpartum haemorrhage and beta2-adrenoceptor agonists used to relax the uterus and prevent premature labour.

POSTPARTUM HAEMORRHAGE. **Ergometrine** and **oxytocin** differ in their actions on the uterus. In moderate doses oxytocin produces slow generalized contractions with full relaxation in between; ergometrine produces faster contractions superimposed on a tonic contraction. High doses of both substances produce sustained tonic contractions. Oxytocin is now recommended for routine use in postpartum and post-abortion haemorrhage since it is more stable than ergometrine. However, ergometrine may be used if oxytocin is not available or in emergency situations.

PREMATURE LABOUR. **Salbutamol** is a beta2-adrenoceptor agonist which relaxes the uterus and can be used to prevent premature labour in uncomplicated cases between 24 and 33 weeks of gestation. Its main purpose is to permit a delay in delivery of at least 48 hours. The greatest benefit is obtained by using this delay to administer corticosteroid therapy or to implement other measures known to improve perinatal health. Prolonged therapy should be avoided since the risks to the mother increase after 48 hours and the response of the myometrium is reduced.

ECLAMPSIA. **Magnesium sulfate** has been shown to have a major role in eclampsia for the prevention of recurrent seizures. Monitoring of blood pressure, respiratory rate and urinary output is carried out, as is monitoring for clinical signs of overdosage (loss of patellar reflexes, weakness, nausea, sensation of warmth, flushing, double vision and slurred speech—calcium gluconate injection (section 27.2) is used for the management of magnesium toxicity).

Ergometrine maleate

Ergometrine is a representative oxytocic drug. Various drugs can serve as alternatives.

Tablets, ergometrine maleate 0.125 mg.

Injection (Solution for injection), ergometrine maleate 200 mcg (0.2 mg)/ml, 1-ml ampoule

NOTE. Injection requires transport by 'cold chain' and refrigerated storage.

Uses: prevention and treatment of postpartum and post-abortion haemorrhage in emergency situations and where oxytocin not available.

Contraindications: induction of labour, first and second stages of labour; vascular disease, severe cardiac disease especially angina pectoris; severe hypertension; impaired respiratory

function; severe renal and hepatic impairment; sepsis; eclampsia.

Precautions: cardiac disease, hypertension, hepatic impairment and renal failure , multiple pregnancy, porphyria.

Dosage:

Prevention and treatment of postpartum haemorrhage, when oxytocin is not available, *by intramuscular injection,* ADULT 200 mcg.

Prevention of postpartum haemorrhage in high risk cases, *by intravenous injection,* ADULT 250–500 mcg Secondary postpartum haemorrhage, *by mouth*, ADULT 400 mcg 3 times daily for 3 days.

Adverse effects: nausea, vomiting, headache, dizziness, tinnitus, abdominal pain, chest pain, palpitations, dyspnoea, bradycardia, transient hypertension, vasoconstriction; stroke, myocardial infarction and pulmonary oedema also reported.

Magnesium sulfate

Injection (Solution for injection), magnesium sulfate 500 mg/ml, 2-ml ampoule, 10-ml ampoule.

Uses: prevention of recurrent seizures in eclampsia.

Precautions: hepatic impairment ; renal failure; in severe hypomagnesaemia administer initially via a controlled infusion device;

Interactions: Appendix 1.

Dosage:

Prevention of recurrent seizures in eclampsia, *by intravenous injection,* ADULT initially 4 g over 5–10 minutes followed *by intravenous infusion* at a rate of 1 g every hour for at least 24 hours after the last seizure; recurrence of seizures may require additional *intravenous bolus* of 2 g

DILUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: generally associated with hypermagnesaemia, nausea, vomiting, thirst, flushing of skin, hypotension, arrhythmias, coma, respiratory depression, drowsiness, confusion, loss of tendon reflexes, muscle weakness; see also Appendix 2.

Oxytocin

Injection (Solution for injection), oxytocin 2, iu/ml, 5 iu/ ml, 10 units/ml, 1-ml ampoule.

Uses: routine prevention and treatment of postpartum and postabortion haemorrhage; induction of labour.

Contraindications: hypertonic uterine contractions, mechanical obstruction to delivery, fetal distress; any condition where spontaneous labour or vaginal delivery inadvisable; avoid prolonged administration in oxytocin-

resistant uterine inertia, in severe pre-eclamptic toxaemia or in severe cardiovascular disease.

Precautions: induction or enhancement of labour in presence of borderline cephalopelvic disproportion (avoid if significant); mild to moderate pregnancy-associated hypertension or cardiac disease; age over 35 years; history of low-uterine segment caesarean section; avoid tumultuous labour if fetal death or meconium-stained amniotic fluid (risk of amniotic fluid embolism);water intoxication and hyponatraemia (avoid large volume infusions and restrict fluid intake); caudal block anaesthesia (risk of severe hypertension due to enhanced vasopressor effect of sympathomimetics).

Interactions: Appendix1.

Dosage:

Induction of labour, *by intravenous infusion,* ADULT, initially 0.0005–0.001 unit/minute increased in 0.001–0.002 unit/minute increments at intervals of 30–60 minutes until labour pattern similar to normal established; no more than 5 units should be administered in 24 hours

Prevention of postpartum haemorrhage, *by slow intravenous injection*, ADULT 5–10 units after placenta is delivered

Postpartum haemorrhage; *by intravenous infusion*, ADULT a total of 40 units should be infused at a rate of 0.02–0.04 units/minute; this should be started after the placenta is delivered.

DILUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: uterine spasm, uterine hyperstimulation; water intoxication and hyponatraemia associated with high doses and large-volume infusions; nausea, vomiting, arrhythmias, rashes and anaphylactoid reactions also reported.

Salbutamol

Salbutamol is a representative myometrial relaxant. Various drugs can serve as alternatives

Tablets, salbutamol (as sulfate) 4 mg.

Injection (Solution for injection), salbutamol (as sulfate) 50 mcg/ml, 5-ml ampoule.

Uses: uncomplicated premature labour between 24–33 weeks gestation; asthma (section 25.1)

Contraindications: first and second trimester of pregnancy; cardiac disease, eclampsia and pre-eclampsia, intra-uterine infection, intra-uterine fetal death, antepartum haemorrhage, placenta praevia, cord compression, ruptured membranes.

Precautions: monitor pulse and blood pressure and avoid overhydration; suspected cardiac disease, hypertension, hyperthyroidism, hypokalaemia, diabetes mellitus; if pulmonary oedema suspected, discontinue immediately and institute diuretic therapy;

Interactions: Appendix 1

Dosage:

Premature labour, 4 mg every 6–8 hours (use for more than 48 hours not recommended)

Adverse effects: nausea, vomiting, flushing, sweating, tremor; hypokalaemia, tachycardia, palpitations, and hypotension, increased tendency to uterine bleeding; pulmonary oedema; chest pain or tightness and arrhythmias; hypersensitivity reactions including bronchospasm, urticaria and angioedema reported.

Isoxsuprine

Isoxsuprine is a selective b stimulant and has direct smooth muscle relaxant property. Losing favour with obstetricians in many parts of the world, it is more used for its vasodilatory role.

Tablet, 10 mg, 20 mg, 40 mg (retard) of Isoxsuprine hydrochloride *Injection,* 5mg/ml.

Uses: threatened abortion, premature labour, cerebral and peripheral vascular insufficiency, and Raynaud's syndrome.

Contraindications: Postpartum; recent arterial haemorrhage; acute coronary thrombosis.

Precautions: severe angina pectoris, hyperthyroidism, recent myocardial lesion, paroxysmal tachycardia. Use with caution in pregnant and breastfeeding mothers.

Dosage:

Adults: Initially 10 to 20 mg 3-4 times daily after meals; reduce gradually following improvement.

Adverse Reaction: nausea, vomiting, dizziness, sinus tachycardia, hypotension, skin, rash, angina.

Section 23: Peritoneal dialysis solution

Reserved for use in higher centers where this procedure is undertaken:

Section 24: Psychotherapeutic drugs

24.1 Drugs used in psychotic disorders

Treatment of psychotic disorders is both pharmacological and psychosocial. Individual and community programmes for relearning old skills and developing new ones and for learning to cope with the illness should be initiated. Classes of antipsychotic drugs include phenothiazines (for example chlorpromazine), butyrophenones (for example haloperidol), thioxanthenes (for example flupentixol) and newer 'atypical' neuroleptics including clozapine and risperidone. The various antipsychotic drugs do not, in general, differ in their antipsychotic activity, but differ in range and quality of adverse effects (see below).

ACUTE PHASE TREATMENT.

The administration of **chlorpromazine** or **haloperidol** will relieve symptoms such as thought disorder, hallucinations and delusions and prevent relapse. They are usually less effective in apathetic, withdrawn patients. However, haloperidol may restore an acutely ill schizophrenic, who was previously withdrawn, or even mute and akinetic, to normal activity and social behaviour. In the acute phase chlorpromazine may be administered by intramuscular injection in a dose of 25–50 mg which can be repeated every 6–8 hours while observing the patient for possible hypotension. In most cases, however, the intramuscular injection is not needed and patients can be treated with an oral dose. Haloperidol may be administered in the acute phase.

MAINTENANCE THERAPY. Long-term treatment in patients with a definite diagnosis of schizophrenia may be necessary after the first episode to prevent the manifest illness from becoming chronic.

The lowest possible dose of antipsychotic drug that will prevent major exacerbations of florid symptoms is used for long-term management. Too rapid a dose reduction should be avoided. Intramuscular depot preparations such as **fluphenazine decanoate** may be used as an alternative to oral maintenance therapy especially when compliance with oral treatment is unreliable. Exacerbations of illness in patients on maintenance drug therapy can be precipitated by stress.

Withdrawal of maintenance drug treatment requires careful surveillance since it is not possible to predict the course of the disease and the patient may suffer a relapse if treatment is withdrawn inappropriately. Further, the need for continuation of treatment may not be evident on withdrawal of treatment because relapse may be delayed for several weeks.

ADVERSE EFFECTS. They are very common with long-term administration of antipsychotic medicines. Hypotension and

interference with temperature regulation, neuroleptic malignant syndrome and bone-marrow depression are the most lifethreatening. Hypotension and interference with temperature regulation are dose-related. They can result in dangerous falls and hypothermia in the elderly and this must be considered before prescribing these drugs for patients over 70 years of age.

Neuroleptic malignant syndrome (hypothermia, fluctuating levels of consciousness, muscular rigidity and autonomic dysfunction with pallor, tachycardia, labile blood pressure, sweating and urinary incontinence) is a rare adverse effect of drugs including haloperidol, chlorpromazine and flupentixol decanoate. It is managed by discontinuation of the antipsychotic medication, attention to fluid and electrolyte balance, and administration of bromocriptine and sometimes dantrolene.

Extrapyramidal symptoms are the most troublesome and are caused most frequently by the piperazine phenothiazines such as fluphenazine, the butyrophenones such as haloperidol and the depot preparations. Although easily recognized, they are not so easy to predict because they depend in part on the dose and patient susceptibility as well as the type of drug. However, there is a general tendency for low-potency drugs to have less extrapyramidal adverse effects, while high-potency drugs such as haloperidol have more extrapyramidal effects but less sedation and anticholinergic (more correctly antimuscarinic) effects. Sedation and anticholinergic effects usually diminish with continued use. Extrapyramidal symptoms consist of parkinsonian-type symptoms including tremor which may occur gradually, dystonia (abnormal face and body movements) which may appear after only a few doses, akathisia (restlessness) and tardive dyskinesia (an orofacial dyskinesia) which usually takes longer to develop. Parkinsonian symptoms are usually reversible on withdrawal of the drug and may be suppressed by anticholinergic (antimuscarinic) drugs but tardive dyskinesia may be irreversible. Tardive dyskinesia is usually associated with long-term treatment and high dosage of neuroleptics, particularly in elderly patients. There is no established treatment for tardive dyskinesias and treatment of all patients on neuroleptic medication must be carefully and regularly reviewed.

Chlorpromazine hydrochloride

Chlorpromazine is a representative antipsychotic. Various drugs can serve as alternatives WARNING. Owing to the risk of contact sensitization, pharmacists, nurses, and other health workers should avoid direct contact with chlorpromazine; tablets should not be crushed and solutions should be handled with care.

Tablets, chlorpromazine hydrochloride 10 mg, 25 mg, 50 mg, 100 mg, 200 mg,

Injection (Solution for injection), chlorpromazine hydrochloride 25 mg/ml, 2- ml ampoule.

Uses: schizophrenia and other psychotic disorders, mania, psychomotor agitation and violent behaviour; adjunct in severe anxiety.

Contraindications: impaired consciousness due to CNS depression; bone-marrow depression; phaeochromocytoma.

Precautions: cardiovascular and cerebrovascular disorders, respiratory disease, parkinsonism, epilepsy, acute infections, pregnancy (Appendix 2), breastfeeding (Appendix 3), renal and hepatic impairment (avoid if severe;), history of jaundice, leukopenia (blood counts if unexplained fever or infection); hypothyroidism, myasthenia gravis, prostatic hypertrophy, angle-closure glaucoma; elderly (particularly in very hot or very cold weather); avoid abrupt withdrawal; patients should remain supine and the blood pressure monitored for 30 minutes after intramuscular injection;

Interactions: Appendix 1

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving.

Dosage:

Schizophrenia and other psychoses, mania, psychomotor agitation, violent behaviour, and severe anxiety (adjunct), *by mouth*, ADULT initially 25 mg 3 times daily (*or* 75 mg at night) adjusted according to response to usual maintenance dose of 100–300 mg daily (but up to 1.2 g daily may be required in psychoses); ELDERLY (or debilitated) third to half adult dose; CHILD (childhood schizophrenia and autism) 1–5 years 500 mcg/kg every 4–6 hours (maximum 40 mg daily); 6–12 years, third to half adult dose (maximum 75 mg daily).

For relief of acute symptoms, *by deep intramuscular injection*, ADULT 25–50 mg every 6–8 hours; CHILD 500 mcg/kg every 6–8 hours (1–5 years, maximum 40 mg daily; 6–12 years, maximum 75 mg daily) (see also Precautions and Adverse effects).

Adverse effects: extrapyramidal symptoms and on prolonged administration, occasionally potentially irreversible tardive dyskinesias (see notes above); hypothermia (occasionally pyrexia), drowsiness, apathy, pallor, nightmares, depression; more rarely, agitation, EEG changes, convulsions, nasal congestion; anticholinergic symptoms including dry mouth, constipation, blurred vision, difficulty in micturition; hypotension, tachycardia and arrhythmias; ECG changes; respiratory depression; menstrual disturbances, galactorrhoea, gynaecomastia, impotence, weight gain; sensitivity reactions such as agranulocytosis, leukopenia,

leukocytosis, haemolytic anaemia, photosensitization, contact sensitization and rashes, jaundice and alterations in liver function; neuroleptic malignant syndrome; lupus erythematosus-like syndrome; with prolonged high dosage, corneal and lens opacities, and purplish pigmentation of the skin, cornea and retina; intramuscular injection may be painful and cause hypotension and tachycardia (see Precautions) and nodule formation.

Haloperidol

Haloperidol is a representative antipsychotic. Various drugs can serve as alternatives.

Tablets, haloperidol 0.25 mg, 1.5 mg, 5 mg, 10 mg, 20 mg *Liquid,* 2 mg/ml *Drop* 2mg/ml, 10 mg/ml

Injection (Solution for injection), haloperidol 5 mg/ml, 1-ml ampoule.

Uses: schizophrenia and other psychotic disorders, mania, psychomotor agitation and violent behaviour; adjunct in severe anxiety

Contraindications: impaired consciousness due to CNS depression; bone-marrow depression; phaeochromocytoma; porphyria; basal ganglia disease.

Precautions: cardiovascular and cerebrovascular disorders, respiratory disease, parkinsonism, epilepsy, acute infections, pregnancy (Appendix 2), breastfeeding (Appendix 3), renal and hepatic impairment (avoid if severe;), history of jaundice, leukopenia (blood counts if unexplained fever or infection); hypothyroidism, myasthenia gravis, prostatic hypertrophy, angle-closure glaucoma; elderly (particularly in very hot or very cold weather); children and adolescents; avoid abrupt withdrawal; patients should remain supine and the blood pressure monitored for 30 minutes after intramuscular injection;

Interactions: Appendix 1

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving.

Dosage:

Schizophrenia and other psychoses, mania, psychomotor agitation, violent behaviour, and severe anxiety (adjunct), *by mouth*, ADULT initially 1.5–3 mg 2–3 times daily *or* 3–5 mg 2– 3 times daily in severely affected or resistant patients (up to30 mg daily in resistant schizophrenia); ELDERLY (or debilitated) initially half adult dose; CHILD initially 25–50 mcg/kg daily in 2 divided doses (maximum 10 mg daily).

Acute psychotic conditions, *by deep intramuscular injection*, ADULT 2–10 mg, subsequent doses every 4–8 hours according to response (up to every hour if necessary) to total maximum of 18 mg; severely disturbed patients may require initial dose of up to 18 mg; CHILD not recommended.

Adverse effects: as for Chlorpromazine Hydrochloride (see above), but less sedating and fewer hypotensive and anticholinergic symptoms; pigmentation and photosensitivity reactions rare; extrapyramidal symptoms are common, particularly acute dystonia and akathisia (especially in thyrotoxic patients); rarely weight loss.

Fluphenazine

Fluphenazine is a representative depot antipsychotic, used if compliance unlikely to be reliable. Various drugs can serve as alternatives.

Oily injection (Solution for injection), fluphenazine decanoate 25 mg/ml, 1- ml ampoule.

Tablet, 1 mg.

Uses: maintenance treatment of schizophrenia and other psychoses.

Contraindications: children; confusional states; impaired consciousness due to CNS depression; parkinsonism; intolerance to antipsychotics; depression;bone-marrow depression; phaeochromocytoma.

Precautions: treatment requires careful monitoring for optimum effect; extrapyramidal symptoms occur frequently; when transferring from oral to depot therapy, dosage by mouth should be gradually phased out; cardiovascular and cerebrovascular disorders, respiratory disease, epilepsy, acute infections, pregnancy (Appendix 2), breastfeeding (Appendix 3), renal and hepatic impairment (avoid if severe;), history of jaundice, leukopenia (blood counts if unexplained fever or infection); hypothyroidism, myasthenia gravis, prostatic hypertrophy, angle-closure glaucoma; elderly (particularly in very hot or very cold weather);

Interactions: Appendix 1

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving.

Dosage:

Maintenance in schizophrenia and other psychoses, *by deep intramuscular injection* into gluteal muscle, ADULT test dose of 12.5 mg (6.25 mg in elderly), then after 4–7 days 12.5–100 mg repeated at intervals of 2–5 weeks, adjusted according to response; CHILD not recommended

ADMINISTRATION. According to manufacturer's directions.

Adverse effects: as for Chlorpromazine Hydrochloride (see above), but less sedating and fewer hypotensive and anticholinergic symptoms; higher incidence of extrapyramidal symptoms (most likely to occur a few hours after injection and continue for about 2 days but may be delayed); pain at injection site, occasionally erythema, swelling, nodules.

24.2 Drugs used in mood disorders

Mood disorders can be classified as depression (unipolar disorder) and mania; alternating episodes of mania and depression (manic depression) are termed bipolar disorder. Electroconvulsive therapy (ECT) has been shown to be rapidly effective in the urgent treatment of severe depression. Counselling and psychotherapy have an important role in treating some forms of depression.

24.2.1 Drugs used in depressive disorders

Tricyclic and related antidepressants and the more recently introduced selective serotonin reuptake inhibitors (SSRIs) are the most widely used drugs in the treatment of depressive disorders. The response to antidepressant therapy is usually delayed with a lag-period of up to two weeks and at least six weeks before maximum improvement occurs. It is important to use doses that are sufficiently high for effective treatment, but not so high as to cause toxic effects. Low doses should be used for initial treatment in the elderly. The use of more than one antidepressant at a time is not recommended since this does not enhance effectiveness and it may result in enhanced adverse effects or interactions. The response of the patient should be monitored carefully especially during the first few weeks after diagnosis to detect any suicidal tendencies. Minimal quantities of antidepressants should be prescribed at any one time since they may be dangerous in overdosage. The natural history of depressive illness suggests that remission usually occurs after three months to one year. Treatment at full therapeutic dose should be continued for at least 6 months after resolution of symptoms. Treatment should not be withdrawn prematurely otherwise symptoms are likely to recur. Reduction in dose should be gradually carried out over a period of about four weeks.

Tricyclic and related antidepressants can be divided into those with more or less sedative effect. Those with sedative properties include **imipramine**. These drugs are most effective in the treatment of depression associated with psychomotor and physiological disturbances. Adverse effects include anticholinergic (more correctly amtimuscarinic) symptoms of dry mouth, blurred vision, constipation and urinary retention. Arrhythmias and heart block can occur.

The SSRIs characteristically cause gastrointestinal disturbances and sleep disturbances but they are less sedating and have fewer anticholinergic (antimuscarinic) and cardiotoxic effects than tricyclic antidepressants. The SSRIs are less toxic in overdose than the older tricyclic compounds. They may be preferred in patients in whom the risk of suicide is strong, although there is some concern that SSRIs, especially fluoxetine, may increase suicidal ideation.

Imipramine

A tricyclic antidepressant drug with many more in its dibenzapine family that are in use.

Tablets, 25 mg, 50 mg, 75 mg.

Capsules 75 mg

Uses: depressive psychosis, nocturnal enuresis, narcolepsy, attention- deficit hyperactivity disorder.

Contraindications: heart block, narrow angle glaucome; severe liver disease, acute recovery period after myocardial infarction; patients with reduced gastrointestinal motility; along with MAO inhibitors or within 14 days of discontinuation; pregnancy; breastfeeding; children below 6 years.

Precautions: do not abruptly stop after high doses for fear of rebound cholinergic activity like vomiting, diarrhoea; decreased mental alertness or depression if alcohol is taken in such patients; may swing the disease to other pole in bipolar disorder; may reduce seizure threshold hence care must be taken in epilepsy patients; may worsen Parkinson's disease symptoms; should be discontinued several day before major surgery for fear of causing hypertension; may get sunburnt on treatment faster than normal, repeated liver function tests are advisable; care to be taekn if giving to children under 12 years and above 65 years.

Dosage:

For major depression *Adults over 18 and less than 65 years:* 25 mg orally thrice daily to start with and then increase every week by 25 to 50 mg per day until 200 mg per day depending on response and adverse effects.

Adults over 65: start with 25 mg at bed time and increase to 10 mg thrice daily and 20 mg orally at bed time.

Children above 12 years: start with 10 mg thrice daily and 20 mg at bed time and increase upto 100 mg per day.

Children 6-12 years: oral 10 to 30 mg or 1-5 mg/kg body weight in three divided doses.

For functional enuresis *Children age 6 to 12 years:* 10 to 30 mg per day or 1 to 5 mg / kg body wt. Given one hour before bedtime or in divided doses, one given mid-afternoon and the other given at bedtime.

Other disorders *Adults:* start with 25 mg orally thrice a day to a maximum of 200 mg depending on response and adverse effects.

Children age 6 to 12 years: 10 to 30 mg per day or 1 to 5 mg / kg body wt.

Adverse Reaction : dry mouth, constipation, urinary retention, blurred vision, vision disturbances; tachycardia, drowsiness, insomnia, nervousnesss, tremors, orthostatic hyppotension, dizziness, weakness, seizures, extrapyramidal symptoms; weight loss or gain; allergic skin reactions, jaundice and liver

disorders, conduction defects, arrhythmias, impotence, decreased libido, schizophrenic symptoms, mania, gynaecomastia.

24.2.2 Drugs used in bipolar disorders

Treatment of bipolar disorders has to take account of three stages: treatment of the acute episode, continuation phase and prophylaxis to prevent further episodes. **Lithium** is effective in acute mania but symptomatic control of the florid symptoms with an antipsychotic or benzodiazepine is often necessary whilst waiting for the antimania drug to exert its effect. Benzodiazepines may be given during the initial stages until lithium becomes effective but they should not be used for long periods because of the risk of dependence. Lithium may be given concurrently with antipsychotics and treatment with the antipsychotic should be tailed off as lithium becomes effective. Alternatively, lithium therapy may be delayed until the patient's mood is stabilized with the antipsychotic. However, there is a risk of interactions including neurotoxicity and increased extrapyramidal disorders when lithium and antipsychotics are used concurrently. Lithium is the mainstay of treatment but its narrow therapeutic range is a disadvantage. **Valproic acid** is effective and **carbamazepine** may also be used and it is a valuable drug in areas where there are few effective treatments.

Treatment of depressive episodes in bipolar disorders will mostly involve combination treatment using either lithium or valproic acid together with a tricyclic antidepressant. Increased adverse effects are a problem which may compromise treatment.

Lithium prophylaxis should usually only be undertaken with specialist advice and consideration of the likelihood of recurrence in the individual patient and with the benefits carefully weighed against the risks. Long-term lithium therapy has been associated with thyroid disorders and mild cognitive and memory impairment. Patients should continue the treatment for longer than three to five years only if, on assessment, benefit persists.

Withdrawal appears to produce high levels of relapse. If lithium is to be discontinued, the dose should be reduced gradually over a period of a few weeks and patients should be warned of possible relapses if discontinued abruptly.

Lithium salts have a narrow therapeutic/toxic ratio and should only be prescribed if there are facilities for monitoring serum lithium concentrations. Doses are adjusted to achieve serumlithium concentrations of 0.4–1 mmol/litre (lower end of range for maintenance therapy and the elderly) on samples

taken 12 hours after the preceding dose. The optimum range for each patient should be determined.

Overdosage with lithium carbonate (plasma concentrations of over 1.5 mmol lithium/litre) may be fatal. Toxic effects include coarse tremor, ataxia, dysarthria, nystagmus, renal impairment and convulsions. If any of these toxic effects occur, treatment should be stopped, plasma lithium levels determined and in mild overdosage large amounts of sodium and fluid should be given to reverse the toxicity; in severe toxicity, haemodialysis may be required.

For patients who are unresponsive to or intolerant of lithium, carbamazepine may be used in the prophylaxis of bipolar illness in patients with rapid cycling affective disorders (more than four affective episodes per year).

Lithium carbonate

Tablets, *capsules,* lithium carbonate 300 mg .

Uses: treatment and prophylaxis of mania, prophylaxis of bipolar disorder and recurrent depression.

Contraindications: renal impairment ; cardiac insufficiency; conditions with sodium imbalance such as Addison disease.

Precautions: measure serum-lithium concentration about 4 days after starting treatment, then weekly until stabilized, then at least every 3 months; monitor thyroid function and renal function; maintain adequate fluid and sodium intake; reduction of dose or discontinuation may be necessary in diarrhoea, vomiting and intercurrent infection (especially if associated with profuse sweating); pregnancy (Appendix 2); breastfeeding (Appendix 3); elderly (reduce dose); diuretic treatment, myasthenia gravis; surgery; if possible, avoid abrupt withdrawal (see notes above);

Interactions: Appendix 1

PATIENT ADVICE. Patients should maintain adequate fluid intake and should avoid dietary changes which may reduce or increase sodium intake

NOTE. Different preparations vary widely in bioavailability; a change in the preparation used requires the same precautions as initiation of treatment.

Dosage:

Treatment of mania (general guidelines only, see also note below) *by mouth*, ADULT initially 0.6–1.8 g daily (elderly 300– 900 mg daily)

Prophylaxis of mania, bipolar disorder and recurrent depression (general guidelines only, see also note below), *by mouth*, ADULT initially 0.6–1.2 g daily (elderly 300–900 mg daily)

NOTE. Dosage of lithium depends on the preparation chosen since different preparations vary widely in bioavailability. Dosage should be adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre (lower end of range for maintenance therapy and in elderly) on samples taken 12 hours after a dose and 4–7 days after starting treatment

For dose information for a specific preparation, consult manufacturer's literature.

Adverse effects: gastrointestinal disturbances, fine tremor, polyuria, polydipsia, weight gain and oedema (may respond to dose reduction); signs of intoxication include blurred vision, muscle weakness, increasing gastrointestinal disturbances (anorexia, vomiting, diarrhoea), increased CNS disturbances (mild drowsiness and sluggishness, increasing to giddiness with ataxia, coarse tremor, lack of co-ordination, dysarthria) and require withdrawal of treatment; with severe overdosage (serum concentrations above 2 mmol/litre), hyperreflexia and hyperextension of the limbs, convulsions, toxic psychoses,syncope, oliguria, circulatory failure, coma, occasionally death; goitre, raised antidiuretic hormone concentration, hypothyroidism, hypokalaemia, ECG changes, exacerbation of psoriasis and kidney changes may occur.

Carbamazepine

Tablets, carbamazepine 100 mg, 200 mg, 400 mg. *Tablet,* sustained release, 200 mg, 400 mg .

Uses: prophylaxis of bipolar disorder unresponsive to or intolerant of lithium; epilepsy, trigeminal neuralgia (section 5.1).

Contraindications: atrioventricular conduction abnormalities; history of bone-marrow depression; porphyria.

Precautions: hepatic impairment ; renal impairment ; cardiac disease (see also Contraindications); skin reactions (see Adverse effects); history of blood disorders (blood counts before and during treatment); glaucoma; pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid sudden withdrawal;

Interactions: Appendix 1

BLOOD, HEPATIC OR SKIN DISORDERS. Patients or their carers should be told how to recognize signs of blood, liver or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising or bleeding develop. Leukopenia which is severe, progressive and associated with clinical symptoms requires withdrawal (if necessary under cover of suitable alternative)

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving.

Dosage:

Prophylaxis of bipolar disorder, *by mouth*, ADULT initially 400 mg daily in divided doses increased until symptoms are controlled to a maximum of 1.6 g daily; usual maintenance range 400–600 mg daily.

Adverse effects: dizziness, drowsiness, headache, ataxia, blurred vision, diplopia (may be associated with high plasma concentrations); gastrointestinal intolerance including

nausea and vomiting, anorexia, abdominal pain, dry mouth, diarrhoea or constipation; commonly, mild transient generalized erythematous rash (withdraw if worsens or is accompanied by other symptoms); leukopenia and other blood disorders (including thrombocytopenia, agranulocytosis and aplastic anaemia); cholestatic jaundice, hepatitis, acute renal failure, Stevens-Johnson syndrome (erythema multiforme), toxic epidermal necrolysis, alopecia, thromboembolism, arthralgia, fever, proteinuria, lymph node enlargement, arrhythmias, heart block and heart failure, dyskinesias, paraesthesia, depression, impotence, male infertility, gynaecomastia, galactorrhoea, aggression, activation of psychosis, photosensitivity, pulmonary hypersensitivity, hyponatraemia, oedema, disturbances of bone metabolism with osteomalacia also reported; confusion and agitation in elderly.

Valproic acid

Enteric-coated tablets (Gastro-resistant tablets), valproic acid 200 mg, 500 mg.

Uses: acute mania; epilepsy (section 5.1)

Contraindications: active liver disease, family history of severe hepatic dysfunction; pancreatitis; porphyria

Precautions: monitor liver function before and during therapy, especially in patients at most risk (those with metabolic disorders, degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation); ensure no undue potential for bleeding before starting and before major surgery or anticoagulant therapy; renal impairment ; pregnancy (Appendix 2 (neural tube screening)); breastfeeding (Appendix 3); systemic lupus erythematosus; false-positive urine tests for ketones; avoid sudden withdrawal;

Interactions: Appendix 1

BLOOD OR HEPATIC DISORDERS. Patients or their carers should be told how to recognize signs of blood or liver disorders, and advised to seek immediate medical attention if symptoms including malaise, weakness, anorexia, lethargy, oedema, vomiting, abdominal pain, drowsiness, jaundice, or spontaneous bruising or bleeding develop.

