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.