Hormones and other endocrine drugs and contraceptives

Adrenal hormones and synthetic substances

Corticosteroids (section 3.1) include hormones secreted by the adrenal cortex and 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 betamethasone, **dexamethasone** and **prednisolone** . Fludrocortisone [not included on WHO Model List] has glucocorticoid properties but it has potent mineralocorticoid properties and is used for its mineralocorticoid effects.

Pharmacology of the corticosteroids is complex and their actions are wide-ranging. In physiological (low) doses, they replace deficient endogenous hormones. In pharmacological (high) doses, glucocorticoids decrease inflammation and suppress the immune response.

In therapeutic doses glucocorticoids suppress release of corticotrophin (adrenocorticotrophic hormone, 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. The mineralocorticoid activity of fludrocortisone is also high and its anti-inflammatory activity is of no clinical relevance. It is used together with glucocorticoids in adrenal insufficiency. **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 suppression

Adrenal suppression occurs during prolonged therapy with corticosteroids, with development of adrenal atrophy which may persist for years after stopping. Abrupt withdrawal after a prolonged period may lead to acute adrenal insufficiency, hypotension or death (see Withdrawal of Systemic Corticosteroids, below). Withdrawal may also be associated with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and weight loss.

CORTICOSTEROID COVER DURING STRESS

To compensate for a diminished adrenocortical response caused by prolonged corticosteroid treatment, any significant intercurrent illness, trauma, or surgery requires a temporary increase in corticosteroid dose, or if already stopped, a temporary re-introduction of corticosteroid treatment. Anaesthetists **must** therefore know whether a patient is taking or has been taking a corticosteroid, to avoid a precipitous fall in blood pressure during anaesthesia or in the immediate postoperative period. A suitable regimen for corticosteroid replacement, in patients who have taken more than 10 mg prednisolone daily (or equivalent) within 3 months of surgery, is:

- *Minor surgery under general anaesthesia* —usual oral corticosteroid dose on the morning of surgery or hydrocortisone 25–50 mg intravenously at induction; the usual oral corticosteroid dose is recommenced after surgery
- *Moderate or major surgery* —usual oral corticosteroid dose on the morning of surgery and hydrocortisone 25–50 mg intravenously at induction, followed by

hydrocortisone 25–50 mg 3 times a day by intravenous injection for 24 hours after moderate surgery or for 48–72 hours after major surgery; the usual preoperative oral corticosteroid dose is recommenced on stopping hydrocortisone injections

Infections

Prolonged courses of corticosteroids increase susceptibility to infections and increase their severity; clinical presentation of infections may also be atypical. Serious infections, for example septicaemia and tuberculosis, may reach an advanced stage before being recognised, and amoebiasis or strongyloidiasis may be activated or exacerbated (exclude before initiating a corticosteroid in those at risk or with suggestive symptoms). Fungal or viral ocular infections may also be exacerbated.

CHICKENPOX

Unless they have had chickenpox, patients receiving oral or parenteral corticosteroids for purposes other than replacement should be regarded as being at risk of severe chickenpox. Manifestations of fulminant illness include pneumonia, hepatitis and disseminated intravascular coagulation; rash is not necessarily a prominent feature.

Passive immunization with varicella–zoster immunoglobulin [not included on WHO Model List] is needed for exposed non-immune patients receiving systemic corticosteroids or for those who have used them within the previous 3 months; varicella–zoster immunoglobulin should preferably be given within 3 days of exposure and no later than 10 days. Confirmed chickenpox warrants specialist care and urgent treatment. Corticosteroids should not be stopped and dosage may need to be increased.

Topical, inhaled or rectal corticosteroids are less likely to be associated with an increased risk of severe chickenpox.

MEASLES

Patients taking corticosteroids should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin [not included on WHO Model List] may be needed.

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 period 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 be needed 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* who 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.

Dexamethasone

Tablets , dexamethasone 500 micrograms, 4 mg [4-mg strength not included on WHO Model List]

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); shock; 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 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; risk of chickenpox and measles increased (see notes above); 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 micrograms/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 [not included on WHO Model List]

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); asthma (section 25.1)

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 (see notes above); 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, 25 mg

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); asthma (section 25.1)

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; risk of chickenpox and measles increased (see notes above); 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 (Appendix 5); 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** 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; **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

Maintenance, *by mouth* , **ADULT** 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

Myasthenia gravis, initially 10 mg on alternate days, increased in steps of 10 mg on alternate days to 1–1.5 mg/kg (maximum 100 mg) on alternate days *or* initially 5 mg daily increased in steps of 5 mg daily to usual dose of 60–80 mg daily (0.75–1 mg/kg daily)