Dosage:

Acute mania, *by mouth*, ADULT initially 750 mg daily in divided doses, increased as quickly as possible to achieve the optimal response (maximum 60 mg/kg daily).

Adverse effects: gastrointestinal irritation, nausea, increased appetite and weight gain, hyperammonaemia; ataxia, tremor; transient hair loss (regrowth may be curly); oedema, thrombocytopenia, inhibition of platelet aggregation; impaired hepatic function and rarely fatal hepatic failure (see Precautions — withdraw treatment immediately if

malaise, weakness, lethargy, oedema, abdominal pain, vomiting, anorexia, jaundice, drowsiness); sedation reported and alsoincreased alertness; behavioural disturbances; rarely pancreatitis(measure plasma amylase if acute abdominal pain), leukopenia, pancytopenia, red cell hypoplasia, fibrinogen reduction; irregular periods, amenorrhoea, gynaecomastia, hearing loss, Fanconi syndrome, dementia, toxic epidermal necrolysis Stevens-Johnson syndrome (erythema multiforme) and vasculitis reported.

24.3 Drugs used in anxiety and sleep disorders

The most widely used anxiolytics and hypnotics are the benzodiazepines. Treatment of anxiety should be limited to the lowest effective dose for the shortest possible time. The cause of insomnia should be established and appropriate treatment for underlying factors instituted before hypnotics are considered. Hypnotics may be of value for a few days but rarely longer than a week.

Tolerance and dependence (both physical and psychological) and subsequent difficulty in withdrawing the drug may occur after regular use for more than a few weeks. Patients with chronic anxiety, alcohol or drug dependence or those with personality disorders are more likely to become dependent. Anxiolytics and hypnotics should be prescribed in carefully individualized dosage and use should be limited to control of acute conditions such as panic attacks and acute anxiety and severe, incapacitating insomnia. There is usually no justification for prolonging treatment with anxiolytics and hypnotics for more than one to two weeks.

If used for longer periods, withdrawal should be gradual by reduction of the dose over a period of weeks or months, as abrupt discontinuation may produce confusion, toxic psychosis, convulsions or a condition resembling delirium tremens. The benzodiazepine withdrawal syndrome may not develop until up to three weeks after stopping a long-acting benzodiazepine but may occur within a few hours in the case of a short-acting one. The syndrome is characterized by insomnia, anxiety, loss of appetite and body-weight, tremor, perspiration, tinnitus and perceptual disturbances. These symptoms may be similar to the original complaint and encourage further prescribing.

Patients should be warned that their ability to drive or operate machinery may be impaired and that the effects of alcohol may be enhanced.

Diazepam

Diazepam is a representative benzodiazepine anxiolytic and hypnotic.Various drugs can serve as alternatives.

Tablets, diazepam 2 mg, 5 mg, 10 mg.
Injection, 5 mg/ml, 2 ml ampoule *Suspension*, 2 mg/5 ml.

Uses: short-term treatment of anxiety and insomnia; status epilepticus, recurrent seizures; febrile convulsions, adjunct in acute alcohol withdrawal (section 5.1); premedication (section 1.3).

Contraindications: respiratory depression; acute pulmonary insufficiency; sleep apnoea; severe hepatic impairment; myasthenia gravis

Precautions: respiratory disease, muscle weakness, history of alcohol or drug abuse, marked personality disorder; pregnancy (Appendix 2); breastfeeding (Appendix 3); reduce dose in elderly or debilitated and in hepatic impairment (avoid if severe,), renal impairment; avoid prolonged use and abrupt withdrawal; porphyria;

Interactions: Appendix 1

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving.

Dosage:

Anxiety, *by mouth*, ADULT 2 mg 3 times daily increased if necessary to 15–30 mg daily in divided doses; ELDERLY (or debilitated) half adult dose Insomnia, *by mouth*, ADULT 5–15 mg at bedtime.

Adverse effects: drowsiness and lightheadedness the next day; confusion and ataxia (especially in the elderly); amnesia; dependence; paradoxical increase in aggression; muscle weakness; occasionally headache, vertigo, salivation changes, gastrointestinal disturbances, visual disturbances, dysarthria, tremor, changes in libido, incontinence, urinary retention; blood disorders and jaundice; skin reactions; raised liver enzymes.

24.4 Obsessive-compulsive disorders and panic attacks

Obsessive-compulsive disorders can be treated with a combination of pharmacological, behavioural and psychological treatments. Antidepressants such as **imipramine** which inhibit reuptake of serotonin have been found to be effective. Panic attacks may be treated with behavioural or cognitive therapy. If this management fails, drug therapy may be tried. Some tricyclic antidepressants including clomipramine, or SSRIs can reduce frequency of attacks or prevent them completely. Benzodiazepines may be used in panic attacks resistant to antidepressants.

Imipramine hydrochloride

Capsules, imipramine hydrochloride 25 mg, 50 mg, 75 mg.

Uses: phobic and obsessional states; panic attacks.

Contraindications: recent myocardial infarction, arrhythmias (especially heart block); manic phase in bipolar disorders; severe liver disease; children; porphyria.

Precautions: cardiac disease (see Contraindications above), history of epilepsy; pregnancy (Appendix 2); breastfeeding (Appendix 3); elderly; hepatic impairment ; thyroid disease; phaeochromocytoma; history of mania, psychoses (may aggravate psychotic symptoms); angleclosure glaucoma, history of urinary retention; concurrent electroconvulsive therapy; avoid abrupt withdrawal; anaesthesia (increased risk of arrhythmias and hypotension);

Interactions: Appendix 1

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving.

Dosage:

Phobic and obsessional states, *by mouth*, ADULT initially 25 mg daily, usually at bedtime (ELDERLY 10 mg daily) increased over 2 weeks to 100–150 mg daily; CHILD not recommended.

Adverse effects: sedation, dry mouth, blurred vision (disturbance of accommodation, increased intra-ocular pressure), constipation, nausea, difficulty in micturition; cardiovascular adverse effects particularly with high dosage including ECG changes, arrhythmias, postural hypotension, tachycardia, syncope; sweating, tremor, rash and hypersensitivity reactions (urticaria, photosensitivity); behavioural disturbances; hypomania or mania, confusion (particularly in elderly), interference with sexual function, blood sugar changes; increased appetite and weight gain (occasional weight loss); endocrine adverse effects such as testicular enlargement, gynaecomastia and galactorrhoea; convulsions, movement disorders and dyskinesias, fever, agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia, hyponatraemia (may be due to inappropriate antidiuretic hormone secretion); abnormal liver function test

Section 25: Drugs acting on the respiratory tract

25.1 Antiasthmatic drugs Asthma

Asthma is a chronic inflammatory disease characterized by episodes of reversible airways obstruction due to bronchial hyperresponsiveness; inflammation may lead to irreversible obstruction in a few patients. A classification based on severity before the start of treatment and disease progression is of importance when decisions have to be made about management. It can be divided by severity into intermittent, mild persistent, moderate persistent and severe persistent. These are useful in the management of the disease since therapy has a stepwise approach which must be discussed with the patient before commencing therapy. The level of therapy is increased as the severity of the asthma increases with stepping-down if control is sustained (see tables on treatment below).

INHALATION. Medications for asthma can be administered in several different ways, including inhaled, oral and parenteral (subcutaneous, intramuscular, or intravenous). The main advantage of delivering drugs directly into the airways via inhalation is that high concentrations can be delivered more effectively and rapidly to the airways, and systemic adverse effects avoided or minimized.

It is important that patients receive careful instruction in the use of pressurized (aerosol) inhalation (using a metered-dose inhaler) to obtain optimum results. Before use, the inhaler should be shaken well. After exhaling as completely as possible, the mouthpiece of the inhaler should be placed well into the mouth and the lips firmly closed around it. The patient should inhale deeply through the mouth while actuating the inhaler. After holding the breath for 10 seconds or as long as is comfortable, the mouthpiece should be removed and the patient should exhale slowly.

It is important to check that patients continue to use their inhalers correctly as inadequate technique may be mistaken for drug failure. Spacing devices provide a space between the inhaler and the mouth. They may be of benefit for patients such as the elderly, small children and the asthmatic who find inhalers difficult to use or for those who have difficulty synchronizing their breathing with administration of the aerosol. A large volume spacing device is also recommended for inhalation of high doses of corticosteroids to reduce oropharyngeal deposition which can cause candidosis. The use of metered-dose inhalers with spacers is less expensive and may be as effective as use of nebulizers, although drug delivery may be affected by choice of spacing device.

PREGNANCY. Poorly controlled asthma in pregnant women can have an adverse effect on the fetus, resulting in perinatal

mortality, increased prematurity and low birth-weight. For this reason using medications to obtain optimal control of asthma is justified. Administration of drugs by inhalation during pregnancy has the advantage that plasma drug concentrations are not likely to be high enough to have an effect on the fetus. Acute exacerbations should be treated aggressively in order to avoid fetal hypoxia.

Acute exacerbation of asthma

Severe asthma can be fatal and **must** be treated promptly and energetically. Acute severe asthma attacks require hospital admission where resuscitation facilities are immediately available.

Severe asthma is characterized by persistent dyspnoea poorly relieved by bronchodilators, exhaustion, a high pulse rate (usually more than 110/minute) and a very low peak expiratory flow.

As asthma becomes more severe, wheezing may be absent. Patients should be given oxygen 40–60% (if available) (see also section 1.1.3) and **corticosteroids;** for adults, prednisolone 30–60 mg by mouth *or* hydrocortisone 200 mg (preferably as sodium succinate) intravenously; for children, prednisolone 1–2 mg/kg by mouth (1–4 years, maximum 20 mg, 5–15 years, maximum 40 mg) *or* hydrocortisone 100 mg (preferably as sodium succinate) intravenously; if the patient experiences vomiting the parenteral route may be preferred for the first dose.

Patients should also be given **salbutamol** or terbutaline via a nebulizer. In emergency situations where delivery via a nebulizer is not available, salbutamol 100 mcg by aerosol inhalation can be repeated 10–20 times preferably using a large volume spacing device.

If there is little response, the following additional treatment should be considered: **aminophylline** by slow intravenous injection if the patient has **not** been receiving theophylline, or administer the beta $_2$-selective adrenoceptor agonist by the intravenous route.

The use of **epinephrine (adrenaline)** (see section 3.1) in asthma has generally been superseded by beta$_2$-selective adrenoceptor agonists.

Treatment should **never** be delayed for investigations, patients should **never** be sedated and the possibility of pneumothorax should also be considered. Patients who deteriorate further despite treatment may need intermittent positive pressure ventilation.

ASTHMA TABLES

TREATMENT OF CHRONIC ASTHMA:
INFANTS AND YOUNG CHILDREN UNDER 5 YEARS OLD
Preferred treatments are in bold print

	Long-term Preventive	*Quick Relief*
STEP 4 Severe Persistent	Daily medications. • **Inhaled corticosteroid,** beclomethasone dipropionate MDI with spacer and face mask > 1 mg daily *or* nebulized beclometasone > 1 mg twice daily Consider short course of soluble prednisolone tablets, regular inhaled long-acting **beta$_2$-agonist** or modified-release theophylline Also, nebulized **beta$_2$- agonist.**	• Inhaled short-acting bronchodilator: **inhaled beta$_2$-agonist** *or* ipratropium bromide as needed for symptoms, not to exceed 3– 4 times daily.
STEP 3 Moderate Persistent	Daily medications. • **Inhaled corticosteroid,** beclomethasone dipropionate MDI with spacer and face mask 400– 800 mcg daily *or* nebulized beclometasone _ 1 mg twice daily Consider short course of soluble prednisolone tablets, regular inhaled long-acting **beta$_2$-agonist** or modified-release theophylline.	• Inhaled shortacting bronchodilator: **inhaled beta$_2$-agonist** *or* ipratropium bromide as needed for symptoms, not to exceed 3– 4 times daily.
STEP 2 Mild Persistent	Daily medications • *Either* **inhaled corticosteroid,** beclometasone dipropionate, 400– 800 mcg, *or* cromoglicate (use MDI with a spacer and face mask *or* use a nebulizer).	• Inhaled short-acting bronchodilator: **inhaled beta$_2$-agonist** *or* ipratropium bromide as needed for symptoms, not to exceed 3–4 times daily.
STEP 1 Intermittent.	• None needed .	• Inhaled short-acting bronchodilator: **inhaled beta$_2$-agonist** *or* ipratropium bromide as needed for symptoms, but not more than once daily. • Intensity of treatment will depend on severity of attack
	Step down Review treatment every 3 to 6 months. If control is sustained for at least 3 months, a gradual stepwise reduction in treatment may be possible.	***Step up*** If control is not achieved, consider step up. But first: review patient medication technique, compliance and environmental *control.*

TREATMENT OF CHRONIC ASTHMA:
ADULTS AND CHILDREN OVER 5 YEARS OLD
Preferred treatments are in bold print

	Long-term Preventive	*Quick Relief*
STEP 4 Severe Persistent	Daily medications. • **Inhaled corticosteroid,** beclomethasone dipropionate 0.8–2mg +. • Long-acting bronchodilator: *either* **long-acting inhaled beta$_2$-agonist,** *and/or* modified-release theophylline, *and/or* long-acting **beta$_2$-agonist** tablets or syrup +. • Corticosteroid tablets or syrup	• Short-acting bronchodilator long term. : **inhaled beta$_2$-agonist** as needed for symptoms
STEP 3 Moderate Persistent	Daily medications. • **Inhaled corticosteroid,** beclomethasone diproprionate 0.8–2mg daily in divided doses + if needed. • Long-acting bronchodilator: *either* **long-acting inhaled beta$_2$-agonist,** modified-release theophylline, *or* long-acting **beta$_2$-agonist** tablets or syrup.	• Short-acting bronchodilator : **inhaled beta$_2$-agonist** as needed forsymptoms, not to exceed 3–4 times daily
STEP 2 Mild Persistent	Daily medications. • *Either* **inhaled corticosteroid,** beclometasone dipropionate 100– 400 mcg twice daily, sodium cromoglicate *or* modifiedrelease theophylline.	• Short-acting bronchodilator: **inhaled beta$_2$-agonist** as needed for symptoms, not to exceed 3–4 times daily
STEP 1 Intermittent.	• None needed.	• Short-acting bronchodilator: **inhaled beta$_2$-agonist** as needed for symptoms (up to oncedaily). • Intensity of treatment will depend on severity of attack . • Inhaled **beta$_2$-agonist** or sodium cromoglicate before exercise or exposure to allergen.
	Step down Review treatment every 3 to 6 months. If control is sustained for at least 3 months, a gradual stepwise reduction in treatment may be possible.	***Step up*** If control is not achieved, consider step up. But first: review patient medication technique, compliance and environmental control.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (chronic bronchitis and emphysema) may be helped by an inhaled short-acting **beta$_2$-adrenoceptor agonist** used as required *or* when the airways obstruction is more severe, by an inhaled **anticholinergic (antimuscarinic) bronchodilator** or both if necessary. Although many patients are treated with an inhaled corticosteroid its role in chronic obstructive pulmonary disease is not clear at present. A limited trial of high-dose inhaled corticosteroid *or* an oral corticosteroid is recommended for patients with moderate airflow obstruction to determine the extent of the airway reversibility and to ensure that asthma has not been overlooked.

Beta$_2$-adrenoceptor agonists (beta$_2$-adrenoceptor stimulants)

The adrenoreceptors in bronchi are mainly beta$_2$ type and their stimulation causes bronchial muscles to relax. The beta$_2$-adrenoceptor agonists include **salbutamol**.

When salbutamol is given by inhalation (100–200 mcg) the effect can last as long as four hours thus making it suitable for both the treatment (see Tables) and prevention of asthma. It can also be taken orally, 2–4 mg up to four times a day but is less effective and causes more adverse effects. It can also be given by injection for severe bronchospasm.

ADVERSE EFFECTS. Cardiovascular adverse effects (arrhythmias, palpitations and tachycardia) may occur with salbutamol, but are infrequent with inhaled preparations. Hypokalaemia may result from beta$_2$-adrenoceptor agonist therapy. Particular caution is required in severe asthma because this effect may be potentiated by concomitant treatment with xanthines (for example theophylline), corticosteroids, diuretics and hypoxia. Plasma potassium concentrations should be monitored in severe asthma.

Xanthines

Xanthines include **theophylline** and **aminophylline**. They relax bronchial smooth muscle. Absorption of theophylline from the gastrointestinal tract is usually rapid and complete. It is metabolized by the liver but its half-life can vary considerably in certain diseases including hepatic impairment and cardiac failure and with some coadministered drugs (see Appendix 1). The half-life variations are important because theophylline has a narrow margin between therapeutic and toxic effects. At therapeutic doses some patients experience nausea and diarrhoea and when plasma concentrations exceed the recommended range of 10–20 mg/litre (55–110 micromol/litre) arrhythmias and convulsions which may be

fatal can occur. Monitoring of plasma concentrations is therefore recommended. Theophylline is used to treat chronic asthma, usually in the form of modifiedrelease preparations which produce adequate plasma concentrations for up to 12 hours. It is used as an adjunct to beta$_2$-agonist or corticosteroid therapy when additional bronchodilation is required but there is an increased risk of adverse effects with beta$_2$-agonists (see above). When given as a single dose at night, modified-release preparations may be useful in controlling nocturnal asthma and early morning wheezing.

The absorption characteristics of modified-release theophylline peparations vary considerably and therefore it is important to keep the patient on the same brand-name formulation.

Theophylline is given by injection as aminophylline (a mixture of theophylline with ethylenediamine) which is 20 times more soluble in water than theophylline alone. It is administered by slow intravenous injection in severe asthma attacks.

Corticosteroids

INHALED CORTICOSTEROIDS as antiinflammatory agents are not cost effective for our conditions however much their relevance.

They include **beclometasone**, budesonide and fluticasone, all of which appear equally effective.

SYSTEMIC CORTICOSTEROIDS. Oral **corticosteroids** may be used as 'maximum therapy' to achieve control of a patient's asthma. This may be useful either when initiating long-term therapy for a patient with uncontrolled asthma or as a short 'rescue' course at any stage for acute exacerbation. Long-term oral corticosteroid therapy may be required to control severe persistent asthma, but its use is limited by the risk of significant adverse effects. In these cases high-dose inhaled corticosteroids should be continued so that oral requirements are reduced to a minimum. Oral doses should be given as a single dose in the morning to reduce the disturbance to the circadian cortisol secretion. Dosage should always be adjusted to the lowest dose which controls symptoms.

Salbutamol

Salbutamol is a representative beta$_2$-adrenoceptor agonist. Various drugs can serve as alternatives.

Tablets, salbutamol (as sulfate) 2 mg, 4 mg.

Syrup, salbutamol (as sulfate) 2 mg/5 ml .

Pressurized inhalation solution *(Aerosol),* salbutamol (as sulfate) 100 mcg/ metered inhalation .

Nebulizer solution, salbutamol (as sulfate) 5 mg/ml, 20-ml ampoules.

Uses: prophylaxis and treatment of asthma; premature labour (section 22.1).

Precautions: hyperthyroidism, myocardial insufficiency, arrhythmias, susceptibility to QT-interval prolongation, hypertension, pregnancy (but appropriate to use; see also notes above); breastfeeding (Appendix 3); diabetes mellitus — especially intravenous administration (monitor blood glucose; ketoacidosis reported);

Interactions: Appendix 1.

Dosage:

Chronic asthma (when inhalation is ineffective), *by mouth*, ADULT 2–4 mg 3 or 4 times daily; in some patients up to maximum of 8 mg 3 or 4 times daily; CHILD under 2 years, 100 mcg/kg 4 times daily, 2–6 years, 1–2 mg 3–4 times daily, 6–12 years, 2 mg 3–4 times daily

Severe acute bronchospasm, *by slow intravenous injection*, ADULT 250 mcg, repeated if necessary

Relief of acute bronchospasm, *by aerosol inhalation*, ADULT 100–200 mcg (1–2 puffs); CHILD 100 mcg (1 puff) increased to 200 mcg (2 puffs) if necessary; *by intramuscular or subcutaneous injection*, ADULT 500 mcg repeated every 4 hours if necessary

Prophylaxis of exercise-induced bronchospasm, *by aerosol inhalation*, ADULT 200 mcg (2 puffs); CHILD 100 mcg (1 puff) increased to 200 mcg (2 puffs) if required

Chronic asthma (as adjunct in stepped treatment), *by aerosol inhalation*, ADULT 100–200 mcg (1–2 puffs) up to 3–4 times daily; CHILD 100 mcg (1 puff) 3–4 times daily, increased to 200 mcg (2 puffs) 3–4 times daily if necessarySevere acute asthma or chronic bronchospasm unresponsive to conventional treatment, *by inhalation of nebulized solution*, ADULT and CHILD over 18 months, 2.5 mg repeated up to 4 times daily; may be increased to 5 mg if necessary — medical assessment should be considered since alternative therapy may be indicated; CHILD under 18 months, clinical efficacy uncertain (transient hypoxaemia may occur — consider oxygen supplementation)

Adverse effects: hypokalaemia after high doses (see notes above); arrhythmias, tachycardia, palpitations, peripheral vasodilation, fine tremor (usually hands), muscle cramps, headache, insomnia, behavioural disturbances in children; hypersensitivity reactions including paradoxical bronchospasm, urticaria and angioedema; slight pain on intramuscular injection.

Beclometasone dipropionate

Beclometasone dipropionate is a representative corticossteroid. Various drugs can serve as alternatives.

Pressurized inhalation solution (aerosol), beclometasone dipropionate 50 micrograms/metered inhalation (standard dose inhaler), 250 micrograms/metered inhalation (high dose inhaler)

Uses : chronic asthma not controlled by short-acting beta2-adrenoceptor agoinsts

Precautions : see notes above; active or quiescent tuberulosis; systemic therapy may be required during periods of stress or when airway obstruction or mucus prevent drug access to smaller airways; not for relief of acute symptoms; monitor height of children receiving prologed treatment- if growth slowed, review therapy.

Dosage:

Chronic asthma, *by aerosol inhalation* (standard dose inhaler),ADULT 200 micrograms twice daily *or* 100 micrograms 3–4 times daily (in more severe cases, initially 600–800 micrograms daily); CHILD 50–100 micrograms 2–4 times daily *or* 100–200 micrograms twice daily; Chronic asthma, *by aerosol inhalation* (high dose inhaler), ADULT 500 micrograms twice daily *or* 250 micrograms 4 times daily; if necessary may be increased to 500 micrograms 4 times daily; CHILD not recommended

Adverse effects: oropharyngeal candidosis, cough and dysphonia (usually only with high doses); adrenal suppression, growth retardation in children and adolescents, impaired bone metabolism, glaucoma and cataract (with high doses, but less frequent than with systemic corticosteroids); paradoxical bronchospasm — requires discontinuation and alternative therapy (if mild, may be prevented by inhalation of beta2-adrenoceptor agonist *or* by transfer from aerosol to powder inhalation); rarely, urticaria, rash, angioedema

CANDIDOSIS. Candidosis can be reduced by use of a spacing device (see notes above); rinsing the mouth with water after inhalation may help to prevent candidosis

Theophylline and Aminophylline

Aminophylline is a representative xanthine bronchodilator. Aminophylline comprises of theophylline and ethylenediamine.

Tablets, theophylline 100 mg.

Modified-release tablets, theophylline 200 mg, 300 mg *Injection* (Solution for injection), aminophylline 25 mg/ml, 10-ml ampoule.

Uses: chronic asthma including nocturnal asthma; acute severe asthma.

Contraindications: porphyria; known hypersensitivity to ethylenediamine (for aminophylline)

Precautions: cardiac disease, hypertension, hyperthyroidism, peptic ulcer, epilepsy, hepatic impairment (Appendix 5), pregnancy (Appendix 2), breastfeeding (Appendix 3), elderly, fever; smokers may require larger or more frequent doses;

Interactions: Appendix 1

Dosage:

Chronic asthma, *by mouth* (as tablets), ADULT and CHILD over 12 years, 100–200 mg 3–4 times daily after food; *by mouth* (as modified-release tablets) ADULT 300–450 mg every 12 hours

Nocturnal asthma, *by mouth* (as modified-release tablets), ADULT total daily requirement as single evening dose

NOTE. Plasma theophylline concentration for optimum response 10–20 mg/ litre (55–110 micromol/litre); narrow margin between therapeutic and toxic dose; see notes above; a range of 5–15 mg/litre (27.5–82.5 micromol/litre) may be effective and associated with fewer adverse effects

Acute severe asthma (**not** previously treated with theophylline), *by slow intravenous injection* (over at least 20 minutes), ADULT and CHILD 5 mg/kg; maintenance, *by intravenous infusion*, ADULT 500 micrograms/kg/hour; CHILD 6 months–9 years, 1 mg/kg/hour, 10–16 years, 800 micrograms/kg/hour, adjusted according to plasma-theophylline concentration.

NOTE. Patients taking oral theophylline (or aminophylline) should not normally receive intravenous aminophylline unless plasma-theophylline concentration is available to guide dosage.

Adverse effects: gastrointestinal irritation, restlessness, anxiety, tremor, palpitations, headache, insomnia, dizziness; convulsions, arrhythmias and hypotension — especially if given by rapid injection; urticaria, erythema and exfoliative dermatitis — resulting from hypersensitivity to ethylene-diamine component of aminophylline.

25.2 Antitussives

Cough is an important physiological protective mechanism, but may also occur as a symptom of an underlying disorder. Treatment of the disease should be the first step in therapy to stop the cough. Upper respiratory tract infections often produce a self-limiting non-productive cough which serves no useful purpose and cough suppressants such as **dextromethorphan** may provide the patient with relief, although they control the cough rather than eliminate it. Cough suppressants must not be used to treat productive cough. For children and the elderly, they are contra-indicated. Cough suppressants should not be combined with expectorants in the treatment of cough since the combination is illogical and there is little evidence for their efficacy, but patients may be exposed to unnecessary adverse effects. Inhibition of cough reflex will lead to retention of phlegm. Although available in the markets, they are best avoided by every practitioner because of their abuse potential and the danger in suppressing productive cough.

25.3 Expectorants

Mucous is produced in the respiratory tract in response to infection, toxic fumes, smoking and to inhalation of drugs, chemicals and as innocuous a thing as air at a temperature

much higher or lower than the body temperature. This mucous not only acts a barrier to the harmful agent causing the excessive production of mucous, but also traps organisms and unwanted particles in the air. The cough reflex, especially in healthy people throws out the harmful material and prevents it from reaching the lower respiratory tract.

Expectorants are natural or manufactured chemicals that decrease the viscosity of the mucous produced and make it easier for the body to cough it out. It is of particular importance in undernourished children – 50% of children in our country are found to be underweight – and the weak and aged.

Vapour – not steam – arising out of heating water when inhaled acts as the best expectorant. Despite a number of expectorants like ammonium citrate and sodium citrate available in the market, most expectorant mixtures irrationally combine drying agents like antihistamines with the expectorant chemical. Further, many studies have questioned the efficacy of these expectorants. Yet, to encourage people to inhale steam as an expectorant, it is proposed to keep compound tincture benzoin that can be added to the water when it is being heated in order to appear of medicinal nature.

Compound Tincture Benzoin

An aromatic expectorant, it is a volatile substance used as expectorant. Although the vapour may contain little of the additive, it encourages deliberate inspiration of warm moist air that is often comforting in bronchitis. *Liquid mixture,* Benzoin tincture, compound, Balsam, balsamic acids approx. 4.5%

Uses: bronchitis, acute sinusitis, acute rhinitis.

Contraindications: not for infants under the age of 3 months

Precautions: use with care in young children as using boiling water may cause scalding of mucosa; vapour – not steam- is intended to be inhaled and does not require heating to the stage of boiling.

Dosage:

Adults: and children over 5 years: add one teaspoonful to a pint of hot, **not** boiling water.

Adverse Reaction: scalding, chemical pneumonia if used in higher doses.

Section 26: Solutions correcting water, electrolyte and acidbase disturbances

26.1 Oral solutions

26.1.1 Oral rehydration

Replacement of fluid and electrolytes orally can be achieved by giving oral rehydration salts — solutions containing sodium, potassium and glucose. Acute diarrhoea in children should always be treated with oral rehydration solution according to plans A, B, or C as shown.

Treatment of : WHO recommendations

According to the degree of dehydration, health professionals are advised to follow one of 3 management plans.

Plan A: no dehydration. Nutritional advice and increased fluid intake are sufficient (soup, rice, water and yoghurt, or even water). For infants aged under 6 months who have not yet started taking solids, oral rehydration solution must be presented before offering milk. Mother's milk or dried cow's milk must be given without any particular restrictions. In the case of mixed breast-milk/formula feeding, the contribution of breastfeeding must be increased.

Plan B: moderate dehydration. Whatever the child's age, a 4-hour treatment plan is applied to avoid short-term problems. Feeding should not therefore be envisaged initially. It is recommended that parents are shown how to give approximately 75 ml/kg of oral rehydration solution with a spoon over a 4-hour period, and it is suggested that parents should be watched to see how they cope at the beginning of the treatment. A larger amount of solution can be given if the child continues to have frequent stools. In case of vomiting, rehydration must be discontinued for 10 minutes and then resumed at a slower rate (about one teaspoonful every 2 minutes). The child's status must be re-assessed after 4 hours to decide on the most appropriate subsequent treatment. Oral rehydration solution should continue to be offered once dehydration has been controlled, for as long as the child continues to have diarrhoea.

Plan C: severe dehydration. Hospitalization is necessary, but most urgent priority is to start rehydration. In hospital (or elsewhere), if the child can drink, oral rehydration solution must be given pending, and even during, intravenous infusion (20 ml/kg every hour by mouth before infusion, then 5 ml/kg every hour by mouth during intravenous rehydration. For intravenous supplementation, it is recommended that compound solution of sodium lactate (see section 26.2) is administered at a rate adapted to the child's age (infant under 12 months: 30 ml/kg over 1 hour then 70 ml/kg over 5 hours; child over 12 months: the same amounts over 30 minutes and 2.5 hours respectively).

If the intravenous route is unavailable, a nasogastric tube is

also suitable for administering oral rehydration solution, at a rate of 20 ml/kg every hour. If the child vomits, the rate of administration of the oral solution should be reduced.

Oral rehydration salts

Glucose salt solution

sodium chloride	3.5 g/litre of clean water
trisodium citrate	2.9 g/litre of clean water
potassium chloride	1.5 g/litre of clean water
glucose (anhydrous)	20.00 g/litre of clean water

When glucose and trisodium citrate are not available, they may be replaced by

sucrose (common sugar)	40.00 g/litre of clean water
sodium bicarbonate	2.5 g/litre of clean water.

NOTE. The solution may be prepared either from prepackaged sugar/salt mixtures or from bulk substances and water. Solutions must be freshly prepared, preferably with recently boiled and cooled water. Accurate weighing and thorough mixing and dissolution of ingredients in the correct volume of clean water is important. Administration of more concentrated solutions can result in hypernatraemia.

