



Recognizing and Managing Iron Toxicity

Christian Balmadrid, MD
Senior Emergency Medicine
Resident

Michael Bono, MD
Professor of Emergency Medicine
Eastern Virginia Medical School
Norfolk, Virginia

Since urgent care physicians will encounter patients suffering from excess iron intake only occasionally, iron toxicity can be challenging when it does present. The authors review the basic science and the signs, symptoms and course of illness and provide an update on the clinical management of these patients.

Acute care settings form the first line of defense against the relatively uncommon problem of toxicity from heavy metals and specifically from iron. If this illness presents to an urgent care physician who has not maintained familiarity with its effects and treatment, the potential for morbidity and mortality due to misdiagnosis or inappropriate treatment is significant.

This article will review the basic science, the identifying signs and symptoms, and the principles of clinical management applicable to patients suffering from iron toxicity. We hope our discussion will help you to be optimally prepared to provide their care, but the relatively low incidence of the diagnosis tends to make these cases challenging by nature. It is strongly recommended that a toxicologist or the regional poison control center always be consulted for suspected poisoning from iron or any other metal.

CAUSES AND PATTERNS OF IRON TOXICITY

Reports of iron exposure collected by the American Association of Poison Control Centers (AAPCC) totaled approximately 35,000 in 2004.¹ More than 100 iron-containing preparations are listed in the *Physicians' Desk Reference*, but the vast majority of cases in 2004 were, as usual, a result of iron-containing multivitamin ingestions.¹ Unintentional ingestions by children younger than 6 years accounted for 83% of those reported cases, while intentional overdoses (suicide attempts) were much more common in adults.¹ Although intentional overdose accounted for only a small fraction of the cases, it accounted for the majority of the admissions (58%), and resulted in a much higher mortality rate (10% vs 1%).² In children, pediatric multivitamin formulations are usually minimally toxic, and life-threatening poisonings are usually the result of ingestion of more potent adult formulations, especially prenatal vitamins, which have the highest iron content. In one case control study, the birth of a sibling within 6 months was identified as a risk factor for iron ingestion in children less than 3 years old.³

Iron is an essential metal, meaning it is an element that the body needs but does not produce and must extract from dietary sources. It acts as

TABLE 1. Common Iron Preparations

Compound	Elemental iron
ferrous sulfate	20%
ferrous fumarate	33%
ferrous gluconate	12%
ferric pyrophosphate	30%
ferrocholate	14%
ferroglycine sulfate	16%
ferrous sulfate, dried	33%
ferrous carbonate, anhydrous	38%
carbonyl iron	100%

Data extracted from: Velez LI and Delaney KA.⁴

an essential cofactor in the normal function of hemoglobin, myoglobin, cytochromes, and numerous other catalytic enzymes. It is absorbed through the digestive tract, then bound to transferrin in the bloodstream. Normally, 15% to 35% of transferrin's iron binding capacity is utilized.⁴ Overdoses of iron, however, can quickly lead to transferrin saturation, resulting in free iron circulating in the serum, which is directly toxic to organs.

The toxicity of iron depends on the amount of elemental iron the ingested formulation contains. Some common iron preparations are listed in Table 1⁴ and the elemental iron content of some popular multivitamin and prenatal vitamin formulations on the market is shown in Table 2.² While the minimum toxic dose and the lethal dose of iron are not firmly established, it can be expected that ingestion of less than 20 mg/kg of elemental iron will usually cause no symptoms, 20 to 40 mg/kg will produce mild toxicity, 40 to 60 mg/kg will provoke moderate symptoms, and levels greater than 60 mg/kg can lead to severe toxicity.⁴

COURSE OF ILLNESS

Iron has two distinct toxic effects. First, it is directly caustic to the GI mucosa, leading to vom-

>>FAST TRACK<<

In children, poisonings are usually the result of ingestion of adult formulations, especially prenatal vitamins.

iting, diarrhea, and abdominal pain. In severe cases, it can result in hemorrhagic necrosis with bleeding, perforation, and peritonitis. Second, it impairs intracellular metabolism, primarily through lipid peroxidation and free radical formation. One of its most important consequences is impairment of adenosine triphosphate synthesis, which results from alteration of the lipid membrane of mitochondria, inhibition of enzymatic processes in the Krebs cycle, and uncoupling of oxidative phosphorylation.^{2,4}

In addition to its effects at the cellular level, iron also acts as a direct vasodilator, can increase capillary permeability, and is directly toxic to the myocardium.² These effects, in addition to the severe GI fluid losses that occur from the vomiting and diarrhea, can lead to shock in severe cases.⁴

Depending on the source, acute iron toxicity is typically described in four or five stages. Signs and symptoms may overlap, however. As noted for each below, there is a classical timeline for these symptoms, but it may be quite accelerated with larger ingestions.

