mano; Jarabe Palto Compuesto con Miel Adulto; Jarabe Palto Compuesto con Miel Infantil; Mielax; Mielito; Paltomiel; Paltomiel Plus; Pulmosina; ***Fr.:*** Feromiel; Taido; ***Indon.:*** Pectum; Sirec; ***Irl.:*** Venos Honey & Lemon; ***Ital.:*** Alvear con Ginseng; Apiserum con Telergon 1; Bebimix; Bioton; Fon Wan Eleuthero†; Fon Wan Ginsenergy; Liozim; Nepiros; Nerex; Nutrigel†; Pollingel Ginseng†; ***Mex.:*** Guayalin-Plus†; ***NZ:*** Lemsip Dry Cough†; Robitussin Honey Cough; ***Pol.:*** Babicum; ***Rus.:*** Bronchicum Husten (Бронхикум Сироп от Кашля); ***S.Afr.:*** Choats Extract of Lettuce Cough Mixture; Enzian Anaemodoron Drops; ***Switz.:*** Neo-Angin au miel et citron; ***UK:*** Adult Meltus for Chesty Coughs & Catarrh; Beehive Balsam; Buttercup Syrup (Honey and Lemon flavour); Herb and Honey Cough Elixir; Honey & Molasses; Jackson's Lemon Linctus; Jackson's Troublesome Coughs; Lemsip Cough & Cold Dry Cough; Lockets; Lockets Medicated Linctus; M & M; Meltus Expectorant; Meltus Honey & Lemon; Potters Children's Cough Pastilles; Potters Gees Linctus; Regina Royal Five; Sanderson's Throat Specific; Throaties Pastilles; Venos Honey & Lemon; Zubes Honey & Lemon; ***Venez.:*** Jengimiel; Jengimiel Sabila; Perebron con Miel†.

Invert Sugar

Azúcar invertido.

CAS — 8013-17-0.

ATC — C05BB03.

ATC Vet — QC05BB03.

Pharmacopoeias. *Br.* and *US* include preparations of invert sugar.

Profile

Invert sugar is an equimolecular mixture of glucose and fructose which may be prepared by the hydrolysis of sucrose with a suitable mineral acid such as hydrochloric acid. Invert sugar has similar actions and uses to those of glucose (p.1945) and fructose (p.1945). It has been used as a 10% solution as an alternative to glucose in parenteral nutrition but, as with fructose, such use cannot be recommended.

A syrup of invert sugar is used as a stabilising agent; when mixed with suitable proportions of sucrose-based syrup it will help to prevent crystallisation of the sucrose.

Preparations

BP 2008: Invert Syrup;
USP 31: Invert Sugar Injection; Multiple Electrolytes and Invert Sugar Injection Type 1; Multiple Electrolytes and Invert Sugar Injection Type 2; Multiple Electrolytes and Invert Sugar Injection Type 3.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***S.Afr.:*** Emex; ***USA:*** Travert.

Iron

Eisen; Fer; Ferro; Ferrum; Hierro; Ijzer; Järn; Rauta; Železo; Železo.

Fe = 55.845.

CAS — 7439-89-6.

Pharmacopoeias. *Eur.* (see p.vii) includes a form for homoeopathic preparations.
Ph. Eur. 6.2 (Iron for Homoeopathic Preparations; Ferrum ad Praeparationes Homoeopathicae). A fine, blackish-grey powder, without metallic lustre, obtained by reduction or sublimation. Practically insoluble in water and in alcohol; it dissolves with heating in dilute mineral acids.

Adverse Effects

The astringent action of **oral** iron preparations sometimes produces gastrointestinal irritation and abdominal pain with nausea and vomiting. These irritant adverse effects are usually related to the amount of elemental iron taken rather than the type of preparation. Other gastrointestinal effects may include either diarrhoea or constipation. Adverse effects can be reduced by giving it with or after food (rather than on an empty stomach) or by beginning therapy with a small dose and increasing gradually. Modified-release products are claimed to produce fewer adverse effects but this may only reflect the lower availability of iron from these preparations. Oral liquid preparations containing iron salts may blacken the teeth and should be drunk through a straw. The faeces of patients taking iron salts may be coloured black.

The adverse effects associated with iron given **parenterally** are described under iron dextran (see p.1951).

Since absorbed iron is conserved by the body, **iron overload**, with increased storage of iron in various tissues (haemosiderosis), may occur as a result of excessive or mistaken therapy, especially parenteral therapy. Patients with pre-existing iron storage or absorption diseases are also at risk.

Acute iron **overdosage** can be divided into four stages.