Uses: dehydration from acute diarrhoea

Precautions: renal impairment

Dosage:

Fluid and electrolyte loss in acute diarrhoea, *by mouth*, ADULT 200–400 ml solution after every loose motion; INFANT and CHILD according to Plans A, B or C (see above)

Adverse effects: vomiting—may indicate too rapid administration; hypernatraemia and hyperkalaemia may result from overdose in renal impairment or administration of too concentrated a solution

26.1.2 Oral potassium

Compensation for potassium loss is necessary in patients taking digoxin or antiarrhythmic drugs where potassium depletion may induce arrhythmias. It is also necessary in patients with secondary hyperaldosteronism (renal artery stenosis, liver cirrhosis, the nephrotic syndrome, severe heart failure) and those with excessive loss of potassium in the faeces (chronic diarrhoea associated with intestinal malabsorption or laxative abuse).

Measures to compensate for potassium loss may also be required in the elderly since they often take inadequate amounts in the diet (but see warning on use in renal insufficiency, below).

Measures may also be required during long-term administration of drugs known to induce potassium loss (for example,

corticosteroids). Potassium supplements are seldom required with the small doses of diuretics given to treat hypertension. Potassium-sparing diuretics (rather than potassium supplements) are recommended for prevention of hypokalaemia due to diuretics such as frusemide or the thiazides when these are given to eliminate oedema (see section 16.3).

For the prevention of hypokalaemia doses of potassium chloride 1.5 g (approximately 20 mmol) daily by mouth are suitable in patients taking a normal diet. Smaller doses must be used if there is renal insufficiency (common in the elderly) otherwise there is a danger of hyperkalaemia.

Larger doses may be required in established potassium depletion, the quantity depending on the severity of any continuing potassium loss (monitoring of plasma potassium and specialist advice required).

Potassium depletion is frequently associated with metabolic alkalosis and chloride depletion and these disorders require correction.

Potassium chloride

Powder for oral solution, potassium chloride 1.5 g (potassium 20 mmol, chloride 20 mmol).

Uses: prevention and treatment of hypokalaemia (see notes above).

Contraindications: severe renal impairment; plasma potassium concentration above 5 mmol/litre

Precautions: elderly , mild to moderate renal impairment (close monitoring required, Appendix 4), history of peptic ulcer; **important:** special hazard if given with drugs liable to raise plasma potassium concentrations such as potassium-sparing diuretics, ACE inhibitors or ciclosporin, for other.

Interactions: Appendix 1

Dosage:

Prevention of hypokalaemia (see notes above), *by mouth*, ADULT 20–50 mmol daily after meals

Potassium depletion (see notes above), *by mouth*, ADULT 40–100 mmol daily in divided doses after meals: adjust dose according to severity of deficiency and any continuing loss of potassium

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions

Adverse effects: nausea and vomiting, gastrointestinal irritation.

26.2 Parenteral solutions

Solutions of electrolytes are given intravenously, to meet normal fluid and electrolyte requirements or to replenish substantial deficits or continuing losses, when the patient is nauseated

or vomiting and is unable to take adequate amounts by mouth.

In an individual patient the nature and severity of the electrolyte imbalance must be assessed from the history and clinical and biochemical examination. Sodium, potassium, chloride, magnesium, phosphate, and water depletion can occur singly and in combination with or without disturbances of acidbase balance.

Isotonic solutions may be infused safely into a peripheral vein. More concentrated solutions, for example 20% glucose, are best given through an indwelling catheter positioned in a large vein.

Sodium chloride in isotonic solution provides the most important extracellular ions in near physiological concentrations and is indicated in *sodium depletion* which may arise from conditions such as gastroenteritis, diabetic ketoacidosis, ileus and ascites. In a severe deficit of from 4 to 8 litres, 2 to 3 litres of isotonic sodium chloride may be given over 2 to 3 hours; thereafter infusion can usually be at a slower rate.

Excessive administration should be avoided; the jugular venous pressure should be assessed; the bases of the lungs should be examined for crepitations, and in elderly or seriously ill patients it is often helpful to monitor the right atrial (central) venous pressure. The more physiologically appropriate **compound solution of sodium lactate** can be used instead of isotonic sodium chloride solution during surgery or in the initial management of the injured or wounded.

Sodium chloride and glucose solutions are indicated when there is *combined water and sodium depletion*. A 1:1 mixture of isotonic sodium chloride and 5% glucose allows some of the water (free of sodium) to enter body cells which suffer most from dehydration while the sodium salt with a volume of water determined by the normal plasma Na+ remains extracellular. Combined sodium, potassium, chloride, and water depletion may occur, for example, with severe diarrhoea or persistent vomiting; replacement is carried out with sodium chloride intravenous infusion 0.9% and glucose intravenous infusion 5% with potassium as appropriate.

Glucose solutions (5%) are mainly used to replace *water deficits* and should be given alone when there is no significant loss of electrolytes. Average water requirement in a healthy adult are 1.5 to 2.5 litres daily and this is needed to balance unavoidable losses of water through the skin and lungs and to provide sufficient for urinary excretion. Water depletion (dehydration) tends to occur when these losses are not matched by a comparable intake, as for example may occur in coma or dysphagia or in the aged or apathetic who may not drink water in sufficient amount on their own initiative.

Excessive loss of water without loss of electrolytes 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 replace deficits varies with the severity of the disorder, but usually lies within the range of 2 to 6 litres.

Glucose solutions are also given in regimens with calcium, bicarbonate, and insulin for the emergency treatment of *hyperkalaemia*. They are also given, after correction of hyperglycaemia, during treatment of diabetic ketoacidosis, when they must be accompanied by continuing insulin infusion. A concentrated solution of glucose (50%) is used to treat *hypoglycaemia*.

Sodium hydrogen carbonate (sodium bicarbonate) is used to control severe *metabolic acidosis* (as in renal failure). Since this condition is usually attended by sodium depletion, it is reasonable to correct this first by the administration of isotonic sodium chloride intravenous infusion, provided the kidneys are not primarily affected and the degree of acidosis is not so severe as to impair renal function. In these circumstances, isotonic sodium chloride alone is usually effective as it restores the ability of the kidneys to generate bicarbonate. In renal acidosis or in severe metabolic acidosis of any origin, for example blood pH < 7.1, sodium hydrogen carbonate (1.4%) may be infused with isotonic sodium chloride when the acidosis remains unresponsive to correction of anoxia or fluid depletion; a total volume of up to 6 litres (4 litres of sodium chloride and 2 litres of sodium hydrogen carbonate) may be necessary in the adult. In severe shock due for example to cardiac arrest, metabolic acidosis may develop without sodium depletion; in these circumstances sodium hydrogen carbonate is best given in a small volume of hypertonic solution (for example 50 ml of 8.4% solution intravenously); plasma pH should be monitored. Sodium hydrogen carbonate is also used in the emergency management of *hyperkalaemia*.

Intravenous **potassium chloride** and sodium chloride infusion is used to correct *severe hypokalaemia* and depletion when sufficient potassium cannot be taken by mouth. Potassium chloride may be added to sodium chloride 0.9% infusion and given slowly over 2 to 3 hours with specialist advice and ECG monitoring in difficult cases. Repeated measurements of plasma potassium are necessary to determine whether further infusions are required and to avoid the development of hyperkalaemia which is especially likely to occur in renal impairment. Initial potassium replacement therapy should **not** involve glucose infusions because glucose may cause a further decrease in the plasma-potassium concentration.

Glucose

Infusion (Solution for infusion), glucose 5% (isotonic), 10% (hypertonic), 50% (hypertonic)

Uses: fluid replacement without significant electrolyte deficit (see notes above); treatment of hypoglycaemia

Precautions: diabetes mellitus (may require additional insulin)

Dosage:

Fluid replacement, *by intravenous infusion*, ADULT and CHILD determined on the basis of clinical and, whenever possible, electrolyte monitoring (see notes above)

Treatment of hypoglycaemia, *by intravenous infusion* of 50% glucose solution into a large vein, ADULT, 25 ml .

Adverse effects: glucose injections, especially if hypertonic, may have a low pH and cause venous irritation and thrombophlebitis; fluid and electrolyte disturbances; oedema or water intoxication (on prolonged administration or rapid infusion of large volumes of isotonic solutions); hyperglycaemia (on prolonged administration of hypertonic solutions).

Glucose with sodium chloride

Infusion (Solution for infusion), glucose 4%, sodium chloride 0.18% (1.8 g, 30 mmol each of Na^+ and Cl^+ /litre).

Uses: fluid and electrolyte replacement

Precautions: restrict intake in impaired renal function, cardiac failure, hypertension, pulmonary oedema, toxaemia of pregnancy.

Dosage:

Fluid replacement, *by intravenous infusion*, ADULT and CHILD determined on the basis of clinical and, whenever possible, electrolyte monitoring (see notes above)

Adverse effects: administration of large doses may give rise to oedema.

Sodium chloride

Infusion (Solution for infusion), sodium chloride 0.9% (9 g, 154 mmol each of Na^+ and Cl^- /litre)

Uses: electrolyte and fluid replacement

Precautions: restrict intake in impaired renal function (Appendix 4), cardiac failure, hypertension, pulmonary oedema, toxaemia of pregnancy

Dosage:

Fluid and electrolyte replacement, *by intravenous infusion*, ADULT and CHILD determined on the basis of clinical and, whenever possible, electrolyte monitoring (see notes above)

Adverse effects: administration of large doses may give rise to sodium accumulation and oedema.

Sodium lactate, compound solution of

Compound solution of sodium lactate is a representative intravenous electrolyte solution. Various solutions can serve as alternatives.

Infusion (Solution for infusion), sodium chloride 0.6%, sodium lactate 0.25%, potassium chloride 0.04%, calcium chloride 0.027% (containing Na^+ 131 mmol, K^+ 5 mmol, Ca^{++} 2 mmol, HCO_3^- (as lactate) 29 mmol, Cl^- 111 mmol/litre).

Uses: pre- and perioperative fluid and electrolyte replacement; hypovolaemic shock

Contraindications: metabolic or respiratory alkalosis; hypocalcaemiaor hypochlorhydria

Precautions: restrict intake in impaired renal function, cardiac failure, hypertension, pulmonary oedema, toxaemia of pregnancy.

Interactions: Appendix 1

Dosage:

Fluid and electrolyte replacement or hypovolaemic shock, *by intravenous infusion*, ADULT and CHILD determined on the basis of clinical and, whenever possible, electrolyte monitoring (see notes above).

Adverse effects: excessive administration may cause metabolic alkalosis; administration of large doses may give rise to oedema.

Sodium hydrogen carbonate

Infusion (Solution for infusion), sodium hydrogen carbonate 1.4% (14 g, 166.7 mmol each of Na^+ and HCO_3^- /litre)

Injection (Solution for injection), sodium hydrogen carbonate 8.4% (840 mg,10 mmol each of Na^+ and HCO_3^- /10 ml)

Uses: metabolic acidosis.

Contraindications: metabolic or respiratory alkalosis, hypocalcaemia, hypochlorhydria.

Precautions: restrict intake in impaired renal function (Appendix 4), cardiac failure, hypertension, pulmonary oedema, toxaemia of pregnancy; monitor electrolytes and acid-base status.

Interactions: Appendix 1

Dosage:

Metabolic acidosis, *by slow intravenous injection*, ADULT and CHILD a strong solution (up to 8.4%) **or** *by continuous intravenous infusion*, ADULT and CHILD a weaker solution (usually 1.4%), an amount appropriate to the body base deficit (see notes above).

Adverse effects: excessive administration may cause hypokalaemia and metabolic alkalosis, especially in renal impairment;large doses may give rise to sodium accumulation and oedema.

Potassium chloride

Concentrate for infusion (Concentrate for solution for infusion), potassium chloride 11.2% (112 mg, approximately 1.5 mmol each of K+ and Cl^-/ml), 20-ml ampoule.

Uses: electrolyte imbalance

Precautions: for intravenous infusion the concentration of solution should not usually exceed 3.2 g (43 mmol)/litre; specialist advice and ECG monitoring (see notes above); renal impairment (Appendix 4).

Interactions: Appendix 1

Dosage:

Electrolyte imbalance, *by slow intravenous infusion*, ADULT and CHILD depending on the deficit or the daily maintenance requirements (see also notes above)

DILUTION AND ADMINISTRATION. **Must** be diluted before use and administered according to manufacturer's directions.

Adverse effects: rapid infusion is toxic to the heart

26.3 Water

Water for injections

Injection, sterile distilled water free from pyrogens, 2-ml, 5-ml, 10-ml ampoules

Uses: in preparations intended for parenteral administration and in other sterile preparations

Section 27: Vitamins and minerals

27.1 Vitamins

Vitamins are used for the prevention and treatment of specific deficiency states or when the diet is known to be inadequate. It has often been suggested but never convincingly proved, that subclinical vitamin deficiencies cause much chronic ill-health and liability to infections. This has led to enormous consumption of vitamin preparations, which have no more than placebo value. Most vitamins are comparatively non-toxic but prolonged administration of high doses of retinol (vitamin A), ergocalciferol (vitamin D2) and pyridoxine (vitamin B6) may have severe adverse effects.

Retinol (vitamin A) is a fat-soluble substance stored in body organs, principally the liver. Periodic high-dose supplementation is intended to protect against vitamin A deficiency which is associated with ocular defects particularly xerophthalmia (including night blindness which may progress to severe eye lesions and blindness), and an increased susceptibility to infections, particularly measles and diarrhoea. Universal vitamin A distribution involves the periodic administration of supplemental doses to all preschool-age children with priority given to age groups, 6 months to 3 years, or regions at greatest risk. All mothers in high-risk regions should also receive a high dose of vitamin A within 8 weeks of delivery. Since vitamin A is associated with a teratogenic effect it should be given in smaller doses (no more than 10 000 IU/day) to women of child-bearing age. It is also used in the treatment of active xerophthalmia. Doses of vitamin A should be administered orally immediately upon diagnosis of xerophthalmia and thereafter patients with acute corneal lesions should be referred to a hospital on an emergency basis. In women of child-bearing age there is a need to balance the possible teratogenic effects of vitamin A should they be pregnant with the serious consequences of xerophthalmia. Where there are severe signs of xerophthalmia high dose treatment as for patients over 1 year should be given. When less severe symptoms are present (for example night blindness) a much lower dose is recommended. Vitamin A therapy should also be given during epidemics of measles to reduce complications.

Vitamin B is composed of widely differing substances which are, for convenience, classed as 'vitamin B complex'. **Thiamine (vitamin B1)** is used orally for deficiency due to to inadequate dietary intake. Severe deficiency may result in 'beri-beri'. Chronic dry 'beri-beri' is characterized by peripheral neuropathy, muscle wasting and weakness, and paralysis; wet 'beriberi' is characterized by cardiac failure and oedema. Wernicke-Korsakoff syndrome (demyelination of the CNS) may develop in severe deficiency. Thiamine is

given by intravenous injection in doses of up to 300 mg daily (parenteral preparations may contain several B group vitamins) as initial treatment in severe deficiency states. Potentially severe allergic reactions may occur after parenteral administration. Facilities for resuscitation should be immediately available. **Riboflavin (vitamin B2)** deficiency may result from reduced dietary intake or reduced absorption due to liver disease, alcoholism, chronic infection or probenecid therapy. It may also occur in association with other deficiency states such as pellagra. **Pyridoxine (vitamin B6)** deficiency is rare as the vitamin is widely distributed in foods, but deficiency may occur during isoniazid therapy and is characterized by peripheral neuritis. High doses are given in some metabolic disorders, such as hyperoxaluria. **Nicotinic acid** inhibits the synthesis of cholesterol and triglyceride and is used in some hyperlipidaemias. Nicotinic acid and **nicotinamide** are used to prevent and treat nicotinic acid deficiency (pellagra). Nicotinamide is generally preferred as it does not cause vasodilation. **Hydroxocobalamin** is the form of **vitamin B12** used to treat vitamin B12 deficiency due to dietary deficiency or malabsorption (see section 10.1).

Folic acid is essential for the synthesis of DNA and certain proteins. Deficiency of folic acid or vitamin B12 is associated with megaloblastic anaemia. Folic acid should not be used in undiagnosed megaloblastic anaemia unless vitamin B12 is administered concurrently, otherwise neuropathy may be precipitated (see section 10.1). Supplementation with folic acid 400 micrograms daily is recommended for women of childbearing potential in order to reduce the risk of serious neural tube defects in their offspring (see section 10.1).

Ascorbic acid (vitamin C) is used for the prevention and treatment of scurvy. Claims that ascorbic acid is of value in the treatment of common colds are unsubstantiated.

The term **vitamin D** covers a range of compounds including **ergocalciferol (vitamin D2)** and **colecalciferol (vitamin D3)**. These two compounds are equipotent and either can be used to prevent and treat rickets. Simple deficiency of vitamin D occurs in those who have an inadequate dietary intake or who fail to produce enough colecalciferol (vitamin D_3) in their skin from the precursor 7-dehydrocholesterol in response to ultraviolet light.

Children with dark skin must continue vitamin D prophylaxis for up to 24 months because of their inability to produce enough vitamin D_3 in their skin. ***Dark skin with a high melanin content must be exposed to daylight longer than light skin in order to obtain the same synthesis of vitamin D3.*** Vitamin D is also used in deficiency states caused by intestinal malabsorption or chronic liver disease and for the

hypocalcaemia of hypoparathyroidism. **Vitamin K** is necessary for the production of blood clotting factors (see section 10.2).

Ascorbic acid
Vitamin C

Tablets, ascorbic acid 50 mg

Uses: prevention and treatment of scurvy

Dosage:

Prophylaxis of scurvy, *by mouth*, ADULT and CHILD 25–75 mg daily

Treatment of scurvy, *by mouth*, ADULT and CHILD not less than 250 mg daily in divided doses

Adverse effects: gastrointestinal disturbances reported with large doses.

Ergocalciferol
Vitamin D_2

Ergocalciferol is a representative vitamin D compound. Various vitamin D compounds can serve as alternatives

Tablets, ergocalciferol 1.25 mg (50 000 units)

Capsules, ergocalciferol 1.25 mg (50 000 units)

Oral solution, ergocalciferol 250 micrograms/ml (10 000 units/ml)

NOTE. There is no plain vitamin D tablet available for the treatment of simple deficiency. Alternatives include calcium and ergocalciferol tablets, although the calcium is unnecessary

Tablets, ergocalciferol 10 micrograms (400 units), calcium lactate 300 mg, calcium phosphate 150 mg.

Uses: prevention of vitamin D deficiency; vitamin D deficiency caused by malabsorption or chronic liver disease; hypocalcaemia of hypoparathyroidism.

Contraindications: hypercalcaemia; metastatic calcification

Precautions: take care to ensure correct dose in infants; monitor plasma calcium at weekly intervals in patients receiving high doses or those with renal impairment; nausea and vomiting—may indicate overdose and hypercalcaemia; pregnancy and breastfeeding (Appendices 2 and 3);

Interactions: Appendix 1

Dosage:

Prevention of vitamin D deficiency, *by mouth*, ADULT and CHILD 10 micrograms (400 units) daily

Treatment of vitamin D deficiency, *by mouth*, ADULT 1.25 mg (50 000 units) daily for a limited period; CHILD 75–125 micrograms (3000–5000 units) daily

Hypocalcaemia associated with hypoparathyroidism, *by mouth*, ADULT 2.5 mg (100 000 units) daily; CHILD up to 1.5 mg (60 000 units) daily.

Adverse effects: symptoms of overdosage include anorexia, lassitude, nausea and vomiting, diarrhoea, weight loss,

polyuria, sweating, headache, thirst, vertigo, and raised concentrations of calcium and phosphate in plasma and urine; calcification of tissues may occur if dose of 1.25 mg continued for several months.

Nicotinamide

Nicotinamide is a representative vitamin B substance. Various compounds can serve as alternatives.

Tablets, nicotinamide 50 mg

Uses: treatment of pellagra

Dosage:

Treatment of pellagra, *by mouth*, ADULT up to 500 mg daily in divided doses.

Pyridoxine hydrochloride
Vitamin B6

Tablets, pyridoxine hydrochloride 25 mg

Uses: treatment of pyridoxine deficiency due to metabolic disorders; isoniazid neuropathy; sideroblastic anaemia.

Precautions: interactions: Appendix 1

Dosage:

Deficiency states, *by mouth*, ADULT 25–50 mg up to 3 times daily

Isoniazid neuropathy, prophylaxis, *by mouth*, ADULT 10 mg daily.

Isoniazid neuropathy, treatment, *by mouth*, ADULT 50 mg 3 times daily.

Sideroblastic anaemia, *by mouth*, ADULT 100–400 mg daily in divided doses

Adverse effects: generally well tolerated, but chronic administration of high doses may cause peripheral neuropathies.

Retinol
Vitamin A

Retinol is a representative vitamin A compound. Various compounds can serve as alternatives

Sugar-coated tablets (Coated tablets), retinol (as palmitate) 10 000 units

Capsules, retinol (as palmitate) 200 000 units

Oral solution (oily), retinol (as palmitate) 100 000 units/ml

Water-miscible injection (Solution for injection), retinol (as palmitate) 50 000 units/ml, 2-ml ampoule.

Uses: prevention and treatment of vitamin A deficiency; prevention of complications of measles.

Precautions: pregnancy (teratogenic; see notes above and Appendix 2); breastfeeding (Appendix 3).

Dosage:

Prevention of vitamin A deficiency (universal or targeted

distribution programmes), *by mouth*, INFANTS less than 6 months, 50 000 units before 6 weeks of age, followed by 2 further doses of 50 000 units at intervals of 1 month (total dose 150 000 units), 6–12 months, 100 000 units, preferably at measles vaccination; CHILD over 1 year (preschool), 200 000 units every 4–6 months; ADULTS women of childbearing age or pregnant, maximum of 10 000 units daily *or* maximum 25 000 units weekly; ADULTS in high-risk regions, mothers at or soon after delivery 200 000 units, then further dose within 6 weeks.

Treatment of xerophthalmia, *by mouth*, INFANTS less than 6 months, 50 000 units on diagnosis, repeated the next day and then after 2 weeks; 6–12 months, 100 000 units immediately on diagnosis, repeated the next day and then after 2 weeks; CHILD over one year and ADULT (except women of child-bearing age) 200 000 units on diagnosis, repeated the next day and then after 2 weeks; ADULT (women of child-bearing age, see notes above), severe signs of xerophthalmia, as for other adults; less severe cases (for example, night blindness), 5000–10 000 units daily for at least 4 weeks *or* up to 25 000 units weekly.

NOTE. Oral vitamin A preparations are preferred for the prevention and treatment of vitamin A deficiency. However, in situations where patients have severe anorexia or vomiting or are suffering from malabsorption, a watermiscible injection preparation may be administered intramuscularly.

Adverse effects: no serious or irreversible adverse effects in recommended doses; high levels may cause birth defects; transient increased intracranial pressure in adults or a tense and bulging fontanelle in infants (with high dosage); massive overdose can cause rough skin, dry hair, an enlarged liver, a raised erythrocyte sedimentation rate, raised serum calcium and raised serum alkaline phosphatase concentrations.

Riboflavin
Vitamin B2

Tablets, riboflavin 5 mg

Uses: vitamin B2 deficiency

Dosage:

Treatment of vitamin B2 deficiency, *by mouth*, ADULT and CHILD up to 30 mg daily in single or divided doses

Prophylaxis of vitamin B2 deficiency, *by mouth*, ADULT and CHILD 1–2 mg daily.

Thiamine hydrochloride
Vitamin B1

Tablets, thiamine hydrochloride 50 mg

Uses: prevention and treatment of vitamin B1 deficiency

Precautions: parenteral administration (see notes above); breastfeeding (Appendix 3)

Dosage:

Mild chronic thiamine deficiency, *by mouth*, ADULT 10–25 mg daily.

27.2 Minerals

Calcium gluconate. Calcium supplements are usually only required where dietary calcium intake is deficient. This dietary requirement varies with age and is relatively greater in childhood, pregnancy and lactation due to an increased demand, and in old age, due to impaired absorption. In osteoporosis, a calcium intake which is double the recommended daily amount reduces the rate of bone loss. In hypocalcaemic tetany calcium gluconate must be given parenterally but plasma calcium must be monitored. Calcium gluconate is also used in cardiac resuscitation.

Iodine is among the body's essential trace elements. The recommended intake of iodine is 150 micrograms daily (200 micrograms daily in pregnant and breastfeeding women); in children the recommended intake of iodine is 50 micrograms daily for infants under 1 year, 90 micrograms daily for children aged 2–6 years, and 120 micrograms daily for children aged 7–12 years. Deficiency causes endemic goitre and results in endemic cretinism (characterized by deaf-mutism, intellectual deficit, spasticity and sometimes hypothyroidism), impaired mental function in children and adults and an increased incidence of still-births and perinatal and infant mortality. Iodine and iodides may suppress neonatal thyroid function and in general iodine compounds should be avoided in pregnancy. Where it is essential to prevent neonatal goitre and cretinism, iodine should not be witheld from pregnant women. Control of iodine deficiency largely depends upon salt iodization with potassium iodide or potassium iodate and through dietary diversification. In areas where iodine deficiency disorders are moderate to severe, **iodized oil** given either before or at any stage of pregnancy is found to be beneficial.

Calcium gluconate

Calcium gluconate is a complementary drug.

Injection (Solution for injection), calcium gluconate (monohydrate) 100 mg (Ca^{2+} 220 micromol)/ml, 10-ml ampoule.

Uses: hypocalcaemic tetany.

Contraindications: conditions associated with hypercalcaemia and hypercalciuria (for example some forms of malignant disease).

Precautions: monitor plasma calcium concentration;

Interactions: Appendix 1

Dosage:

Hypocalcaemic tetany, *by slow intravenous injection*, ADULT 1 g (2.2 mmol) followed *by continuous intravenous infusion* of about 4 g (8.8 mmol) daily

DILUTION AND ADMINISTRATION. According to manufacturer's directions

Adverse effects: mild gastrointestinal disturbances; bradycardia, arrhythmia; irritation at injection site.

Iodine

Oily injection (Solution for injection), iodine (as iodized oil) 240 mg/ml, 480 mg/ml.

NOTE. Iodized oil may also be given by mouth.

Uses: prevention and treatment of iodine deficiency.

Contraindications: breastfeeding (Appendix 3).

Precautions: over 45 years old or with nodular goitre (especially susceptible to hyperthyroidism when given iodine supplements — iodized oil may not be appropriate); may interfere with thyroid-function tests; pregnancy (see notes above and Appendix 2).

Dosage:

Endemic moderate to severe iodine deficiency, *by intramuscular injection*, ADULT women of child-bearing age, including any stage of pregnancy, 480 mg once each year; *by mouth*, ADULT during pregnancy and one year postpartum, 300–480 mg once a year *or* 100–300 mg every 6 months; women of child-bearing age, 400–960 mg once a year *or* 200–480 mg every 6 months

Iodine deficiency, *by intramuscular injection*, INFANT up to 1 year, 190 mg; CHILD and ADULT 380 mg (aged over 45 years or with nodular goitre, 76 mg but see also Precautions) (provides up to 3 years protection).

Iodine deficiency, *by mouth*, ADULT (except during pregnancy) and CHILD above 6 years, 400 mg once a year; ADULT during pregnancy, single dose of 200 mg; INFANT under 1 year, single dose of 100 mg; CHILD 1–5 years, 200 mg once a year.

Adverse effects: hypersensitivity reactions; goitre and hypothyroidism; hyperthyroidism.

Appendix 1 : Interactions

Two or more drugs given at the same time may exert their effects independently or may interact. The interaction may be potentiation or antagonism of one drug by another, or occasionally some other effect. Drug interactions may be pharmacodynamic or pharmacokinetic.

Pharmacodynamic interactions occur between drugs which have similar or antagonistic pharmacological effects or adverse effects. They are usually predictable from a knowledge of the pharmacology of the interacting drugs and an interaction occurring with one drug is likely to occur with a related drug.

Pharmacodynamic interactions may be due to

+ competition at receptor sites.
+ Drugs acting on the same physiological system

Pharmacodynamic interactions usually occur in most patients who receive the interacting drugs.

Pharmacokinetic interactions occur when one drug increases or reduces the amount of another drug available to produce its pharmacological action. They are not easily predicted and an interaction occurring with one drug cannot be assumed to occur with a related drug unless their pharmacokinetic properties are known to be similar. Pharmacokinetic interactions may be due to.

+ Interference with absorption
+ changes in protein binding
+ modification of drug metabolism
+ interference with renal excretion.

Many pharmacokinetic interactions affect only a small proportion of patients taking the combination of drugs.

Many drug interactions do not have serious consequences and many which are potentially harmful occur only in a small proportion of patients. A known interaction will not necessarily occur to the same extent in all patients. Drugs with a small therapeutic ratio (such as phenytoin) and drugs which require careful dose control (such as anticoagulants, antihypertensives or antidiabetics) are most often involved.

Patients at increased risk from drug interactions include the elderly and those with impaired renal or liver function.

In the following table the symbol * indicates a **potentially hazardous interaction** and the combined administration of the drugs involved should be **avoided**, or only taken with caution and appropriate monitoring. Interactions with no symbol do not usually have serious consequences.

Acetazolamide

Acetylsalicylic acid: Reduced excretion of acetazolamide (risk of toxicity) Alcohol: Enhanced hypotensive effect Imipramine: Increased risk of postural hypotension Atenolol: Enhanced hypotensive effect.

* Enalapril: Enhanced hypotensive effect (can be extreme)

* Carbamazepine: Increased risk of hyponatraemia; acetazolamide increases plasma-Carbamazepine concentra ion Chloral hydrate: Enhanced hypotensive effect

Chlorpromazine: Enhanced hypotensive effect

Cisplatin: In creased risk of nephrotoxicity and ototoxicity

Clomipramine: Increased risk of postural hypotension.

Clonazepam: Enhanced hypotensive effect

Contraceptives, Oral: Antagonism of diuretic effect Dexamethasone: Increased risk of hypokalaemia; antagonism of diuretic effect

Diazepam: Enhanced hypotensive effect

* Digoxin: Cardiac toxicity of digoxin increased if hypokalaemia occurs Ether,

Anaesthetic: Enhanced hypotensive effect

Fludrocortisone: Increased risk of hypokalaemia; antagonism of diuretic effect

Fluphenazine: Enhanced hypotensive effect

Frusemide: Increased risk of hypokalaemia

Glyceryl trinitrate: Enhanced hypotensive effect

Halothane: Enhanced hypotensive effect

Hydralazine: Enhanced hypotensive effect

Hydrochlorothiazide: Increased risk of hypokalaemia.

Hydrocortisone: Increased risk of hypokalaemia; antagonism of diuretic effect

Ibuprofen: Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect

Isosorbide dinitrate: Enhanced hypotensive effect.

Ketamine: Enhanced hypotensive effect.

