IRON POISONING - AN OVERVIEW

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ABSTRACT

Iron is one of the most widespread elements in the earth crust. Its presence in soils has long been a forgone pedological fact. Iron toxicity occurs when, under the reductive effect of the environment, bacteria cause anaerobic respiration by releasing large quantities of ferrous ions (Fe2+) in the solution. The objective of this paper is to present an overview of the iron poisoning, etiology, pharmacology, metabolism, clinical features, diagnosis and therapy. The information has been obtained by searching relevant literature using Chemical abstract, Pubmed, Delnet, Science direct, Dove press, Medline and other data bases. This review discusses aspects of chronic and acute exposures of iron toxicity management. However, treatment comprises fluid and electrolyte resuscitation in an ICU and iron chelating agents. Commonly used iron chelators are Desferrioxamine, or CAVH (Continuous arteriovenous haemofiltration) may be helpful in cases of severe poisoning.

Keywords: Desferrioxamine, Ferrous, Ferric, Metabolism and Toxicity.

INTRODUCTION

Iron is an essential element (Symbol Fe; atomic no.26) for all mammals and its biological roles include those of enzyme co-factor, oxygen transport and redox reactions. The symbol is derived from the Latin word for iron, ferrum. Iron (Fe) forms ferrous (2+) and ferric (3+) compounds. Ferrous compounds are easily oxidized to ferric compounds. Ferrous sulfate (green vitriol), the most important of the ferrous compounds, usually occurs as pale-green crystals. The ferrous and ferric ions combine with cyanides to form complex cyanide compounds. Chronic exposure of heavy metals, iron and other metals, has been linked to the development of severe, often irreversible, neurological disorders. Although the biochemical and molecular mechanisms by which these metals elicit CNS cell loss are likely to be different, neurotoxicity is invariably mediated by a number of common features, one of which is their transport across the blood–brain barrier and their subsequent uptake into targeted cells within the brain. Once inside the cells, these heavy metals provoke a series of biochemical and molecular events leading to cell death induced by apoptosis and/or necrosis. [1] Iron preparations are available in three salt formulations: fumarate (33% iron), sulfate (20% iron) and gluconate (12% iron). The fumarate salt may cause a greater incidence of gastrointestinal irritation due to the higher concentration of the fumarate salt. Iron is also available in a time-released preparation which is promoted to cause less incidence of gastrointestinal upset. The preparation may cause less stomach upset since iron absorption occurs in the upper part of the small intestine and the time released preparations permits iron to be released past the site of iron absorption [2]. (Table.1)

PHYSICAL APPEARANCE

Iron is one of the most widespread elements in the earth crust. Its presence in soils has long been a forgone pedological fact. Iron toxicity occurs when, under the reductive effect of the environment, bacteria cause anaerobic respiration by releasing large quantities of ferrous ions (Fe2+) in the solution. These soluble ferrous ions cause in turn an imbalance in soil solution elements, which is replicated at plant level.
Metallic iron is silvery white in colour, occurring naturally as haematite, magnetite etc., and usually causes no problems. Even if there is more than the required intake daily, the excess is excreted. But in some individuals with inborn errors, even normal dietary iron can cause toxic effects due to accumulation e.g., haemochromatosis (bronze diabetes).

Various iron salts are administered therapeutically in individuals with iron deficiency anaemia which can result from a wide variety of causes. Iron poisoning is related in most instances to overdose of such salts. One of the commonest is ferrous sulfate (green vitriol) which occurs as bluish green crystals. Iron (ferric) oxide i.e., rust does not cause iron poisoning.

USES & SOURCES
Iron is primarily used in powder metallurgy and serves as a catalyst in chemical reactions. Iron is a component of carbon steels, cast iron, high-speed steels, high strength low-alloy steels, manganese alloy steels, and stainless steels. The use of iron cooking utensils is often considered a useful source of supplementary iron in the diet. Iron oxides and hydroxides are used as pigments in cosmetics.

Potassium ferricyanide (red prussiaste of potash) is obtained from ferrous ferricyanide (Turnbull’s blue) and is used in processing blueprint paper. Ferric ferrocyanide, a dark-blue, amorphous solid formed by the reaction of potassium ferrocyanide with a ferric salt (Prussian blue) is used as a pigment in paint and in laundry bluing.

Steel is the most important alloy of iron. It contains 0.25% -2% of carbon. Allowed with Carbon (C), Manganese (Mn), Chromium (Cr), Nickel (Ni) and other elements, iron is used as steel. Wrought iron is almost pure iron.

Iron uses, include magnets, dyes, pigments, and abrasives.

Biological uses
Iron is essential to life. It is a constituent of biological pigments such as haemoglobin, cytochromes and ferrichromes.

Recommended Daily intake
Adults require 10-20mg of elemental iron daily. This amount is supplied through average diet. During pregnancy the daily requirement increases to 30mg.