- In the first phase, which occurs up to 6 hours after oral ingestion, gastrointestinal toxicity, notably vomiting and diarrhoea, predominates. Other effects may include cardiovascular disorders such as hypotension, metabolic changes including acidosis and hyperglycaemia, and CNS depression ranging from lethargy to coma. Patients with only mild to moderate poisoning do not generally progress past this first phase.
- The second phase, which is not always seen, may occur at 6 to 24 hours after ingestion and is characterised by a temporary remission or clinical stabilisation.
- In the third phase, 12 to 48 hours after ingestion, gastrointestinal toxicity recurs together with shock, metabolic acidosis, severe lethargy or coma, hepatic necrosis and jaundice, hypoglycaemia, coagulation disorders, oliguria or renal failure, and possible myocardial dysfunction.
- The fourth phase may occur several weeks after ingestion and is characterised by gastrointestinal obstruction and possibly late hepatic damage.

Relatively small amounts of iron may produce symptoms of toxicity. It has been stated that more than the equivalent of 20 mg/kg of iron could lead to some symptoms of toxicity and that in a young child the equivalent of about 60 mg/kg of iron should be regarded as extremely dangerous. Estimates of acute lethal dosages have ranged from the equivalent of 150 mg/kg of iron upwards. Serum-iron concentrations have also been used as an indication of the severity of overdosage: a peak concentration of 5 micrograms/mL or more is reportedly associated with severe poisoning in many patients.

Effects on the cardiovascular system. For a suggestion that iron overload may contribute to ischaemic heart disease, see Effects in Non-deficient Subjects, below.

Effects on growth. Iron supplementation in iron-replete children has been reported to adversely affect their growth—see Effects in Non-deficient Subjects, below.

Iron overload. Because the body lacks a mechanism for the excretion of excess iron, abnormally high absorption or repeated blood transfusion will result in iron overload (p.1442), leading eventually to haemochromatosis. The consequences of haemochromatosis include pigment deposition in skin and other organs, mild liver dysfunction, endocrine dysfunction (failure of the adolescent growth spurt, hypogonadism, sometimes diabetes and hypothyroidism), and heart disease (pericarditis, heart failure, and arrhythmias). If unchecked, the iron build-up can lead to death, mainly through heart failure or arrhythmia. Where iron overload is due to increased absorption, phlebotomy is the treatment of choice; however, if phlebotomy is not tolerated or in patients who are transfusion-dependent (as in β-thalassaemia—see p.1045) treatment with iron chelators such as desferrioxamine is used to retard accumulation.

Treatment of Adverse Effects

In treating acute iron poisoning, speed is essential to reduce absorption of iron from the gastrointestinal tract. Activated charcoal is ineffective, but gastric lavage should be considered in those who have ingested the equivalent of more than 60 mg/kg of elemental iron within 1 hour of presentation. Serum-iron concentrations may be an aid to estimating the severity of poisoning. Although these do not correlate well with symptoms, the UK Poisons Information Service considers that concentrations taken about 4 hours after ingestion generally indicate the severity of poisoning as follows:

- less than 3 micrograms/mL, mild poisoning
- 3 to 5 micrograms/mL, moderate poisoning
- 5 micrograms/mL or more, severe poisoning

In patients with moderate poisoning, or severe asymptomatic poisoning, the measurement should be repeated after a further 2 hours, and chelation therapy with desferrioxamine (p.1441) should be considered if the concentration is rising. In patients with severe symptomatic poisoning, chelation therapy should be considered straight away.

Other measures include the symptomatic management and therapy of metabolic and cardiovascular disorders.

◊ General references.

1. Proudfoot AT, *et al.* Management of acute iron poisoning. *Med Toxicol* 1986; **i:** 83–100.
2. Mann KV, *et al.* Management of acute iron overdose. *Clin Pharm* 1989; **8:** 428–40.
3. Mills KC, Curry SC. Acute iron poisoning. *Emerg Med Clin North Am* 1994; **12:** 397–413.
4. Fine JS. Iron poisoning. *Curr Probl Pediatr* 2000; **30:** 71–90.

Overdosage. References highlighting the specific problem of iron overdose in children.[1-4] Child-resistant packaging and warning labels may be helpful in reducing the problem.

1. Anonymous. Iron-containing drugs and supplements: accidental poisoning. *WHO Drug Inf* 1995; **9:** 159–60.
2. Fitzpatrick R, Murray V. Iron toxicity: dietary supplements. *Pharm J* 1996; **256:** 666.
3. Committee on Safety of Medicines/Medicines Control Agency. Oral iron supplements: accidental overdose may be fatal in children. *Current Problems* 2001; **27:** 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 08/11/05)
4. Singhi SC, *et al.* Acute iron poisoning: clinical picture, intensive care needs and outcome. *Indian Pediatr* 2003; **40:** 1177–82.

Overdosage in pregnancy. Limited data on the treatment of iron overdose in pregnancy from the UK National Teratology Information Service, suggested that treatment with desferrioxamine should not be withheld if clinically indicated.[1-3] Most pregnancies had a normal outcome. A literature review[4] of iron overdose in pregnant women found that women with peak serum-iron concentrations greater than or equal to 4 micrograms/mL were more frequently symptomatic, but that there was no relationship between peak iron level and frequency of spontaneous abortion, preterm delivery, congenital anomalies, or perinatal or maternal death. However, women with stage 3 iron toxicity, defined as those manifesting with hepatic, renal, or cardiac failure, were more likely to spontaneously abort, deliver preterm, or die.