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

Androgens

Androgens are secreted by the testes and weaker androgens by the adrenal cortex and ovaries. In the male, they are responsible for the development and maintenance of the sex organs and the secondary sexual characteristics, normal reproductive function, and sexual performance ability in addition to stimulating the growth and development of the skeleton and skeletal muscle during puberty. At high doses in the normal male androgens inhibit pituitary gonadotrophin secretion and depress spermatogenesis. **Testosterone** is used as replacement therapy in those who are hypogonadal due to either pituitary (secondary hypogonadism) or testicular disease (primary hypogonadism). Androgens are useless as a treatment of impotence and impaired spermatogenesis unless there is associated hypogonadism; they should not be given until the hypogonadism has been properly investigated and treatment should always be under expert supervision. When given to patients with hypopituitarism they can lead to normal sexual development and potency but not fertility. If fertility is desired, the usual treatment is with gonadotrophins or pulsatile gonadotrophin-releasing hormone which will stimulate spermatogenesis as well as androgen production. Androgens cannot induce fertility in men with primary hypogonadism. Caution should be used in treating boys with delayed puberty with excessive doses of testosterone since the fusion of epiphyses is hastened and may result in short stature. Androgens, including testosterone have also been used in postmenopausal women for the palliative treatment of androgen-responsive, advanced, metastatic breast cancer; care is required to prevent masculinizing effects.

Testosterone enantate

Testosterone enantate is a complementary androgenic drug

Oily injection (Solution for injection), testosterone enantate 200 mg/ml, 1-ml ampoule; 250 mg/ml, 1-ml ampoule [250 mg/ml not included on WHO Model List]

Uses:

hypogonadism; palliative treatment of advanced breast cancer in women

Contraindications:

breast cancer in men, prostate cancer, hypercalcaemia, pregnancy (Appendix 2), breastfeeding (Appendix 3), nephrosis, history of primary liver tumours

Precautions:

cardiac, renal or hepatic impairment (Appendix 5), elderly, ischaemic heart disease, hypertension, epilepsy, migraine, diabetes mellitus, skeletal metastases (risk of

hypercalcaemia); regular examination of prostate during treatment; prepubertal boys; **interactions** : Appendix 1

Dosage:

Hypogonadism, *by slow intramuscular injection* ; **ADULT** (males), initially 200–250 mg every 2–3 weeks; maintenance 200–250 mg every 3–6 weeks

Breast cancer, *by slow intramuscular injection* , **ADULT** (females) 250 mg every 2–3 weeks

Adverse effects:

prostate abnormalities and prostate cancer, headache, depression, gastrointestinal bleeding, nausea, polycythaemia, cholestatic jaundice, changes in libido, gynaecomastia, anxiety, asthenia, generalized paraesthesia, electrolyte disturbances including sodium retention with oedema and hypercalcaemia; increased bone growth; androgenic effects such as hirsutism, male-pattern baldness, seborrhoea, acne, priapism, precocious sexual development and premature closure of epiphyses in pre-pubertal males, virilism in females, and suppression of spermatogenesis in men

Contraceptives

Hormonal contraceptives

Hormonal contraception is one of the most effective methods of reversible fertility control.

COMBINED ORAL CONTRACEPTIVES

Estrogen plus progestogen combinations are the most widely used hormonal contraceptives. 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.

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; anovulation and amenorrhoea persisting for six months or longer requires investigation and appropriate treatment if necessary.

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 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 in migraine with aura, in severe migraine without aura regularly lasting over 72 hours despite treatment and in migraine treated with ergot derivatives.

SURGERY

Estrogen-containing oral contraceptives should preferably be discontinued (and adequate alternative contraceptive arrangements made) 4 weeks before major elective surgery and all surgery to the legs or surgery which involves prolonged immobilization of a lower limb. They should normally be restarted at the first menses occuring at least 2 weeks after full mobilization. When discontinuation is not possible thromboprophylaxis (with heparin and graduated compression hosiery) is advised.