Dietary Sources
The required daily amount of iron of 10-20mg, for adults is supplied through average diet.
The average daily intake for adults is 15mg

Environmental Sources
Iron is found in 5.1% of the earth’s crust. It is the second most abundant metal, and the fourth most abundant element. The content in the earth’s crust is 50,000 ppm. It is believed that the earth’s core consists mainly of iron [4] SOURCES (Table .2).

TOXICOKINETICS
Fe metabolism is unique in that it operates primarily as a closed system, with Fe stores being efficiently reused by the body. Fe losses are minimal (<1mg/day), but absorption is usually poor. The metal generally is present in foods in the ferric form, bound to proteins and organic acids. Release of Fe from these carriers is a prerequisite for Fe to be absorbed. While only 10% of Fe ingested in the diet is absorbed, severe deficiency increases absorption to about 30%.

Low pH in the stomach reduces the ferric form to the ferrous form, which is then absorbed by the intestinal mucosal cells. Under the influence of apoferritin, ferrous Fe is converted back to the ferric form and eventually enters the plasma. Transferrin transports Fe to the liver, where it is bound to ferritin and hemosiderin. Fe is transported via transferring from the liver to the bone marrow for the production of hemoglobin and myoglobin and to other tissues for the incorporation into cytochromes and nonheme Fe [6].

CLINICAL FEATURES
Stage 1: Gastrointestinal effects, 30 minutes to 6 hours.
Stage 1 is characterized primarily by GI effects, and is the result of iron’s direct toxic effects on the GI mucosa. Vomiting will usually occur within the first 1 to 1.5 hours following the ingestion in severe toxicity, but may be delayed up to 6 hours with enteric-coated iron tablets. Vomiting is the most sensitive indicator of severe toxicity. Other symptoms can include abdominal pain, diarrhea, hematemesis, melena, and lethargy. Lab results will show a metabolic acidosis. If death occurs in this stage, it is usually secondary to hypovolemic shock. Patients with mild to moderate toxicity usually will not progress beyond Stage 1 and if a patient remains asymptomatic for 6 hours after a presumed iron ingestion, it is unlikely that any serious side effects will occur (again, unless enteric coated iron tablets were ingested, which may have delayed effects).

Stage 2: Latent phase, 6 to 24 hours. This is a period of apparent recovery in which the patient’s GI symptoms have resolved because the circulating free iron has redistributed into the reticulo-endothelial system, where it no longer produces its toxic GI effects. In severe toxicity, this stage may not occur at all. The challenge, clinically, is to distinguish between the patient in a true latent phase that may progress to more serious stages and the patient who only had mild GI toxicity that has now resolved. Careful examination and assessment may produce clues. Although patients in the latent phase may appear stable, they are not necessarily asymptomatic. There may still be poor perfusion, hyperventilation (Secondary to metabolic acidosis), or Oliguria (secondary to hypovolemia).
Stage 3: Shock and metabolic acidosis, 6 to 72 hours. Patients will have severe metabolic acidosis in this stage, partly as a result of hydration of absorbed ferric ions, which releases hydrogen ions as a by-product of the reaction. Additionally, lactic acidosis results secondary to hypovolemia and poor tissue perfusion as well as iron-induced mitochondrial dysfunction. Different types of shock may occur in this stage, including hypovolemic, distributive, and cardiogenic shock. Gastrointestinal symptoms from Stage 1 may recur within the first few hours, resulting in further hypovolemia and hypovolemic shock. A few hours later, distributive shock may occur secondary to iron’s effect as a vasodilator and its tendency to increase vascular permeability. Also of concern is iron’s direct toxicity to the myocardium, which may lead to cardiogenic shock within 1 to 2 days. Other symptoms at this stage may include GI hemorrhage, bowel perforation, iron-induced coagulopathy (iron causes thrombin dysfunction), renal and hepatic dysfunction (leading to jaundice, coma, and worsening coagulopathy), and adult respiratory distress syndrome (from direct lung toxicity, hypotension, and metabolic acidosis). Death may occur from widespread cellular dysfunction, which is primarily a result of mitochondrial injury. Once a critical amount of iron has reached the mitochondria, therapy has little effect and prognosis is poor.

Stage 4: Hepatotoxicity/hepatic necrosis, 12 to 96 hours. Fulminant hepatic failure can occur within 4 hours after a severe iron overdose. The liver is particularly vulnerable to iron toxicity because of the high iron concentrations that circulate through the portal circulation. Also, hepatocytes have a high metabolic activity putting them at higher risk to be damaged by iron’s disruptive effects on enzymatic reactions. Fulminant hepatic failure after iron ingestion is rare, but if it does occur it will often be fatal. It is the second most common cause of death from iron poisoning.

Stage 5: Bowel obstruction, 2 to 8 weeks. As the GI mucosa heals, scarring can result in bowel obstruction [7] (Table 3).

DIAGNOSIS

Iron in water can be determined by atomic absorption spectrometry (detection limit 1 μg/litre) or by colorimetric methods (detection limit 5 μg/litre) [8].