1. McElhatton PR, *et al.* The consequences of iron overdose and its treatment with desferrioxamine in pregnancy. *Hum Exp Toxicol* 1991; **10:** 251–9.
2. McElhatton PR, *et al.* Outcome of pregnancy following deliberate iron overdose by the mother. *Hum Exp Toxicol* 1993; **12:** 579.
3. McElhatton PR, *et al.* The outcome of pregnancy following iron overdose by the mother. *Br J Clin Pharmacol* 1998; **45:** 212P–213P.
4. Tran T, *et al.* Intentional iron overdose in pregnancy—management and outcome. *J Emerg Med* 2000; **18:** 225–8.

Precautions

Iron compounds should not be given to patients receiving repeated blood transfusions or to patients with anaemias not produced by iron deficiency unless iron deficiency is also present. Oral and parenteral iron therapy should not be used together. Care should be taken in patients with iron-storage or iron-absorption diseases such as haemochromatosis, haemoglobinopathies, or existing gastrointestinal diseases such as inflammatory bowel disease, intestinal strictures and diverticulae.

Liquid preparations containing iron salts should be well diluted with water and swallowed through a straw to prevent discoloration of the teeth.

Effects in non-deficient subjects. There has been concern about the potential consequences of iron supplementation in individuals and groups who are not actually iron-deficient. Apart from the suggestion that certain populations may be at somewhat increased risk of microbial *infection* after supplementation (see Infections, below), there is some evidence that supplementation in children without iron deficiency may *retard their growth*.[1,2] It has also been proposed that iron may be associated with *ischaemic heart disease*, by modifying low-density lipoprotein in ways which increase its atherogenic potential and by sensitising the myocardium to ischaemic injury.[3,4] However, conclusions of a cohort study[5] and a systematic review[6] did not support any correlation between iron status and coronary heart disease. There is some suggestion that an excess of iron may be *carcinogenic*;[7,8] conclusive studies are lacking.

1. Idjradinata P, *et al.* Adverse effect of iron supplementation on weight gain of iron-replete young children. *Lancet* 1994; **343:** 1252–4.
2. Dewey KG, *et al.* Iron supplementation affects growth and morbidity of breast-fed infants: results of a randomized trial in Sweden and Honduras. *J Nutr* 2002; **132:** 3249–55.
3. Burt MJ, *et al.* Iron and coronary heart disease: iron's role is undecided. *BMJ* 1993; **307:** 575–6.
4. Sullivan JL. Iron and coronary heart disease: iron makes myocardium vulnerable to ischaemia. *BMJ* 1993; **307:** 1066–7.
5. Sempos CT, *et al.* Serum ferritin and death from all causes and cardiovascular disease: the NHANES II Mortality Study. *Ann Epidemiol* 2000; **10:** 441–8.

6. Danesh J, Appleby P. Coronary heart disease and iron status: meta-analyses of prospective studies. *Circulation* 1999; **99:** 852–4.
7. Deugnier Y. Iron and liver cancer. *Alcohol* 2003; **30:** 145–50.
8. Huang X. Iron overload and its association with cancer risk in humans: evidence for iron as a carcinogenic metal. *Mutat Res* 2003; **533:** 153–71.

INFECTIONS. Iron is not only an essential element for humans but is also essential for many micro-organisms. Thus, it has been suggested that persons with either adequate iron stores or iron overload may provide optimum conditions for microbial growth and therefore be susceptible to an increased incidence and severity of infection; conversely, iron-deficiency anaemia may offer some protection against infections. The topic has been reviewed[1,2] and although there is no evidence that small amounts of iron supplements or iron-fortified food in normal people will render them more prone to infection[3] there is some evidence that in populations with a high prevalence of endemic infectious disease such as malaria, iron therapy may be followed by a higher incidence of infectious complications or by a flare-up of existing low-grade disease. Therefore, the routine use of iron supplements in such communities has been questioned,[4,5] although an increasing number of studies failed to demonstrate a detrimental effect.[6-10] A subsequent systematic review[11] concluded that, while iron supplementation slightly increases the risk of developing diarrhoea, it has no apparent harmful effect on the overall incidence of infectious illnesses in children. More recently, a controlled study found that supplementation with iron and folic acid increased the risk of severe illness and death in pre-school children in a population with high rates of malaria. The authors concluded that, while iron-deficient children can benefit from supplementation in the presence of active prophylaxis and treatment of malaria, supplementation in non-deficient subjects might be harmful.[12] Data conflict on the association between parenteral iron and infection in dialysis patients; some consider that treatment with parenteral iron should be avoided during active infection.[13,14]