REASONS TO STOP COMBINED ORAL CONTRACEPTIVES IMMEDIATELY

Combined estrogen-containing oral contraceptives should be stopped immediately if any of the following symptoms occur and resumed only after consultation with a health care provider:

- 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;
- Blood pressure above systolic 160 mmHg and diastolic100 mmHg;

- Detection of 2 or more risk factors for venous thromboembolism or arterial disease, see notes above

PROGESTOGEN-ONLY CONTRACEPTIVES

Progestogen-only contraceptives, such as oral **levonorgestrel** may offer a suitable alternative when estrogens are contraindicated but the oral progestogen-only preparations do not prevent ovulation in all cycles and have a higher failure rate than combined estrogen-containing preparations. Progestogen-only contraceptives carry less risk of thromboembolic and cardiovascular disease than combined oral contraceptives and are preferable for women at increased risk of such complications, for example smokers over 35 years. They can be used as an alternative to estrogen-containing combined preparations prior to major surgery. Oral progestogen-only contraceptives may be started 3 weeks after birth; breastfeeding women should preferably start at least 6 weeks after birth. Menstrual irregularities (oligomenorrhoea, menorrhagia, amenorrhoea) are common. Injectable preparations of **medroxyprogesterone acetate** or **norethisterone enantate** may be given intramuscularly. They have prolonged action and should only be given with full counselling and manufacturer's information leaflet.

EMERGENCY CONTRACEPTION

Levonorgestrel is used for emergency contraception. Levonorgestrel 1.5 mg should be taken as a single dose within 120 hours of unprotected intercourse; alternatively, levonorgestrel 750 micrograms can be taken within 72 hours of unprotected intercourse followed 12 hours later by another 750 micrograms. Under these circumstances levonorgestrel prevents about 86% of pregnancies that would have occurred if no treatment had been given. Adverse effects include nausea, vomiting, headache, dizziness, breast discomfort, and menstrual irregularities. If vomiting occurs within 2–3 hours of taking the tablets, replacement tablets can be given with an antiemetic.

It should be explained to the woman that her next period may be early or late; that she needs to use a barrier contraceptive method until her next period, and that she should return promptly if she has any lower abdominal pain or if the subsequent menstrual bleed is abnormally light, heavy, brief or absent. There is no evidence of harmful effects to the fetus if pregnancy should occur.

Combined oral contraceptives

Ethinylestradiol with levonorgestrel and ethinylestradiol with norethisterone are representative combined oral contraceptive preparations. Various combinations can serve as alternatives

Tablets , ethinylestradiol 30 micrograms, levonorgestrel 150 micrograms

Tablets , ethinylestradiol 35 micrograms, norethisterone 1 mg

Uses:

contraception; menstrual symptoms; endometriosis (see also progestogens, section 18.5)

Contraindications:

use within 3 weeks of birth; breastfeeding until weaning or for first 6 months after birth (Appendix 3); personal history of or 2 or more risk factors for venous or arterial thrombosis (see notes above); 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 with oral contraceptives; 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; severe depression; long-term immobilization (see also Travel below); sickle-cell disease; inflammatory bowel disease including Crohn disease; **interactions:** Appendix 1

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); **contraindications:** migraine with typical focal aura; migraine without aura regularly lasting over 72 hours duration despite treatment; migraine treated with ergot derivatives; **precautions:** migraine without focal aura or controlled with $5HT_1$ agonist

TRAVEL. Women taking oral contraceptives may be at increased risk of deep-vein thrombosis during travel involving long periods of immobility (over 5 hours). The risk may be reduced by appropriate exercise during the journey and possibly by wearing elastic hosiery

Dosage:

Contraception (21-day combined (monophasic) preparations), *by mouth* , **ADULT** (female), 1 tablet ('pill') daily for 21 days; subsequent courses repeated after 7-day pill-free interval (during which withdrawal bleeding occurs)

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)

MISSED PILL. If a pill is not taken on time, it should be taken as soon as possible, and the next one taken at the usual time. If administration is delayed by more than 12 hours, the woman should resume taking the pill at the usual time as soon as possible; furthermore, because contraceptive efficacy is reduced, an additional method of contraception such as the condom

is required for 7 days—if the 7 days extend beyond the end of the packet, a new packet is started without leaving a gap between packets. Emergency contraception is recommended if either 2 or more pills are missed from the first 7 pills in a packet *or* 4 or more consecutive pills are missed mid-packet

DIARRHOEA AND VOMITING. Vomiting up to 3 hours after taking an oral contraceptive *or* very severe diarrhoea can interfere with the absorption of the pill. Additional precautions should be used during and for 7 days after recovery. If vomiting and diarrhoea occur during the last 7 pills, the next pill-free period should be omitted

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 which persists after stopping)

Levonorgestrel

Tablets , levonorgestrel 30 micrograms

Tablets , levonorgestrel 750 micrograms, 2-tablet pack

Tablets , levonorgestrel 1.5 mg, 1-tablet pack

Uses:

contraception (particularly when estrogens are contraindicated); emergency hormonal contraception

Contraindications:

progestogen-only oral contraceptives: 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:* severe liver disease; porphyria