X-ray: Like all other heavy metals, iron and its compounds are radiopaque. However, chewable iron tablets and liquid iron formulations are usually not visualized on X-ray. Tablet may remain in the gut and an abdominal X-ray should be obtained to determine if further lavage is necessary. As dissolution occurs, a diffuse density rather than discrete tablets may be seen. Completely dissolved iron tablets/capsules may not be radiopaque. A positive abdominal radiograph is more likely to be associated with severe toxicity.

Acute iron poisoning guaiac test of stools for the presence of blood.

Qualitative desferrioxamine colour test (QDCT): 2ml of gastric fluid and 2 drops of 30% hydrogen peroxide are placed in 2 plastic tubes. 0.5 mL of solution of desferrioxamine (500mg in 4mL distilled water) is added into one tube and the resulting colour change is compared with the other tube (Control). If the test is positive, an orange to red colour will develop in the tube in which desferrioxamine was added. The test must be done within 2 hours of ingestion of iron.

Chelation of challenge test: Desferrioxamine in a dose of 25mg/kg (maximum 1g) is given IM. If the serum iron has exceeded iron binding capacity, the excess iron is chelated to desferrioxamine and the complex is excreted as a pinkish (Vinrose) colour in the urine. But a negative result does not rule out iron poisoning.

Acute iron poisoning abdominal radiograph to detect solid iron tablets in gastrointestinal tract.

All IV iron agents are colloids with spheroidal iron carbohydrate nanoparticles. Each particle consists of an iron-oxyhydroxide core (Fe3+) and a carbohydrate shell that stabilizes the iron-oxyhydroxide core. Differences in core size and carbohydrate chemistry determine pharmacological and biologic differences between the different iron complexes, including clearance after injection, iron release in vitro, early evidence of iron bioactivity in vivo, and maximum tolerated dose and rate of infusion [8,9]. Complexes can generally be classified as labile or robust (kinetic variability), and as weak or strong (thermodynamic variability), with all possible intermediates. Four different products are mostly used in clinical practice: iron gluconate, iron sucrose, iron dextran, and iron carboxymaltose [9-11].

PHARMACOLOGY

Iron is present in all cells and has several vital functions. Ionic iron is component of a number of enzymes necessary for energy transfer (e.g. Cytochrome oxidase, Xanthine oxidase, Succinic dehydrogenase) and is also present in compounds necessary for transport medium for electrons within cells. Haemoglobin is a carrier of oxygen from the lungs to tissues and myoglobin facilitates oxygen use and storage in muscle. Iron deficiency can interfere with these vital functions and lead to morbidity and mortality. Administration of iron preparations corrects haemoglobin disturbances not caused by iron deficiency. Administration of iron also relieves other manifestations of iron deficiency such as soreness of the tongue, dysphagia, dystrophy of the nails and skin and fissuring of the angles of the lips [12].

Nowadays accidental poisonings have become a major pediatric health problem, particularly in children who are 1-3 years old. Acute iron poisoning and chronic iron overload result in significant morbidity and mortality worldwide. Treatment of acute iron poisoning and chronic
Iron overload can be challenging and care providers are often confronted with management dilemmas. Oral iron supplements are commonly prescribed for patients with iron deficiency anemia. The wide availability of iron supplements and iron-containing multivitamins provide easy accessibility for both adults and children. The approach to treatment of acute iron toxicity involves providing adequate supportive care, optimizing hemodynamic status and antidotal therapy with IV desferrioxamine, when indicated. Early following an acute ingestion gastrointestinal (GI) decontamination can be potentially beneficial. Multiple options exist including: syrup of ipecac, gastric lavage, and whole bowel irrigation (WBI). Although definitive evidence that GI decontamination decreases morbidity and mortality is lacking it is often considered to be beneficial. The decision to initiate GI decontamination should be made on an individual case basis. In addition to conventional GI decontamination other methods to prevent absorption have been investigated. Likewise, several small studies have investigated the use of other oral agent/chelators for the treatment of acute iron poisoning. Chronic iron overload associated with red cell disorders (i.e. sickle cell anemia and thalassemia) and other myelodysplastic syndromes affect a significantly larger number of individuals. The body does not have an efficient mechanism to excrete iron. Thus, in those patients requiring multiple transfusions iron accumulates and is deposited into multiple organ systems. The long term consequences of chronic iron overload include multiple organ dysfunction (heart, liver, and endocrine) and/or failure [13-16].

