Iron

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Abstract

Iron poisoning causes its metabolic effects in proportion to the concentrations of free iron. Toxicity is therefore related to the dose ingested. The amount of iron in different salts varies, and iron concentrations may rise and fall, making plasma concentrations difficult to interpret in acute poisoning. Clinical features include severe gastrointestinal irritation, cardiovascular collapse and direct organ damage to liver and kidneys. Unconsciousness occurs in severe cases. The chelating agent, desferrioxamine, is the antidote used, although there remains uncertainty about the optimal dose in individual patients.

Keywords chelating agents; desferrioxamine; iron poisoning

Numerous iron preparations are available on prescription and over the counter, the latter types being commonly co-formulated with vitamins. Acute iron poisoning occurs mainly in childhood, partly because iron preparations are usually brightly coloured tablets indistinguishable from sweets.[1–3] Adults occasionally ingest large quantities in self-poisoning episodes.

Iron content — a distinction must be made between the amount of iron salt contained in a tablet or syrup and the elemental iron content, because elemental iron content is a better guide to toxicity than weight of iron salt.

- A 200 mg ferrous fumarate tablet contains 65 mg elemental iron.
- A 200 mg ferrous sulphate tablet contains 60 mg.
- A 300 mg ferrous gluconate tablet contains only 35 mg.

Such differences become more important as the number of tablets involved in a poisoning episode increases. Some combined iron and vitamin preparations contain toxicologically insignificant amounts of iron, but others contain as much as ferrous sulphate — this should be checked with a poisons information service. Serious toxicity is unlikely unless more than 60 mg elemental iron/kg body weight has been ingested; 180–300 mg/kg body weight is potentially fatal.

Mechanism of toxicity

The pathophysiology of poisoning with acute iron, which acts as a cellular toxin, is incompletely understood. Iron preparations permeate and stain the upper gastrointestinal mucosa, sometimes causing ulceration and haemorrhage. Absorbed iron is initially bound to transferrin; however, in large overdoses, the iron-binding capacity of transferrin may be exceeded, leaving the toxicologically more important free iron circulating in the plasma. The iron is then taken up by the reticulo-endothelial system and transferred to hepatocytes, where it appears to concentrate around the mitochondrial cristae, disrupting metabolic processes and causing cell death, which is most marked in the periportal regions.[4]

Circulating free iron is a potent vasodilator, and contributes to the development of hypotension and shock.

Clinical features

The course of acute iron poisoning is commonly said to have four phases (Table 1), but the clinical value of this is doubtful. It is more important to appreciate that the initial gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhoea and bleeding) result from the direct effects of iron on the gut mucosa. Shock (only rarely caused by blood loss), acidosis, impaired consciousness, convulsions and features of hepatocellular necrosis and its complications reflect systemic toxicity secondary to absorption of excessive amounts of elemental iron. In most patients with iron poisoning, only the signs of gut irritation are present. Systemic toxicity is uncommon and death seldom occurs.

Assessment of severity of poisoning is essential to identify patients in whom the benefits of the antidote outweigh the dangers. Desferrioxamine is the standard antidote but has potential adverse effects (mainly hypotension), may complicate assessment of the serum iron concentration, and should not be given indiscriminately.

Shock and/or coma indicates severe poisoning and the need for immediate treatment with desferrioxamine. Most patients do not exhibit these features, however, and are more difficult to assess. There is no single or simple test of poisoning severity. A straight abdominal radiograph may indicate the approximate number of tablets ingested, but this approach is contraindicated in women of child-bearing age and is not fail-safe.

Measurement of serum iron concentration is the usual method of assessing the severity of poisoning, but interpretation of the results is difficult, and haemolysis in severe iron poisoning may interfere with the assay preventing a result being obtained. There have been few studies of iron kinetics in acute overdose. Plasma concentrations probably peak within 4 hours and decline rapidly thereafter; it is therefore difficult to use a single concentration, particularly in the first few hours after ingestion, as a method of assessing severity. Even less is known about the serum iron concentration following overdose with modified-release formulations. Only free, circulating iron is toxic, but it is not helpful to measure the patient's total iron-binding capacity because this may be falsely raised after acute overdose. On the basis of limited data, it has been recommended that treatment with desferrioxamine is indicated if the initial serum iron concentration is 5000 μg/litre (90 μmol/litre) or more and the patient has clinical features to suggest significant iron poisoning.[5,6]

Management

Minor overdoses (<20 mg elemental iron/kg body weight) do not require treatment. Children taking such quantities do not require admission to hospital.

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Time course of acute iron intoxication

	Time after ingestion	Features
Phase 1	< 6 hours	• Vomiting and diarrhoea are common; vomit and stools are often dark grey or black as a result of the presence of disintegrating iron tablets — these features are often associated with abdominal pain • In more severe poisoning, vomit and stools may become bloodstained if there is ulceration of the upper gastrointestinal mucosa • Drowsiness, coma, convulsions, metabolic acidosis and shock may develop; shock is disproportionate to the amount of gastrointestinal fluid and blood lost • Progressive circulatory failure and coma may cause death
Phase 2	6—12 hours	• Symptoms improve or disappear, particularly in mild cases, but will persist and deteriorate in severe cases, and reappear in moderate poisoning.
Phase 3	12—48 hours	• Severe shock, metabolic acidosis and the development of jaundice caused by hepatocellular necrosis and encephalopathy are the principal features • Liver failure with haemorrhage, hypoglycaemia and renal failure may supervene • Intestinal infarction and infection with *Yersinia enterocolitica* occur rarely • Mortality is high
Phase 4	2—5 weeks	• Vomiting caused by gastric stricture or pyloric stenosis is the main symptom

Table 1

Preventing absorption — patients who have ingested 20 mg elemental iron/kg body weight or more should be admitted to hospital. Gastric aspiration or lavage should be considered if they present within 1 hour of ingestion, though the value of this procedure is unproven and many patients with severe poisoning will be vomiting, making this procedure difficult and probably unnecessary. There is no advantage in adding desferrioxamine, sodium bicarbonate or disodium phosphate solutions to the lavage fluid in the hope of preventing absorption of iron remaining in the stomach nor should desferrioxamine be left in the stomach after gastric decontamination has been completed. If a modified-release iron formulation has been ingested and tablets remain in the bowel after gastric lavage, whole-bowel irrigation may be considered, although its efficacy is debated. Activated charcoal adsorbs iron poorly and is not used.

Desferrioxamine given intravenously is indicated in clinically severe iron poisoning (defined by the presence of coma or shock). It is unjustifiable to wait for the determination of serum iron concentration before treating such patients. Desferrioxamine is usually given as an intravenous infusion at a rate of 15 mg/kg/hour; the data sheet indicates the total dose should not exceed 80 mg/kg in 24 hours, although this may be necessary in severe poisoning with expert advice. Administration may be stopped when clinical improvement occurs. This dose of desferrioxamine binds relatively small quantities of iron. There are case reports where much larger doses have been administered with apparent success.

The iron—desferrioxamine complex (ferrioxamine) is excreted in the urine, which becomes orange-red, and may be eliminated by dialysis if renal failure develops.[7]

Supportive measures are required in severe iron poisoning only; they include replacement of fluid and blood losses, and conventional measures for liver and renal failure.

Acute iron overdose in pregnancy is not uncommon, and is occasionally fatal for the mother and fetus. It must, therefore, be managed as outlined above. Limited evidence suggests that concern over possible teratogenicity from desferrioxamine is unjustified.[8] ◆

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