Precautions:

possible small increase in risk of breast cancer; cardiac disease; sex-steroid dependent cancer; past ectopic pregnancy; malabsorption syndrome; ovarian cysts; active liver disease, recurrent cholestatic jaundice, history of jaundice in pregnancy (Appendix 5); increase in frequency or severity of headache (discontinue pending investigation); breastfeeding (Appendix 3); **interactions:** Appendix 1

Dosage:

Contraception, *by mouth* , **ADULT** (female), 1 tablet ('pill') (30 micrograms) 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

MISSED PILL. If a pill is not taken on time, it should be taken as soon as possible, and the next one taken at the usual time. If administration is delayed by more than 3 hours, the woman should resume taking the pill at the usual time as soon as possible; furthermore, because contraceptive efficacy is reduced, an additional method of contraception such as the condom is required for 2 days. Emergency contraception may be considered if 1 or more progestogen-only contraceptive pills are missed or taken more than 3 hours late

DIARRHOEA AND VOMITING. Vomiting up to 3 hours after taking an oral contraceptive *or* very severe diarrhoea can interfere with the absorption of the pill. Additional precautions should be used during and for 7 days after recovery

Emergency (post-coital) contraception, *by mouth* , **ADULT** (female), 1.5 mg as a single dose (taken within 120 hours (5 days) of unprotected intercourse); alternatively 750 micrograms (taken within 72 hours of unprotected intercourse) followed by a second dose of 750 micrograms 12 hours later

ADMINISTRATION. Taking as soon as possible after unprotected intercourse 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

Medroxyprogesterone acetate

Medroxyprogesterone acetate is a complementary drug

Injection (Suspension for injection), medroxyprogesterone acetate 150 mg/ml, 1-ml vial

Uses:

parenteral progestogen-only contraception (short-term or long-term); menstrual symptoms and endometriosis (section 18.5)

Contraindications:

pregnancy (Appendix 2); hormone-dependent breast or genital neoplasms; undiagnosed vaginal bleeding; hepatic impairment or active liver disease (Appendix 5); severe arterial disease; porphyria

Precautions:

small increase in possible risk of breast cancer; migraine; liver disease; thromboembolic or coronary vascular disease; diabetes mellitus; trophoblastic disease; hypertension; renal disease; **interactions:** Appendix 1

Dosage:

Contraception (short-term), *by deep intramuscular injection* , **ADULT** (female) 150 mg within first 5 days of cycle or within first 5 days after parturition (delay until 6 weeks after parturition if breastfeeding)

Contraception (long-term), *by deep intramuscular injection* , **ADULT** (female) as for short-term, repeated every 3 months

ADMINISTRATION. If interval between injections is greater than 3 months and 14 days, exclude pregnancy before next injection and advise patient to use additional contraceptive measures (for example barrier) for 7 days after the injection

Patient Advice. Women must receive full counselling (backed by manufacturer's approved leaflet) before treatment, concerning menstrual irregularities and because of prolonged activity and the potential for a delay in return to full fertility

Adverse effects:

menstrual irregularities; delayed return to fertility; reduction in bone mineral density; weight gain; depression; rarely, anaphylaxis

Norethisterone enantate

Oily injection (Solution for injection), norethisterone enantate 200 mg/ml, 1-ml ampoule

Uses:

parenteral progestogen-only contraception (short-term)

Contraindications:

pregnancy (Appendix 2); breast or endometrial cancer; severe liver disease (Dubin-Johnson or Rotor syndromes) (Appendix 5); history during pregnancy of jaundice, pruritus, herpes or of deteriorating otosclerosis; severe diabetes mellitus with vascular changes; hypertension; 12 weeks before planned surgery and during immobilization; thromboembolic disease; disturbances of lipid metabolism; undiagnosed vaginal bleeding; porphyria

Precautions:

possible small increase in risk of breast cancer; migraine; liver dysfunction; depression; diabetes mellitus; previous ectopic pregnancy; cardiac and renal disease; **interactions:** Appendix 1

Dosage:

Short-term contraception, *by deep intramuscular injection* into gluteal muscle, **ADULT** (female) 200 mg within 5 days of cycle or immediately after parturition; repeated after 2 months

Administration. If interval between injections is greater than 2 months and 14 days, exclude pregnancy before next injection and advise patient to use additional contraceptive measures (for example barrier) for 7 days after the injection

Patient Advice. Women must receive full counselling (backed by manufacturer's approved leaflet) before treatment, concerning possible menstrual irregularities and because of prolonged activity

Adverse effects:

bloating, breast discomfort, headache, dizziness, depression, nausea, menstrual irregularities; rarely, weight gain

Intrauterine contraceptive devices

Copper-bearing intrauterine contraceptive 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 normally between 3 and 8 years. Fertility declines with age and therefore a copper intrauterine device fitted in a woman over 40 years of age, may remain in the uterus until menopause.