Levodopa: Enhanced hypotensive effect

* Lidocaine: Action of lidocaine antagonised by hypokalaemia

* Lithium: Excretion of lithium increased

Methyldopa: Enhanced hypotensive effect

Nifedipine: Enhanced hypotensive effect

Nitrous oxide: Enhanced hypotensive effect

Phenytoin: Increased risk of osteomalacia

* Prazosin: Enhanced hypotensive effect; increased risk of first-dose hypotensive effect of prazosin Prednisolone: Increased risk of hypokalaemia; antagonism of diuretic effect. Propranolol: Enhanced hypotensive effect

* Quinidine: Cardiac toxicity of quinidine increased if hypokalaemia occurs; acetazolamide reduces excretion of quinidine (occasionally increased plasma concentration)

Reserpine: Enhanced hypotensive effect

Salbutamol: Increased risk of hypokalaemia with high doses of salbutamol Sodium nitroprusside: Enhanced hypotensive effect

Theophylline: Increased risk of hypokalaemia

Thiopentone: Enhanced hypotensive effect

Timolol: Enhanced hypotensive effect

Verapamil: Enhanced hypotensive effect

Acetylsalicylic acid

Acetazolamide: Reduced excretion of acetazolamide (risk of toxicity)

Antacids (Aluminium hydroxide; Magnesium hydroxide): Excretion of acetylsalicylic acid increased in alkaline urine

* Enalapril: Antagonism of hypotensive effect; increased risk of renal impairment

Dexamethasone: Increased risk of gastrointestinal bleeding and ulceration; dexamethasone reduces plasma-salicylate concentration

Fludrocortisone: Increased risk of gastrointestinal bleeding and ulceration; fludrocortisone reduces plasma-salicylate concentration.

* Heparin: Enhanced anticoagulant effect

Hydrocortisone: Increased risk of gastrointestinal bleeding and ulceration; hydrocortisone reduces plasma-salicylate concentration

* Ibuprofen: Avoid concurrent administration (increased adverse effects, including gastrointestinal damage)

* Methotrexate: Reduced excretion of methotrexate (increased toxicity)

Metoclopramide: Enhanced effect of acetylsalicylic acid (increased rate of absorption)

Phenytoin: Enhancement of effect of phenytoin

Prednisolone: Increased risk of gastrointestinal bleeding and ulceration; prednisolone reduces plasma-salicylate concentration

Spironolactone: Antagonism of diuretic effect Valproic acid: Enhancement of effect of valproic acid.

* Warfarin: Increased risk of bleeding due to antiplatelet effect

Alcohol

Acetazolamide: Enhanced hypotensive effect

Amiloride: Enhanced hypotensive effect

* Imipramine: Enhanced sedative effect

Atenolol: Enhanced hypotensive effect

Enalapril: Enhanced hypotensive effect

Carbamazepine: Possibly enhanced CNS adverse effects of carbamazepine

Chloral hydrate: Enhanced sedative effect

Chlorphenamine: Enhanced sedative effect

Chlorpromazine: Enhanced sedative effect

* Clomipramine: Enhanced sedative effect

Clonazepam: Enhanced sedative effect

Codeine: Enhanced sedative and hypotensive effect

Diazepam: Enhanced sedative effect

Fluphenazine: Enhanced sedative effect

Frusemide: Enhanced hypotensive effect

Glibenclamide: Enhanced hypoglycaemic effect

Glyceryl trinitrate: Enhanced hypotensive effect

Haloperidol: Enhanced sedative effect

Hydralazine: Enhanced hypotensive effect

Hydrochlorothiazide: Enhanced hypotensive effect

Insulins: Enhanced hypoglycaemic effect

Isosorbide dinitrate: Enhanced hypotensive effect

Metformin: Enhanced hypoglycaemic effect; increased risk of lactic acidosis

Methyldopa: Enhanced hypotensive effect

Metronidazole: Disulfiram-like reaction

Morphine: Enhanced sedative and hypotensive effect

Nifedipine: Enhanced hypotensive effect

Paracetamol: Increased risk of liver damage with regular large amounts of alcohol

Pethidine: Enhanced sedative and hypotensive effect

Phenobarbitone: Enhanced sedative effect
Phenytoin: Plasma-phenytoin concentration reduced with regular large amounts of alcohol
Prazosin: Enhanced hypotensive effect
Procarbazine: Disulfiram-like reaction
Promethazine: Enhanced sedative effect
Propranolol: Enhanced hypotensive effect
Reserpine: Enhanced hypotensive effect
Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Enhanced hypotensive effect
Timolol: Enhanced hypotensive effect
Verapamil: Enhanced hypotensive effect; plasma concentration of alcohol possibly increased by verapamil
* Warfarin: Enhanced anticoagulant effect with large amounts of alcohol; major changes in alcohol consumption may affect anticoagulant control

Aluminium hydroxide see Antacids

Aminophylline see Theophylline

Amlodipine
Acetazolamide: Enhanced hypotensive effect
Alcohol: Enhanced hypotensive effect
Alcuronium: Enhanced muscle relaxant effect
Amiloride: Enhanced hypotensive effect
* Atenolol: Severe hypotension and heart failure occasionally
Enalapril: Enhanced hypotensive effect
Carbamazepine: Probably reduced effect of nifedipine
Chloral hydrate: Enhanced hypotensive effect
Chlorpromazine: Enhanced hypotensive effect
Ciclosporin: Possibly increased plasma-nifedipine concentration (increased risk of adverse effects such as gingival hyperplasia)
Cimetidine: Metabolism of nifedipine possibly inhibited (increased plasma concentration)
Clonazepam: Enhanced hypotensive effect
Contraceptives, Oral: Antagonism of hypotensive effect
Dexamethasone: Antagonism of hypotensive effect
Diazepam: Enhanced hypotensive effect
* Digoxin: Possibly increased plasma concentration of digoxin
Ether, Anaesthetic: Enhanced hypotensive effect
Fludrocortisone: Antagonism of hypotensive effect
Fluphenazine: Enhanced hypotensive effect
Frusemide: Enhanced hypotensive effect
Glyceryl trinitrate: Enhanced hypotensive effect
Grapefruit juice: Increased plasma-nifedipine concentration
Haloperidol: Enhanced hypotensive effect
Halothane: Enhanced hypotensive effect
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Enhanced hypotensive effect
Hydrocortisone: Antagonism of hypotensive effect
Ibuprofen: Antagonism of hypotensive effect
Insulins: Occasionally impaired glucose tolerance
Isosorbide dinitrate: Enhanced hypotensive effect
Ketamine: Enhanced hypotensive effect
Levodopa: Enhanced hypotensive effect
* Magnesium (parenteral): Profound hypotension reported with nifedipine and intravenous magnesium sulfate in pre-eclampsia

Mefloquine: Possibly increased risk of bradycardia
Methyldopa: Enhanced hypotensive effect
Nitrous oxide: Enhanced hypotensive effect
* Phenobarbitone: Effect of nifedipine probably reduced
* Phenytoin: Increased plasma-phenytoin concentration; probably reduced effect of nifedipine
* Prazosin: Enhanced hypotensive effect; increased risk of first-dose hypotensive effect of prazosin
Prednisolone: Antagonism of hypotensive effect.
* Propranolol: Severe hypotension and heart failure occasionally
Quinidine: Reduced plasma-quinidine concentration
Reserpine: Enhanced hypotensive effect
* Ritonavir: Plasma concentration possibly increased by ritonavir
* Rifampicin: Accelerated metabolism of nifedipine (plasma concentration significantly reduced)
Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Enhanced hypotensive effect
* Theophylline: Possibly enhanced theophylline effect (possibly increased plasma-theophylline concentration)
Thiopentone: Enhanced hypotensive effect
* Timolol: Severe hypotension and heart failure occasionally
Vecuronium: Enhanced muscle relaxant effect

Amoxicillin

Allopurinol: Increased risk of rash
* Contraceptives, Oral: Possibility of reduced contraceptive effect
Methotrexate: Reduced excretion of methotrexate (increased risk of toxicity)
Warfarin: Studies have failed to demonstrate an interaction, but common experience in anticoagulant clinics is that INR can be altered by a course of amoxicillin

Amoxicillin+Clavulanic acid *see* Amoxicillin

Amphotericin

NOTE. Close monitoring required with concomitant administration of nephrotoxic drugs or cytotoxics
* Ciclosporin: Increased risk of nephrotoxicity
* Dexamethasone: Increased risk of hypokalaemia (avoid concomitant use unless dexamethasone needed to control reactions)
* Digoxin: Increased digoxin toxicity if hypokalaemia occurs
Fluconazole: Possible antagonism of effect of amphotericin
Flucytosine: Renal excretion of flucytosine decreased and cellular uptake increased (flucytosine toxicity possibly increased)
* Fludrocortisone: Increased risk of hypokalaemia
Frusemide: Increased risk of hypokalaemia
Gentamicin: Increased risk of nephrotoxicity
Hydrochlorothiazide: Increased risk of hypokalaemia
* Hydrocortisone: Increased risk of hypokalaemia (avoid concomitant use unless hydrocortisone needed to control reactions)
* Prednisolone: Increased risk of hypokalaemia (avoid concomitant use unless prednisolone needed to control reactions) Streptomycin: Increased risk of nephrotoxicity

Ampicillin

Allopurinol: Increased risk of rash
* Contraceptives, Oral: Possibility of reduced contraceptive effect
Methotrexate: Reduced excretion of methotrexate (increased risk of toxicity)

Warfarin: Studies have failed to demonstrate an interaction, but common experience in anticoagulant clinics is that INR can be altered by a course of ampicillin

Antacids (Aluminium hydroxide; Magnesium hydroxide)

NOTE. Antacids should preferably not be taken at the same time as other drugs since they may impair absorption Acetylsalicylic acid: Excretion of acetylsalicylic acid increased in alkaline urine
Enalapril: Absorption of enalapril reduced
Chloroquine: Reduced absorption
Chlorpromazine: Reduced absorption of chlorpromazine
Ciprofloxacin: Reduced absorption of ciprofloxacin
Digoxin: Possibly reduced absorption of digoxin
Doxycycline: Reduced absorption of doxycycline
Isoniazid: Reduced absorption of isoniazid
Minocycline: Reduced absorption of minocycline
Ofloxacin: Reduced absorption of ofloxacin
Penicillamine: Reduced absorption of penicillamine
Phenytoin: Reduced absorption of phenytoin
Quinidine: Reduced quinidine excretion in alkaline urine (plasmaquinidine concentration occasionally increased)
Rifampicin: Reduced absorption of rifampicin

Atenolol

Acetazolamide: Enhanced hypotensive effect
Alcohol: Enhanced hypotensive effect
Amiloride: Enhanced hypotensive effect
Enalapril: Enhanced hypotensive effect
Chloral hydrate: Enhanced hypotensive effect
Chlorpromazine: Enhanced hypotensive effect
Clonazepam: Enhanced hypotensive effect
Contraceptives, Oral: Antagonism of hypotensive effect
Dexamethasone: Antagonism of hypotensive effect
Diazepam: Enhanced hypotensive effect
Digoxin: Increased AV block and bradycardia
* Epinephrine: Severe hypertension
Ergotamine: Increased peripheral vasoconstriction
Ether, Anaesthetic: Enhanced hypotensive effect
Fludrocortisone: Antagonism of hypotensive effect
Fluphenazine: Enhanced hypotensive effect
Frusemide: Enhanced hypotensive effect
Glibenclamide: Masking of warning signs of hypoglycaemia such as tremor
Glyceryl trinitrate: Enhanced hypotensive effect
Halothane: Enhanced hypotensive effect
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Enhanced hypotensive effect
Hydrocortisone: Antagonism of hypotensive effect
Ibuprofen: Antagonism of hypotensive effect
Insulins: Enhanced hypoglycaemic effect; masking of warning signs of hypoglycaemia such as tremor
Isosorbide dinitrate: Enhanced hypotensive effect
Ketamine: Enhanced hypotensive effect
Levodopa: Enhanced hypotensive effect
* Lidocaine: Increased risk of myocardial depression
Mefloquine: Increased risk of bradycardia
Metformin: Masking of warning signs of hypoglycaemia such as tremor
Methyldopa: Enhanced hypotensive effect

* Nifedipine: Severe hypotension and heart failure occasionally
Nitrous oxide: Enhanced hypotensive effect
* Prazosin: Enhanced hypotensive effect; increased risk of first-dose hypotensive effect of prazosin
Prednisolone: Antagonism of hypotensive effect
* Procainamide: Increased risk of myocardial depression
* Quinidine: Increased risk of myocardial depression
Reserpine: Enhanced hypotensive effect
Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Enhanced hypotensive effect
Theophylline: Avoid concomitant use on pharmacological grounds (bronchospasm)
Thiopentone: Enhanced hypotensive effect
* Verapamil: Asystole, severe hypotension and heart failure

Bisacodyl

Antacids: increase in gastric pH may dissolve enteric coating to cause gastric irrritation.

Dicyclomine

Imipramine: Increased antimuscarinic adverse effects
Chlorphenamine: Increased antimuscarinic adverse effects
Chlorpromazine: Increased antimuscarinic adverse effects of chlorpromazine (but reduced plasma concentration)
Clomipramine: Increased antimuscarinic adverse effects
Fluphenazine: Increased antimuscarinic adverse effects of fluphenazine (but reduced plasma concentration)
Glyceryl trinitrate: Possibly reduced effect of sublingual nitrates (failure to dissolve under the tongue owing to dry mouth)
Isosorbide dinitrate: Possibly reduced effect of sublingual nitrates (failure to dissolve under the tongue owing to dry mouth)
Levodopa: Absorption of levodopa possibly reduced
Metoclopramide: Antagonism of effect on gastrointestinal activity
Neostigmine: Antagonism of effect
Promethazine: Increased antimuscarinic adverse effects
Pyridostigmine: Antagonism of effect

Benzathine benzylpenicillin *see* Benzylpenicillin

Benzylpenicillin

Methotrexate: Reduced excretion of methotrexate (increased risk of toxicity)

BCG vaccine *see* Vaccine, live

Bupivacaine

Lidocaine: Increased myocardial depression
Procainamide: Increased myocardial depression
* Propranolol: Increased risk of bupivacaine toxicity
Quinidine: Increased myocardial depression

Calcium gluconate *see* Calcium salts

Calcium salts

Digoxin: Large intravenous doses of calcium can precipitate arrhythmias
Hydrochlorothiazide: Increased risk of hypercalcaemia

Carbamazepine

* Acetazolamide: Increased risk of hyponatraemia; acetazolamide increases plasma-carbamazepine concentration
Alcohol: Possibly enhanced CNS adverse effects of carbamazepine
Alcuronium: Antagonism of muscle relaxant effect (recovery from neuromuscular blockade accelerated)

Amiloride: Increased risk of hyponatraemia
* Imipramine: Antagonism (convulsive threshold lowered); possibly accelerated metabolism of imipramine (reduced plasma concentration; reduced antidepressant effect)
* Chloroquine: Antagonism of anticonvulsant effect
* Chlorpromazine: Antagonism of anticonvulsant effect (convulsive threshold lowered)
* Ciclosporin: Accelerated metabolism (reduced plasma-ciclosporin concentration)
* Cimetidine: Metabolism of carbamazepine inhibited (increased plasmacarbamazepine concentration)
* Clomipramine: Antagonism (convulsive threshold lowered); possibly accelerated metabolism of clomipramine (reduced plasma concentration;reduced antidepressant effect)
* Clonazepam: May be enhanced toxicity without corresponding increasein antiepileptic effect; plasma concentration of clonazepam often lowered
* Contraceptives, Oral: Accelerated metabolism (reduced contraceptive effect)
* Dexamethasone: Accelerated metabolism of dexamethasone (reduced effect)
Doxycycline: Accelerated doxycycline metabolism (reduced effect)
Ergocalciferol: Ergocalciferol requirements possibly increase
* Erythromycin: Increased plasma-carbamazepine concentration
* Ethosuximide: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of ethosuximide sometimes lowered
* Fludrocortisone: Accelerated metabolism of fludrocortisone (reduced effect)
* Fluphenazine: Antagonism of anticonvulsant effect (convulsive threshold lowered)
Frusemide: Increased risk of hyponatraemia
* Haloperidol: Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration)
Hydrochlorothiazide: Increased risk of hyponatraemia
* Hydrocortisone: Accelerated metabolism of hydrocortisone (reduced effect)
Indinavir: Possibly reduced plasma-indinavir concentration
* Isoniazid: Increased plasma-carbamazepine concentration (also isoniazid hepatotoxicity possibly increased)
* Levonorgestrel: Accelerated metabolism (reduced contraceptive effect)
Levothyroxine: Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism)
Lithium: Neurotoxicity may occur without increased plasma-lithium concentration
Lopinavir: Possibly reduced plasma-lopinavir concentration
* Medroxyprogesterone: Accelerated metabolism (reduced contraceptive effect)
* Mefloquine: Antagonism of anticonvulsant effect
Nelfinavir: Possibly reduced plasma-nelfinavir concentration
Nifedipine: Probably reduced effect of nifedipine
* Norethisterone: Accelerated metabolism (reduced contraceptive effect)

* Phenobarbitone: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of carbamazepine often lowered
* Phenytoin: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of carbamazepine often lowered
Praziquantel: Plasma-praziquantel concentration reduced
* Prednisolone: Accelerated metabolism of prednisolone (reduced effect)
* Ritonavir: Plasma concentration possibly increased by ritonavir
Saquinavir: Possibly reduced plasma-saquinavir concentration
Spironolactone: Increased risk of hyponatraemia
Theophylline: Accelerated metabolism of theophylline (reduced effect)
* Valproic acid: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid often lowered; plasma concentration of active metabolite of carbamazepine often raised
Vecuronium: Antagonism of muscle relaxant effect (recovery from neuromuscular blockade accelerated)
* Verapamil: Enhanced effect of carbamazepine
* Warfarin: Accelerated metabolism of warfarin (reduced anticoagulant effect)
Chloral hydrate
Acetazolamide: Enhanced hypotensive effect
Alcohol: Enhanced sedative effect
Amiloride: Enhanced hypotensive effect
Imipramine: Enhanced sedative effect
Atenolol: Enhanced hypotensive effect
Enalapril: Enhanced hypotensive effect
Chlorphenamine: Enhanced sedative effect
Chlorpromazine: Enhanced sedative effect
Clomipramine: Enhanced sedative effect
Codeine: Enhanced sedative effect
Ether, Anaesthetic: Enhanced sedative effect
Fluphenazine: Enhanced sedative effect
Frusemide: Administration of chloral hydrate with parenteral frusemide may displace thyroid hormone from binding sites; enhanced hypotensive effect
Glyceryl trinitrate: Enhanced hypotensive effect
Haloperidol: Enhanced sedative effect
Halothane: Enhanced sedative effect
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Enhanced hypotensive effect
Isosorbide dinitrate: Enhanced hypotensive effect
Ketamine: Enhanced sedative effect
Methyldopa: Enhanced hypotensive effect
Morphine: Enhanced sedative effect
Nifedipine: Enhanced hypotensive effect
Nitrous oxide: Enhanced sedative effect
Pethidine: Enhanced sedative effect
Prazosin: Enhanced hypotensive and sedative effects
Promethazine: Enhanced sedative effect
Propranolol: Enhanced hypotensive effect
Reserpine: Enhanced hypotensive effect

* Ritonavir: Plasma concentration possibly increased by ritonavir
Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Enhanced hypotensive effect
Thiopentone: Enhanced sedative effect
Timolol: Enhanced hypotensive effect
Verapamil: Enhanced hypotensive effect
Warfarin: May transiently enhance anticoagulant effect
Chloroquine
Antacids (Aluminium hydroxide; Magnesium hydroxide): Reduced absorption
* Artemether+Lumefantrine: Increased risk of ventricular arrhythmias
* Carbamazepine: Antagonism of anticonvulsant effect
* Ciclosporin: Increased plasma-ciclosporin concentration (increased risk of toxicity)
Cimetidine: Inhibition of chloroquine metabolism (increased plasma concentration)
* Digoxin: Plasma-digoxin concentration possibly increased
* Ethosuximide: Antagonism of anticonvulsant effect
* Mefloquine: Increased risk of convulsions
Neostigmine: Chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of neostigmine
* Phenytoin: Antagonism of anticonvulsant effect
Pyridostigmine: Chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of pyridostigmine
Quinidine: Increased risk of ventricular arrhythmias
Quinine: Increased risk of ventricular arrhythmias Vaccine, Rabies: Concomitant administration of chloroquine may affect antibody response
* Valproic acid: Antagonism of anticonvulsant effect
Chlorphenamine (Chlorpheniramine)
Alcohol: Enhanced sedative effect
Imipramine: Increased antimuscarinic and sedative effects
Atropine: Increased antimuscarinic adverse effects
Biperiden: Increased antimuscarinic adverse effects
Chloral hydrate: Enhanced sedative effect
Clomipramine: Increased antimuscarinic and sedative effects
Clonazepam: Enhanced sedative effect
Diazepam: Enhanced sedative effect
Chlorpromazine
Acetazolamide: Enhanced hypotensive effect
Alcohol: Enhanced sedative effect
Amiloride: Enhanced hypotensive effect
* Imipramine: Increased antimuscarinic adverse effects; increased plasma-imipramine concentration; possibly increased risk of ventricular arrhythmias Antacids (Aluminium hydroxide; Magnesium hydroxide): Reduced absorption of chlorpromazine
* Artemether+Lumefantrine: Increased risk of ventricular arrhythmias
Atenolol: Enhanced hypotensive effect
Atropine: Increased antimuscarinic adverse effects of chlorpromazine (but reduced plasma concentration)
Biperiden: Increased antimuscarinic adverse effects of chlorpromazine (but reduced plasma concentration)
Enalapril: Enhanced hypotensive effect
* Carbamazepine: Antagonism of anticonvulsant effect (convulsive threshold lowered)

Chloral hydrate: Enhanced sedative effect
Cimetidine: Possibly enhanced effects of chlorpromazine
* Clomipramine: Increased antimuscarinic adverse effects; increased plasma-clomipramine concentration; possibly increased risk of ventricular arrhythmias
Clonazepam: Enhanced sedative effect
Codeine: Enhanced sedative and hypotensive effect
Diazepam: Enhanced sedative effect
Dopamine: Antagonism of pressor action
Ephedrine: Antagonism of pressor action
Epinephrine: Antagonism of pressor action
* Ether, Anaesthetic: Enhanced hypotensive effect
* Ethosuximide: Antagonism (convulsive threshold lowered)
Frusemide: Enhanced hypotensive effect
Glibenclamide: Possible antagonism of hypoglycaemic effect
Glyceryl trinitrate: Enhanced hypotensive effect
* Halothane: Enhanced hypotensive effect
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Enhanced hypotensive effect
Isoprenaline: Antagonism of pressor action
Isosorbide dinitrate: Enhanced hypotensive effect
* Ketamine: Enhanced hypotensive effect
Levodopa: Antagonism of effects of levodopa
Lithium: Increased risk of extrapyramidal effects and possibility of neurotoxicity
Methyldopa: Enhanced hypotensive effect; increased risk of extrapyramidal effects
Metoclopramide: Increased risk of extrapyramidal effects
Morphine: Enhanced sedative and hypotensive effect
Nifedipine: Enhanced hypotensive effect
* Nitrous oxide: Enhanced hypotensive effect
Pethidine: Enhanced sedative and hypotensive effect
* Phenobarbitone: Antagonism of anticonvulsant effect (convulsive threshold lowered)
* Phenytoin: Antagonism of anticonvulsant effect (convulsive threshold lowered)
Prazosin: Enhanced hypotensive effect
* Procainamide: Increased risk of ventricular arrhythmias
* Propranolol: Concomitant administration may increase plasma concentration of both drugs; enhanced hypotensive effect
* Quinidine: Increased risk of ventricular arrhythmias
Reserpine: Enhanced hypotensive effect; increased risk of extrapyramidal effects
* Ritonavir: Plasma concentration possibly increased by ritonavir
Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Enhanced hypotensive effect
* Thiopentone: Enhanced hypotensive effect
Timolol: Enhanced hypotensive effect
* Valproic acid: Antagonism of anticonvulsant effect (convulsive threshold lowered)
Verapamil: Enhanced hypotensive effect

Ciprofloxacin

Antacids (Aluminium hydroxide; Magnesium hydroxide): Reduced absorption of ciprofloxacin
* Ciclosporin: Increased risk of nephrotoxicity

Ferrous salts: Absorption of ciprofloxacin reduced by oral ferrous salts
Glibenclamide: Possibly enhanced effect of glibenclamide
* Ibuprofen: Possibly increased risk of convulsions
Morphine: Manufacturer of ciprofloxacin advises avoid premedication with morphine (reduced plasma-ciprofloxacin concentration)
Pethidine: Manufacturer of ciprofloxacin advises avoid premedication with pethidine (reduced plasma-ciprofloxacin concentration)
Phenytoin: Plasma-phenytoin concentration possibly altered by ciprofloxacin
* Theophylline: Increased plasma-theophylline concentration; possible increased risk of convulsions
* Warfarin: Enhanced anticoagulant effect
Cloxacillin *see* **Benzylpenicillin**
Contraceptives, Oral
NOTE. **Interactions also apply to ethinylestradiol** taken alone. In hormone replacement therapy low dose unlikely to induce interactions
Acetazolamide: Antagonism of diuretic effect
Amiloride: Antagonism of diuretic effect
Imipramine: Antagonism of antidepressant effect but adverse effects possibly increased due to increased plasma concentration of imipramine
* Amoxicillin: Possibility of reduced contraceptive effect
* Ampicillin: Possibility of reduced contraceptive effect
Atenolol: Antagonism of hypotensive effect
Enalapril: Antagonism of hypotensive effect
* Carbamazepine: Accelerated metabolism (reduced contraceptive effect)
Ceftazidime: Possibility of reduced contraceptive effect
Ceftriaxone: Possibility of reduced contraceptive effect
Ciclosporin: Possibly increased plasma-ciclosporin concentration
Clomipramine: Antagonism of antidepressant effect but adverse effects possibly increased due to increased plasma concentration of clomipramine
Dexamethasone: Oral contraceptives increase plasma concentration of dexamethasone
* Doxycycline: Possibility of reduced contraceptive effect
Efavirenz: Efficacy of oral contraceptives possibly reduced
Fluconazole: Anecdotal reports of contraceptive failure
Fludrocortisone: Oral contraceptives increase plasma concentration of fludrocortisone
Frusemide: Antagonism of diuretic effect
Glibenclamide: Antagonism of hypoglycaemic effect
Glyceryl trinitrate: Antagonism of hypotensive effect
* Griseofulvin: Accelerated metabolism (reduced contraceptive effect)
Hydralazine: Antagonism of hypotensive effect
Hydrochlorothiazide: Antagonism of diuretic effect
Hydrocortisone: Oral contraceptives increase plasma concentration of hydrocortisone
Insulins: Antagonism of hypoglycaemic effect
Isosorbide dinitrate: Antagonism of hypotensive effect
Metformin: Antagonism of hypoglycaemic effect
Methyldopa: Antagonism of hypotensive effect
* Minocycline: Possibility of reduced contraceptive effect

* Nelfinavir: Accelerated metabolism (reduced contraceptive effect)
* Nevirapine: Accelerated metabolism (reduced contraceptive effect)
Nifedipine: Antagonism of hypotensive effect
* Phenobarbitone: Metabolism accelerated (reduced contraceptive effect)
* Phenytoin: Accelerated metabolism (reduced contraceptive effect)
Prazosin: Antagonism of hypotensive effect
Prednisolone: Oral contraceptives increase plasma concentration of prednisolone
Propranolol: Antagonism of hypotensive effect
Reserpine: Antagonism of hypotensive effect
* Rifampicin: Accelerated metabolism of oral contraceptives (reduced contraceptive effect)
* Ritonavir: Accelerated metabolism (reduced contraceptive effect)
Sodium nitroprusside: Antagonism of hypotensive effect
Spironolactone: Antagonism of diuretic effect
Theophylline: Delayed excretion of theophylline (increased plasma concentration)
Verapamil: Antagonism of hypotensive effect
* Warfarin: Antagonism of anticoagulant effect

Dapsone

Rifampicin: Reduced plasma-dapsone concentration

Daunorubicin

Vaccine, Live: Avoid use of live vaccines with daunorubicin (impairment of immune response)

Dexamethasone

Acetazolamide: Increased risk of hypokalaemia; antagonism of diureticeffect
Acetylsalicylic acid: Increased risk of gastrointestinal bleeding and ulceration; dexamethasone reduces plasma-salicylate concentration
Amiloride: Antagonism of diuretic effect
* Amphotericin: Increased risk of hypokalaemia (avoid concomitant use unless dexamethasone needed to control reactions)
Atenolol: Antagonism of hypotensive effect
Enalapril: Antagonism of hypotensive effect
* Carbamazepine: Accelerated metabolism of dexamethasone (reduced effect)
Contraceptives, Oral: Oral contraceptives increase plasma concentration of dexamethasone
Digoxin: Increased risk of hypokalaemia
Ephedrine: Metabolism of dexamethasone accelerated
Erythromycin: Erythromycin possibly inhibits metabolism of dexamethasone
Frusemide: Antagonism of diuretic effect; increased risk of hypokalaemia
Glibenclamide: Antagonism of hypoglycaemic effect
Glyceryl trinitrate: Antagonism of hypotensive effect
Hydralazine: Antagonism of hypotensive effect
Hydrochlorothiazide: Antagonism of diuretic effect; increased risk of hypokalaemia
Indinavir: Possibly reduced plasma-indinavir concentration
Ibuprofen: Increased risk of gastrointestinal bleeding and ulceration
Insulins: Antagonism of hypoglycaemic effect

Isosorbide dinitrate: Antagonism of hypotensive effect
Levonorgestrel: Levonorgestrel increases plasma concentration of dexamethasone
Lopinavir: Possibly reduced plasma-lopinavir concentration
Medroxyprogesterone: Medroxyprogesterone increases plasma concentration of dexamethasone
Metformin: Antagonism of hypoglycaemic effect
Methotrexate: Increased risk of haematological toxicity
Methyldopa: Antagonism of hypotensive effect
Nifedipine: Antagonism of hypotensive effect
Norethisterone: Norethisterone increases plasma concentration of dexamethasone
* Phenobarbitone: Metabolism of dexamethasone accelerated (reduced effect)
* Phenytoin: Metabolism of dexamethasone accelerated (reduced effect)
Praziquantel: Plasma-praziquantel concentration reduced
Prazosin: Antagonism of hypotensive effect
Propranolol: Antagonism of hypotensive effect
Reserpine: Antagonism of hypotensive effect
* Rifampicin: Accelerated metabolism of dexamethasone (reduced effect)
Ritonavir: Plasma concentration possibly increased by ritonavir
Salbutamol: Increased risk of hypokalaemia if high doses of dexamethasone given with high doses of salbutamol
Saquinavir: Possibly reduced plasma-saquinavir concentration
Sodium nitroprusside: Antagonism of hypotensive effect
Spironolactone: Antagonism of diuretic effect
Theophylline: Increased risk of hypokalaemia
Vaccine, Live: High doses of dexamethasone impair immune response; avoid use of live vaccines
Verapamil: Antagonism of hypotensive effect
* Warfarin: Anticoagulant effect possibly altered

Diazepam

Acetazolamide: Enhanced hypotensive effect
Alcohol: Enhanced sedative effect
Amiloride: Enhanced hypotensive effect
Imipramine: Enhanced sedative effect
Atenolol: Enhanced hypotensive effect
Enalapril: Enhanced hypotensive effect
Chlorphenamine: Enhanced sedative effect
Chlorpromazine: Enhanced sedative effect
Cimetidine: Inhibition of diazepam metabolism (increased plasma concentration)
Clomipramine: Enhanced sedative effect
Codeine: Enhanced sedative effect
Ether, Anaesthetic: Enhanced sedative effect
Fluphenazine: Enhanced sedative effect
Frusemide: Enhanced hypotensive effect
Glyceryl trinitrate: Enhanced hypotensive effect
Haloperidol: Enhanced sedative effect
Halothane: Enhanced sedative effect
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Enhanced hypotensive effect
Isoniazid: Metabolism of diazepam inhibited
Isosorbide dinitrate: Enhanced hypotensive effect