IRON METABOLISM AND TOXICITY

The average human male contains approximately 4.5 g of iron. About 65% of the iron is bound to haemoglobin, 10% is a constituent of myoglobin, cytochromes, and iron-containing enzymes, and 20/30% is bound to the iron storage proteins, ferritin and hemosiderin. Ferritin, a low affinity, high-capacity storage protein, can store up to 4500 atoms of iron per molecule. Another protein relevant in iron homeostasis is transferrin, a high-affinity, low-capacity protein (two atoms of iron per molecule) that transports iron in the plasma. It is thought that only trace amounts of the metal remain free as non-chelated or loosely chelated iron. To prevent the potential health disturbances produced by both iron deficiency and iron overload, mammals have evolved with numerous, integrated mechanisms to regulate iron metabolism. The body store of iron is divided between essential iron-containing compounds and excess iron, which is held in storage. Quantitatively, hemoglobin dominates the essential fraction (Table 4). This protein, with a molecular weight of 64,500, contains four atoms of iron per molecule, amounting to 1.1mg of iron per milliliter of red blood cells (20mmol). Other forms of essential iron include myoglobin and a variety of heme and nonheme iron-dependent enzymes. Ferritin is a protein-iron storage complex that exists as individual molecules or as aggregates. Apoferritin has a molecular weight of about 450,000 and is composed of 24 polypeptide subunits that form an outer shell, within which resides a storage cavity for polynuclear hydrous ferric oxide phosphate.

Ferritin aggregates, referred to as hemosiderin and visible by light microscopy, constitute about one-third of normal stores a fraction that increase as stores enlarge. The two predominant sites of iron storage are the reticuloendothelial system and the hepatocytes, although some storage also occurs in muscle.

Iron deficiency, is a widely spread condition that affects approximately 500 million people around the world. The consequences of iron deficiency can range from anemia to mental retardation in growing children. Iron overload is a less frequent condition, but high contents of tissue iron has been associated with several pathological conditions, including liver and heart disease cancer, neurodegenerative disorders, diabetes, hormonal abnormalities, and immune system abnormalities, shows a comprehensive list of pathological conditions associated with iron overload. In terms of toxicity, chronic iron toxicity is a condition that can be associated with: (a) primary hemochromatosis, a genetic disorder related to increased intestinal absorption of iron; (b) high dietary iron intake; and (c) frequent blood transfusions (often required for the treatment of certain refractory anemias). Cases of acute iron toxicity are rare and mostly related to hepatotoxicity (Table 5).

Desferrioxamine

Desferrioxamine is a water-soluble organic compound with a high affinity for iron, binding 8.5 mg of iron to 100 mg desferrioxamine. It is colourless in solution but its complex with iron (ferrioxamine) has a pink colour and is freely excreted in the urine, giving it the colour of rose wine. This colour change can be used as a diagnostic test for iron overload. Desferrioxamine is safe and virtually free of side-effects, when given at the recommended dose of 90 mg/kg intramuscularly followed by the intravenous infusion of 15mg/kg/h. Hypotension has been noted in animal studies, but in studies reporting the rare occurrence of hypotension in children infusion rates were excessive, and adequate fluid replacement may not have been given. [27]

SUGGESTED MANAGEMENT OF A CHILD WITH SUSPECTED IRON INGESTION

Induce emesis and rush patient to hospital, after correcting any hypovolaemia. Patient fully conscious, circulation normal
1. Administer desferrioxamine 90 mg/kg by intramuscular injection.
2. Give syrup of ipecac 15-20 ml orally with water.
3. Attach urine bag, check for vinrose colour, measure specific gravity and volume.
4. Check acid-base status and plasma iron level.
5. Take a radiograph of the abdomen.
6. If urine shows no vinrose colour after 6 hours, and radiograph shows no iron tablets in abdomen, the patient has not ingested a dangerous dose of iron. Otherwise, proceed as described below, with gastric aspiration, lavage and intravenous desferrioxamine.

   Level of consciousness depressed and/or circulation impaired
   1. Give intravenous fluids to restore circulation.
   2. Administer desferrioxamine 90 mg/kg intramuscularly, followed by 15 mg/kg/h by intravenous infusion.
   3. Perform gastric aspiration, through a size 16F gauge or larger intragastric tube, followed by lavage. Use aliquots of 5 ml/kg body weight of lavage fluid containing 2 g desferrioxamine and 50 ml 8% sodium bicarbonate per litre of water. When return is clear leave behind 10 g desferrioxamine diluted in 5 ml/kg of the lavage fluid to retard absorption of any remaining iron.
   4. Take a radiograph of the abdomen. If large numbers of tablets remain in the stomach and cannot be washed out, they should be removed by gastrotomy.
   5. Continue infusion of desferrioxamine 15 mg/kg/h until urine is clear of vinrose colour.

