

Drugs affecting the blood

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. Ferric salts are much less well absorbed. 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).

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 3 months to replenish the iron stores.

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 but an improvement in tolerance may be due to lower content of elemental iron. Gastrointestinal irritation may occur with iron salts. Nausea and epigastric pain are dose-related. Iron preparations taken orally may be constipating, particularly in the elderly, occasionally leading to faecal impaction. Oral iron may exacerbate diarrhoea in patients with inflammatory bowel disease but care is also needed in patients with intestinal strictures and diverticula. Iron as iron dextran (a complex of ferric hydroxide with dextrans) [not included on WHO Model List] should be given parenterally only if the patient cannot tolerate oral iron, or does not take it reliably or there is continuing severe blood loss or malabsorption. Many patients with chronic renal failure who are receiving haemodialysis (and some on peritoneal dialysis) require intravenous iron on a regular basis. Parenteral iron may cause more harm than benefit. With the exception of patients on haemodialysis the haemoglobin response is not significantly faster with the parenteral route than the oral route.

MEGALOBLASTIC ANAEMIAS

Megaloblastic anaemias result from a 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 establish the underlying cause in every case. **Hydroxocobalamin** is used to treat vitamin B₁₂ deficiency whether due to dietary deficiency or malabsorption including pernicious anaemia (due to a lack of intrinsic factor, which is essential for vitamin B₁₂ absorption).

Folate deficiency due to poor nutrition, pregnancy, antiepileptics or malabsorption is treated with **foliac 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 foliac acid** are used for the prevention of megaloblastic anaemia in pregnancy. The low doses of foliac acid in these preparations are inadequate for the treatment of megaloblastic anaemias.

PREVENTION OF NEURAL TUBE DEFECTS

An adequate intake of **foliac acid** before conception and during early pregnancy reduces the risk of neural tube defects in babies. Therefore, women planning a pregnancy should receive sufficient foliac acid before conception and in the first 12 weeks of pregnancy; foliac acid may be given as a food or a medicinal supplement in a dose of 400–500 micrograms daily. A woman who has not received supplementary foliac acid and suspects that she might be pregnant should start taking foliac acid at once and continue until week 12 of pregnancy.

Women at increased risk of giving birth to a baby with neural tube defects (for example history of neural tube defect in a previous child) should receive a higher dose of foliac acid of approximately 5 mg daily, starting before conception and continuing for 12 weeks after conception. Women taking antiepileptic medication should be counselled by their doctor before starting foliac acid.

Ferrous salts

Tablets , dried ferrous sulfate 200 mg (65 mg iron); ferrous sulfate 300 mg (60 mg iron); ferrous fumarate 210 mg (68 mg iron); ferrous gluconate 300 mg (35 mg iron)

Oral solution , ferrous sulfate (25 mg iron)/mL

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, diverticula; **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

Prevention of iron deficiency anaemia (in those at particular risk), *by mouth* , **adult** (woman) elemental iron 60 mg daily; **child** under 5 years elemental iron 2 mg/kg (maximum 30 mg) daily, over 5 years elemental iron 30 mg daily; in women and children over 5 years, folic acid may also be given

PATIENT ADVICE. Although iron preparations are best absorbed on an empty stomach they may be taken after food to reduce gastrointestinal adverse effects; they may discolour stools. Liquid preparations containing iron salts should be well diluted with water (and if possible swallowed through a drinking straw to prevent discoloration of the teeth)

Adverse effects:

constipation, diarrhoea, dark stools, nausea, epigastric pain, gastrointestinal irritation; long-term or excessive administration may cause haemosiderosis

Folic acid

Tablets , folic acid 1 mg, 5 mg

Uses:

treatment of folate-deficiency megaloblastic anaemia; prevention of neural tube defect in pregnancy (see notes above)

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** 400–500 micrograms 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

Ferrous salt with folic acid

Tablets , dried ferrous sulfate 325 mg (105 mg iron), folic acid 350 micrograms; dried ferrous sulfate 160 mg (50 mg iron), folic acid 400 micrograms; ferrous fumarate 322 mg (105 mg iron), folic acid 350 micrograms

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:

Severe anaemia, *by mouth* , **adult** elemental iron 120 mg daily with folic acid 400 micrograms daily for 3 months; **child** under 2 years elemental iron 25 mg daily with folic acid 100–400 micrograms daily for 3 months, 2–12 years elemental iron 60 mg daily with folic acid 400 micrograms daily for 3 months

Prevention of iron and folic acid deficiencies in pregnancy, *by mouth* **ADULT** the equivalent of about 100 mg elemental iron with 350–400 micrograms folic acid daily throughout pregnancy

Adverse effects:

see Ferrous salts

Hydroxocobalamin

Injection (Solution for injection), hydroxocobalamin 1 mg/ml, 1-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 1 mg 3 times a week for 2 weeks, then 1 mg every 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

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 5 days, until the oral anticoagulant has taken effect and the INR (international normalized ratio) has been in the therapeutic range for 2 consecutive days. 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 deep-vein 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 major 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 48–72 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, for patients with atrial fibrillation who are at risk of embolization and for those with mechanical prosthetic heart valves (to prevent emboli developing on the valves); 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 (usually reported as INR, international normalized ratio) 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

Desmopressin [not included on WHO Model List] by injection may aid haemostasis and be useful in mild forms of haemophilia. For minor procedures including dental surgery, it may circumvent the need for factor VIII. 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, 1-ml ampoule; 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 (Appendix 5) and renal failure (Appendix 4); 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 (Appendix 5) or renal failure (Appendix 4), 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 3–9 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 (including angioedema, anaphylaxis)

Phytomenadione

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 micrograms *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* , 2.5–5 mg; very rarely up to 50 mg (but risk of overcorrection with high dosage)

Haemorrhagic disease of the newborn, treatment, *by intravenous or intramuscular injection* , **NEONATE** 1 mg with further doses if necessary at 8-hour intervals

Haemorrhagic disease of the newborn, 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 breastfed 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