Ketamine: Enhanced sedative effect
Levodopa: Occasional antagonism of levodopa effects
Methyldopa: Enhanced hypotensive effect
Morphine: Enhanced sedative effect
Nifedipine: Enhanced hypotensive effect
Nitrous oxide: Enhanced sedative effect
Pethidine: Enhanced sedative effect
Phenytoin: Plasma-phenytoin concentrations increased or decreased by diazepam
Prazosin: Enhanced hypotensive and sedative effects
Promethazine: Enhanced sedative effect
Propranolol: Enhanced hypotensive effect
Reserpine: Enhanced hypotensive effect
Rifampicin: Metabolism of diazepam accelerated (reduced plasma concentration)
* Ritonavir: Plasma concentration possibly increased by ritonavir (risk of extreme sedation and respiratory depression—avoid concomitant use)
Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Enhanced hypotensive effect
Thiopentone: Enhanced sedative effect
Timolol: Enhanced hypotensive effect
Verapamil: Enhanced hypotensive effect
Dicyclomine
Amantadine, increased adverse effects of dicyclomine.
Antacids:may decrease effect of dicyclomine – space the two drugs.
Benzodiazepines& narcotics: drowsiness may be increased
Digoxin: digoxin absorption may increase, hence close monitoring
Disopyramide, increased adverse effects of dicyclomine
H2 antagonists, increased adverse effects of dicyclomine
Phenothiazines, increased adverse effects of dicyclomine
Sympathomimetics, atropine etc: increased adverse effects of dicyclomine
Tricyclic antidepressants, increased adverse effects of dicyclomine

Digoxin

* Acetazolamide: Cardiac toxicity of digoxin increased if hypokalaemia occurs
* Amphotericin: Increased digoxin toxicity if hypokalaemia occurs
Antacids (Aluminium hydroxide; Magnesium hydroxide): Possibly reduced absorption of digoxin
Atenolol: Increased AV block and bradycardia
Calcium salts: Large intravenous doses of calcium can precipitate arrhythmias
Enalapril: Plasma concentration of digoxin possibly increased
* Chloroquine: Plasma-digoxin concentration possibly increased
Dexamethasone: Increased risk of hypokalaemia
Erythromycin: Enhanced effect of digoxin
Fludrocortisone: Increased risk of hypokalaemia
* Frusemide: Cardiac toxicity of digoxin increased if hypokalaemia occurs
* Hydrochlorothiazide: Cardiac toxicity of digoxin increased if hypokalaemia occurs
Hydrocortisone: Increased risk of hypokalaemia
Ibuprofen: Possibly exacerbation of heart failure, reduced GFR, and increased plasma-digoxin concentration

Mefloquine: Possibly increased risk of bradycardia
* Nifedipine: Possibly increased plasma concentration of digoxin
Prednisolone: Increased risk of hypokalaemia
Propranolol: Increased AV block and bradycardia
* Quinidine: Plasma concentration of digoxin increased (halve maintenance dose of digoxin)
* Quinine: Plasma concentration of digoxin increased
* Spironolactone: Enhanced effect of digoxin
Sulfamethoxazole+Trimethoprim: Plasma concentration of digoxin possibly increased
Sulfasalazine: Absorption of digoxin possibly reduced
Suxamethonium: Risk of arrhythmias
Timolol: Increased AV block and bradycardia
Trimethoprim: Plasma concentration of digoxin possibly increased
* Verapamil: Increased plasma concentration of digoxin; increased AV block and bradycardia

Dopamine

Chlorpromazine: Antagonism of pressor action
Fluphenazine: Antagonism of pressor action
Haloperidol: Antagonism of pressor action
Doxycycline
Antacids (Aluminium hydroxide; Magnesium hydroxide): Reduced absorption of doxycycline
Carbamazepine: Accelerated doxycycline metabolism (reduced effect)
* Ciclosporin: Possibly increased plasma-ciclosporin concentration
* Contraceptives, Oral: Possibility of reduced contraceptive effect
Ferrous salts: Reduced absorption of oral ferrous salts by doxycycline; reduced absorption of doxycycline by oral ferrous salts
Phenobarbitone: Metabolism of doxycycline accelerated (reduced plasma concentration)
Phenytoin: Increased metabolism of doxycycline (reduced plasma concentration)
Rifampicin: Plasma-doxycycline concentration possibly reduced
* Warfarin: Anticoagulant effect possibly enhanced

Enalapril

* Acetazolamide: Enhanced hypotensive effect (can be extreme)
* Acetylsalicylic acid: Antagonism of hypotensive effect; increased risk of renal impairment
Alcohol: Enhanced hypotensive effect
Allopurinol: Increased risk of toxicity especially in renal impairment
* Amiloride: Enhanced hypotensive effect (can be extreme); risk of severe hyperkalaemia
Antacids (Aluminium hydroxide; Magnesium hydroxide): Absorption of enalapril reduced
Atenolol: Enhanced hypotensive effect
Azathioprine: Increased risk of leukopenia
Chloral hydrate: Enhanced hypotensive effect
Chlorpromazine: Enhanced hypotensive effect
* Ciclosporin: Increased risk of hyperkalaemia
Clonazepam: Enhanced hypotensive effect
Contraceptives, Oral: Antagonism of hypotensive effect
Dexamethasone: Antagonism of hypotensive effect
Diazepam: Enhanced hypotensive effect
Digoxin: Plasma concentration of digoxin possibly increased
Ether, Anaesthetic: Enhanced hypotensive effect

Fludrocortisone: Antagonism of hypotensive effect
Fluphenazine: Enhanced hypotensive effect
* Frusemide: Enhanced hypotensive effect (can be extreme)
Glibenclamide: Hypoglycaemic effect possibly enhanced
Glyceryl trinitrate: Enhanced hypotensive effect
Halothane: Enhanced hypotensive effect
Heparin: Increased risk of hyperkalaemia
Hydralazine: Enhanced hypotensive effect
* Hydrochlorothiazide: Enhanced hypotensive effect (can be extreme)
Hydrocortisone: Antagonism of hypotensive effect
Ibuprofen: Antagonism of hypotensive effect, increased risk of renal impairment
Insulins: Hypoglycaemic effect possibly enhanced
Isosorbide dinitrate: Enhanced hypotensive effect
Ketamine: Enhanced hypotensive effect
Levodopa: Enhanced hypotensive effect
* Lithium: Enalapril reduces excretion of lithium (increased plasma-lithium concentration)
Metformin: Hypoglycaemic effect possibly enhanced
Methyldopa: Enhanced hypotensive effect
Nifedipine: Enhanced hypotensive effect
Nitrous oxide: Enhanced hypotensive effect
* Potassium salts: Risk of severe hyperkalaemia
Prazosin: Enhanced hypotensive effect
Prednisolone: Antagonism of hypotensive effect
Procainamide: Increased risk of toxicity, especially in renal impairment
Propranolol: Enhanced hypotensive effect
Reserpine: Enhanced hypotensive effect
Sodium nitroprusside: Enhanced hypotensive effect
* Spironolactone: Enhanced hypotensive effect (can be extreme); risk of severe hyperkalaemia
Thiopentone: Enhanced hypotensive effect
Timolol: Enhanced hypotensive effect
Verapamil: Enhanced hypotensive effect

Epinephrine

* Imipramine: Hypertension and arrhythmias (but local anaesthetics with epinephrine appear to be safe)
* Atenolol: Severe hypertension
Chlorpromazine: Antagonism of pressor action
* Clomipramine: Hypertension and arrhythmias (but local anaesthetics with epinephrine appear to be safe)
* Ether, Anaesthetic: Risk of arrhythmias
Fluphenazine: Antagonism of pressor action
Haloperidol: Antagonism of pressor action
* Halothane: Risk of arrhythmias
Oxytocin: Hypertension due to enhanced vasopressor effect of epinephrine
* Propranolol: Severe hypertension
* Timolol: Severe hypertension

Ergocalciferol

Carbamazepine: Ergocalciferol requirements possibly increase
Hydrochlorothiazide: Increased risk of hypercalcaemia
Phenobarbitone: Ergocalciferol requirements possibly increased
Phenytoin: Ergocalciferol requirements possibly increased

Erythromycin

* Carbamazepine: Increased plasma-carbamazepine concentration
* Ciclosporin: Increased plasma-ciclosporin concentration (inhibition of metabolism)
Cimetidine: Increased plasma-erythromycin concentration (increased risk of toxicity, including deafness)
Dexamethasone: Erythromycin possibly inhibits metabolism of dexamethasone
Digoxin: Enhanced effect of digoxin
* Ergotamine: Risk of ergotism (avoid concomitant use)
Fludrocortisone: Erythromycin possibly inhibits metabolism of fludrocortisone
Hydrocortisone: Erythromycin possibly inhibits metabolism of hydrocortisone
Prednisolone: Erythromycin possibly inhibits metabolism of prednisolone
Ritonavir: Plasma concentration possibly increased by ritonavir
* Theophylline: Inhibition of theophylline metabolism (increased plasmatheophylline concentration); if erythromycin given by mouth, also decreased plasma-erythromycin concentration
Valproic acid: Metabolism of valproic acid possibly inhibited (increased plasma concentration)
* Warfarin: Enhanced anticoagulant effect

Ether, Anaesthetic

Acetazolamide: Enhanced hypotensive effect
Amiloride: Enhanced hypotensive effect
Imipramine: Increased risk of arrhythmias and hypotension
Atenolol: Enhanced hypotensive effect
Enalapril: Enhanced hypotensive effect
Chloral hydrate: Enhanced sedative effect
* Chlorpromazine: Enhanced hypotensive effect
Clomipramine: Increased risk of arrhythmias and hypotension
Clonazepam: Enhanced sedative effect
Diazepam: Enhanced sedative effect
* Epinephrine: Risk of arrhythmias
* Fluphenazine: Enhanced hypotensive effect
Frusemide: Enhanced hypotensive effect
Glyceryl trinitrate: Enhanced hypotensive effect
* Haloperidol: Enhanced hypotensive effect
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Enhanced hypotensive effect
Isoniazid: Possible potentiation of isoniazid hepatotoxicity
* Isoprenaline: Risk of arrhythmias
Isosorbide dinitrate: Enhanced hypotensive effect
* Levodopa: Risk of arrhythmias
Methyldopa: Enhanced hypotensive effect
Nifedipine: Enhanced hypotensive effect
Oxytocin: Oxytocic effect possibly reduced; enhanced hypotensive effect and risk of arrhythmias
* Prazosin: Enhanced hypotensive effect
Propranolol: Enhanced hypotensive effect
Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Enhanced hypotensive effect
Timolol: Enhanced hypotensive effect

Vancomycin: Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin
* Verapamil: Enhanced hypotensive effect and AV delay

Ethinylestradiol *see* Contraceptives, Oral

Ferrous salt and Folic acid *see* Ferrous salts; Folic acid

Ferrous salts

Ciprofloxacin: Absorption of ciprofloxacin reduced by oral ferrous salts
Doxycycline: Reduced absorption of oral ferrous salts by doxycycline; reduced absorption of doxycycline by oral ferrous salts
Levodopa: Absorption of levodopa may be reduced
Methyldopa: Reduced hypotensive effect of methyldopa
Minocycline: Reduced absorption of oral ferrous salts by minocycline; reduced absorption of minocycline by oral ferrous salts
Ofloxacin: Absorption of ofloxacin reduced by oral ferrous salts
Penicillamine: Reduced absorption of penicillamine
Fluconazole
Amphotericin: Possible antagonism of effect of amphotericin
* Ciclosporin: Metabolism of ciclosporin possibly inhibited (possibly increased plasma concentration)
Contraceptives, Oral: Anecdotal reports of contraceptive failure
* Glibenclamide: Plasma concentration of glibenclamide increased
Hydrochlorothiazide: Plasma concentration of fluconazole increased
* Phenytoin: Effect of phenytoin enhanced; plasma concentration increased
* Rifampicin: Accelerated metabolism of fluconazole (reduced plasma concentration)
* Ritonavir: Plasma concentration possibly increased by ritonavir
Saquinavir: Plasma concentration of saquinavir possibly increased
* Theophylline: Plasma-theophylline concentration possibly increased
* Warfarin: Enhanced anticoagulant effect
* Zidovudine: Increased plasma concentration of zidovudine (increased risk of toxicity)

Folic acid and Folinic acid

Phenobarbitone: Plasma concentration of phenobarbitone possibly reduced
Phenytoin: Plasma-phenytoin concentration possibly reduced
Frusemide
Acetazolamide: Increased risk of hypokalaemia
Alcohol: Enhanced hypotensive effect
Imipramine: Increased risk of postural hypotension
Amphotericin: Increased risk of hypokalaemia
* Artemether+Lumefantrine: Increased risk of ventricular arrhythmias if electrolyte disturbance occurs
Atenolol: Enhanced hypotensive effect
* Enalapril: Enhanced hypotensive effect (can be extreme)
Carbamazepine: Increased risk of hyponatraemia
Ceftazidime: Nephrotoxicity of ceftazidime possibly increased
Ceftriaxone: Nephrotoxicity of ceftriaxone possibly increased
Chloral hydrate: Administration of chloral hydrate with parenteral frusemide may displace thyroid hormone from binding sites;enhanced hypotensive effect
Chlorpromazine: Enhanced hypotensive effect
Cisplatin: Increased risk of nephrotoxicity and ototoxicity
Clomipramine: Increased risk of postural hypotension

Clonazepam: Enhanced hypotensive effect
Contraceptives, Oral: Antagonism of diuretic effect
Dexamethasone: Antagonism of diuretic effect; increased risk of hypokalaemia
Diazepam: Enhanced hypotensive effect
* Digoxin: Cardiac toxicity of digoxin increased if hypokalaemia occurs
Ether, Anaesthetic: Enhanced hypotensive effect
Fludrocortisone: Antagonism of diuretic effect; increased risk of hypokalaemia
Fluphenazine: Enhanced hypotensive effect
* Gentamicin: Increased risk of ototoxicity
Glibenclamide: Antagonism of hypoglycaemic effect
Glyceryl trinitrate: Enhanced hypotensive effect
Halothane: Enhanced hypotensive effect
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Increased risk of hypokalaemia
Hydrocortisone: Antagonism of diuretic effect; increased risk of hypokalaemia
Ibuprofen: Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
Insulins: Antagonism of hypoglycaemic effect
Isosorbide dinitrate: Enhanced hypotensive effect
Ketamine: Enhanced hypotensive effect
Levodopa: Enhanced hypotensive effect
* Lidocaine: Action of lidocaine antagonised by hypokalaemia
* Lithium: Reduced lithium excretion (increased plasma-lithium concentration and risk of toxicity); frusemide safer than hydrochlorothiazide
Metformin: Antagonism of hypoglycaemic effect
Methyldopa: Enhanced hypotensive effect
Nifedipine: Enhanced hypotensive effect
Nitrous oxide: Enhanced hypotensive effect
* Prazosin: Enhanced hypotensive effect; increased risk of first-dose hypotensive effect of prazosin
Prednisolone: Antagonism of diuretic effect; increased risk of hypokalaemia
Propranolol: Enhanced hypotensive effect
* Quinidine: Cardiac toxicity of quinidine increased if hypokalaemia occurs
Reserpine: Enhanced hypotensive effect
Salbutamol: Increased risk of hypokalaemia with high doses of salbutamol
Sodium nitroprusside: Enhanced hypotensive effect
* Streptomycin: Increased risk of ototoxicity
Theophylline: Increased risk of hypokalaemia
Thiopentone: Enhanced hypotensive effect
Timolol: Enhanced hypotensive effect
* Vancomycin: Increased risk of ototoxicity
Verapamil: Enhanced hypotensive effect

Furazolidone

Ethanol: Disulfiram like reaction
Levodopa: Efficacy/side effects of levodopa increased
MAOIs: hypertensive crisis
Pethidine: may cause agitation, seizures, diaphoresis, fever, coma, apnoea

Sedatives/antihistaminics: hypotension, hypoglycaemia
Sympathomimetics: increases their effect
Tricyclic antidepressants: hypertension, hyperpyrexia, seizurs, tachycardia, acute psychosis

Gentamicin

* Alcuronium: Enhanced muscle relaxant effect
Amphotericin: Increased risk of nephrotoxicity
* Ciclosporin: Increased risk of nephrotoxicity
* Cisplatin: Increased risk of nephrotoxicity and possibly of ototoxicity
* Frusemide: Increased risk of ototoxicity
* Neostigmine: Antagonism of effect of neostigmine
Polygeline: Increased risk of nephrotoxicity
* Pyridostigmine: Antagonism of effect of pyridostigmine
* Suxamethonium: Enhanced muscle relaxant effect
Vancomycin: Increased risk of nephrotoxicity and ototoxicity
* Vecuronium: Enhanced muscle relaxant effect

Glibenclamide

Alcohol: Enhanced hypoglycaemic effect
Atenolol: Masking of warning signs of hypoglycaemia such as tremor
Enalapril: Hypoglycaemic effect possibly enhanced
* Chloramphenicol: Enhanced effect of glibenclamide
Chlorpromazine: Possible antagonism of hypoglycaemic effect
Cimetidine: Enhanced hypoglycaemic effect
Ciprofloxacin: Possibly enhanced effect of glibenclamide
Contraceptives, Oral: Antagonism of hypoglycaemic effect
Dexamethasone: Antagonism of hypoglycaemic effect
* Fluconazole: Plasma concentration of glibenclamide increased
Fludrocortisone: Antagonism of hypoglycaemic effect
Fluphenazine: Possible antagonism of hypoglycaemic effect
Frusemide: Antagonism of hypoglycaemic effect
Hydrochlorothiazide: Antagonism of hypoglycaemic effect
Hydrocortisone: Antagonism of hypoglycaemic effect
* Ibuprofen: Possibly enhanced effect of glibenclamide
Levonorgestrel: Antagonism of hypoglycaemic effect
Lithium: May occasionally impair glucose tolerance
Medroxyprogesterone: Antagonism of hypoglycaemic effect
Norethisterone: Antagonism of hypoglycaemic effect
Prednisolone: Antagonism of hypoglycaemic effect
Propranolol: Masking of warning signs of hypoglycaemia such as tremor
* Rifampicin: Possibly accelerated metabolism (reduced effect) of glibenclamide
* Sulfadiazine: Enhanced effect of glibenclamide
* Sulfadoxine+Pyrimethamine: Enhanced effect of glibenclamide
* Sulfamethoxazole+Trimethoprim: Enhanced effect of glibenclamide
Testosterone: Hypoglycaemic effect possibly enhanced
Timolol: Masking of warning signs of hypoglycaemia such as tremor
* Warfarin: Possibly enhanced hypoglycaemic effects and changes to anticoagulant effect

Glyceryl trinitrate

Acetazolamide: Enhanced hypotensive effect
Alcohol: Enhanced hypotensive effect
Amiloride: Enhanced hypotensive effect
Imipramine: Reduced effect of sublingual glyceryl trinitrate (owing to dry mouth)

Atenolol: Enhanced hypotensive effect
Atropine: Possibly reduced effect of sublingual nitrates (failure to dissolve under the tongue owing to dry mouth)
Biperiden: Possibly reduced effect of sublingual nitrates (failure to dissolve under the tongue owing to dry mouth)
Enalapril: Enhanced hypotensive effect
Chloral hydrate: Enhanced hypotensive effect
Chlorpromazine: Enhanced hypotensive effect
Clomipramine: Reduced effect of sublingual glyceryl trinitrate (owing to dry mouth)
Clonazepam: Enhanced hypotensive effect
Contraceptives, Oral: Antagonism of hypotensive effect
Dexamethasone: Antagonism of hypotensive effect
Diazepam: Enhanced hypotensive effect
Ether, Anaesthetic: Enhanced hypotensive effect
Fludrocortisone: Antagonism of hypotensive effect
Fluphenazine: Enhanced hypotensive effect
Frusemide: Enhanced hypotensive effect
Halothane: Enhanced hypotensive effect
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Enhanced hypotensive effect
Hydrocortisone: Antagonism of hypotensive effect
Ibuprofen: Antagonism of hypotensive effect
Ketamine: Enhanced hypotensive effect
Levodopa: Enhanced hypotensive effect
Methyldopa: Enhanced hypotensive effect
Nifedipine: Enhanced hypotensive effect
Nitrous oxide: Enhanced hypotensive effect
Prazosin: Enhanced hypotensive effect
Prednisolone: Antagonism of hypotensive effect
Propranolol: Enhanced hypotensive effect
Reserpine: Enhanced hypotensive effect
Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Enhanced hypotensive effect
Thiopentone: Enhanced hypotensive effect
Timolol: Enhanced hypotensive effect
Verapamil: Enhanced hypotensive effect

Haloperidol

Alcohol: Enhanced sedative effect
* Imipramine: Increased plasma-imipramine concentration; possibly increased risk of ventricular arrhythmias
* Carbamazepine: Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration)
Chloral hydrate: Enhanced sedative effect
Cimetidine: Possibly enhanced effects of haloperidol
* Clomipramine: Increased plasma-clomipramine concentration; possibly increased risk of ventricular arrhythmias
Clonazepam: Enhanced sedative effect
Codeine: Enhanced sedative and hypotensive effect
Diazepam: Enhanced sedative effect
Dopamine: Antagonism of pressor action
Ephedrine: Antagonism of pressor action
Epinephrine: Antagonism of pressor action
* Ether, Anaesthetic: Enhanced hypotensive effect

* Ethosuximide: Antagonism (convulsive threshold lowered)
* Halothane: Enhanced hypotensive effect
Isoprenaline: Antagonism of pressor action
* Ketamine: Enhanced hypotensive effect
Levodopa: Antagonism of effects of levodopa
Lithium: Increased risk of extrapyramidal effects and possibility of neurotoxicity
Methyldopa: Enhanced hypotensive effect; increased risk of extrapyramidal effects
Metoclopramide: Increased risk of extrapyramidal effects
Morphine: Enhanced sedative and hypotensive effect
Nifedipine: Enhanced hypotensive effect
* Nitrous oxide: Enhanced hypotensive effect
Pethidine: Enhanced sedative and hypotensive effect
* Phenobarbitone: Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration)
* Phenytoin: Antagonism of anticonvulsant effect (convulsive threshold lowered)
Prazosin: Enhanced hypotensive effect
* Procainamide: Increased risk of ventricular arrhythmias
* Quinidine: Increased risk of ventricular arrhythmias
Reserpine: Enhanced hypotensive effect; increased risk of extrapyramidal effects
* Rifampicin: Accelerated metabolism of haloperidol (reduced plasmahaloperidolconcentration)
* Ritonavir: Plasma concentration possibly increased by ritonavir
* Thiopentone: Enhanced hypotensive effect
* Valproic acid: Antagonism of anticonvulsant effect (convulsive threshold lowered)
Verapamil: Enhanced hypotensive effect

Halothane

Acetazolamide: Enhanced hypotensive effect
Amiloride: Enhanced hypotensive effect
Imipramine: Increased risk of arrhythmias and hypotension
Atenolol: Enhanced hypotensive effect
Enalapril: Enhanced hypotensive effect
Chloral hydrate: Enhanced sedative effect
* Chlorpromazine: Enhanced hypotensive effect
Clomipramine: Increased risk of arrhythmias and hypotension
Clonazepam: Enhanced sedative effect
Diazepam: Enhanced sedative effect
* Epinephrine: Risk of arrhythmias
* Fluphenazine: Enhanced hypotensive effect
Frusemide: Enhanced hypotensive effect
Glyceryl trinitrate: Enhanced hypotensive effect
* Haloperidol: Enhanced hypotensive effect
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Enhanced hypotensive effect
Isoniazid: Possible potentiation of isoniazid hepatotoxicity
* Isoprenaline: Risk of arrhythmias
Isosorbide dinitrate: Enhanced hypotensive effect
* Levodopa: Risk of arrhythmias
Methyldopa: Enhanced hypotensive effect
Nifedipine: Enhanced hypotensive effect

Oxytocin: Oxytocic effect possibly reduced; enhanced hypotensive effect and risk of arrhythmias
* Prazosin: Enhanced hypotensive effect
Propranolol: Enhanced hypotensive effect
Reserpine: Enhanced hypotensive effect
Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Enhanced hypotensive effect
Theophylline: Increased risk of arrhythmias
Timolol: Enhanced hypotensive effect
Vancomycin: Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin
* Verapamil: Enhanced hypotensive effect and AV delay

Heparin

* Acetylsalicylic acid: Enhanced anticoagulant effect
Enalapril: Increased risk of hyperkalaemia
Ibuprofen: Possibly increased risk of bleeding
Hydrochlorothiazide
Acetazolamide: Increased risk of hypokalaemia
Alcohol: Enhanced hypotensive effect
Imipramine: Increased risk of postural hypotension
Amphotericin: Increased risk of hypokalaemia
* Artemether+Lumefantrine: Increased risk of ventricular arrhythmias if electrolyte disturbance occurs
Atenolol: Enhanced hypotensive effect
Calcium salts: Increased risk of hypercalcaemia
* Enalapril: Enhanced hypotensive effect (can be extreme)
Carbamazepine: Increased risk of hyponatraemia
Chloral hydrate: Enhanced hypotensive effect
Chlorpromazine: Enhanced hypotensive effect
Cisplatin: Increased risk of nephrotoxicity and ototoxicity
Clomipramine: Increased risk of postural hypotension
Clonazepam: Enhanced hypotensive effect
Contraceptives, Oral: Antagonism of diuretic effect
Dexamethasone: Antagonism of diuretic effect; increased risk of hypokalaemia
Diazepam: Enhanced hypotensive effect
* Digoxin: Cardiac toxicity of digoxin increased if hypokalaemia occurs
Ergocalciferol: Increased risk of hypercalcaemia
Ether, Anaesthetic: Enhanced hypotensive effect
Fluconazole: Plasma concentration of fluconazole increased
Fludrocortisone: Antagonism of diuretic effect; increased risk of hypokalaemia
Fluphenazine: Enhanced hypotensive effect
Frusemide: Increased risk of hypokalaemia
Glibenclamide: Antagonism of hypoglycaemic effect
Glyceryl trinitrate: Enhanced hypotensive effect
Halothane: Enhanced hypotensive effect
Hydralazine: Enhanced hypotensive effect
Hydrocortisone: Antagonism of diuretic effect; increased risk of hypokalaemia
Ibuprofen: Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
Insulins: Antagonism of hypoglycaemic effect
Isosorbide dinitrate: Enhanced hypotensive effect
Ketamine: Enhanced hypotensive effect
Levodopa: Enhanced hypotensive effect

* Lidocaine: Action of lidocaine antagonised by hypokalaemia
* Lithium: Reduced lithium excretion (increased plasma-lithium concentration and risk of toxicity); frusemide safer than hydrochlorothiazide
Metformin: Antagonism of hypoglycaemic effect
Methyldopa: Enhanced hypotensive effect
Nifedipine: Enhanced hypotensive effect
Nitrous oxide: Enhanced hypotensive effect
* Prazosin: Enhanced hypotensive effect; increased risk of first-dose hypotensive effect of prazosin
Prednisolone: Antagonism of diuretic effect; increased risk of hypokalaemia
Propranolol: Enhanced hypotensive effect
* Quinidine: Cardiac toxicity of quinidine increased if hypokalaemia occurs
Reserpine: Enhanced hypotensive effect
Salbutamol: Increased risk of hypokalaemia with high doses of salbutamol
Sodium nitroprusside: Enhanced hypotensive effect
Theophylline: Increased risk of hypokalaemia
Thiopentone: Enhanced hypotensive effect
Timolol: Enhanced hypotensive effect
Verapamil: Enhanced hypotensive effect

Hydrocortisone

NOTE. Interactions do not generally apply to hydrocortisone used for topical application
Acetazolamide: Increased risk of hypokalaemia; antagonism of diuretic effect
Acetylsalicylic acid: Increased risk of gastrointestinal bleeding and ulceration; hydrocortisone reduces plasma-salicylate concentration
Amiloride: Antagonism of diuretic effect
* Amphotericin: Increased risk of hypokalaemia (avoid concomitant use unless hydrocortisone needed to control reactions)
Atenolol: Antagonism of hypotensive effect
Enalapril: Antagonism of hypotensive effect
* Carbamazepine: Accelerated metabolism of hydrocortisone (reduced effect)
Contraceptives, Oral: Oral contraceptives increase plasma concentration of hydrocortisone
Digoxin: Increased risk of hypokalaemia
Erythromycin: Erythromycin possibly inhibits metabolism of hydrocortisone
Frusemide: Antagonism of diuretic effect; increased risk of hypokalaemia
Glibenclamide: Antagonism of hypoglycaemic effect
Glyceryl trinitrate: Antagonism of hypotensive effect
Hydralazine: Antagonism of hypotensive effect
Hydrochlorothiazide: Antagonism of diuretic effect; increased risk of hypokalaemia
Ibuprofen: Increased risk of gastrointestinal bleeding and ulceration
Insulins: Antagonism of hypoglycaemic effect
Isosorbide dinitrate: Antagonism of hypotensive effect
Levonorgestrel: Levonorgestrel increases plasma concentration of hydrocortisone
Medroxyprogesterone: Medroxyprogesterone increases plasma concentration of hydrocortisone

Metformin: Antagonism of hypoglycaemic effect
Methotrexate: Increased risk of haematological toxicity
Methyldopa: Antagonism of hypotensive effect
Nifedipine: Antagonism of hypotensive effect
Norethisterone: Norethisterone increases plasma concentration of hydrocortisone
* Phenobarbitone: Metabolism of hydrocortisone accelerated (reduced effect)
* Phenytoin: Metabolism of hydrocortisone accelerated (reduced effect)
Prazosin: Antagonism of hypotensive effect
Propranolol: Antagonism of hypotensive effect
Reserpine: Antagonism of hypotensive effect
* Rifampicin: Accelerated metabolism of hydrocortisone (reduced effect)
Ritonavir: Plasma concentration possibly increased by ritonavir
Salbutamol: Increased risk of hypokalaemia if high doses of hydrocortisone given with high doses of salbutamol
Sodium nitroprusside: Antagonism of hypotensive effect
Spironolactone: Antagonism of diuretic effect
Theophylline: Increased risk of hypokalaemia
Vaccine, Live: High doses of hydrocortisone impair immune response; avoid use of live vaccines
Verapamil: Antagonism of hypotensive effect
* Warfarin: Anticoagulant effect possibly altered

Ibuprofen

Acetazolamide: Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
* Acetylsalicylic acid: Avoid concurrent administration (increased adverse effects, including gastrointestinal damage)
Amiloride: Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect; possibly increased risk of hyperkalaemia
Atenolol: Antagonism of hypotensive effect
Enalapril: Antagonism of hypotensive effect, increased risk of renal impairment
* Ciclosporin: Increased risk of nephrotoxicity
* Ciprofloxacin: Possibly increased risk of convulsions
Dexamethasone: Increased risk of gastrointestinal bleeding and ulceration
Digoxin: Possibly exacerbation of heart failure, reduced GFR, and increased plasma-digoxin concentration
Fludrocortisone: Increased risk of gastrointestinal bleeding and ulceration
Frusemide: Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
* Glibenclamide: Possibly enhanced effect of glibenclamide
Glyceryl trinitrate: Antagonism of hypotensive effect
Heparin: Possibly increased risk of bleeding
Hydralazine: Antagonism of hypotensive effect
Hydrochlorothiazide: Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
Hydrocortisone: Increased risk of gastrointestinal bleeding and ulceration
Isosorbide dinitrate: Antagonism of hypotensive effect
* Lithium: Reduced excretion of lithium (risk of toxicity)
* Methotrexate: Excretion of methotrexate reduced (increased risk of toxicity)