**IRON AND OXYGEN INTERACTION**

Free radicals derived from the reaction of iron and oxygen causes drastic tissue damage. Iron can accelerate oxidative damage for macromolecules, leading both to inflammatory and neoplastic disorders. When iron and oxygen react together, iron is the reducing agent and oxygen is the oxidizing agent; electrons have been removed by oxygen. Iron facilitates DNA mutation through augmentation of oxygen radical synthesis via the Harber–Weiss reaction or Fenton chemistry:

\[
\begin{align*}
Fe^{2+} + O_2 & \rightarrow Fe^{3+} + O_2^- \\
Fe^{2+} + O_2^- + 2H^+ & \rightarrow Fe^{3+} + H_2O_2 \\
Fe^{3+} + H_2O_2 & \rightarrow Fe^{3+} + OH^- + OH^-
\end{align*}
\]

Therefore, metal-catalyzed generation of superoxide, hydrogen peroxide and hydroxyl radical, as well as production of ferryl and perferryl radicals, can cause oxidative stress. Superoxide radicals are capable of reducing Fe\(^{3+}\), bound to ferritin, to Fe\(^{2+}\) and thus release it from ferritin storage. The reduced iron released from ferritin storage may participate in Fenton reactions, reduce hydrogen peroxide and generate highly reactive hydroxyl radicals. A comparison of the effects of Fe\((3+)\)-NTA on cells cultured in 1% and 20% oxygen environments showed that the following features were more prominent with concentrations of 20% oxygen: (1) cytotoxicity, (2) increase in intracellular reactive oxygen species, (3) increase in H2O2 production in the cells, and (4) formation of 8-hydroxydeoxyguanosine. Enhanced cytotoxic effects of Fe\((3+)\)-NTA at 20% oxygen are due to endogenously produced hydroxyl radicals. Iron mediated the production of single and double strand breaks in supercoiled DNA while H2O2 and OH are involved in the DNA damaging process. Accumulation of intracellular iron induces the generation of reactive oxygen species and that the increased oxidative stress may cause apoptosis of cancer cells [18].

**MANAGEMENT OF ACUTE AND CHRONIC IRON POISONING**

1) A stomach wash with 1% sodiumbicarbonate solution should be administered to remove undissolved iron tablets. The lavage should not be carried out later than 1 hour after ingestion of iron for fear of perforation.
2) With the tube still in place, 1 percent solution of sodium bicarbonate or preferably an iron binding chelating agent like desferrioxamine mesylate (5 to 10 g. in 100ml.isotonic saline), calcium diethylenetriamine pentaacetate (DTPA 35 to 40mg/kg) or calcium disodium edentate (35 to 40mg/kg) should be administered to retard the absorption of iron from the gastrointestinal tract.
3) Correction of hypovolaemia and metabolic acidosis
4) Magnesium hydroxide solution (1%) administered orally may help reduce absorption of iron by precipitating the formation of ferrous hydroxide. Magnesium hydroxide and calcium carbonate containing antacids may safely be used in therapeutic doses to help reduce iron absorption.
5) Obtain serum iron levels, creatinine, electrolytes, blood haemoglobin concentration, blood prothrombin time, baseline hepatic function tests and arterial blood gases in seriously poisoned patients.
6) Continuous arteriovenous haemofiltration (CAVH) may be helpful in severe poisoning.
7) Early replacement of body fluids and electrolytes using isotonic saline, correction of metabolic acidosis and hypotension by using ringer lactate and vasopressor agents, respectively are indicated.
8) Liver transplantation is the only therapeutic avenue open in the presence of fluminant hepatic failure.
9) An intravenous infusion of desferrioxamine
10) Diazepam, paraldehyde and other anticonvulsants may be necessary to control convulsions.
11) Chelation therapy:

Desferrioxamine mesylate (desferal) : This compound, obtained from streptomycyes pilosus, is a potent and specific chelator or iron. It readily binds ferric iron to form ferrioxamine, a stable and water soluble chelate. Ferrioxamine is excreted 2/3 in the urine and 1/3 in the bile. It colours the urine reddish brown. Deferrioxamine also removes iron from hemosiderin except that in the bone marrow. One hundred milligrams of desferrioxamine bind 8.5 mg of iron.
The drug is generally well tolerated. Rapid IV injection can produce hypotension, tachycardia and anaphylactoid reactions and urticaria. Allergic reactions and cataract formation are known to occur during its chronic administration in the treatment of iron storage diseases. The drug is contraindicated in patients with severe renal disease or anuria and in pregnant women.

The drug is available as lyophilized powder (500mg) for solution. It is administered by IV infusion and by IM injection [19]. (Table 6)

PREVENTION OF IRON LOADING
- Industrial workers exposed to airborne iron should be advised to wear masks.
- Home owners should be warned against applying tremolite paint to the inner and outer walls of their houses.
- Curtailment of active and passive inhalation of tobacco smoke is essential for the prevention of iron toxicity to respiratory tract tissue.
- Diet include high amounts of non-heme iron can lower the quantity absorbed by concurrent consumption of the natural phenolic iron chelators in tea and of phytates in whole grains.
- A reduction in heme iron intake can be achieved by lowering the ingestion of red meat.
- Men of all ages, as well as post-menopausal women, should consider periodic donations of blood; each unit drawn results in a reduction in the iron burden of 250mg.
- In hereditary hemochromatosis, hemoglobin is normal; thus blood transfusions are not required and iron loading can be treated appropriately by phlebotomies [22].
- Iron dextran may be administered by slow intravenous injection at a rate of no more than 1ml/min or by deep intramuscular injection into the upper outer quadrant of the buttck.
- Iron dextran has also been administered by intravenous infusion over one to six hours after dilution in sodium chloride 0.9%. A test dose of 25mg should be given over five minutes, with the remainder given after one hour has elapsed if no hypersensitivity reaction occurs [23].