1. Hershko C, *et al.* Iron and infection. *BMJ* 1988; **296:** 660–4.
2. Oppenheimer SJ. Iron and its relation to immunity and infectious disease. *J Nutr* 2001; **131** (suppl): 616S–633S.
3. Bullen JJ, Ward CG. Iron and infection. *BMJ* 1988; **296:** 1539.
4. Oppenheimer SJ, *et al.* Iron supplementation increases prevalence and effects of malaria: report on clinical studies in Papua New Guinea. *Trans R Soc Trop Med Hyg* 1986; **80:** 603–12.
5. Smith AW, *et al.* The effects on malaria of treatment of iron-deficiency anaemia with oral iron in Gambian children. *Ann Trop Paediatr* 1989; **9:** 17–23.
6. Harvey PWJ, *et al.* The effect of iron therapy on malarial infection in Papua New Guinean schoolchildren. *Am J Trop Med Hyg* 1989; **40:** 12–18.
7. Boele van Hensbroek M, *et al.* Iron, but not folic acid, combined with effective antimalarial therapy promotes haematological recovery in African children after acute falciparum malaria. *Trans R Soc Trop Med Hyg* 1995; **89:** 672–6.
8. van den Hombergh J, *et al.* Does iron therapy benefit children with severe malaria-associated anaemia? A clinical trial with 12 weeks supplementation of oral iron in young children from the Turiani Division, Tanzania. *J Trop Pediatr* 1996; **42:** 220–7.
9. Menendez C, *et al.* Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. *Lancet* 1997; **350:** 844–50.
10. Mebrahtu T, *et al.* Low-dose daily iron supplementation for 12 months does not increase the prevalence of malarial infection or density of parasites in young Zanzibari children. *J Nutr* 2004; **134:** 3037–41.
11. Gera T, Sachdev HPS. Effect of iron supplementation on incidence of infectious illness in children: systematic review. *BMJ* 2002; **325:** 1142.
12. Sazawal S, *et al.* Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. *Lancet* 2006; **367:** 133–43.
13. Brewster UC, Perazella MA. Intravenous iron and the risk of infection in end-stage renal disease patients. *Semin Dial* 2004; **17:** 57–60.
14. Maynor L, Brophy DF. Risk of infection with intravenous iron therapy. *Ann Pharmacother* 2007; **41:** 1476–80.

Interference with diagnostic tests. Although studies *in vitro* found that iron (ferrous sulfate) caused a false-positive result in the Hemoccult test for blood in faeces, this did not occur *in vivo* in persons receiving oral iron therapy.[1-3] An explanation for the difference in these findings was that hydrogen peroxide in the Hemoccult developer converted ferrous ions in solution to ferric ions, which caused oxidation in the test, whereas *in vivo* the iron was probably eliminated in the faeces in the form of non-reactive insoluble iron precipitates.[2]

1. Kulbaski MJ, *et al.* Oral iron and the Hemoccult test: a controversy on the teaching wards. *N Engl J Med* 1989; **320:** 1500.
2. McDonnell M, Elta G. More on oral iron and the Hemoccult test. *N Engl J Med* 1989; **321:** 1684.
3. Anderson GD, *et al.* An investigation into the effects of oral iron supplementation on in vivo Hemoccult stool testing. *Am J Gastroenterol* 1990; **85:** 558–61.

Porphyria. Erythropoietic protoporphyria was exacerbated by oral iron therapy in 4 patients;[1] a further patient had a variable reaction to iron, being able to tolerate it on some occasions but suffering from exacerbation of porphyria on others.[2] Intravenous iron precipitated porphyria cutanea tarda in one patient on haemodialysis.[3]

1. Milligan A, *et al.* Erythropoietic protoporphyria exacerbated by oral iron therapy. *Br J Dermatol* 1988; **119:** 63–6.
2. McClements BM, *et al.* Erythropoietic protoporphyria and iron therapy. *Br J Dermatol* 1990; **122:** 423–6.
3. McKane W, *et al.* Porphyria cutanea tarda precipitated by intravenous iron in a haemodialysis patient. *Nephrol Dial Transplant* 2001; **16:** 1936–8.

Interactions

Iron salts are not well absorbed by mouth, and food may further impair their absorption.

Compounds containing calcium and magnesium, including antacids and mineral supplements, and bicarbonates, carbonates, oxalates, or phosphates, may impair the absorption of iron by the formation of insoluble complexes. Zinc salts may also decrease the absorption of iron. The absorption of both iron salts and tetracyclines is diminished when taken together orally. If treatment with both drugs is required, a time interval of about 2 to 3 hours should be allowed between them. A suitable interval is also advised if an iron supplement is needed in patients given trientine. Iron is chelated by acetohydroxamic acid, reducing the absorption of both. Iron should not be given with dimercaprol as toxic complexes may form.

The response to iron may be delayed in patients receiving systemic chloramphenicol.

Some agents, such as ascorbic acid and citric acid, may actually increase the absorption of iron.

In addition to those already mentioned, iron salts can also decrease the absorption of other drugs and thus reduce their bioavailability and clinical effect. Drugs so affected include cefdinir, bisphosphonates, entacapone, fluoroquinolones, levodopa, methyldopa, mycophenolate mofetil, and penicillamine. Iron salts may reduce the efficacy of levothyroxine (p.2173).