Methyldopa: Antagonism of hypotensive effect
* Nalidixic acid: Possibly increased risk of convulsions
Nifedipine: Antagonism of hypotensive effect
* Ofloxacin: Possible increased risk of convulsions
* Phenytoin: Effect of phenytoin possibly enhanced
Prazosin: Antagonism of hypotensive effect
Prednisolone: Increased risk of gastrointestinal bleeding and ulceration
Propranolol: Antagonism of hypotensive effect
Ritonavir: Plasma concentration possibly increased by ritonavir
Sodium nitroprusside: Antagonism of hypotensive effect
Spironolactone: Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect; possibly increased risk of hyperkalaemia
Verapamil: Antagonism of hypotensive effect
* Warfarin: Anticoagulant effect possibly enhanced
Zidovudine: Increased risk of haematological toxicity

Imipramine

Acetazolamide: Increased risk of postural hypotension
* Alcohol: Enhanced sedative effect
Amiloride: Increased risk of postural hypotension
* Artemether+Lumefantrine: Increased risk of ventricular arrhythmias
Atropine: Increased antimuscarinic adverse effects
Biperiden: Increased antimuscarinic adverse effects
* Carbamazepine: Antagonism (convulsive threshold lowered); possibly accelerated metabolism of imipramine (reduced plasma concentration; reduced antidepressant effect)
Chloral hydrate: Enhanced sedative effect
Chlorphenamine: Increased antimuscarinic and sedative effects
* Chlorpromazine: Increased antimuscarinic adverse effects; increased plasma-imipramine concentration; possibly increased risk of ventricular arrhythmias
Cimetidine: Plasma concentration of imipramine increased (inhibition of metabolism)
Clonazepam: Enhanced sedative effect
Codeine: Possibly increased sedation
Contraceptives, Oral: Antagonism of antidepressant effect but adverse effects possibly increased due to increased plasma concentration of imipramine
Diazepam: Enhanced sedative effect
* Epinephrine: Hypertension and arrhythmias (but local anaesthetics with epinephrine appear to be safe)
Ether, Anaesthetic: Increased risk of arrhythmias and hypotension
* Ethosuximide: Antagonism (convulsive threshold lowered)
* Fluphenazine: Increased antimuscarinic adverse effects; increased plasma-imipramine concentration; possibly increased risk of ventricular arrhythmias
Frusemide: Increased risk of postural hypotension
Glyceryl trinitrate: Reduced effect of sublingual glyceryl trinitrate (owing to dry mouth)
* Haloperidol: Increased plasma-imipramine concentration; possibly increased risk of ventricular arrhythmias
Halothane: Increased risk of arrhythmias and hypotension
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Increased risk of postural hypotension
Isosorbide dinitrate: Reduced effect of sublingual isosorbide dinitrate (owing to dry mouth)

Ketamine: Increased risk of arrhythmias and hypotension
Methyldopa: Enhanced hypotensive effect
Morphine: Possibly increased sedation
Nitrous oxide: Increased risk of arrhythmias and hypotension
Pethidine: Possibly increased sedation
* Phenobarbitone: Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of imipramine possibly accelerated (reduced plasma concentration)
* Phenytoin: Antagonism (convulsive threshold lowered); possibly reduced plasma-imipramine concentration
* Procainamide: Increased risk of ventricular arrhythmias
Promethazine: Increased antimuscarinic and sedative effects
* Quinidine: Increased risk of ventricular arrhythmias
Reserpine: Enhanced hypotensive effect
Rifampicin: Plasma concentration of imipramine possibly reduced (reduced antidepressant effect)
Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Increased risk of postural hypotension
Thiopentone: Increased risk of arrhythmias and hypotension
* Valproic acid: Antagonism (convulsive threshold lowered)
Verapamil: Possibly increased plasma concentration of imipramine
Immunoglobulin, Anti-D
* Vaccine, MMR: Avoid use of MMR vaccine during *3 weeks before* or during *3 months after* injection of anti-D immunoglobulin (impairment of immune response)

Insulins

Alcohol: Enhanced hypoglycaemic effect
Atenolol: Enhanced hypoglycaemic effect; masking of warning signs of hypoglycaemia such as tremor
Enalapril: Hypoglycaemic effect possibly enhanced
Contraceptives, Oral: Antagonism of hypoglycaemic effect
Dexamethasone: Antagonism of hypoglycaemic effect
Fludrocortisone: Antagonism of hypoglycaemic effect
Frusemide: Antagonism of hypoglycaemic effect
Hydrochlorothiazide: Antagonism of hypoglycaemic effect
Hydrocortisone: Antagonism of hypoglycaemic effect
Levonorgestrel: Antagonism of hypoglycaemic effect
Lithium: May occasionally impair glucose tolerance
Medroxyprogesterone: Antagonism of hypoglycaemic effect
Nifedipine: Occasionally impaired glucose tolerance
Norethisterone: Antagonism of hypoglycaemic effect
Prednisolone: Antagonism of hypoglycaemic effect
Propranolol: Enhanced hypoglycaemic effect; masking of warning signs of hypoglycaemia such as tremor
Testosterone: Hypoglycaemic effect possibly enhanced
Timolol: Enhanced hypoglycaemic effect; masking of warning signs of hypoglycaemia such as tremor

Isoniazid

Antacids (Aluminium hydroxide; Magnesium hydroxide): Reduced absorption of isoniazid
* Carbamazepine: Increased plasma-carbamazepine concentration (also isoniazid hepatotoxicity possibly increased)
Diazepam: Metabolism of diazepam inhibited
Ether, Anaesthetic: Possible potentiation of isoniazid hepatotoxicity

* Ethosuximide: Metabolism of ethosuximide inhibited (increased plasmaethosuximide concentration and risk of toxicity)
Halothane: Possible potentiation of isoniazid hepatotoxicity
Ketamine: Possible potentiation of isoniazid hepatotoxicity
Nitrous oxide: Possible potentiation of isoniazid hepatotoxicity
* Phenytoin: Metabolism of phenytoin inhibited (enhanced effect)
Theophylline: Plasma-theophylline concentration possibly increased
Thiopentone: Possible potentiation of isoniazid hepatotoxicity

Isophane insulin *see* Insulins

Isosorbide dinitrate

Acetazolamide: Enhanced hypotensive effect
Alcohol: Enhanced hypotensive effect
Amiloride: Enhanced hypotensive effect
Imipramine: Reduced effect of sublingual isosorbide dinitrate (owing to dry mouth)
Atenolol: Enhanced hypotensive effect
Atropine: Possibly reduced effect of sublingual nitrates (failure to dissolve under the tongue owing to dry mouth)
Biperiden: Possibly reduced effect of sublingual nitrates (failure to dissolve under the tongue owing to dry mouth)
Enalapril: Enhanced hypotensive effect
Chloral hydrate: Enhanced hypotensive effect
Chlorpromazine: Enhanced hypotensive effect
Clomipramine: Reduced effect of sublingual isosorbide dinitrate (owing to dry mouth)
Clonazepam: Enhanced hypotensive effect
Contraceptives, Oral: Antagonism of hypotensive effect
Dexamethasone: Antagonism of hypotensive effect
Diazepam: Enhanced hypotensive effect
Ether, Anaesthetic: Enhanced hypotensive effect
Fludrocortisone: Antagonism of hypotensive effect
Fluphenazine: Enhanced hypotensive effect
Frusemide: Enhanced hypotensive effect
Halothane: Enhanced hypotensive effect
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Enhanced hypotensive effect
Hydrocortisone: Antagonism of hypotensive effect
Ibuprofen: Antagonism of hypotensive effect
Ketamine: Enhanced hypotensive effect
Levodopa: Enhanced hypotensive effect
Methyldopa: Enhanced hypotensive effect
Nifedipine: Enhanced hypotensive effect
Nitrous oxide: Enhanced hypotensive effect
Prazosin: Enhanced hypotensive effect
Prednisolone: Antagonism of hypotensive effect
Propranolol: Enhanced hypotensive effect
Reserpine: Enhanced hypotensive effect
Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Enhanced hypotensive effect
Thiopentone: Enhanced hypotensive effect
Timolol: Enhanced hypotensive effect
Verapamil: Enhanced hypotensive effect

Ketamine

Acetazolamide: Enhanced hypotensive effect
Amiloride: Enhanced hypotensive effect

Imipramine: Increased risk of arrhythmias and hypotension
Atenolol: Enhanced hypotensive effect
Enalapril: Enhanced hypotensive effect
Chloral hydrate: Enhanced sedative effect
* Chlorpromazine: Enhanced hypotensive effect
Clomipramine: Increased risk of arrhythmias and hypotension
Clonazepam: Enhanced sedative effect
Diazepam: Enhanced sedative effect
* Fluphenazine: Enhanced hypotensive effect
Frusemide: Enhanced hypotensive effect
Glyceryl trinitrate: Enhanced hypotensive effect
* Haloperidol: Enhanced hypotensive effect
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Enhanced hypotensive effect
Isoniazid: Possible potentiation of isoniazid hepatotoxicity
Isosorbide dinitrate: Enhanced hypotensive effect
Methyldopa: Enhanced hypotensive effect
Nifedipine: Enhanced hypotensive effect
* Prazosin: Enhanced hypotensive effect
Propranolol: Enhanced hypotensive effect
Reserpine: Enhanced hypotensive effect
Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Enhanced hypotensive effect
Theophylline: Increased risk of convulsions
Timolol: Enhanced hypotensive effect
Vancomycin: Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin
* Verapamil: Enhanced hypotensive effect and AV delay

Levodopa

Acetazolamide: Enhanced hypotensive effect
Amiloride: Enhanced hypotensive effect
Atenolol: Enhanced hypotensive effect
Atropine: Absorption of levodopa possibly reduced
Biperiden: Absorption of levodopa possibly reduced
Enalapril: Enhanced hypotensive effect
Chlorpromazine: Antagonism of effects of levodopa
Clonazepam: Possibly occasional antagonism of levodopa effects
Diazepam: Occasional antagonism of levodopa effects
* Ether, Anaesthetic: Risk of arrhythmias
Ferrous salts: Absorption of levodopa may be reduced
Fluphenazine: Antagonism of effects of levodopa
Frusemide: Enhanced hypotensive effect
Glyceryl trinitrate: Enhanced hypotensive effect
Haloperidol: Antagonism of effects of levodopa
* Halothane: Risk of arrhythmias
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Enhanced hypotensive effect
Isosorbide dinitrate: Enhanced hypotensive effect
Methyldopa: Enhanced hypotensive effect; antagonism of antiparkinsonian effect
Nifedipine: Enhanced hypotensive effect
Prazosin: Enhanced hypotensive effect
Propranolol: Enhanced hypotensive effect
Pyridoxine: Antagonism of levodopa unless carbidopa also given
Reserpine: Enhanced hypotensive effect; antagonism of antiparkinsonian effect

Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Enhanced hypotensive effect
Timolol: Enhanced hypotensive effect
Verapamil: Enhanced hypotensive effect

Levonorgestrel *see* also *Contraceptives, Oral*

* Carbamazepine: Accelerated metabolism (reduced contraceptive effect)
* Ciclosporin: Inhibition of ciclosporin metabolism (increased plasmaciclosporin concentration)
Dexamethasone: Levonorgestrel increases plasma concentration of dexamethasone
Fludrocortisone: Levonorgestrel increases plasma concentration of fludrocortisone
Glibenclamide: Antagonism of hypoglycaemic effect
* Griseofulvin: Accelerated metabolism (reduced contraceptive effect)
Hydrocortisone: Levonorgestrel increases plasma concentration of hydrocortisone
Insulins: Antagonism of hypoglycaemic effect
Metformin: Antagonism of hypoglycaemic effect
* Nevirapine: Accelerated metabolism (reduced contraceptive effect)
* Phenobarbitone: Accelerated metabolism (reduced contracep tive effect)
* Phenytoin: Accelerated metabolism (reduced contraceptive effect)
Prednisolone: Levonorgestrel increases plasma concentration of prednisolone
* Rifampicin: Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
* Warfarin: Antagonism of anticoagulant effect

Levothyroxine

Carbamazepine: Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism)
Phenobarbitone: Metabolism of levothyroxine accelerated (may increase levothyroxine requirements in hypothyroidism)
Phenytoin: Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism)
Propranolol: Metabolism of propranolol accelerated (reduced effect)
Rifampicin: Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism)
* Warfarin: Enhanced anticoagulant effect

Lidocaine

* Acetazolamide: Action of lidocaine antagonised by hypokalaemia
* Atenolol: Increased risk of myocardial depression
Bupivacaine: Increased myocardial depression
* Cimetidine: Increased plasma concentration of lidocaine (increased risk of toxicity)
* Frusemide: Action of lidocaine antagonised by hypokalaemia
* Hydrochlorothiazide: Action of lidocaine antagonised by hypokalaemia
* Procainamide: Increased myocardial depression
* Propranolol: Increased risk of myocardial depression; increased risk of lidocaine toxicity
* Quinidine: Increased myocardial depression
Suxamethonium: Action of suxamethonium prolonged
* Timolol: Increased risk of myocardial depression

Magnesium hydroxide *see* Antacids

Magnesium (parenteral)

Alcuronium: Enhanced muscle relaxant effect
* Nifedipine: Profound hypotension reported with nifedipine and intravenous magnesium sulfate in pre-eclampsia
Suxamethonium: Enhanced muscle relaxant effect
Vecuronium: Enhanced muscle relaxant effect
Magnesium sulfate *see* Magnesium (parenteral)
Measles vaccine *see* Vaccine, live

Metformin

Alcohol: Enhanced hypoglycaemic effect; increased risk of lactic acidosis
Atenolol: Masking of warning signs of hypoglycaemia such as tremor
Enalapril: Hypoglycaemic effect possibly enhanced
Cimetidine: Renal excretion of metformin inhibited; increased plasmametformin concentration
Contraceptives, Oral: Antagonism of hypoglycaemic effect
Dexamethasone: Antagonism of hypoglycaemic effect
Fludrocortisone: Antagonism of hypoglycaemic effect
Frusemide: Antagonism of hypoglycaemic effect
Hydrochlorothiazide: Antagonism of hypoglycaemic effect
Hydrocortisone: Antagonism of hypoglycaemic effect
Levonorgestrel: Antagonism of hypoglycaemic effect
Lithium: May occasionally impair glucose tolerance
Medroxyprogesterone: Antagonism of hypoglycaemic effect
Norethisterone: Antagonism of hypoglycaemic effect
Prednisolone: Antagonism of hypoglycaemic effect
Propranolol: Masking of warning signs of hypoglycaemia such as tremor
Testosterone: Hypoglycaemic effect possibly enhanced
Timolol: Masking of warning signs of hypoglycaemia such as tremor

Methotrexate

* Acetylsalicylic acid: Reduced excretion of methotrexate (increased toxicity)
Amoxicillin: Reduced excretion of methotrexate (increased risk of toxicity)
Ampicillin: Reduced excretion of methotrexate (increased risk of toxicity)
Benzylpenicillin: Reduced excretion of methotrexate (increased risk of toxicity)
* Ciclosporin: Increased toxicity
Dexamethasone: Increased risk of haematological toxicity
Fludrocortisone: Increased risk of haematological toxicity
Hydrocortisone: Increased risk of haematological toxicity
* Ibuprofen: Excretion of methotrexate reduced (increased risk of toxicity)
Phenoxymethylpenicillin: Reduced excretion of methotrexate (increased risk of toxicity)
Phenytoin: Reduced absorption of phenytoin; antifolate effect of methotrexate increased
Prednisolone: Increased risk of haematological toxicity
* Pyrimethamine: Antifolate effect of methotrexate increased
Sulfadiazine: Risk of methotrexate toxicity increased
* Sulfadoxine+Pyrimethamine: Antifolate effect of methotrexate increased; risk of methotrexate toxicity increased
* Sulfamethoxazole+Trimethoprim: Antifolate effect of methotrexate increased; risk of methotrexate toxicity increased

* Trimethoprim: Antifolate effect of methotrexate increased
Vaccine, Live: Avoid use of live vaccines with methotrexate (impairment of immune response)

Methyldopa

Acetazolamide: Enhanced hypotensive effect
Alcohol: Enhanced hypotensive effect
Amiloride: Enhanced hypotensive effect
Imipramine: Enhanced hypotensive effect
Atenolol: Enhanced hypotensive effect
Enalapril: Enhanced hypotensive effect
Chloral hydrate: Enhanced hypotensive effect
Chlorpromazine: Enhanced hypotensive effect; increased risk of extrapyramidal effects
Clomipramine: Enhanced hypotensive effect
Clonazepam: Enhanced hypotensive effect
Contraceptives, Oral: Antagonism of hypotensive effect
Dexamethasone: Antagonism of hypotensive effect
Diazepam: Enhanced hypotensive effect
Ether, Anaesthetic: Enhanced hypotensive effect
Ferrous salts: Reduced hypotensive effect of methyldopa
Fludrocortisone: Antagonism of hypotensive effect
Fluphenazine: Enhanced hypotensive effect; increased risk of extrapyramidal effects
Frusemide: Enhanced hypotensive effect
Glyceryl trinitrate: Enhanced hypotensive effect
Haloperidol: Enhanced hypotensive effect; increased risk of extrapyramidal effects
Halothane: Enhanced hypotensive effect
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Enhanced hypotensive effect
Hydrocortisone: Antagonism of hypotensive effect
Ibuprofen: Antagonism of hypotensive effect
Isosorbide dinitrate: Enhanced hypotensive effect
Ketamine: Enhanced hypotensive effect
Levodopa: Enhanced hypotensive effect; antagonism of antiparkinsonian effect
* Lithium: Neurotoxicity may occur without increased plasma-lithium concentration
Nifedipine: Enhanced hypotensive effect
Nitrous oxide: Enhanced hypotensive effect
Prazosin: Enhanced hypotensive effect
Prednisolone: Antagonism of hypotensive effect
Propranolol: Enhanced hypotensive effect
Reserpine: Enhanced hypotensive effect; increased risk of extrapyramidal effects
* Salbutamol: Acute hypotension reported with salbutamol infusion
Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Enhanced hypotensive effect
Thiopentone: Enhanced hypotensive effect
Timolol: Enhanced hypotensive effect
Verapamil: Enhanced hypotensive effect

Metoclopramide

Acetylsalicylic acid: Enhanced effect of acetylsalicylic acid (increased rate of absorption)
Atropine: Antagonism of effect on gastrointestinal activity

Biperiden: Antagonism of effect on gastrointestinal activity
Chlorpromazine: Increased risk of extrapyramidal effects
Codeine: Antagonism of effect of metoclopramide on gastrointestinal activity
Fluphenazine: Increased risk of extrapyramidal effects
Haloperidol: Increased risk of extrapyramidal effects
Morphine: Antagonism of effect of metoclopramide on gastrointestinal activity
Paracetamol: Increased absorption of paracetamol (enhanced effect)
Pethidine: Antagonism of effect of metoclopramide on gastrointestinal activity

Metronidazole

Alcohol: Disulfiram-like reaction
Cimetidine: Metabolism of metronidazole inhibited (increased plasmametronidazole concentration)
Fluorouracil: Metabolism of fluorouracil inhibited (increased toxicity)
Lithium: Increased lithium toxicity reported
Phenobarbitone: Metabolism of metronidazole accelerated (reduced plasma concentration)
* Phenytoin: Metabolism of phenytoin inhibited (increased plasma-phenytoin concentration)
* Warfarin: Enhanced anticoagulant effect

Minocycline

Antacids (Aluminium hydroxide; Magnesium hydroxide): Reduced absorption of minocycline
* Contraceptives, Oral: Possibility of reduced contraceptive effect
Ferrous salts: Reduced absorption of oral ferrous salts by minocycline; reduced absorption of minocycline by oral ferrous salts
* Warfarin: Anticoagulant effect possibly enhanced

Morphine

Alcohol: Enhanced sedative and hypotensive effect
Imipramine: Possibly increased sedation
Chloral hydrate: Enhanced sedative effect
Chlorpromazine: Enhanced sedative and hypotensive effect
Cimetidine: Metabolism of morphine inhibited (increased plasma concentration)
Ciprofloxacin: Manufacturer of ciprofloxacin advises avoid premedication with morphine (reduced plasma-ciprofloxacin concentration)
Clomipramine: Possibly increased sedation
Clonazepam: Enhanced sedative effect
Diazepam: Enhanced sedative effect
Fluphenazine: Enhanced sedative and hypotensive effect
Haloperidol: Enhanced sedative and hypotensive effect
Metoclopramide: Antagonism of effect of metoclopramide on gastrointestinal activity
* Ritonavir: Ritonavir possibly increases plasma concentration of morphine

Nalidixic acid

* Ibuprofen: Possibly increased risk of convulsions
* Theophylline: Possible increased risk of convulsions
* Warfarin: Enhanced anticoagulant effect

Neostigmine

Alcuronium: Antagonism of muscle relaxant effect
Atropine: Antagonism of effect

Biperiden: Antagonism of effect
Chloroquine: Chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of neostigmine
Clindamycin: Antagonism of effects of neostigmine
* Gentamicin: Antagonism of effect of neostigmine
Lithium: Antagonism of effect of neostigmine
Procainamide: Antagonism of effect of neostigmine
Propranolol: Antagonism of effect of neostigmine
Quinidine: Antagonism of effect of neostigmine
* Streptomycin: Antagonism of effect of neostigmine
Suxamethonium: Effect of suxamethonium enhanced
Vecuronium: Antagonism of muscle relaxant effect

Nitrous oxide

Acetazolamide: Enhanced hypotensive effect
Amiloride: Enhanced hypotensive effect
Imipramine: Increased risk of arrhythmias and hypotension
Atenolol: Enhanced hypotensive effect
Enalapril: Enhanced hypotensive effect
Chloral hydrate: Enhanced sedative effect
* Chlorpromazine: Enhanced hypotensive effect
Clomipramine: Increased risk of arrhythmias and hypotension
Clonazepam: Enhanced sedative effect
Diazepam: Enhanced sedative effect
* Fluphenazine: Enhanced hypotensive effect
Frusemide: Enhanced hypotensive effect
Glyceryl trinitrate: Enhanced hypotensive effect
* Haloperidol: Enhanced hypotensive effect
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Enhanced hypotensive effect
Isoniazid: Possible potentiation of isoniazid hepatotoxicity
Isosorbide dinitrate: Enhanced hypotensive effect
Methyldopa: Enhanced hypotensive effect
Nifedipine: Enhanced hypotensive effect
* Prazosin: Enhanced hypotensive effect
Propranolol: Enhanced hypotensive effect
Reserpine: Enhanced hypotensive effect
Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Enhanced hypotensive effect
Timolol: Enhanced hypotensive effect
Vancomycin: Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin
* Verapamil: Enhanced hypotensive effect and AV delay

Norethisterone *see also* Contraceptives, Oral

* Carbamazepine: Accelerated metabolism (reduced contraceptive effect)
* Ciclosporin: Inhibition of ciclosporin metabolism (increased plasmaciclosporin concentration)
Dexamethasone: Norethisterone increases plasma concentration of dexamethasone
Fludrocortisone: Norethisterone increases plasma concentration of fludrocortisone
Glibenclamide: Antagonism of hypoglycaemic effect
* Griseofulvin: Accelerated metabolism (reduced contraceptive effect)
Hydrocortisone: Norethisterone increases plasma concentration of hydrocortisone

Insulins: Antagonism of hypoglycaemic effect
Metformin: Antagonism of hypoglycaemic effect
* Nevirapine: Accelerated metabolism (reduced contraceptive effect)
* Phenobarbitone: Accelerated metabolism (reduced contracep tive effect)
* Phenytoin: Accelerated metabolism (reduced contraceptive effect)
* Prednisolone: Norethisterone increases plasma concentration of prednisolone
* Rifampicin: Accelerated metabolism of norethisterone (reduced contraceptive effect)
* Warfarin: Antagonism of anticoagulant effect

Ofloxacin

Antacids (Aluminium hydroxide; Magnesium hydroxide): Reduced absorption of ofloxacin
* Ciclosporin: Increased risk of nephrotoxicity
Ferrous salts: Absorption of ofloxacin reduced by oral ferrous salts
* Ibuprofen: Possible increased risk of convulsions
* Theophylline: Possible increased risk of convulsions
* Warfarin: Enhanced anticoagulant effect

Oxygen

* Bleomycin: Increased risk of pulmonary toxicity

Oxytocin

Ephedrine: Hypertension due to enhanced vasopressor effect of ephedrine
Epinephrine: Hypertension due to enhanced vasopressor effect of epinephrine
Ether, Anaesthetic: Oxytocic effect possibly reduced; enhanced hypotensive effect and risk of arrhythmias
Halothane: Oxytocic effect possibly reduced; enhanced hypotensive effect and risk of arrhythmias

Paracetamol

Alcohol: Increased risk of liver damage with regular large amounts of alcohol
Metoclopramide: Increased absorption of paracetamol (enhanced effect)
Warfarin: Prolonged regular use of paracetamol possibly enhances anticoagulant effect

Pethidine

Alcohol: Enhanced sedative and hypotensive effect
Imipramine: Possibly increased sedation
Chloral hydrate: Enhanced sedative effect
Chlorpromazine: Enhanced sedative and hypotensive effect
Cimetidine: Metabolism of pethidine inhibited (increased plasma concentration)
Ciprofloxacin: Manufacturer of ciprofloxacin advises avoid premedication with pethidine (reduced plasma-ciprofloxacin concentration)
Clomipramine: Possibly increased sedation
Clonazepam: Enhanced sedative effect
Diazepam: Enhanced sedative effect
Fluphenazine: Enhanced sedative and hypotensive effect
Haloperidol: Enhanced sedative and hypotensive effect
Metoclopramide: Antagonism of effect of metoclopramide on gastrointestinal activity

* Ritonavir: Increased plasma-pethidine concentration (risk of toxicity—avoid concomitant use)

Phenobarbitone

Alcohol: Enhanced sedative effect
* Imipramine: Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of imipramine possibly accelerated (reduced plasma concentration)
* Carbamazepine: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of carbamazepine often lowered
* Chloramphenicol: Metabolism of chloramphenicol accelerated (reduced chloramphenicol concentration)
* Chlorpromazine: Antagonism of anticonvulsant effect (convulsive threshold lowered)
* Ciclosporin: Metabolism of ciclosporin accelerated (reduced effect)
* Clomipramine: Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of clomipramine possibly accelerated (reduced plasma concentration)
* Clonazepam: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of clonazepam often lowered
* Contraceptives, Oral: Metabolism accelerated (reduced contraceptive effect)
* Dexamethasone: Metabolism of dexamethasone accelerated (reduced effect)
Doxycycline: Metabolism of doxycycline accelerated (reduced plasma concentration)
Ergocalciferol: Ergocalciferol requirements possibly increased
* Ethosuximide: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of ethosuximide sometimes lowered
* Fludrocortisone: Metabolism of fludrocortisone accelerated (reduced effect)
* Fluphenazine: Antagonism of anticonvulsant effect (convulsive threshold lowered)
Folic acid and Folinic acid: Plasma concentration of phenobarbitone possibly reduced
Griseofulvin: Reduction in absorption of griseofulvin (reduced effect)
* Haloperidol: Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration)
* Hydrocortisone: Metabolism of hydrocortisone accelerated (reduced effect)
* Indinavir: Plasma concentration of indinavir possibly reduced
* Levonorgestrel: Accelerated metabolism (reduced contraceptive effect)
Levothyroxine: Metabolism of levothyroxine accelerated (may increase levothyroxine requirements in hypothyroidism)
* Lopinavir: Plasma concentration of lopinavir possibly reduced
* Medroxyprogesterone: Accelerated metabolism (reduced contraceptive effect)
Metronidazole: Metabolism of metronidazole accelerated (reduced plasma concentration)
* Nelfinavir: Plasma concentration of nelfinavir possibly reduced
* Nifedipine: Effect of nifedipine probably reduced

* Norethisterone: Accelerated metabolism (reduced contraceptive effect)
* Phenytoin: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of phenobarbitone often raised
* Prednisolone: Metabolism of prednisolone accelerated (reduced effect)

Quinidine: Metabolism of quinidine accelerated (reduced plasma concentration)

* Saquinavir: Plasma concentration of saquinavir possibly reduced

Theophylline: Metabolism of theophylline accelerated (reduced effect)

* Valproic acid: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid often lowered; phenobarbitone concentration often raised
* Verapamil: Effect of verapamil probably reduced
* Warfarin: Metabolism of warfarin accelerated (reduced anticoagulant effect)

Phenoxymethylpenicillin

Methotrexate: Reduced excretion of methotrexate (increased risk of toxicity)

Phenytoin

Acetazolamide: Increased risk of osteomalacia

Acetylsalicylic acid: Enhancement of effect of phenytoin

Alcohol: Plasma-phenytoin concentration reduced with regular large amounts of alcohol

Alcuronium: Antagonism of muscle relaxant effect (accelerated recovery from neuromuscular blockade)

* Imipramine: Antagonism (convulsive threshold lowered); possibly reduced plasma-imipramine concentration

Antacids (Aluminium hydroxide; Magnesium hydroxide): Reduced absorption of phenytoin

Azathioprine: Reduced absorption of phenytoin

* Carbamazepine: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of carbamazepine often lowered
* Chloramphenicol: Plasma-phenytoin concentration increased (risk of toxicity)
* Chloroquine: Antagonism of anticonvulsant effect
* Chlorpromazine: Antagonism of anticonvulsant effect (convulsive threshold lowered)
* Ciclosporin: Accelerated metabolism (reduced plasma-ciclosporin concentration)
* Cimetidine: Metabolism of phenytoin inhibited (increased plasma concentration)

Ciprofloxacin: Plasma-phenytoin concentration possibly altered by ciprofloxacin

Cisplatin: Reduced absorption of phenytoin

* Clomipramine: Antagonism (convulsive threshold lowered); possibly reduced plasma- clomipramine concentration
* Clonazepam: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of clonazepam often lowered

* Contraceptives, Oral: Accelerated metabolism (reduced contraceptive effect)

Cyclophosphamide: Reduced absorption of phenytoin

Cytarabine: Reduced absorption of phenytoin

* Dexamethasone: Metabolism of dexamethasone accelerated (reduced effect)

Diazepam: Plasma-phenytoin concentrations increased or decreased by diazepam

Doxorubicin: Reduced absorption of phenytoin

Doxycycline: Increased metabolism of doxycycline (reduced plasma concentration)

Ergocalciferol: Ergocalciferol requirements possibly increased

* Ethosuximide: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of phenytoin sometimes raised; plasma concentration of ethosuximide sometimes lowered
* Fluconazole: Effect of phenytoin enhanced; plasma concentration increased
* Fludrocortisone: Metabolism of fludrocortisone accelerated (reduced effect)