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Air
In remote areas, iron levels in air are about 50–90 ng/m3; at urban sites, levels are about 1.3 μg/m3. Concentrations up to 12 μg/m3 have been reported in the vicinity of iron- and steel producing plants.

Water
The median iron concentration in rivers has been reported to be 0.7 mg/litre. In anaerobic groundwater where iron is in the form of iron(II), concentrations will usually be 0.5–10 mg/litre, but concentrations up to 50 mg/litre can sometimes be found. Concentrations of iron in drinking-water are normally less than 0.3 mg/litre but may be higher in countries where various iron salts are used as coagulating agents in water-treatment plants and where cast iron, steel, and galvanized iron pipes are used for water distribution.

Food
Iron occurs as a natural constituent in plants and animals. Liver, kidney, fish, and green vegetables contain 20–150 mg/kg, whereas red meats and egg yolks contain 10–20 mg/kg. Rice and many fruits and vegetables have low iron contents (1–10 mg/kg). Estimated total exposure and relative contribution of drinking-water Reported daily intakes of iron in food — the major source of exposure range from 10 to 14 mg. Drinking-water containing 0.3 mg/litre would contribute about 0.6 mg to the daily intake. Intake of iron from air is about 25 μg/day in urban areas [24].

Iron dextran
Administration and Adult Dosage. The total cumulative amount required for restoration of hemoglobin (Hb) in g/dL and body stores of iron can be approximated using lean body weight (LBW) in kg (or actual body weight if less than LBW) from the formula:

\[
\text{Total mg Iron} = (0.0442 \times \text{desired Hb- Observed Hb}) \times \text{LBW} + [0.26 \times \text{LBW}] \times 50
\]

To calculate dose in mL, divide the result by 50. Usual Hb target for adults is 14.8g/dL. The dose of iron required secondary to blood loss can be estimated from the formula:

\[
\text{Total mg Iron} = \text{Blood Loss (mL)} \times \text{Hematocrit (Observed, as decimal fraction)}
\]

SOME POISONS DATABASES OF INTERNATIONAL RESOURCES FOR MANAGEMENT OF POISONS
- TOXBASE
Primary toxicology database of the United Kingdom, produced by the National Poisons Information Service Centres; free access to healthcare professionals (in viewdata format but internet version available soon). Contact Scottish Poisons Information Bureau (tel 0131 536 2303)
- CD Roms
Poisonous plants in Britain and Ireland and Poisonous fungi in Britain and Ireland. Contact National Poisons Information Service (London) (tel 0171 771 5383)
- toxnet.nlm.nih.gov/servlets/simple-search
Toxicology database of the National Library of Medicine—access to Pubmed, Toxline, and hazardous substance databank
- www.pharmacy.arizona.edu/centers/poison-center/
Arizona Poisons Centre
- World Health Organisation and international programme on chemical safety
Global information network on chemicals
- www.nihs.go.jp/GINC/webguide/csinfo.html
Comprehensive global information network on chemicals
- www.rmpcdc.org/poisoncenter/index.cfm
- Rocky Mountain Poisons Center
- www.atstdr.cdc.gov/atstdrhome.html
- Agency for Toxic Substance and Disease Registry; slow access from NHS Net [25].

Special Situation: Pregnant Patients

The frequent diagnosis of iron-deficiency anemia during pregnancy is associated with access to iron preparations with resultant serious, and even fatal, iron ingestions in pregnant women. Neither iron nor deferoxamine is transferred to the fetus in appreciable quantities. Fetal demise presumably results from maternal iron toxicity and not from direct iron toxicity to the fetus. Consequently, deferoxamine should be used to treat serious maternal iron poisoning and never withheld because of concern for fetal exposure to deferoxamine.

Alternative Therapies

One other treatment modality used experimentally for iron intoxication is continuous arteriovenous hemofiltration (CAVH). In the animal model, increased elimination of ferrioxamine was demonstrated in the ultrafiltrate when increasing doses of deferoxamine were increasing doses of deferoxamine were infused into the arterial side of the system. This technique is not described in iron-poisoned humans. In toddlers with severe poisoning, exchange transfusion may help to physically remove free iron from the blood while replacing it with normal blood. However, because iron-poisoned patients tend to have hemodynamic instability, removing blood volume may not be well tolerated. The decision to use these alternative therapies should be based on a risk-to-benefit analysis [26].

AUTOPSY FEATURES

- Haemorrhagic necrosis of gastric mucosa. In ferrous sulfate poisoning gastric contents may appear bluish green in colour.
- Hepatic and renal necrosis

GENERAL METHOD TO ANALYSIS OF A POISONING SITUATION – TYPES OF FREQUENTLY ASKED QUESTIONS?