Interactions with parenteral iron are mentioned under Iron Dextran, p.1952.

◊ Reviews.

1. Campbell NRC, Hasinoff BB. Iron supplements: a common cause of drug interactions. *Br J Clin Pharmacol* 1991; **31:** 251–5.

Pharmacokinetics

Iron is irregularly and incompletely absorbed from the gastrointestinal tract, the main sites of absorption being the duodenum and jejunum. Absorption is aided by the acid secretion of the stomach and by some dietary acids (such as ascorbic acid) and occurs more readily when the iron is in the ferrous state or is part of the haem complex (haem-iron). Absorption is also increased in conditions of iron deficiency or in the fasting state but is decreased if the body stores are overloaded. Normally only about 5 to 15% of the iron ingested in food is absorbed.

Most absorbed iron is bound to transferrin and transported to the bone marrow where it is incorporated into haemoglobin; the remainder is contained within the storage forms, ferritin (p.1938) or haemosiderin, or as myoglobin, with smaller amounts occurring in haem-containing enzymes or in plasma bound to transferrin.

Only very small amounts of iron are excreted as the majority released after the destruction of the haemoglobin molecule is re-used. This conservation of body iron, and lack of an excretory mechanism for excess iron, is the reason for the development of iron overload with excessive iron therapy or repeated transfusions.

◊ General references.

1. Harju E. Clinical pharmacokinetics of iron preparations. *Clin Pharmacokinet* 1989; **17:** 69–89.

Human Requirements

The body contains about 4 g of iron most of which is present as haemoglobin.

Apart from haemorrhage, iron is mainly lost from the body in the faeces, urine, from skin, and sweat, but the total loss is very small. Iron is also lost in small amounts in breast milk and in menstrual blood. In healthy men and postmenopausal women the loss is replaced by the absorption of about 1 mg of iron daily; about 1.5 to 2 mg needs to be absorbed daily by premenopausal women. In childhood and adolescence, the need is proportionately greater because of growth. Iron absorption is variable but is usually between 5 and 15% and therefore a dietary allowance containing the equivalent of about 10 mg of iron daily is usually sufficient for men and postmenopausal women; up to 15 mg daily may be necessary for premenopausal women with normal menstrual blood losses; some authorities recommend higher amounts or supplements during pregnancy. For further details concerning dietary requirements, see below and for a discussion of prophylactic iron given during pregnancy, see Iron-deficiency Anaemia, under Uses and Administration, below.

Good dietary sources of haem-iron are animal products such as meat and fish; non-haem-iron is also found in animal products and in vegetable products such as legumes and some leafy vegetables, but some vegetable products with a high iron content also contain phosphates or phytates which inhibit absorption by the formation of unabsorbable complexes.

UK and US recommended dietary intake. In the UK, dietary reference values (DRV)[1] and in the USA, recommended dietary allowances (RDA)[2] have been published for iron.

In the UK the estimated average requirement (EAR) for adult males and postmenopausal females is 6.7 mg daily and the reference nutrient intake (RNI) is 8.7 mg daily; for premenopausal females, but without heavy menstrual blood losses, the EAR and RNI are 11.4 and 14.8 mg daily respectively. Amounts for infants, children, and adolescents, which are proportionately higher than those for adults, are also given. No increase is considered necessary during pregnancy or lactation.[1]

In the USA the RDA for adult males and postmenopausal females is 8 mg daily and that for premenopausal women is 18 mg. The tolerable upper intake level is 45 mg daily. Amounts for infants, children, and adolescents, again proportionately higher than for adults, are also provided. The RDA for pregnant women is 27 mg daily. An RDA of 9 mg for lactating adult women has been estimated from the EAR of non-menstruating women plus the average iron content of human milk.[2]

The Food and Agriculture Organization of the United Nations and the WHO have together published guidelines concerning iron requirements and these take into account many factors including bioavailability of iron in the diet.[3]

For the definitions of DRV, EAR, RNI, and RDA, see under Vitamins, p.1925.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. FAO/WHO. *Requirements of vitamin A, iron, folate and vitamin B : report of a joint FAO/WHO expert consultation*. Rome: Food and Agriculture Organization of the United Nations, 1988.

Uses and Administration

Iron is an essential constituent of the body, being necessary for haemoglobin formation and for the oxidative processes of living tissues. Iron deficiency results in defective erythropoiesis and anaemia. Iron and iron salts should only be given for the treatment or prophylaxis of iron-deficiency anaemias (see below). They should not be given for the treatment of other types of anaemia except where iron deficiency is also present. Iron-deficiency anaemias respond readily to iron therapy but the underlying cause of the anaemia should be determined and treated.