Fluorouracil: Reduced absorption of phenytoin

* Fluphenazine: Antagonism of anticonvulsant effect (convulsive threshold lowered)

Folic acid and Folinic acid: Plasma-phenytoin concentration possibly reduced

* Haloperidol: Antagonism of anticonvulsant effect (convulsive threshold lowered)
* Hydrocortisone: Metabolism of hydrocortisone accelerated (reduced effect)
* Ibuprofen: Effect of phenytoin possibly enhanced

Indinavir: Plasma-indinavir concentration possibly reduced

* Isoniazid: Metabolism of phenytoin inhibited (enhanced effect)
* Levonorgestrel: Accelerated metabolism (reduced contraceptive effect)

Levothyroxine: Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism)

Lithium: Neurotoxicity may occur without increased plasma-lithium concentration

Lopinavir: Plasma-lopinavir concentration possibly reduced

* Medroxyprogesterone: Accelerated metabolism (reduced contraceptive effect)
* Mefloquine: Antagonism of anticonvulsant effect

Mercaptopurine: Reduced absorption of phenytoin

Methotrexate: Reduced absorption of phenytoin; antifolate effect of methotrexate increased

* Metronidazole: Metabolism of phenytoin inhibited (increased plasmaphenytoin concentration)

Nelfinavir: Possibly reduced plasma-nelfinavir concentration

* Nifedipine: Increased plasma-phenytoin concentration; probably reduced effect of nifedipine
* Norethisterone: Accelerated metabolism (reduced contraceptive effect)
* Phenobarbitone: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of phenobarbitone often raised

Praziquantel: Plasma-praziquantel concentration reduced
* Prednisolone: Metabolism of prednisolone accelerated (reduced effect)
Procarbazine: Reduced absorption of phenytoin
* Pyrimethamine: Antagonism of anticonvulsant effect; increased antifolate effect
* Quinidine: Accelerated metabolism (reduced plasma-quinidine concentration)
* Rifampicin: Accelerated metabolism of phenytoin (reduced plasma concentration)
Saquinavir: Plasma-saquinavir concentration possibly reduced
Sulfadiazine: Plasma-phenytoin concentration possibly increased
* Sulfadoxine+Pyrimethamine: Plasma-phenytoin concentration possibly increased; increased antifolate effect
* Sulfamethoxazole+Trimethoprim: Antifolate effect and plasma-phenytoin concentration increased
Theophylline: Accelerated metabolism of theophylline (reduced plasma concentration)
* Trimethoprim: Antifolate effect and plasma-phenytoin concentration increased
Vaccine, Influenza: Enhanced effect of phenytoin
* Valproic acid: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid often lowered; plasma concentration of phenytoin often raised (but may also be lowered)
Vecuronium: Antagonism of muscle relaxant effect (accelerated recovery from neuromuscular blockade)
Verapamil: Reduced effect of verapamil
Vincristine: Reduced absorption of phenytoin
* Warfarin: Accelerated metabolism of warfarin (possibility of reduced anticoagulant effect, but enhancement also reported)
Zidovudine: Plasma-phenytoin concentration increased or decreased by zidovudine

Phytomenadione

* Warfarin: Antagonism of anticoagulant effect by phytomenadione

Poliomyelitis, oral vaccine *see* Vaccine, live

Polygeline

Gentamicin: Increased risk of nephrotoxicity

Potassium chloride *see* Potassium salts

Potassium salts

* Amiloride: Risk of hyperkalaemia
* Enalapril: Risk of severe hyperkalaemia
* Ciclosporin: Increased risk of hyperkalaemia
* Spironolactone: Risk of hyperkalaemia

Pralidoxime

Atropine: potentiates antimuscarinic effects of Atropine.
Barbiturates: smaller doses required to handle convulsions
* Morphine: worsens OP poisoning
Neostigmine/pyridostigmine: may reduce their effect
* Phenothiazine: worsens OP poisoning
Reserpine: worsens OP poisoning – contraindicated
Succinyl choline: worsens OP poisoning
Theophylline: worsens OP poisoning
Praziquantel

Carbamazepine: Plasma-praziquantel concentration reduced
Dexamethasone: Plasma-praziquantel concentration reduced
Phenytoin: Plasma-praziquantel concentration reduced

Prednisolone

Acetazolamide: Increased risk of hypokalaemia; antagonism of diuretic effect
Acetylsalicylic acid: Increased risk of gastrointestinal bleeding and ulceration; prednisolone reduces plasma-salicylate concentration
Amiloride: Antagonism of diuretic effect
* Amphotericin: Increased risk of hypokalaemia (avoid concomitant use unless prednisolone needed to control reactions)
Atenolol: Antagonism of hypotensive effect
Enalapril: Antagonism of hypotensive effect
* Carbamazepine: Accelerated metabolism of prednisolone (reduced effect)
Ciclosporin: Increased plasma concentration of prednisolone
Contraceptives, Oral: Oral contraceptives increase plasma concentration of prednisolone
Digoxin: Increased risk of hypokalaemia
Erythromycin: Erythromycin possibly inhibits metabolism of prednisolone
Frusemide: Antagonism of diuretic effect; increased risk of hypokalaemia
Glibenclamide: Antagonism of hypoglycaemic effect
Glyceryl trinitrate: Antagonism of hypotensive effect
Hydralazine: Antagonism of hypotensive effect
Hydrochlorothiazide: Antagonism of diuretic effect; increased risk of hypokalaemia
Ibuprofen: Increased risk of gastrointestinal bleeding and ulceration
Insulins: Antagonism of hypoglycaemic effect
Isosorbide dinitrate: Antagonism of hypotensive effect
Levonorgestrel: Levonorgestrel increases plasma concentration of prednisolone
* Medroxyprogesterone: Medroxyprogesterone increases plasma concentration of prednisolone
Metformin: Antagonism of hypoglycaemic effect
Methotrexate: Increased risk of haematological toxicity
Methyldopa: Antagonism of hypotensive effect
Nifedipine: Antagonism of hypotensive effect
* Norethisterone: Norethisterone increases plasma concentration of prednisolone
* Phenobarbitone: Metabolism of prednisolone accelerated (reduced effect)
* Phenytoin: Metabolism of prednisolone accelerated (reduced effect)
Prazosin: Antagonism of hypotensive effect
Propranolol: Antagonism of hypotensive effect
Reserpine: Antagonism of hypotensive effect
* Rifampicin: Accelerated metabolism of prednisolone (reduced effect)
Ritonavir: Plasma concentration possibly increased by ritonavir
Salbutamol: Increased risk of hypokalaemia if high doses of prednisolone given with high doses of salbutamol
Sodium nitroprusside: Antagonism of hypotensive effect
Spironolactone: Antagonism of diuretic effect
Theophylline: Increased risk of hypokalaemia
Vaccine, Live: High doses of prednisolone impair immune response; avoid use of live vaccines

Verapamil: Antagonism of hypotensive effect
* Warfarin: Anticoagulant effect possibly altered

Procaine benzylpenicillin *see* Benzylpenicillin

Promethazine

Alcohol: Enhanced sedative effect
Imipramine: Increased antimuscarinic and sedative effects
Atropine: Increased antimuscarinic adverse effects
Biperiden: Increased antimuscarinic adverse effects
Chloral hydrate: Enhanced sedative effect
Clomipramine: Increased antimuscarinic and sedative effects
Clonazepam: Enhanced sedative effect
Diazepam: Enhanced sedative effect
Pyridostigmine
Alcuronium: Antagonism of muscle relaxant effect
Atropine: Antagonism of effect
Biperiden: Antagonism of effect
Chloroquine: Chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of pyridostigmine
Clindamycin: Antagonism of effects of pyridostigmine
* Gentamicin: Antagonism of effect of pyridostigmine
Lithium: Antagonism of effect of pyridostigmine
Procainamide: Antagonism of effect of pyridostigmine
Propranolol: Antagonism of effect of pyridostigmine
Quinidine: Antagonism of effect of pyridostigmine
* Streptomycin: Antagonism of effect of pyridostigmine
Suxamethonium: Effect of suxamethonium enhanced
Vecuronium: Antagonism of muscle relaxant effect

Pyridoxine

Levodopa: Antagonism of levodopa unless carbidopa also given

Pyrimethamine

* Methotrexate: Antifolate effect of methotrexate increased
* Phenytoin: Antagonism of anticonvulsant effect; increased antifolate effect
* Sulfadiazine: Increased risk of antifolate effect
* Sulfamethoxazole+Trimethoprim: Increased antifolate effect
* Trimethoprim: Increased antifolate effect

Pyrimethamine+Sulfadoxine *see* Sulfadoxine+Pyrimethamine

Quinine

* Artemether+Lumefantrine: Increased risk of ventricular arrhythmias
Chloroquine: Increased risk of ventricular arrhythmias
Cimetidine: Metabolism of quinine inhibited (increased plasma concentration)
* Digoxin: Plasma concentration of digoxin increased
* Mefloquine: Increased risk of convulsions, but should not prevent the use of intravenous quinine in severe cases

Ranitidine

* Carbamazepine: Metabolism of carbamazepine inhibited (increased plasma-carbamazepine concentration)
Chloroquine: Inhibition of chloroquine metabolism (increased plasma concentration)
Chlorpromazine: Possibly enhanced effects of chlorpromazine
* Ciclosporin: Possibly increased plasma-ciclosporin concentration
Clomipramine: Plasma concentration of clomipramine possibly increased

Clonazepam: Inhibition of clonazepam metabolism (increased plasma concentration)
Codeine: Metabolism of codeine inhibited (increased plasma concentration)
Diazepam: Inhibition of diazepam metabolism (increased plasma concentration)
Erythromycin: Increased plasma-erythromycin concentration (increased risk of toxicity, including deafness)
Fluorouracil: Metabolism of fluorouracil inhibited (increased plasmafluorouracil concentration)
Fluphenazine: Possibly enhanced effects of fluphenazine
Glibenclamide: Enhanced hypoglycaemic effect
Haloperidol: Possibly enhanced effects of haloperidol
Imipramine: Plasma concentration of imipramine increased (inhibition of metabolism)
* Lidocaine: Increased plasma concentration of lidocaine (increased risk of toxicity)
Mebendazole: Metabolism of mebendazole possibly inhibited (increased plasma concentration)
Metformin: Renal excretion of metformin inhibited; increased plasmametformin concentration
Metronidazole: Metabolism of metronidazole inhibited (increased plasma-metronidazole concentration)
Morphine: Metabolism of morphine inhibited (increased plasma concentration)
Nifedipine: Metabolism of nifedipine possibly inhibited (increased plasma concentration)
Pethidine: Metabolism of pethidine inhibited (increased plasma concentration)
* Phenytoin: Metabolism of phenytoin inhibited (increased plasma concentration)
* Procainamide: Increased plasma concentration of procainamide
Propranolol: Increased plasma-propranolol concentration
* Quinidine: Increased plasma concentration of quinidine
Quinine: Metabolism of quinine inhibited (increased plasma concentration)
Rifampicin: Accelerated metabolism of cimetidine (reduced plasmacimetidine concentration)
* Theophylline: Metabolism of theophylline inhibited (plasma-theophylline concentration increased)
* Valproic acid: Metabolism of valproic acid inhibited (increased plasma concentration)
Verapamil: Metabolism of verapamil possibly inhibited (increased plasma concentration)
* Warfarin: Enhanced anticoagulant effect (inhibition of metabolism)

Rifampicin

Imipramine: Plasma concentration of imipramine possibly reduced (reduced antidepressant effect)
Antacids (Aluminium hydroxide; Magnesium hydroxide): Reduced absorption of rifampicin
* Azathioprine: Manufacturer reports interaction (transplants possibly rejected)
Chloramphenicol: Accelerated metabolism of chloramphenicol (reduced plasma-chloramphenicol concentration)
* Ciclosporin: Accelerated metabolism (reduced plasma-ciclosporin concentration)

Cimetidine: Accelerated metabolism of cimetidine (reduced plasmacimetidine concentration)
Clomipramine: Plasma concentration of clomipramine possibly reduced (reduced antidepressant effect)
Clonazepam: Metabolism of clonazepam possibly accelerated (possibly reduced plasma concentration)
* Contraceptives, Oral: Accelerated metabolism of oral contraceptives (reduced contraceptive effect)
Dapsone: Reduced plasma-dapsone concentration
* Dexamethasone: Accelerated metabolism of dexamethasone (reduced effect)
Diazepam: Metabolism of diazepam accelerated (reduced plasma concentration)
Doxycycline: Plasma-doxycycline concentration possibly reduced
Efavirenz: Reduced plasma concentration of efavirenz (increase efavirenz dose)
* Fluconazole: Accelerated metabolism of fluconazole (reduced plasma concentration)
* Fludrocortisone: Accelerated metabolism of fludrocortisone (reduced effect)
* Glibenclamide: Possibly accelerated metabolism (reduced effect) of glibenclamide
* Haloperidol: Accelerated metabolism of haloperidol (reduced plasmahaloperidol concentration)
* Hydrocortisone: Accelerated metabolism of hydrocortisone (reduced effect)
* Indinavir: Metabolism enhanced by rifampicin (plasma-indinavir concentration significantly reduced—avoid concomitant use)
* Levonorgestrel: Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
Levothyroxine: Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism)
* Lopinavir: Reduced plasma concentration of lopinavir (avoid concomitant use)
* Medroxyprogesterone: Accelerated metabolism of medroxy-progesterone (reduced contraceptive effect)
* Nelfinavir: Plasma concentration of nelfinavir significantly reduced (avoid concomitant use)
Nevirapine: Reduced plasma concentration of nevirapine
* Nifedipine: Accelerated metabolism of nifedipine (plasma concentration significantly reduced)
* Norethisterone: Accelerated metabolism of norethisterone (reduced contraceptive effect)
* Phenytoin: Accelerated metabolism of phenytoin (reduced plasma concentration)
* Prednisolone: Accelerated metabolism of prednisolone (reduced effect)
Propranolol: Metabolism of propranolol accelerated (significantly reduced plasma concentration)
* Quinidine: Accelerated metabolism (reduced plasma-quinidine concentration)
* Saquinavir: Accelerated metabolism of saquinavir (reduced plasma concentration—avoid concomitant use)
Theophylline: Accelerated metabolism of theophylline (reduced plasmatheophylline concentration)

* Verapamil: Accelerated metabolism of verapamil (plasma concentration significantly reduced)
* Warfarin: Accelerated metabolism of warfarin (reduced anticoagulant effect)

Salbutamol

Acetazolamide: Increased risk of hypokalaemia with high doses of salbutamol
Dexamethasone: Increased risk of hypokalaemia if high doses of dexamethasone given with high doses of salbutamol
Fludrocortisone: Increased risk of hypokalaemia if high doses of fludrocortisone given with high doses of salbutamol
Frusemide: Increased risk of hypokalaemia with high doses of salbutamol
Hydrochlorothiazide: Increased risk of hypokalaemia with high doses of salbutamol
Hydrocortisone: Increased risk of hypokalaemia if high doses of hydrocortisone given with high doses of salbutamol
* Methyldopa: Acute hypotension reported with salbutamol infusion
Prednisolone: Increased risk of hypokalaemia if high doses of prednisolone given with high doses of salbutamol
Theophylline: Increased risk of hypokalaemia with concomitant use of high doses of salbutamol

Sodium valproate *see* Valproic acid

Soluble insulin *see* Insulins

Streptomycin

* Alcuronium: Enhanced muscle relaxant effect
Amphotericin: Increased risk of nephrotoxicity
* Ciclosporin: Increased risk of nephrotoxicity
* Cisplatin: Increased risk of nephrotoxicity and possibly of ototoxicity
* Frusemide: Increased risk of ototoxicity
* Neostigmine: Antagonism of effect of neostigmine
* Pyridostigmine: Antagonism of effect of pyridostigmine
* Suxamethonium: Enhanced muscle relaxant effect
Vancomycin: Increased risk of nephrotoxicity and ototoxicity
* Vecuronium: Enhanced muscle relaxant effect

Sulfadiazine

* Ciclosporin: Plasma-ciclosporin concentration possibly reduced; increased risk of nephrotoxicity
* Glibenclamide: Enhanced effect of glibenclamide
Methotrexate: Risk of methotrexate toxicity increased
Phenytoin: Plasma-phenytoin concentration possibly increased
* Pyrimethamine: Increased risk of antifolate effect
* Sulfadoxine+Pyrimethamine: Increased risk of antifolate effect
Thiopentone: Enhanced effects of thiopentone
* Warfarin: Enhanced anticoagulant effect

Sulfadoxine+Pyrimethamine

* Ciclosporin: Increased risk of nephrotoxicity
* Glibenclamide: Enhanced effect of glibenclamide
* Methotrexate: Antifolate effect of methotrexate increased; risk of methotrexate toxicity increased
* Phenytoin: Plasma-phenytoin concentration possibly increased; increased antifolate effect
* Sulfadiazine: Increased risk of antifolate effect
* Sulfamethoxazole+Trimethoprim: Increased antifolate effect
Thiopentone: Enhanced effects of thiopentone

* Trimethoprim: Increased antifolate effect
* Warfarin: Enhanced anticoagulant effect

Sulfamethoxazole+Trimethoprim

* Azathioprine: Increased risk of haematological toxicity
* Ciclosporin: Increased risk of nephrotoxicity; plasma-ciclosporin concentration possibly reduced by intravenous trimethoprim
Digoxin: Plasma concentration of digoxin possibly increased
* Glibenclamide: Enhanced effect of glibenclamide
Lamivudine: Plasma concentration of lamivudine increased (avoid concomitant use of high-dose sulfamethoxazole+trimethoprim)
* Mercaptopurine: Increased risk of haematological toxicity
* Methotrexate: Antifolate effect of methotrexate increased; risk of methotrexate toxicity increased
* Phenytoin: Antifolate effect and plasma-phenytoin concentration increased
Procainamide: Increased plasma-procainamide concentration
* Pyrimethamine: Increased antifolate effect
* Sulfadoxine+Pyrimethamine: Increased antifolate effect
Thiopentone: Enhanced effects of thiopentone
* Warfarin: Enhanced anticoagulant effect

Sulfasalazine

Digoxin: Absorption of digoxin possibly reduced

Suxamethonium

Cyclophosphamide: Enhanced effect of suxamethonium
Digoxin: Risk of arrhythmias
* Gentamicin: Enhanced muscle relaxant effect
Lidocaine: Action of suxamethonium prolonged
Lithium: Enhanced muscle relaxant effect
Magnesium (parenteral): Enhanced muscle relaxant effect
Neostigmine: Effect of suxamethonium enhanced
* Procainamide: Enhanced muscle relaxant effect
Propranolol: Enhanced muscle relaxant effect
Pyridostigmine: Effect of suxamethonium enhanced
* Quinidine: Enhanced muscle relaxant effect
* Streptomycin: Enhanced muscle relaxant effect

Theophylline

Acetazolamide: Increased risk of hypokalaemia
Allopurinol: Plasma-theophylline concentration possibly increased
Atenolol: Avoid concomitant use on pharmacological grounds (bronchospasm)
Carbamazepine: Accelerated metabolism of theophylline (reduced effect)
* Cimetidine: Metabolism of theophylline inhibited (plasma-theophylline concentration increased)
* Ciprofloxacin: Increased plasma-theophylline concentration; possible increased risk of convulsions
Contraceptives, Oral: Delayed excretion of theophylline (increased plasma concentration)
Dexamethasone: Increased risk of hypokalaemia
* Erythromycin: Inhibition of theophylline metabolism (increased plasmatheophylline concentration); if erythromycin given by mouth, also decreased plasma-erythromycin concentration
* Fluconazole: Plasma-theophylline concentration possibly increased
Fludrocortisone: Increased risk of hypokalaemia
Frusemide: Increased risk of hypokalaemia

Halothane: Increased risk of arrhythmias
Hydrochlorothiazide: Increased risk of hypokalaemia
Hydrocortisone: Increased risk of hypokalaemia
Isoniazid: Plasma-theophylline concentration possibly increased
Ketamine: Increased risk of convulsions
Lithium: Increased lithium excretion (reduced plasma-lithium concentration)
* Nalidixic acid: Possible increased risk of convulsions
* Nifedipine: Possibly enhanced theophylline effect (possibly increased plasma-theophylline concentration)
* Ofloxacin: Possible increased risk of convulsions
Phenobarbitone: Metabolism of theophylline accelerated (reduced effect)
Phenytoin: Accelerated metabolism of theophylline (reduced plasma concentration)
Prednisolone: Increased risk of hypokalaemia
Propranolol: Avoid concomitant use on pharmacological grounds (bronchospasm)
Rifampicin: Accelerated metabolism of theophylline (reduced plasmatheophylline concentration)
* Ritonavir: Accelerated theophylline metabolism (reduced plasma concentration)
Salbutamol: Increased risk of hypokalaemia with concomitant use of high doses of salbutamol
Timolol: Avoid concomitant use on pharmacological grounds (bronchospasm)
Tobacco: Tobacco smoking increases theophylline metabolism (reduced plasma-theophylline concentration)
Vaccine, Influenza: Plasma-theophylline concentration occasionally increased
* Verapamil: Enhanced theophylline effect (increased plasma-theophylline concentration)

Thiopentone

Acetazolamide: Enhanced hypotensive effect
Amiloride: Enhanced hypotensive effect
Imipramine: Increased risk of arrhythmias and hypotension
Atenolol: Enhanced hypotensive effect
Enalapril: Enhanced hypotensive effect
Chloral hydrate: Enhanced sedative effect
* Chlorpromazine: Enhanced hypotensive effect
Clomipramine: Increased risk of arrhythmias and hypotension
Clonazepam: Enhanced sedative effect
Diazepam: Enhanced sedative effect
* Fluphenazine: Enhanced hypotensive effect
Frusemide: Enhanced hypotensive effect
Glyceryl trinitrate: Enhanced hypotensive effect
* Haloperidol: Enhanced hypotensive effect
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Enhanced hypotensive effect
Isoniazid: Possible potentiation of isoniazid hepatotoxicity
Isosorbide dinitrate: Enhanced hypotensive effect
Methyldopa: Enhanced hypotensive effect
Nifedipine: Enhanced hypotensive effect
* Prazosin: Enhanced hypotensive effect
Propranolol: Enhanced hypotensive effect

Reserpine: Enhanced hypotensive effect
Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Enhanced hypotensive effect
Sulfadiazine: Enhanced effects of thiopentone
Sulfadoxine+Pyrimethamine: Enhanced effects of thiopentone
Sulfamethoxazole+Trimethoprim: Enhanced effects of thiopentone
Timolol: Enhanced hypotensive effect
Vancomycin: Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin
* Verapamil: Enhanced hypotensive effect and AV delay

Timolol

NOTE. Systemic absorption may follow topical application of timolol to the eye
Acetazolamide: Enhanced hypotensive effect
Alcohol: Enhanced hypotensive effect
Amiloride: Enhanced hypotensive effect
Enalapril: Enhanced hypotensive effect
Chloral hydrate: Enhanced hypotensive effect
Chlorpromazine: Enhanced hypotensive effect
Clonazepam: Enhanced hypotensive effect
Diazepam: Enhanced hypotensive effect
Digoxin: Increased AV block and bradycardia
* Epinephrine: Severe hypertension
Ergotamine: Increased peripheral vasoconstriction
Ether, Anaesthetic: Enhanced hypotensive effect
Fluphenazine: Enhanced hypotensive effect
Frusemide: Enhanced hypotensive effect
Glibenclamide: Masking of warning signs of hypoglycaemia such as tremor
Glyceryl trinitrate: Enhanced hypotensive effect
Halothane: Enhanced hypotensive effect
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Enhanced hypotensive effect
Insulins: Enhanced hypoglycaemic effect; masking of warning signs of hypoglycaemia such as tremor
Isosorbide dinitrate: Enhanced hypotensive effect
Ketamine: Enhanced hypotensive effect
Levodopa: Enhanced hypotensive effect
* Lidocaine: Increased risk of myocardial depression
Mefloquine: Increased risk of bradycardia
Metformin: Masking of warning signs of hypoglycaemia such as tremor
Methyldopa: Enhanced hypotensive effect
* Nifedipine: Severe hypotension and heart failure occasionally
Nitrous oxide: Enhanced hypotensive effect
* Prazosin: Enhanced hypotensive effect; increased risk of first-dose hypotensive effect of prazosin
* Procainamide: Increased risk of myocardial depression
* Quinidine: Increased risk of myocardial depression
Reserpine: Enhanced hypotensive effect
Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Enhanced hypotensive effect
Theophylline: Avoid concomitant use on pharmacological grounds (bronchospasm)
Thiopentone: Enhanced hypotensive effect
* Verapamil: Asystole, severe hypotension and heart failure

Trimethoprim

* Azathioprine: Increased risk of haematological toxicity
* Ciclosporin: Increased risk of nephrotoxicity; plasma-ciclosporin concentration possibly reduced by intravenous trimethoprim
Digoxin: Plasma concentration of digoxin possibly increased
Lamivudine: Plasma concentration of lamivudine increased (avoid concomitant use of high-dose trimethoprim)
* Mercaptopurine: Increased risk of haematological toxicity
* Methotrexate: Antifolate effect of methotrexate increased
* Phenytoin: Antifolate effect and plasma-phenytoin concentration increased
Procainamide: Increased plasma-procainamide concentration
* Pyrimethamine: Increased antifolate effect
* Sulfadoxine+Pyrimethamine: Increased antifolate effect
Warfarin: Possibly enhanced anticoagulant effect

Vaccine, Live

Asparaginase: Avoid use of live vaccines with asparaginase (impairment of immune response)
* Azathioprine: Avoid use of live vaccines with azathioprine (impairment of immune response)
Bleomycin: Avoid use of live vaccines with bleomycin (impairment of immune response)
Chlorambucil: Avoid use of live vaccines with chlorambucil (impairment of immune response)
Chlormethine: Avoid use of live vaccines with chlormethine (impairment of immune response)
* Ciclosporin: Avoid use of live vaccines with ciclosporin (impairment of immune response)
Cisplatin: Avoid use of live vaccines with cisplatin (impairment of immune response)
Cyclophosphamide: Avoid use of live vaccines with cyclophosphamide (impairment of immune response)
Cytarabine: Avoid use of live vaccines with cytarabine (impairment of immune response)
Dacarbazine: Avoid use of live vaccines with dacarbazine (impairment of immune response)
Dactinomycin: Avoid use of live vaccines with dactinomycin (impairment of immune response)
Daunorubicin: Avoid use of live vaccines with daunorubicin (impairment of immune response)
Dexamethasone: High doses of dexamethasone impair immune response; avoid use of live vaccines
Doxorubicin: Avoid use of live vaccines with doxorubicin (impairment of immune response)
Etoposide: Avoid use of live vaccines with etoposide (impairment of immune response)
Fludrocortisone: High doses of fludrocortisone impair immune response; avoid use of live vaccines
Fluorouracil: Avoid use of live vaccines with fluorouracil (impairment of immune response)
Hydrocortisone: High doses of hydrocortisone impair immune response; avoid use of live vaccines
* Immunoglobulin, Normal: Avoid use of live vaccine during *3 weeks before* or during *3 months after* injection of normal immunoglobulin (impairment of immune response)

Mercaptopurine: Avoid use of live vaccines with mercaptopurine (impairment of immune response)
Methotrexate: Avoid use of live vaccines with methotrexate (impairment of immune response)
Prednisolone: High doses of prednisolone impair immune response; avoid use of live vaccines
Procarbazine: Avoid use of live vaccines with procarbazine (impairment of immune response)
Vinblastine: Avoid use of live vaccines with vinblastine (impairment of immune response)
Vincristine: Avoid use of live vaccines with vincristine (impairment of immune response)
Vaccine, Rabies
Chloroquine: Concomitant administration of chloroquine may affect antibody response

Valproic acid

Acetylsalicylic acid: Enhancement of effect of valproic acid
* Imipramine: Antagonism (convulsive threshold lowered)
* Carbamazepine: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid often lowered; plasma concentration of active metabolite of carbamazepine often raised
* Chloroquine: Antagonism of anticonvulsant effect
* Chlorpromazine: Antagonism of anticonvulsant effect (convulsive threshold lowered)
* Cimetidine: Metabolism of valproic acid inhibited (increased plasma concentration)
* Clomipramine: Antagonism (convulsive threshold lowered)
Erythromycin: Metabolism of valproic acid possibly inhibited (increased plasma concentration)
* Ethosuximide: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of ethosuximide sometimes raised
* Fluphenazine: Antagonism of anticonvulsant effect (convulsive threshold lowered)
* Haloperidol: Antagonism of anticonvulsant effect (convulsive threshold lowered)
* Mefloquine: Antagonism of anticonvulsant effect
* Phenobarbitone: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid often lowered; phenobarbitone concentration often raised
* Phenytoin: May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid often lowered; plasma concentration of phenytoin often raised (but may also be lowered)
Warfarin: Anticoagulant effect possibly enhanced
Zidovudine: Plasma concentration of zidovudine possibly increased (risk of toxicity)

Verapamil

Acetazolamide: Enhanced hypotensive effect
Alcohol: Enhanced hypotensive effect; plasma concentration of alcohol possibly increased by verapamil
Alcuronium: Enhanced muscle relaxant effect
Amiloride: Enhanced hypotensive effect
Imipramine: Possibly increased plasma concentration of imipramine

* Atenolol: Asystole, severe hypotension and heart failure
Enalapril: Enhanced hypotensive effect
* Carbamazepine: Enhanced effect of carbamazepine
Chloral hydrate: Enhanced hypotensive effect
Chlorpromazine: Enhanced hypotensive effect
* Ciclosporin: Increased plasma-ciclosporin concentration
Cimetidine: Metabolism of verapamil possibly inhibited (increased plasma concentration)
Clomipramine: Possibly increased plasma concentration of clomipramine
Clonazepam: Enhanced hypotensive effect
Contraceptives, Oral: Antagonism of hypotensive effect
Dexamethasone: Antagonism of hypotensive effect
Diazepam: Enhanced hypotensive effect
* Digoxin: Increased plasma concentration of digoxin; increased AV block and bradycardia
* Ether, Anaesthetic: Enhanced hypotensive effect and AV delay
Fludrocortisone: Antagonism of hypotensive effect
Fluphenazine: Enhanced hypotensive effect
Frusemide: Enhanced hypotensive effect
Glyceryl trinitrate: Enhanced hypotensive effect
Grapefruit juice: Increased plasma-verapamil concentration
Haloperidol: Enhanced hypotensive effect
* Halothane: Enhanced hypotensive effect and AV delay
Hydralazine: Enhanced hypotensive effect
Hydrochlorothiazide: Enhanced hypotensive effect
Hydrocortisone: Antagonism of hypotensive effect
Ibuprofen: Antagonism of hypotensive effect
Isosorbide dinitrate: Enhanced hypotensive effect
* Ketamine: Enhanced hypotensive effect and AV delay
Levodopa: Enhanced hypotensive effect
Lithium: Neurotoxicity may occur without increased plasma-lithium concentration
Mefloquine: Possibly increased risk of bradycardia
Methyldopa: Enhanced hypotensive effect
* Nitrous oxide: Enhanced hypotensive effect and AV delay
* Phenobarbitone: Effect of verapamil probably reduced
Phenytoin: Reduced effect of verapamil
* Prazosin: Enhanced hypotensive effect; increased risk of first-dose hypotensive effect of prazosin
Prednisolone: Antagonism of hypotensive effect
* Propranolol: Asystole, severe hypotension and heart failure
* Quinidine: Increased plasma-quinidine concentration (extreme hypotension may occur)
Reserpine: Enhanced hypotensive effect
* Rifampicin: Accelerated metabolism of verapamil (plasma concentration significantly reduced)
* Ritonavir: Plasma concentration possibly increased by ritonavir
Sodium nitroprusside: Enhanced hypotensive effect
Spironolactone: Enhanced hypotensive effect
* Theophylline: Enhanced theophylline effect (increased plasma-theophylline concentration)
* Thiopentone: Enhanced hypotensive effect and AV delay
* Timolol: Asystole, severe hypotension and heart failure
Vecuronium: Enhanced muscle relaxant effect

Vitamin D *see* Ergocalciferol

Warfarin

NOTE. **Major changes in diet (especially involving salads and vegetables) and in alcohol consumption may affect anticoagulant control**

* Acetylsalicylic acid: Increased risk of bleeding due to antiplatelet effect
* Alcohol: Enhanced anticoagulant effect with large amounts of alcohol; major changes in alcohol consumption may affect anticoagulant control

Allopurinol: Anticoagulant effect possibly enhanced

Amoxicillin: Studies have failed to demonstrate an interaction, but common experience in anticoagulant clinics is that INR can be altered by a course of amoxicillin

Ampicillin: Studies have failed to demonstrate an interaction, but common experience in anticoagulant clinics is that INR can be altered by acourse of ampicillin

* Azathioprine: Anticoagulant effect possibly reduced
* Carbamazepine: Accelerated metabolism of warfarin (reduced anticoagulant effect)
* Ceftazidime: Possibly enhanced anticoagulant effect
* Ceftriaxone: Possibly enhanced anticoagulant effect

Chloral hydrate: May transiently enhance anticoagulant effect

* Chloramphenicol: Enhanced anticoagulant effect
* Cimetidine: Enhanced anticoagulant effect (inhibition of metabolism)
* Ciprofloxacin: Enhanced anticoagulant effect
* Contraceptives, Oral: Antagonism of anticoagulant effect
* Dexamethasone: Anticoagulant effect possibly altered
* Doxycycline: Anticoagulant effect possibly enhanced
* Erythromycin: Enhanced anticoagulant effect
* Fluconazole: Enhanced anticoagulant effect
* Fludrocortisone: Anticoagulant effect possibly altered
* Glibenclamide: Possibly enhanced hypoglycaemic effects and changes to anticoagulant effect
* Griseofulvin: Metabolism of warfarin accelerated (reduced anticoagulant effect)
* Hydrocortisone: Anticoagulant effect possibly altered
* Ibuprofen: Anticoagulant effect possibly enhanced
* Levonorgestrel: Antagonism of anticoagulant effect
* Levothyroxine: Enhanced anticoagulant effect
* Medroxyprogesterone: Antagonism of anticoagulant effect
* Metronidazole: Enhanced anticoagulant effect
* Minocycline: Anticoagulant effect possibly enhanced
* Nalidixic acid: Enhanced anticoagulant effect
* Norethisterone: Antagonism of anticoagulant effect
* Ofloxacin: Enhanced anticoagulant effect

Paracetamol: Prolonged regular use of paracetamol possibly enhances anticoagulant effect

* Phenobarbitone: Metabolism of warfarin accelerated (reduced anticoagulant effect)
* Phenytoin: Accelerated metabolism of warfarin (possibility of reduced anticoagulant effect, but enhancement also reported)
* Phytomenadione: Antagonism of anticoagulant effect by phytomenadione
* Prednisolone: Anticoagulant effect possibly altered

* Proguanil: Possibly enhanced anticoagulant effect
* Quinidine: Anticoagulant effect may be enhanced
* Rifampicin: Accelerated metabolism of warfarin (reduced anticoagulant effect)
* Ritonavir: Plasma concentration possibly increased by ritonavir
* Sulfadiazine: Enhanced anticoagulant effect
* Sulfadoxine+Pyrimethamine: Enhanced anticoagulant effect
* Sulfamethoxazole+Trimethoprim: Enhanced anticoagulant effect
* Tamoxifen: Enhanced anticoagulant effect
* Testosterone: Enhanced anticoagulant effect

Trimethoprim: Possibly enhanced anticoagulant effect

Vaccine, Influenza: Effect of warfarin occasionally enhanced

Valproic acid: Anticoagulant effect possibly enhanced

Appendix 2:Pregnancy

During pregnancy the mother and the fetus form a nonseparable functional unit. Maternal well-being is an absolute prerequisite for the optimal functioning and development of both parts of this unit. Consequently, it is important to treat the mother whenever needed while protecting the unborn to the greatest possible extent.