In many poisoning calls, the caller does not volunteer enough information initially for the clinical pharmacist to assess the situation. The fact that an overdose has occurred is not always obvious in the hospital or home. Occasionally a poisoning situation can be uncovered only by persistent questions. Inquires relating to table identification may involve a poisoning, and this information can be elicited by determine why the caller needs the information.

In addition, poisoning should be considered in the differential diagnosis whenever there is an abrupt onset of illness with multiple organ system involvement, especially if the patient is a child under 5 years of age or has a history of a previous ingestion.

When a poisoning is suspected, the following information must be obtained to “analyze” a poisoning situation.

1. Name of substance: This information should include ingredients and their percentage. The substance involved may be unknown in patients who are comatose or who ingest tablets or capsules from an unmarked container, or who ingest an unidentified plant.
2. Amount: If an accurate determination of the amount ingested is impossible, and the product is potentially toxic amount was ingested, or that the total amount originally in the container was ingested.
3. Time since exposure: By knowing about the onset and duration of action of the substance, one can determine whether the symptoms are consistent with the history of the amount and the time since exposure. In addition, treatment recommendations, such as, whether or not to empty the stomach, may be influenced by the length of time since ingestion.
4. Symptoms: Determine whether symptoms are consistent with the substance involved; if not, determine what other substances or medical conditions may be responsible for these symptoms. Severe signs and symptoms, such as respiratory and cardiovascular collapse, may necessitate immediate treatment. Some treatment modalities are contraindicated when certain signs or symptoms are present (e.g., emetics in the comatose patients).
5. Age and Weight of patient: These are important considerations in determining the toxicity of the substance as well as for dosing antidotes.
6. Past Medical History and Prior Therapy: The patient’s medical history may influence the severity of the intoxication or treatment. Some home remedies may complicate therapy whereas other prior treatment may influence subsequent recommendations. [27]

Table 1. Some commonly used iron preparations [3]

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Tablet Size</th>
<th>Elemental Iron per Tablet</th>
<th>Usual adult (Tablets per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous Sulfate hydrated</td>
<td>325mg</td>
<td>65mg</td>
<td>3-4</td>
</tr>
<tr>
<td>Ferrous Sulfate Desiccated</td>
<td>200mg</td>
<td>65mg</td>
<td>3-4</td>
</tr>
<tr>
<td>Ferrous Gluconate</td>
<td>325mg</td>
<td>36mg</td>
<td>3-4</td>
</tr>
<tr>
<td>Ferrous Fumarate</td>
<td>200mg</td>
<td>66mg</td>
<td>3-4</td>
</tr>
<tr>
<td>Ferrous Fumarate</td>
<td>325mg</td>
<td>106mg</td>
<td>2-3</td>
</tr>
</tbody>
</table>
Table 2. Iron is found widespread in nature in ores [5]

<table>
<thead>
<tr>
<th>Iron Compound</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Almandine hercynite</td>
<td>Iron aluminate</td>
<td>Scorodite</td>
<td>Iron arsenate</td>
</tr>
<tr>
<td>Pyrites</td>
<td>Iron disulfide</td>
<td>Laternite</td>
<td>Iron hydroxide</td>
</tr>
<tr>
<td>Columbite</td>
<td>Iron niobate</td>
<td>Chromite, Hematite, Ilmenite, Limonite, Magnetite, Mugerite, Stilpnosiderite &amp; Umbre</td>
<td>Iron oxides</td>
</tr>
<tr>
<td>Lazulite</td>
<td>Iron phosphate</td>
<td>Babingtonite, Crocidolite, Cummingtonite, Pidote, Eudalyte, Fayalite, Gadolinite, Glauconite, Hornblende, Hypersthenes, Olivine, Pennine, Piedmontite &amp; Riebeckite</td>
<td>Iron silicates</td>
</tr>
<tr>
<td>Coquimbite, Inkstone, and Jarlfosite</td>
<td>Iron sulfates</td>
<td>Ankerite, Arsenopyrites, Bornite, Chalcopyrite, Pentlandite and Pyrrhotite</td>
<td>Iron sulfides</td>
</tr>
<tr>
<td>Marcasite</td>
<td>Iron sulfite</td>
<td>Wolframite</td>
<td>Iron tungstate</td>
</tr>
</tbody>
</table>

Table 3. Peak serum iron in correlation with toxicity in humans

<table>
<thead>
<tr>
<th>Peak serum iron (μg/dL)</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-150</td>
<td>None</td>
</tr>
<tr>
<td>150-300</td>
<td>Mild</td>
</tr>
<tr>
<td>300-500</td>
<td>Moderate (rarely develop serious complications)</td>
</tr>
<tr>
<td>&gt;500</td>
<td>Severe (serious systemic toxicity)</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>Significant morbidity and Mortality</td>
</tr>
</tbody>
</table>

Data extracted from: Liebelt LL and Kronfol R2; Velez LI and Delaney KA.