The intrauterine device is appropriate for women who expect to use it for continuous long-term contraception. It is suitable for older parous women; intrauterine devices should be used with caution in young nulliparous women because of the increased risk of expulsion. Young women at risk of sexually transmitted infections are also at risk of pelvic inflammatory disease.

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 device can be inserted between 4 and 12 days after the start of menstruation; for emergency contraception the device can be inserted at any time in the menstrual cycle within 5 days of unprotected intercourse. 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 and gonorrhoea) 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) post-coital contraception should be considered. If the woman becomes pregnant, the device should be removed in the first trimester and the possibility of ectopic pregnancy considered; if the threads of the intrauterine device are already missing on presentation, the pregnancy is at risk of second trimester abortion, haemorrhage, pre-term delivery and infection.

EMERGENCY CONTRACEPTION

Insertion of a copper intrauterine contraceptive device is a highly effective method of emergency contraception and is more effective than hormonal methods of emergency contraception. Sexually transmitted diseases should be tested for and insertion of the device should usually be covered by antibacterial prophylaxis.

Copper-containing IUD

Uses:

contraception; emergency contraception

Contraindications:

pregnancy; severe anaemia; 48 hours–4 weeks post partum; puerperal sepsis; postseptic 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, fertility problems, nulliparity and young age, severely scarred uterus or severe cervical stenosis, valvular heart disease (requires antibacterial cover)—avoid if prosthetic valve or history of endocarditis; HIV infection or immunosuppressive therapy (risk of infection—avoid if marked immunosuppression); joint and other prostheses; increased risk of expulsion if inserted before uterine involution; gynaecological examination before insertion and 4–6 weeks afterwards—counsel women to see doctor promptly if significant symptoms such as pain; anticoagulant therapy; remove if pregnancy occurs (consider possibility of ectopic pregnancy)

Administration:

Contraception (see also notes above), the device can be inserted at any time between day 4 and day 12 after the start of menstrual bleeding; not to be fitted during heavy menstrual bleeding

Emergency contraception (see also notes above), the device may be inserted up to 120 hours (5 days) after unprotected intercourse, at any time of menstrual cycle; if intercourse has occurred more than 5 days previously, device can still be inserted up to 5 days after the earliest likely calculated day of ovulation; device can be removed at the beginning of menstruation if no longer required

Adverse effects:

uterine or cervical perforation, displacement, expulsion; pelvic infection exacerbated; heavy menstrual bleeding; dysmenorrhoea; pain and bleeding and occasionally epileptic seizure or vasovagal attack on insertion

Barrier 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; diaphragm or cervical caps

Uses: contraception; for condoms, also to decrease risk of transmission of HIV 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 infections (including HIV); 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; spermicides or diaphragm not suitable for women at high risk of HIV infection or with HIV infection

Adverse effects: vaginal and cervical irritation (spermicides), toxic shock syndrome (diaphragm, cap)

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. 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 principally for contraception and for 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 (or of endometrial foci in women who have had a hysterectomy) and possible transformation to cancer.

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. HRT should

not be prescribed with the aim of reducing the incidence of heart disease. Hormone replacement therapy may be used for menopausal women whose lives are unduly 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 and other symptoms of estrogen deficiency and can be given for up to 2–3 years; in women with a uterus (or endometrial foci), a progestogen should be added to reduce the risk of endometrial cancer. Medroxyprogesterone acetate (see also section 18.5) may be given in a dose of 10 mg daily for the last 12–14 days of each estrogen HRT cycle. Alternatively, norethisterone 1 mg daily may be given on the last 12–14 days of each 28-day estrogen cycle.

HRT should be considered for women with early natural or surgical menopause (before age 45 years) because they have a high risk of osteoporosis. Small doses of estrogen given systemically in the perimenopausal and postmenopausal period also diminish osteoporosis, but the slight increased risk of breast cancer needs to be taken into account. For early menopause, HRT can be given until the approximate age of natural menopause (until age 50 years).

For longer-term use of HRT in postmenopausal women (with a uterus or without a uterus), women must be made aware of the increased incidence of breast cancer and other adverse effects. Each decision to start HRT should be made on an individual basis, and treatment should be regularly reappraised (at least once a year). Factors such as corticosteroid therapy, family history of osteoporosis, thinness, lack of exercise, alcoholism or smoking, early menopause, fractures to the hip or forearm before age 65 years should be taken into account when considering the use of HRT; women of African origin appear to be less susceptible to osteoporosis than those who are white or of Asian origin.