Drugs can have harmful effects on the fetus at any time during pregnancy. It is important to remember this when prescribing for a woman of childbearing age. However, irrational fear of using drugs during pregnancy can also result in harm. This includes untreated illness, impaired maternal adherence, suboptimal treatment and treatment failures. Such approaches may impose risk to maternal well-being, and may also affect the unborn child. It is important to know the 'background risk' in the context of the prevalence of druginduced adverse pregnancy outcomes. Major congenital malformations occur in 2–4% of all live births. Up to 15% of all diagnosed pregnancies will result in fetal loss. The cause of these adverse pregnancy outcomes is understood in only a minority of the incidents.

During the *first trimester* drugs may produce congenital malformations (teratogenesis), and the greater risk is from third to the eleventh week of pregnancy. During the *second* and *third trimester* drugs may affect the growth and functional development of the fetus or have toxic effects on fetal tissues. Drugs given shortly before term or during labour may have adverse effects on labour or on the neonate after delivery. Few drugs have been shown conclusively to be teratogenic in man but no drug is safe beyond all doubt in early pregnancy. Screening procedures are available where there is a known risk of certain defects.

Prescribing in pregnancy

If possible counselling of women before a planned pregnancy should be carried out including discussion of risks associated with specific therapeutic agents, traditional medicines and abuse of substances such as smoking and alcohol. Folic acid supplements should be given during pregnancy planning because periconceptual use of folic acid reduces neural tube defects.

Drugs should be prescribed in pregnancy only if the expected benefits to the mother are thought to be greater than the risk to the fetus. All drugs should be avoided if possible during the first trimester. Drugs which have been used extensively in pregnancy and appear to be usually safe should be prescribed in preference to new or untried drugs and the

smallest effective dose should be used. Well known single component drugs should usually be preferred to multi-component drugs.

The following list includes drugs which may have harmful effects in pregnancy and indicates the trimester of risk. It is based on human data but information on animal studies has been included for some newer drugs when its omission might be misleading.

Absence of a drug from the list does not imply safety.

Table of drugs to be avoided or used with caution in Pregnancy

Drug	Comment
Acetazolamide	Not used to treat hypertension in pregnancy First trimester: Avoid (toxicity in *animal* studies)
Acetylsalicylic acid	Third trimester: Impaired platelet function and risk of haemorrhage; delayed onset and increased duration of labour with in creased blood loss; avoid analgesic doses if possible in last few weeks (low doses probably not harm ful); with high doses,closure of fetal ductus arteriosus *in utero* and possibly persistent pulmonary hypertension of newborn; kernict erus in jaundiced neonates
Albendazole	Contraindicated in cestode infections; *see* section 6.1.1.1. First trimester: avoid in nematode infections; *see* section 6.1.1.2
Alcohol	First, second trimesters: Regular daily drinking is teratogenic (fetal alcohol syndrome) and may cause growth retardation; occasional single drinks are probably safe Third trimester: Withdrawal may occur in babies of alcoholic mothers
Aminophylline	Third trimester: Neonatal irritability and apnoea have been reported Amlodipine May inhibit labour; some dihydropyridines are teratogenic in *animals*, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension
Amoxicillin	Not known to be harmful Amoxicillin + Clavulanic acid No evidence of teratogenicity
Amphotericin	Not known to be harmful but use only if potential benefit outweighs risk
Ampicillin	Not known to be harmful
Artesunate	First trimester: Avoid
Atenolol	May cause intrauterine growth restriction, neonatal hypoglycaemia, and bradycardia; risk greater in severe hypertension; *see also* section 12.3
Benzathine benzylpenicillin	Not known to be harmful
Benzylpenicillin	Not known to be harmful

Drug	Comment
Betamethasone	Benefit of treatment, for example in asthma, outweighs risk Bisacodyl: safe; give caution in first trimester
Carbamazepine	First trimester: Risk of teratogenesis including increased risk of neural tube defects (counselling and screening and adequate folate supplements advised, for example 5 mg daily); risk of teratogenicity greater if more than one antiepileptic used;*see also* section 5.1 Third trimester: May possibly cause vitamin K deficiency and risk of neonatal bleeding; if vitamin K not given at birth, neonate should be monitored closely for signs of bleeding Chloral hydrate Avoid
Chloramphenicol	Third trimester: Neonatal 'grey' syndrome
Chloroquine	First, third trimesters: Benefit of pro phylaxis and treatment in malaria outweighs risk; important: *see also* section 6.4.3
Chlorphenamine	No evidence of teratogenicity
Chlorpromazine	Third trimester: Extrapyramidal effects in neonate occasionally reported
Ciprofloxacin	All trimesters: Avoid—arthropathy in *animal* studies; safer alternatives available
Cloxacillin	Not known to be harmful
Contraceptives, oral	Epidemiological evidence suggests no harmful effects on fetus
Dapsone	Third trimester: Neonatal haemolysis and methaemoglobinaemia; adequate folate supplements should be given to mother
Diazepam	Avoid regular use (risk of neonatal withdrawal symptoms); use only if clear indication such as seizure control (high doses during late pregnancy or labour may cause neonatal hypothermia, hypotonia and respiratory depression)
Diethylcarbamazine	Avoid: Delay treatment until after delivery
Digoxin	May need dosage adjustment
Diloxanide	Defer treatment until after first trimester
Doxycycline	First trimester: Effects on skeletal development in *animal* studies Second, third trimesters: Dental discoloration; maternal hepatotoxicity with large parenteral doses
Enalapril	All trimesters: Avoid; may adversely affect fetal and neonatal blood pressure control and renal function; also possible skull defects and oligohydramnios; toxicity in *animal* studies
Ergocalciferol	High doses teratogenic in *animals* but therapeutic doses unlikely to be harmful

Drug	Comment
Erythromycin	Not known to be harmful
Ether, anaesthetic	Third trimester: Depresses neonatal respiration
Ethinylestradiol	Epidemiological evidence suggests no harmful effects on fetus
Fluconazole	Avoid in first trimester—multiple congenital abnormalities reported with long-term high doses
Frusemide	Not used to treat hypertension in pregnancy
Furazolidone:	May be harmful to foetus; use with caution
Gentamicin	Second, third trimesters: Auditory or vestibular nerve damage, risk probably very small with gentamicin, but use only if potential benfit outweighs risk (if given, serum-gentamicin concentration monitoring essential)
Glibenclamide	Third trimester: Neonatal hypoglycaemia; insulin is normally substituted in all diabetics; if oral drugs are used therapy should be stopped at least 2 days before delivery
Griseofulvin	Avoid (fetotoxicity and teratogenicity in *animals*); effective contraception required during and for at least 1 month after adminis tration (**important:** effectiveness of oral contraceptives reduced, *see* Appendix 1); also men should avoid fathering a child during and for at least 6 months after administration
Haloperidol	Third trimester: Extrapyramidal effects in neonate occasionally reported
Halothane	Third trimester: Depresses neonatal respiration
Heparin	All trimesters: Osteoporosis has been reported afterprolonged use; multidose vials may contain benzyl alcohol—some manufacturers advise avoid
Hydrochlorothiazide	Not used to treat hypertension in pregnancy Third trimester: May cause neonatal thrombocytopenia
Hydrocortisone	Benefit of treatment, for example in asthma outweighs risk; risk of in trauterine growth retardation on prolonged or repeated systemic treatment;corticosteroid cover re quired by mother during labour; monitor closely if fluid retention Ibuprofen Third trimester: With regular use closure of fetal ductus arteriosus *in utero* and possibly per sistent pulmo nary hypertension of the newborn. Delayed onset and in creased dura tion of labour
Imipramine	Manufacturer advises avoid unless essential, particularly during first and third trimesters

Drug	Comment
Insulin	All trimesters: Insulin requirements should be assessed frequently by an experienced diabetic clinician
Iodine	Second, third trimesters: Neonatal goitre and hypothyroidism
Ketamine	Third trimester: Depresses neonatal respirationLevodopa+Carbidopa Toxicity in *animal* studies
Levonorgestrel	In oral contraceptives, epidemiologi cal evidence suggests no harmful ef fects on fetus In high doses, may possibly be teratogenic in first trimester
Levothyroxine	Monitor maternal serum-thyrotro phin concentration — dosage adjust ment may be necessary
Lidocaine	Third trimester: With large doses, neonatal respiratory depression, hypotonia, and bradycardia after paracervical or epidural block solution due to high propylene glycol content; *see* section 6.5.2
Magnesium sulfate	Follow hospital regimen in eclamp sia; long-term infusion may cause sustained fetal hypocalcaemia
Metformin	All trimesters: Avoid; insulin is nor mally substituted in all diabetics
Methotrexate	Avoid (teratogenic; fertility may be reduced during therapy but this may bereversible); use effective contraception during and for at least 6 months after administration to men or women; *see also* section 8.2
Methyldopa	Not known to be harmful
Metoclopramide	Not known to be harmful
Metronidazole	Avoid high-dose regimens
Minocycline	First trimester: Effects on skeletal development in *animal* studies Second, third trimesters: Dental discoloration; maternal hepatotoxicity with large parenteral doses
Morphine	Third trimester: Depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour
Nalidixic acid	All trimesters: Avoid — arthropathy in *animal* studies; safer alternatives available
Naloxone	Use only if potential benefit out weighs risk
Neostigmine	Third trimester: Neonatal myasthenia with large doses
Nitrofurantoin	Third trimester: May produce neonatal haemolysis if used at term

Drug	Comment
Nitrous oxide	Third trimester: Depresses neonatal respiration
Norethisterone	In oral contraceptives, epidemiological evidence suggests no harmful effects on fetus In high doses, may possibly be teratogenic in first trimester
Nystatin	No information available, but absorption from gastrointestinal tract negligible
Ofloxacin	All trimesters: Avoid — arthropathy in *animal* studies; safer alternatives available
Paracetamol	Not known to be harmful
Pentamidine isetionate	Potentially fatal visceral leishmaniasis must be treated without delay. Should not be withheld in trypanosomiasis even if evidence of meningoencephalitic involvement.
Potentially fatal	*P. carinii* pneumonia must be treated without delay
Pentavalent antimony	Potentially fatal visceral leishmaniasis must be compounds treated without delay
Pethidine	Third trimester: Depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour
Phenobarbitone	First, third trimesters: Congenital malformations; risk of teratogenicity greater if more than one antiepileptic used. May possibly cause vitamin K deficiency and risk of neonatal bleeding; if vitamin K not given at birth, neonate should be monitored closely for signs of bleeding; *see* section 5.1
Phenoxymethylpenicillin	Not known to be harmful
Phenytoin	First, third trimesters: Congenital malformations (screening advised); adequate folate supplements should be given to mother (for example folic acid 5 mg daily); risk of teratogenicity greater if more than one antiepileptic used. May possibly cause vitamin K deficiency and risk of neonatal bleeding; if vitamin K not given at birth, neonate should be monitored closely for signs of bleeding. Caution in interpreting plasma concentrations — bound may be reduced but free (or effective) unchanged; *see also* section 5.1
Phytomenadione	Use only if potential benefit out weighs risk — no specific information available
Podophyllum resin	All trimesters: Avoid — neonatal death and teratogenesis have been reported
Polyvidone–iodine	Second, third trimesters: Sufficient iodine may be absorbed to affect the fetal thyroid

Drug	Comment
Potassium iodide	Second, third trimesters: Neonatal goitre and hypothyroidism
Pralidoxime:	Use with caution as safety not tested; however poisoning more dangerous.
Praziquantel	*T. solium* infections in pregnancy should be treated immediately; *see* section 6.1.1.1. If immediate treatment not considered essential for Fluke infections or Schistosomiasis, treatment should be delayed until after delivery Prednisolone Benefit of treatment, for example in asthma, outweighs risk; risk of in trauterine growth retardation on prolonged or repeated systemic treatment; corticosteroid cover required by mother during labour; monitor closely if fluid retention
Primaquine	Third trimester: Neonatal haemolysis and methaemoglobinaemia. delay treatment until after delivery
Promethazine	No evidence of teratogenicity
Propylthiouracil	Second, third trimesters: Neonatal goitre and hypothyroidism
Pyridostigmine	Third trimester: Neonatal myasthenia with large doses
Pyrimethamine	First trimester: Theoretical teratogenic risk (folate antagonist); adequate folate supplements should be given to the mother. First trimester: avoid in Pneumocystosis and toxoplasmosis; *see also* Sulfadiazine
Quinine	First trimester: High doses are teratogenic; but in malaria benefit of treatment outweighs risk
Ranitidine	Use only if potential benefit out weighs risk; use if necessary - no effects found in animals
Retinol	First trimester: Excessive doses may be teratogenic; *see also* section 27.1 [text]
Rifampicin	First trimester: Very high doses teratogenic in *animal* studies Third trimester:Risk of neonatal bleeding may be increased Salbutamol For use in asthma *see* section 25.1 [text] Third trimester: For use in premature labour *see* section 22.1
Silver sulfadiazine	Third trimester: Neonatal haemolysis and methaemoglobinaemia; fear of increased risk of kernicterus in neonates appears to be unfounded
Sodium valproate	*see* Valproic acid
Streptokinase	All trimesters: Possibility of premature

Drug	Comment
	separation of placenta in first 18 weeks; theoretical possibility of fetal haemorrhage throughout pregnancy; avoid postpartum use – maternal haemorrhage
Streptomycin	Second, third trimesters: Auditory or vestibular nerve damage; avoid unless essential (if given, serum-streptomycin concentration monitoring essential)
Sulfadiazine	Third trimester: Neonatal haemolysis and methaemoglobinaemia;fear of increased risk of kernicterus in neonates appears to be unfounded In toxoplasmosis, avoid in first trimester, but may be given in second and third trimester if danger of congenital transmission
Sulfadoxine+	In malaria, benefit of prophylaxis Pyrimethamine and treatment outweigh risk. First trimester: Possible teratogenic risk (pyrimethamine a folate antagonist) Third trimester: Neonatal haemolysis and methaemoglobinaemia; fear of increased risk of kernicterus in neonates appears to be unfounded *See also* section 6.4.3
Sulfamethoxazole + Trimethoprim	First trimester: Theoretical teratogenic risk (trimethoprima folate antagonist) Third trimester: Neonatal haemolysis and methaemoglobinaemia; fear of increased risk of kernicterus in neonates appears to be unfounded
Sulfasalazine	Third trimester: Theoretical risk of neonatal haemolysis; adequate folate supplements should be given to mother
Suxamethonium	Mildly prolonged maternal paralysis may occur
Testosterone	All trimesters: Masculinization of female fetus
Tetracycline	First trimester: Effects on skeletal development in *animal* studies second, third trimesters: Dental discoloration; maternal hepatotoxicity with large parenteral doses
Theophylline	Third trimester: Neonatal irritability and apnoea have been reported
Thiopentone	Third trimester: Depresses neonatal respiration
Trimethoprim	First trimester: Theoretical teratogenic risk (folate antagonist)
Vaccine, BCG	First trimester: Theoretical risk of congenital malformations, but need for vaccination may outweigh possible risk to fetus (*see also* section 19.3 [contraindications])

Drug	Comment
Vaccine, Measles	First trimester: Theoretical risk of congenital malformations, but need for vaccination may outweigh possible risk to fetus (*see also* section 19.3 [contraindications and precautions]); avoid MMR
Vaccine, Poliomyelitis,	live First trimester: Theoretical risk of congenital malformations, but need for vaccination may outweigh possible risk to fetus (*see also* section 19.3 [contraindications and precautions])
Valproic acid	First, third trimesters: Increased risk of neural tube defects (counselling and screening advised); risk of teratogenicity greater if more than one antiepileptic used; neonatal bleeding (related to hypofibrinaemia) and neonatal hepatotoxicity also reported; *see also* section 5.1 (sodium valproate)
Verapamil	*Animal* studies have not shown teratogenic effect; possibility that verapamil can relax uterine muscles should be considered at term; risk to fetus should be balanced against risk of uncontrolled maternal hypertension
Warfarin	All trimesters: Congenital malformations; fetal and neonatal haemorrhage *See also* section 10.2

Appendix 3: Breastfeeding

Administration of some drugs (for example, ergotamine) to nursing mothers may cause toxicity in the infant, whereas administration of others (for example, digoxin) has little effect.

Some drugs inhibit lactation (for example, estrogens). Toxicity to the infant can occur if the drug enters the milk in pharmacologically significant quantities. The concentration in milk of some drugs (for example, iodides) may exceed those in the maternal plasma so that therapeutic doses in the mother may cause toxicity to the infant. Some drugs inhibit the infant's sucking reflex (for example, phenobarbitone). Drugs in breast milk may, at least theoretically, cause hypersensitivity in the infant even when concentrations are too low for a pharmacological effect.

The following table lists drugs:

- which should be used with caution or which are contraindicated in breastfeeding for the reasons given above;
- which, on present evidence, may be given to the mother during breastfeeding, because they appear in milk in amounts which are too small to be harmful to the infant;
- which are not known to be harmful to the infant although they are present in milk in significant amounts.

For many drugs insufficient evidence is available to provide guidance and it is advisable to administer only drugs essential to a mother during breastfeeding. Because of the inadequacy of information on drugs in breast milk the following table should be used only as a guide; absence from the table does not imply safety.

WHO POLICY. It is WHO policy to encourage breastfeeding whenever possible, particularly in situations where there is no safe alternative. Advice in the table may differ from other sources, including manufacturer's product literature.

For further information on use of drugs during breastfeeding, see also the WHO document 'Breastfeeding and Maternal Medication', WHO/CDR/95.11.

Table of drugs present in breast milk

Drug	Comment
Acetazolamide	Amount too small to be harmful
Acetylsalicylic acid	Short course safe in usual dosage; monitor infant; regular use of high doses could impair platelet function and produce hypoprothrombinaemia in infant if neonatal vitamin K stores

Drug	Comment
	low; possible risk of Reye syndrome
Alcohol	Large amounts may affect infant and reduce milk consumption
Aminophylline	Present in milk—irritability in infant reported
Amlodipine	Small amount in milk; continue breastfeeding; monitor infant
Amoxicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Amoxicillin+ Clavulanic acid	Trace amounts in milk
Ampicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Artemether+	Significant amounts in milk;
Atenolol	safe in usual dosage; monitor infant
Atropine	Small amount present in milk; monitor infant
Benzathine benzylpenicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Benzylpenicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Betamethasone	Systemic effects in infant unlikely with maternal dose of *less than equivalent* of prednisolone 40 mg daily; monitor infant's adrenal function with higher doses
Bisacodyl Safe	Carbamazepine Continue breastfeeding; adverse effects possible (severe skin reaction reported in 1 infant); monitor infant for drowsiness; *see also* section 5.1
Chloral hydrate	Sedation in infant
Chloramphenicol	Continue breastfeeding; use alterna tive drug if possible; may cause bone-marrow toxicity in infant; concentration in milk usually insufficient to cause 'grey syndrome'
Chloroquine	Amount probably too small to be harmful; inadequate for reliable protection against malaria, *see also* section 6.4.3
Chlorphenamine	Safe in usual dosage; monitor infant for drowsiness
Chlorpromazine	Continue breastfeeding; adverse ef fects possible; monitor infant for drowsiness

Drug	Comment
Ciclosporin	Present in milk—manufacturer ad vises avoid
Ciprofloxacin	Continue breastfeeding; use alterna tive drug if possible; high concentrations in breast milk
Cloxacillin	Trace amounts in milk; safe in usual dosage; monitor infant
Codeine	Amount too small to be harmful
Contraceptives, oral	Combined oral contraceptives may inhibit lactation—use alternative drug; progestogen-only contraceptives do not affect lactation (start 3 weeks after birth or later)
Dapsone	Although significant amount in milk risk to infant very small; continue breastfeeding; monitor infant for jaundice
Dexamethasone	Systemic effects in infant unlikely with maternal dose of *less than equivalent* of prednisolone 40 mg daily; monitor infant's adrenal func tion with higher doses
Diazepam	Continue breastfeeding; adverse ef fects possible; monitor infant for drowsiness; *see also* section 5.1
Dicyclomine	Use with caution as safety not tested; however poisoning more dangerous.
Digoxin	Amount too small to be harmful
Diloxanide	Manufacturer advises avoid
Doxycycline	Continue breastfeeding; use alternative drug if possible (absorption and therefore discoloration of teeth in infant probably usually prevented by chelation with calcium in milk)
Ergocalciferol	Caution with high doses; may cause hypercalcaemia in infant
Ergotamine	Use alternative drug; ergotism may occur in infant; repeated doses may inhibit lactation
Erythromycin	Only small amounts in milk; safe in usual dosage; monitor infant
Ethambutol	Amount too small to be harmful
Ethinylestradiol	Use alternative drug; may inhibit lactation; *see also* Contraceptives, Oral

Drug	Comment
Fluconazole	Present in milk; safe in usual dosage; monitor infant
Frusemide	Amount too small to be harmful
Furazolidone	Use with caution
Glibenclamide	Theoretical possibility of hypoglycaemia in infant
Haloperidol	Amount excreted in milk probably too small to be harmful; continue breastfeeding; adverse effects possible; monitor infant for drowsiness
Halothane	Excreted in milk
Hydrochlorothiazide	Use alternative drug; may inhibitlactation
Hydrocortisone	Systemic effects in infant unlikely with maternal dose of *less than equivalent* of prednisolone 40 mg daily; monitor infant's adrenal function with higher doses
Ibuprofen	Amount too small to be harmful; short courses safe in usual doses
Imipramine	Detectable in breast milk; continue breastfeeding; adverse effects possible, monitor infant for drowsiness
Insulin	Amount too small to be harmful
Iodine	Stop breastfeeding; danger of neonatal hypothyroidism or goitre; appears to be concentrated in milk
Isoniazid	Monitor infant for possible toxicity; theoretical risk of convulsions and neuropathy; prophylactic pyridoxine advisable in mother and infant
Levodopa+Carbidopa	No information available
Levonorgestrel	Combined oral contraceptives may inhibit lactation — use alternative drug; progestogen-only contraceptives do not affect lactation (start 3 weeks after birth or later)
Levothyroxine	Amount too small to affect tests for neonatal hypothyroidism
Lidocaine	Amount too small to be harmful
Metformin	Safe in usual doses; monitor infant
Methotrexate	Breastfeeding contraindicated
Methyldopa	Amount too small to be harmful
Metoclopramide	Present in milk; adverse effects

Drug	Comment
	possible; monitor infant for adverse effects
Metronidazole	Significant amount in milk; continue breastfeeding; use alternative drug if possible
Minocycline	Continue breastfeeding; use alternative drug if possible (absorption and therefore discoloration of teeth in infant probably usually prevented by chelation with calcium in milk)
Morphine	Short courses safe in usual doses; monitor infant
Nalidixic acid	Continue breastfeeding; use alternative drug if possible; one case of haemolytic anaemia reported
Naloxone	No information available
Neostigmine	Amount probably too small to be harmful; monitor infant
Nitrofurantoin	Only small amounts in milk but could be enough to produce haemolysis in G6PD-deficient infants
Norethisterone	Combined oral contraceptives may inhibit lactation — use alternative drug; progestogen-only contraceptives do not affect lactation (start 3 weeks after birth or later)
Nystatin	No information available, but absorption from gastrointestinal tract negligible
Ofloxacin	Continue breastfeeding; use alternative drug if possible
Paracetamol	Small amount present in milk: short courses safe in usual dosage; monitor infant
Pentamidine isetionate	Manufacturer advises avoid unless essential
Pentavalent antimony compounds	Avoid
Pethidine	Short courses safe in usual dosage; monitor infant
Phenobarbitone	Continue breastfeeding; adverse effects possible; monitor infant for drowsiness; *see also* section 5.1
Phenoxymethylpenicillin	Trace amounts in milk; safe in usual

Drug	Comment
	dosage; monitor infant
Phenytoin	Small amount present in milk; continue breastfeeding; adverse effects possible; monitor infant for drowsiness; *see also* section 5.1
Polyvidone–iodine	Avoid; iodine absorbed from vaginal preparations is concentrated in milk
Potassium iodide	Stop breastfeeding; danger of neonatal hypothyroidism or goitre; appears to be concentrated in milk
Pralidoxime	Use with caution as safety not tested; however poisoning more dangerous.
Praziquantel	Avoid breastfeeding during and for 72 hours after treatment
Prednisolone	Systemic effects in infant unlikely with maternal dose of *less than* prednisolone 40 mg daily; monitor infant's adrenal function with higher doses
Primaquine	Avoid; risk of haemolysis in G6PD-deficient infants
Promethazine	Safe in usual dosage; monitor infant for drowsiness
Propylthiouracil	Monitor infant's thyroid status but amounts in milk probably too small to affect infant; high doses might affect neonatal thyroid function
Pyrazinamide	Amount too small to be harmful
Pyridostigmine	Amount probably too small to be harmful
Pyrimethamine	Significant amount—avoid administration of other folate antagonists to infant
Ranitidine	Significant amount—not known to be harmful; monitor infant
Retinol	Theoretical risk of toxicity in infants of mothers taking large doses
Rifampicin	Amount too small to be harmful
Salbutamol	Safe in usual dosage; monitor infant
Silver sulfadiazine	Continue breastfeeding; monitor infant for jaundice—small risk of kernicterus in jaundiced infants particularly with long-acting sulphonamides, and of haemolysis in G6PD-deficient infants
	Sodium valproate *see* Valproic acid
Sulfadiazine	Continue breastfeeding; monitor infant for jaundice—small risk of

Drug	Comment
	kernicterus in jaundiced infants particularly with long-acting sulphonamides, and of haemolysis in G6PD-deficient infants
Sulfadoxine+ Pyrimethamine	Continue breastfeeding; monitor infant for jaundice—small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants (due to sulfadoxine)
Sulfamethoxazole+ Trimethoprim	Continue breastfeeding; monitor infant for jaundice—small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants (due to sulfamethoxazole)
Sulfasalazine	Continue breastfeeding; monitor infant for jaundice—small amounts in milk (1 report of bloody diarrhoea and rashes); theoretical risk of neonatal haemolysis especially in G6PD-deficient infants
Tetracaine	No information available
Tetracycline	Continue breastfeeding; use alternative drug if possible (absorption and therefore discoloration of teeth in infant probably usually prevented by chelation with calcium in milk)
Theophylline	Present in milk—irritability in infant reported; modified-release preparations preferable
Thiamine	Severely thiamine-deficient mothers should avoid breastfeeding as toxic methyl-glyoxal excreted in milk
Trimethoprim	Present in milk; safe in usual doage; monitor infant
Valproic acid	Present in milk; continue breastfeeding; adverse effects possible; monitor infant for drowsiness; *see also* section 5.1 (sodium valproate)
Verapamil	Amount too small to be harmful
Warfarin	Risk of haemorrhage; increased by vitamin-K deficiency; warfarin appears safe

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QUICK REFRENCE FOR EMERGENCIES