Table 4. The Body Content of Iron

<table>
<thead>
<tr>
<th>Contents</th>
<th>MG/KG of body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>Essential Iron</td>
<td>31</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>06</td>
</tr>
<tr>
<td>Myoglobin and enzymes</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 5. Examples of diseases for which excessive/misplaced iron can be a risk factor [21].

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Atherosclerosis cardiomypathy hypertension</th>
<th>Neurologic</th>
<th>ALS, Alzheimer’s Depression, Friedreich’s ataxia Huntington’s multiple sclerosis PKAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermal</td>
<td>Porphyria cutanea tarda</td>
<td>Obstetric</td>
<td>Neonatal hemochromatosis pre-eclampsia</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Diabetes growth deficiency hypogonadism hypothyroidism</td>
<td>Orthopedic</td>
<td>Gout, hemophilic synovitis, osteoarthritis Osteoporosis</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Colorectal cancer</td>
<td>Ophthalmic</td>
<td>Macular degeneration</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Cirrhosis Hepatoma Steatohepatitis Viral hepatitis</td>
<td>Pediatric &amp; Neonatal</td>
<td>Down syndrome epilepsy sudden infant death</td>
</tr>
<tr>
<td>Infectious</td>
<td>Microbial infections of all body systems</td>
<td>Otologic and Renal</td>
<td>Aminoglycoside toxicity</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Cystic fibrosis Lung cancer Pneumoconiosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 6. Iron content and dosage of some oral and parenteral iron preparations [20]

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Iron content a</th>
<th>Daily adult dose b</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral preparations- Conventional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium iron edentate, 190 mg/5ml</td>
<td>27.5mg/5ml</td>
<td>5-10mltid</td>
<td>Nausea, Diarrhoea and/or constipation</td>
</tr>
<tr>
<td>Ferrous gluconate, 300mg</td>
<td>37mg</td>
<td>1-2tid</td>
<td></td>
</tr>
<tr>
<td>Ferrous succinate, 106mg/5ml</td>
<td>60mg</td>
<td>5-10mltid</td>
<td></td>
</tr>
<tr>
<td>Ferrous sulfate, 300mg</td>
<td>65mg</td>
<td>1-2tid</td>
<td></td>
</tr>
<tr>
<td>Ferrous fumarate, 200mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Preparations- Sustained release</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrous glycine sulfate</td>
<td>100mg</td>
<td>1-2od</td>
<td>As above</td>
</tr>
<tr>
<td>Ferrous sulfate, dried</td>
<td>47mg</td>
<td>1-2od</td>
<td></td>
</tr>
<tr>
<td>Ferrous sulfate, dried</td>
<td>105mg</td>
<td>1-2od</td>
<td></td>
</tr>
<tr>
<td>Parenteral Preparations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextriferron</td>
<td>20mg/ml</td>
<td>1.5-5ml slow IV</td>
<td>Intravenous: Venous spasm; Systemic chills, fever,</td>
</tr>
<tr>
<td>Iron dextran</td>
<td>50mg/ml</td>
<td>(not for IM use)</td>
<td>nausea, chest, lumbar and loin pain</td>
</tr>
<tr>
<td>Iron polymaltose</td>
<td>50mg/ml</td>
<td>2-5ml deep IM; also</td>
<td>Intramuscular: Local pain and inflammation; skin</td>
</tr>
<tr>
<td>Iron sorbitol (Iron Sorbitol</td>
<td>50mg/ml</td>
<td>by IV infusion</td>
<td>staining (if administration not correct); Systemic</td>
</tr>
<tr>
<td>citric acid complex)</td>
<td></td>
<td>2-5ml deep IM; also</td>
<td>reactions, metallic taste</td>
</tr>
<tr>
<td></td>
<td></td>
<td>by IV infusion</td>
<td></td>
</tr>
</tbody>
</table>

a As elemental iron per tablet, capsule or specified volume of liquid  
b The daily therapeutic adult dose for optimum haemoglobin response is usually in the range 180 to 270mg elemental iron. The daily prophylactic dose (e.g. in pregnancy) is about 60 to 100mg elemental iron. Parenteral dosage can be calculated by a formula based on the severity of the anaemia and size of the patient. One formula which has been used to calculate the approximate total amount is: Total ml to be injected = body weight in kg x haemoglobin deficiency (100% - actual concentration) x 0.0132. An empirical intramuscular dosage is to give an initial 1ml trial dose, followed by 2 to 5ml daily into alternate buttocks. In practice, a course of 1.5 to 3g elemental iron will be required. Abbreviations: od = once daily; tid = 3 times daily; IV = intravenous; IM = intramuscular; SC = Subcutaneous.

CONCLUSION
This review discusses aspects of chronic and acute exposures of iron toxicity management. However, treatment comprises fluid and electrolyte resuscitation in an ICU and iron chelating agents. Commonly used iron chelators are Desferrioxamine, or CAVH (Continuous arteriovenous haemofiltration) may be helpful in cases of severe poisoning.

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CONFLICT OF INTEREST
The authors declare that there are no conflicts of interest, financial or others.

REFERENCES