There is an increased risk of deep-vein thrombosis and of pulmonary embolism in women taking HRT. 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.

Using HRT increases the risk of breast cancer slightly. The increased risk is related to the duration of HRT use and this excess risk disappears within about 5 years of stopping. The risk of breast cancer is greater with combined HRT (an estrogen and a progestogen) than with estrogen-only HRT (but estrogen alone may not be suitable for women with intact uterus, see above).

Epidemological studies indicate that in women aged between 50 and 65 years *not using HRT* , about 32 cases of breast cancer will be diagnosed in every 1000 women. In those using HRT, the risk of breast cancer is increased as follows:

- Women using *combined HRT* with an estrogen and a progestogen for 5 years, about 6 additional cases in 1000; in those using combined HRT for 10 years, about 19 additional cases in 1000
- Women using *estrogen-only HRT* for 5 years, about 2 additional cases in 1000; in those using estrogen-only HRT for 10 years, about 5 additional cases in 1000.

HRT does not provide contraception. If a potentially fertile woman needs to use HRT, non-hormonal contraceptive measures are necessary.

Precautions for patients on HRT undergoing surgery and reasons to stop HRT are the same as those for hormonal contraceptives (see notes in section 18.3.1).

Ethinylestradiol

Ethinylestradiol is a representative estrogen. Various drugs can serve as alternatives

Tablets , ethinylestradiol 10 micrograms, 50 micrograms

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; estrogen-dependent cancer; active thrombophlebitis or thromboembolic disorders or history of recent venous thromboembolism (unless already on anticoagulant therapy); 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 (or migraine-like headache); history of breast nodules of fibrocystic disease—closely monitor breast status (risk of breast cancer, see notes above); uterine fibroids may increase in size; symptoms of endometriosis may be exacerbated; predisposition to thromboembolism (see notes above); presence of antiphospholipid antibodies; increased risk of gallbladder disease; hypophyseal tumours; porphyria; **interactions:** Appendix 1

Dosage:

Hormone replacement, *by mouth* , **ADULT** (female) 10–20 micrograms 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; thromboembolism (see notes above); altered blood lipids; cholestatic jaundice; rashes and chloasma; changes in libido; depression, headache, migraine, dizziness, leg cramps (rule out venous thrombosis); contact lenses may irritate

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** , **norethisterone** 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, 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 contraceptives (section 18.3.1).

Medroxyprogesterone acetate

Medroxyprogesterone acetate is a complementary progestogenic drug

Tablets , medroxyprogesterone acetate 5 mg

Uses:

endometriosis; dysfunctional uterine bleeding; secondary amenorrhoea; contraception (section 18.3.1); adjunct in HRT (section 18.4)

Contraindications:

pregnancy (Appendix 2); hormone-dependent breast or genital neoplasms; undiagnosed vaginal bleeding; hepatic impairment or active liver disease (Appendix 5); severe arterial disease; porphyria

Precautions:

small increase in possible risk of breast cancer; migraine; depression; thromboembolic or coronary vascular disease; diabetes mellitus; trophoblastic disease; hypertension; renal disease; breastfeeding (Appendix 3); **interactions:** Appendix 1

Dosage:

Mild to moderate endometriosis, *by mouth* , **adult** 10 mg 3 times daily for 90 consecutive days, beginning on day 1 of cycle

Dysfunctional uterine bleeding, *by mouth* , **adult** 2.5–10 mg daily for 5 to 10 days beginning on day 16 to 21 of cycle for 2 cycles

Secondary amenorrhoea, *by mouth* , **adult** 2.5–10 mg daily for 5–10 days beginning on day 16 to 21 of cycle for 3 cycles

Adverse effects:

acne, urticaria, fluid retention, weight gain, gastrointestinal disturbances, changes in libido, breast discomfort, premenstrual symptoms, irregular menstrual cycles; depression, insomnia, somnolence, headache, alopecia, hirsutism; anaphylactoid reactions; rarely jaundice

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 (Appendix 5); 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 and those susceptible to thromboembolism; depression; 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, headache, dizziness, alopecia, hirsutism, anaphylactoid-like reactions; exacerbation of epilepsy and migraine; rarely jaundice

Ovulation inducers

The anti-estrogen, **clomifene** is used in the treatment of female infertility due to disturbances in ovulation. It induces gonadotrophin release by occupying estrogen receptors in the hypothalamus, thereby interfering with feedback mechanisms. Patients should be carefully counselled and should be fully aware of the potential adverse effects, including a risk of multiple pregnancy (rarely more than twins), of this treatment. Most patients who are going to respond will do so to the first course; 3 courses should be adequate; long-term cyclical therapy (more than 6 cycles) is not recommended as it may increase risk of ovarian cancer.