The preferred route for giving iron is oral, usually as soluble ferrous salts which are better absorbed than ferric salts. The usual adult dose for the treatment of iron-deficiency anaemia is 100 to 200 mg of iron daily in divided doses. The usual adult prophylactic dose is about 60 to 120 mg of iron daily. There are various recommendations for children's doses and up to 2 mg/kg of iron three times daily for treatment, and 1 to 2 mg/kg daily for prophylaxis of iron-deficiency anaemia (usually to a maximum of 30 mg) has been used. Therapy is generally continued until haemoglobin concentrations reach normal values, which may take some weeks, and then for a further 3 months or more to restore body-iron stores.

Further information concerning the dosage of iron salts and compounds used is provided in the individual monographs; this information, however, tends to reflect the amounts of iron contained in different salts or available commercial preparations and therefore, in some instances, may not be within the general range of iron dosages as quoted above.

The iron content of various iron salts is tabulated in Table 1, below.

Modified-release dosage forms of iron are claimed to result in reduced gastrointestinal adverse effects and have the advantage of once-daily dosage. The preparations are designed to release the iron gradually along the gut but in some instances the iron may not be released until the preparation reaches a part of the gut where absorption is poor thus resulting in sub-optimal dosing.

Iron can also be given parenterally in circumstances where oral therapy cannot be undertaken and such use is typified by iron dextran (see p.1951).

Administration in the elderly. Patients over 80 years of age with iron-deficiency anaemia (below) were randomised to elemental iron therapy in daily doses of 15 mg, 50 mg (as liquid ferrous gluconate), or 150 mg (as tablets of calcium ferrous citrate) and treated for 2 months.[1] Serum haemoglobin and ferritin concentrations increased significantly in all patients, without significant differences between the 3 doses. The authors concluded that, while these results may not apply to patients with iron deficiency due to malabsorption, chronic disease, or untreated *Helicobacter pylori* infection, low-dose therapy is an effective option for elderly patients with iron-deficiency anaemia, in whom the adverse effects of iron could cause considerable morbidity and impaired compliance. Younger patients could also probably be treated effectively with low-dose iron therapy.

1. Rimon E, *et al.* Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. *Am J Med* 2005; **118:** 1142–7.

Anoxic seizures. Reductions in the frequency of breath-holding episodes in children treated with iron,[1] and especially in those with iron-deficiency anaemia,[2,3] suggest that there might be a relationship between anoxic seizures (p.1221) and iron deficiency.[4]

1. Daoud AS, *et al.* Effectiveness of iron therapy on breath-holding spells. *J Pediatr* 1997; **130:** 547–50.
2. Mocan H, *et al.* Breath holding spells in 91 children and response to treatment with iron. *Arch Dis Child* 1999; **81:** 261–2.
3. Pedersen KW, Knudsen FU. Skal børn med affektkramper behandles med jern? *Ugeskr Laeger* 2004; **166:** 2789–91.
4. Hannon DW. Breath-holding spells: waiting to inhale, waiting for systole, or waiting for iron therapy? *J Pediatr* 1997; **130:** 510–12.

Cough. In a small study[1] of 19 patients, iron supplementation with ferrous sulfate successfully reduced the cough associated with ACE inhibitors (see p.1194). The authors hypothesised that this effect was due to the inhibition by iron of nitric oxide synthase. However, there are some concerns[2] about the effect of giving a nitric oxide synthase inhibitor to hypertensive patients, as it has been found to increase blood pressure in *animal* studies.

1. Lee S-C, *et al.* Iron supplementation inhibits cough associated with ACE inhibitors. *Hypertension* 2001; **38:** 166–70.
2. Lev I, Rian AJJT. Iron supplementation in ACE inhibition as a treatment for cough: is it really inoffensive? *Hypertension* 2001; **38:** e38.

Iron-deficiency anaemia. The iron content of the body is normally kept constant by regulation of the amount absorbed to balance the amount lost. If loss is increased, and/or intake inadequate, a negative iron-balance may lead by degrees to depletion of body iron stores, iron deficiency, and eventually to anaemia. Iron requirements are increased during infancy, puberty, pregnancy, and during menstruation, and iron-deficiency anaemias are most common in women and children; the most common cause in adult males and postmenopausal women is blood loss, usually from the gastrointestinal tract.

Iron deficiency usually results in a microcytic, hypochromic anaemia, but the diagnosis of iron deficiency should be confirmed, if there is any doubt, by measurement of serum ferritin, erythrocyte protoporphyrin, or total iron binding capacity (transferrin). Iron therapy can begin once deficiency is confirmed, but the underlying cause of the deficiency should still be sought and treated.

Table 1. Approximate amounts of different iron salts that supply 60 mg of elemental iron.