Clomifene citrate

Clomifene citrate is a complementary drug for fertility treatment

Tablets , clomifene citrate 50 mg

Uses:

anovulatory infertility

Contraindications:

hepatic disease; ovarian cysts; hormone dependent tumours or uterine bleeding of undetermined cause; pregnancy (exclude before treatment, Appendix 2)

Precautions:

visual disturbances (discontinue and initiate eye examination) and ovarian hyperstimulation syndrome (discontinue treatment immediately); polycystic ovary syndrome (cysts may enlarge during treatment); uterine fibroids, ectopic pregnancy, incidence of multiple births increased (consider ultrasound monitoring); breastfeeding (Appendix 3)

Dosage:

Anovulatory infertility, *by mouth* , **ADULT** (female) 50 mg daily for 5 days, starting within 5 days of onset of menstruation, preferably on the second day, or at any time if cycles have ceased; a second course of 100 mg daily for 5 days may be given in the absence of ovulation

Adverse effects:

visual disturbances, ovarian hyperstimulation, hot flushes, abdominal discomfort, occasional nausea and vomiting, depression, insomnia, breast tenderness, headache, intermenstrual spotting, menorrhagia, endometriosis, convulsions, weight gain, rashes, dizziness and hair loss

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

Appropriate insulin regimens should be worked out for each patient. Insulin requirements may be affected by variations in lifestyle (diet and exercise)—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.

If possible patients should monitor their own blood-glucose concentration using blood glucose strips. Since blood-glucose concentration varies throughout the day, patients should aim to maintain blood-glucose concentration between 4 and 10 mmol/litre for most of the day while accepting that on occasions it will be higher; strenuous efforts should be made to prevent blood-glucose concentrations falling below 4 mmol/litre because of the risk of hypoglycaemia. 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 to optimise blood-glucose concentration while avoiding hypoglycaemia.

In the absence of blood-glucose monitoring strips, urine-glucose monitoring strips can be used; in fact this 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 concentration daily.

Hypoglycaemia is a potential complication in all patients treated with insulin or oral hypoglycaemic agents. The consequences of hypoglycaemia, include confusion, seizures, coma and cerebral infarction.

Loss of warning of hypoglycaemia is common among insulin-treated patients and can be a serious hazard especially for drivers and those in dangerous occupations. 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. Beta-blockers can also blunt hypoglycaemic awareness (and delay recovery). Some patients report loss of hypoglycaemic warning after transfer to human insulin. Clinical studies do not confirm that human insulin decreases hypoglycaemic awareness. If a patient believes that human insulin is responsible for loss of warning it is reasonable to revert to animal insulin. To restore warning signs, episodes of hypoglycaemia must be reduced to a minimum; this involves appropriate adjustment of insulin dose and frequency, and suitable timing and quantity of meals and snacks.

Drivers need to be particularly careful to avoid hypoglycaemia. They should check their blood-glucose concentration 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 stop the vehicle in a safe place, ingest a suitable sugar supply and wait until recovery is complete (may be 15 minutes or longer). Driving is particularly hazardous when hypoglycaemic awareness is impaired.

For sporadic physical activity, 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, but this is uncommon and usually indicates excessive dosage. Sulfonylurea-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; it commonly occurs when adjustments to insulin dosage fail to compensate for increases in insulin requirements, for example during severe infection or major intercurrent illness. Diabetes ketoacidosis occurs mostly in patients with Type 1 diabetes mellitus. It also occurs in Type 2 diabetics who have a temporary need for insulin. Diabetic ketoacidosis is characterized by hyperglycaemia, hyperketonaemia and acidaemia with dehydration and electrolyte disturbances. It is essential that soluble insulin (and intravenous fluids) is 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 paid to insulin requirements when a patient with diabetes undergoes surgery that is likely to need an intravenous infusion of insulin for longer than 12 hours. Soluble insulin should be given in intravenous infusion of glucose and potassium chloride (provided the patient is not

hyperkalaemic), 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 hypoglycaemic drugs having been omitted).

Insulin must be given by injection because it is inactivated by gastrointestinal enzymes. Generally, insulin is given by subcutaneous injection into the upper arms, thighs, buttocks, or abdomen. There may be increased absorption from a limb, 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, for example soluble or neutral 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 , when injected subcutaneously, 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. Soluble insulin by the intravenous route is reserved for urgent treatment and fine control in serious illness and perioperatively. When injected intravenously, soluble insulin has a very short half-life of only about 5 minutes.