Iron salt	Amount
Ferrous ascorbate (anhydrous)	437 mg
Ferrous aspartate (tetrahydrate)	422 mg
Ferrous chloride (tetrahydrate)	214 mg
Ferrous fumarate (anhydrous)	183 mg
Ferrous gluconate (dihydrate)	518 mg
Ferrous succinate (anhydrous)	185 mg
Ferrous sulfate (dried)	186 mg
Ferrous sulfate (heptahydrate)	300 mg

Treatment. The prevention and control of iron-deficiency anaemias has been reviewed.[1-4] Almost all iron-deficiency anaemias respond readily to treatment with iron. The treatment of choice is an oral ferrous salt (ferrous iron is better absorbed than ferric iron).[1] Many iron compounds have been used for this purpose, but do not offer any real advantage over the simple ferrous fumarate, gluconate, or sulfate salts. The usual adult dose is sufficient of these salts to supply about 100 to 200 mg of elemental iron daily (for the elemental iron content of various iron salts, see above), with the aim of increasing haemoglobin concentrations by about 1 g/litre daily or about 20 g/litre every 3 weeks.[1] Haemoglobin response is greatest in the first few weeks of therapy and is proportional to the severity of the original anaemia. Once haemoglobin concentrations have risen to the normal range, iron therapy should be continued for a further 3 months to aid replenishment of iron stores.[1,3] For the view that low-dose iron therapy may be as effective as higher doses, see Administration in the Elderly, above.

Oral iron has been given with agents such as ascorbic acid to enhance iron absorption, and modified-release preparations have been used in patients intolerant of ordinary formulations of iron but the *BNF* considers them to have no therapeutic advantage.

Failure to respond to oral iron after about 3 weeks of therapy may be indicative of non-compliance, continued blood loss with inadequate replacement of iron, malabsorption, wrong diagnosis, or other complicating factors, and the treatment should be reassessed.

Parenteral iron therapy is rarely indicated, may produce severe adverse effects, and should be reserved for patients who are genuinely intolerant of oral iron, persistently non-compliant,[3] who have gastrointestinal disorders exacerbated by oral iron therapy, continuing blood loss too severe for oral treatment to provide sufficient iron, or for those unable to absorb iron adequately from the gastrointestinal tract. Patients with chronic renal failure on haemodialysis (and some on peritoneal dialysis) require regular iron. US guidelines[5] suggest that intravenous use is preferred in haemodialysis patients, but that iron may be given either intravenously or orally in predialysis and peritoneal dialysis patients. The most common parenteral forms are iron dextran, iron sorbitol, iron sucrose, and sodium ferric gluconate complex.

Exceptionally, in patients with profound anaemia, blood transfusion may be necessary to restore dangerously low concentrations of haemoglobin. This may be the case, for example, in cases of worsening angina or severe coexisting pulmonary disease.[1] However, transfusion should always be avoided if possible.

Prophylaxis. Prophylaxis may be desirable in some groups at risk of iron deficiency and consequent anaemia, and may include therapy with oral iron supplements, measures to improve dietary iron intake, fortification of food staples, or control of infection. For the possible problems associated with iron supplementation in those who are not deficient, see Effects in Non-deficient Subjects, under Precautions, above.

WHO[2] recommends that universal supplementation of iron and folic acid should be implemented for pregnant women, starting as soon as possible after gestation starts and continuing for the rest of the pregnancy. WHO also recommends that where anaemia prevalence is above 40%, women of child-bearing age and lactating women should be given 3 months of iron and folic acid supplementation. However, the US Preventive Services Task Force has reviewed the subject of iron supplementation during pregnancy,[6] and concluded that there was insufficient evidence for or against routine supplementation.[7]

Iron supplementation is accepted in menorrhagia, after gastrectomy, and in the management of low birth-weight infants such as the premature. Iron deficiency in infants and children may result in developmental delay or impairment of cognitive function.[2] Breast feeding should be encouraged during the first year of life.[1] WHO has suggested[2] that low birth-weight infants be given universal supplementation. Where the diet does not include foods fortified with iron or where anaemia prevalence is above 40%, iron supplementation should be given to all children between 6 and 23 months of age; for children aged 24 months and above, a 3-month course of iron supplementation should be given where the anaemia prevalence is above 40%.

The usual prophylactic dose in adults suggested by WHO is about 60 mg of elemental iron daily. Doses of about 2 mg/kg of elemental iron daily (up to 30 mg) have been suggested for prophylaxis in children (see also Uses and Administration, above).

Dietary measures, such as addition of vitamin-C-rich foods, or other enhancers of iron absorption including iron in the form of haem (found in meat or fish) to the diet, control of parasitic infections such as hookworm (which are responsible for considerable occult blood loss), and malaria prophylaxis are particularly important for the general community in developing countries. Fortification of food staples poses technical problems as iron salts react with food components and may produce rancidity or other undesirable changes on storage. Nonetheless, wheat or maize flour, rice, and milk products have been fortified in some countries, and consideration has also been given to fortification of salt or sugar.