When injected 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 pre-mixed short- and medium-acting insulins (for example 30% soluble insulin with 70% isophane insulin) given twice daily. The proportions of soluble insulin can be increased in patients with excessive post-prandial hyperglycaemia.

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 (Appendix 4); 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 zinc suspension

Injection (Suspension for injection), insulin zinc (mixed) 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 (Appendix 4); pregnancy and breastfeeding (Appendix 2 and Appendix 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

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 (Appendix 4); 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

Oral antidiabetic drugs

Oral antidiabetic (hypoglycaemic) 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 such as myocardial infarction, coma, infection, and trauma, 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 (such as 3 g daily) are given. In order to reduce gastrointestinal effects, treatment should be initiated with a low dose which may be gradually increased. Metformin may provoke lactic acidosis which is most likely to occur in patients with renal impairment; it should not be used in patients with even mild renal impairment. 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 possibility of increased adverse effects with such combinations). During medical and surgical emergencies insulin treatment is almost always required; insulin should be substituted for metformin before elective surgery and in pregnancy.

Glibenclamide

Tablets , glibenclamide 2.5 mg, 5 mg

Uses:

diabetes mellitus

Contraindications:

ketoacidosis; porphyria; pregnancy (Appendix 2); breastfeeding (Appendix 3)

Precautions:

renal impairment (Appendix 4); hepatic impairment (Appendix 5); 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 or immediately after 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; liver disorders; hypersensitivity reactions usually in first 6–8 weeks; rarely, erythema multiforme, exfoliative dermatitis, fever and jaundice; hypoglycaemia, particularly in the elderly; rarely blood disorders including leukopenia, thrombocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia, and aplastic anaemia

Metformin hydrochloride

Tablets , metformin hydrochloride 500 mg, 850 mg [850-mg strength not included on WHO Model List]

Uses:

diabetes mellitus (see notes above)

Contraindications:

renal impairment (withdraw if renal impairment suspected; Appendix 4); withdraw if tissue hypoxia likely (for example sepsis, respiratory failure, recent myocardial infarction, hepatic impairment), use of iodine-containing X-ray contrast media (do not restart metformin until renal function returns to normal) and use of general anaesthesia (suspend metformin 2 days beforehand and restart when renal function returns to normal); alcohol dependence; pregnancy (Appendix 2)

Precautions:

measure serum creatinine before treatment and once or twice annually during treatment; substitute insulin during severe infection, trauma, surgery (see notes above and contraindications); breastfeeding (Appendix 3); **interactions:** Appendix 1

Dosage:

Diabetes mellitus, *by mouth* , **ADULT** initially 500 mg with breakfast for at least 1 week then 500 mg with breakfast and evening meal for at least 1 week, then 500 mg with breakfast, lunch and evening meal *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), abdominal pain, metallic taste; lactic acidosis most likely in patients with renal impairment (discontinue); decreased vitamin B_{12} absorption

Thyroid hormones and antithyroid drugs

Thyroid hormones

Thyroid agents are natural or synthetic agents containing **levothyroxine** (thyroxine) or **liothyronine** (tri-iodothyronine). 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.

Levothyroxine sodium

Tablets , levothyroxine sodium 25 micrograms, 50 micrograms, 100 micrograms [25-mg strength not included on WHO Model List]

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 (Appendix 3); **interactions:** Appendix 1

Dosage:

Hypothyroidism, *by mouth* , **ADULT** initially 50–100 micrograms daily (25–50 micrograms for those over 50 years) before breakfast, increased by 25–50 micrograms every 3–4 weeks until normal metabolism maintained (usual maintenance dose, 100–200 micrograms daily); where there is cardiac disease, initially 25 micrograms daily *or* 50 micrograms on alternate days, adjusted in steps of 25 micrograms every 4 weeks

Congenital hypothyroidism and juvenile myxoedema (see notes above), *by mouth* , **CHILD** up to 1 month, initially 5–10 micrograms/kg daily, **CHILD** over 1 month, initally 5 micrograms/kg daily, adjusted in steps of 25 micrograms 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

Antithyroid drugs

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 long-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.

Propylthiouracil

Propylthiouracil is a representative antithyroid drug. Various drugs can serve as alternatives

Tablets , propylthiouracil 50 mg

Uses:

hyperthyroidism

Precautions:

large goitre; pregnancy and breastfeeding (see also notes; Appendices 2 and 3); hepatic impairment (Appendix 5)—withdraw treatment if hepatic function deteriorates (fatal reactions reported); renal impairment—reduce dosage (Appendix 4)

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, hepatic necrosis, encephalopathy, nephritis

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