1. Provan D. Iron deficiency anaemia. In: Provan D, ed. *ABC of clinical haematology.* 2nd ed. London: BMJ Books, 2003: 1–4.
2. World Health Organization. *Iron deficiency anaemia assessment, prevention, and control: a guide for programme managers.* Geneva: WHO, 2001. Available at: http://www.who.int/entity/nutrition/publications/en/ida_assessment_prevention_control.pdf (accessed 11/07/06)
3. British Society of Gastroenterology. Guidelines for the management of iron deficiency anaemia (issued May 2005). Available at: http://www.bsg.org.uk/pdf_word_docs/iron_def.pdf (accessed 09/11/05)
4. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. *Lancet* 2007; **370:** 511–20.
5. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in adults. *Am J Kidney Dis* 2006; **47** (suppl 3): S16–S85. Correction. *ibid.*; **48:** 518. Also available at: http://www.kidney.org/professionals/KDOQI/guidelines_anemia/index.htm (accessed 04/12/06)
6. US Preventive Services Task Force. Routine iron supplementation during pregnancy: review article. *JAMA* 1993; **270:** 2848–54.
7. US Preventive Services Task Force. Routine iron supplementation during pregnancy: policy statement. *JAMA* 1993; **270:** 2846–8.

Restless legs syndrome. Iron deficiency is present in about a quarter of people with restless legs syndrome (see Sleep-associated Movement Disorders, p.958), particularly older people, and serum ferritin concentrations are inversely correlated with the severity of symptoms. Iron may have a role in the pathophysiology of the disorder, and treatment of iron deficiency may reduce symptoms.[1]

1. Medcalf P, Bhatia KP. Restless legs syndrome. *BMJ* 2006; **333:** 457–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Celloids IP 82; ***Austria:*** Liquifer†; ***Braz.:*** Ferrini; ***Indon.:*** Ferromia; ***Ital.:*** Liquifer†; Profer; ***Jpn:*** Ferromia; ***Malaysia:*** Ferrocyte; ***Mex.:*** Unifer; ***Singapore:*** Ferrocyte; ***Thai.:*** Ferrocyte; ***USA:*** EZFE; Icar; Ircon.

Multi-ingredient: ***Arg.:*** Hierroquick; ***Austral.:*** Celloid Compounds Magcal Plus; Celloid Compounds Sodical Plus; Clements Iron; Duo Celloids CPIP; Duo Celloids PCIP; Duo Celloids PPIP; Duo Celloids SPIP; Iron Compound†; ***Austria:*** China-Eisenwein; ***Braz.:*** Fernni Folico; Ferrumvit†; Folifer; Hemofer†; Olohepat†; Sadol; Sangotone†; Vi-Ferrin; ***Cz.:*** Homeovox; ***Ger.:*** Biovital Classic; Ferrodix†; Folicombin; ***Hung.:*** Biovital†; ***India:*** Cafe-Kit†; Carboflot†; Cofol Z; Fexid-Z; Imax; Probofex; Tonoferon; ***Indon.:*** Ferlin; Ferofort; Incremin with Iron; ***Ital.:*** Carfosid; Evafer; ***Mex.:*** Ferricol; Forta; Intrafer; Intrafer F-800; Intrafer TF; Uniferfol; ***NZ:*** Incremin with Iron; ***Philipp.:*** Incremin; Odiron; Odiron-C; ***Singapore:*** Memolobat†; ***Switz.:*** Elixir tonique N; ***Thai.:*** Hemo-Cyto-Serum; ***Turk.:*** Blood Builder; ***UK:*** Hematinic; ***USA:*** Centurion A–Z†; Feocyte; FeoGen; Geritol Complete; I-L-X; Icar-C Plus; Ircon-FA†; Renatabs with Iron; Tandem F; Theravee Hematinic; Ultra-Natal.

Iron Dextran

Demir Dekstran; Hierro dextrano; Iron-Dextran Complex.
CAS — 9004-66-4.
ATC Vet — QB03AB90; QB03AC90.

Pharmacopoeias. *Br.*, *Chin.*, and *US* include injections.
BP 2008 (Iron Dextran Injection). A sterile colloidal solution containing a complex of ferric hydroxide and dextrans of weight average molecular weight between 5000 and 7000. It contains 4.75 to 5.25% of iron and 17.0 to 23.0% of dextrans. pH 5.2 to 6.5.
USP 31 (Iron Dextran Injection). A sterile colloidal solution of ferric hydroxide in complex with partially hydrolysed dextran of low molecular weight. It may contain not more than 0.5% of phenol as a preservative. pH 5.2 to 6.5.

Adverse Effects and Treatment

Severe anaphylactoid reactions may occur with iron dextran and fatalities have been reported. It is therefore recommended that it be given where there are facilities for the emergency treatment of such reactions, that certain precautions be observed, and that test doses be used (see Precautions, below).

Rapid intravenous use may be associated with vascular flushing and hypotension. Thrombophlebitis may occur at the site of injection, although the incidence can be reduced by giving iron dextran in sodium chloride 0.9% rather than glucose 5%. Intramuscular injection is associated with local reactions, pain, and staining at the site of injection; leakage along the injection track may occur unless the proper technique is used (see Uses and Administration, below). Cardiovascular effects such as chest pain or tightness, shock, myocardial infarction, hypertension, tachycardia, bradycardia, and arrhythmias may occur with either route. Rashes, urticaria, purpura, and pruritus have been reported. Other reactions include gastrointestinal disturbances, haematuria, dyspnoea, and taste disturbance.