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).^{2,4}

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 circulat-

TABLE 2. Elemental Iron Content of Select Multivitamin Formulations

Preparation	Elemental iron
PRENATAL VITAMINS	
NataChew Prenatal Vitamins	29 mg
Natalins Rx	60 mg
Natalins	45 mg
CHILDREN'S MULTIVITAMINS	
Bugs Bunny With Iron	18 mg
Centrum Jr. Plus Iron	18 mg
Centrum Kids Complete Rugsrats®	18 mg
Flintstones® With Iron	18 mg
Poly-Vi-Sol With Iron	
Tablet	12 mg
Drops	10 mg/mL
Shamu and His Crew® Plus Iron	18 mg
Sunkist® Complete	18 mg
ADULT MULTIVITAMINS	
Centrum®	18 mg
Centrum® Silver	4 mg
Complete for Men	5 mg
Complete for Women	10 mg
Natural MD	
Men/Basic Life Prescription	5 mg
Women/Basic Life Prescription	5 mg
Women/Standard Life Prescription	10 mg
One-A-Day® Maximum	18 mg
One-A-Day® Women's	27 mg
Stresstabs® Plus Iron	18 mg

Data extracted from: Liebelt LL and Kronfol R.²

ing free iron has redistributed into the reticuloendothelial 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).^{2,4}

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.² Additionally, lactic acidosis results secondary to hypovolemia and poor tissue perfusion as well as iron-induced mitochondrial dysfunction.²

Different types of shock may occur in this stage, including hypovolemic, distributive, and cardiogenic shock. Gastrointestinal symptoms

TABLE 3. Peak Serum Iron in Correlation with Toxicity

Peak serum iron (µg/dL)	Toxicity
50-150	none
150-300	mild
300-500	moderate (rarely develop serious complications)
>500	severe (serious systemic toxicity)
>1000	significant morbidity and mortality

Data extracted from: Liebelt LL and Kronfol R²; Velez LI and Delaney KA.⁴

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.²

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.²

Stage 4: Hepatotoxicity/hepatic necrosis, 12 to 96 hours. Fulminant hepatic failure can occur within 4 hours after a severe iron overdose.² 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.⁵ It is the second most common cause of death from iron poisoning.²

Stage 5: Bowel obstruction, 2 to 8 weeks. As the GI mucosa heals, scarring can result in bowel obstruction.

CLINICAL ASSESSMENT

Iron poisoning is primarily a clinical diagnosis. Patients will often present knowing that they ingested iron, either with suicidal intent or accidentally (as is often

>>FAST TRACK<<
Fulminant hepatic failure after iron ingestion is rare, but if it does occur it will often be fatal.

the case in children). It is essential to probe motivation, type of iron ingested, and the timing and quantity of the ingestion. When

that information is unavailable, as in cases of a patient being found unresponsive or a child with no witnesses to an ingestion, the diagnosis requires a high index of suspicion because its presenting symptoms of nausea, vomiting, and abdominal pain are so nonspecific. A good history and physical exam is required in these patients to gauge the probability of excessive iron exposure.

The most useful laboratory value to follow in acute iron toxicity is the serum iron level. Peak serum iron levels usually correlate with toxicity as shown in Table 3.^{2,4} It is important to note, however, that measurements of serum iron level reflect free iron circulating in the blood. Iron is rapidly cleared from the serum and enters tissues intracellularly, so concentrations measured more than 8 hours past ingestion may be deceptively low.⁴

The other laboratory studies that should be ordered are:

- basic metabolic panel to check for electrolyte abnormalities, anion gap metabolic acidosis, hyperglycemia, and assess fluid status;
- arterial blood gases in moderately to severely poisoned patients to check for degree of acidosis;
- aminotransferases and bilirubin to assess hepatic function;
- prothrombin time/partial thromboplastin time to assess hepatic function;
- complete blood count w/differential (leukocytosis is a nonspecific marker of iron toxicity); and
- type and crossmatch.

Certain additional assessments may be of little or no value, such as total iron binding capacity (TIBC), which measures the amount of iron bound to transferrin. Theoretically, if TIBC is higher than the serum iron levels, there should be no free iron circulating to cause its toxic effects. Unfortunately, this theory has not been clinically supported, as measurements of TIBC can often be inaccurate, especially if patients are receiving deferoxamine therapy. Also, there have been documented cases of iron toxicity in which TIBC was greater than the serum iron levels.² These cases likely illustrate the above-mentioned problem of serum iron becoming deceptively low after ingested iron has redistributed into the tissues.

Plain radiographs can sometimes reveal the presence of iron tablets in the GI tract, which can confirm the diagnosis. However, the radiopacity of iron tablets depends on the type of formulation and content of elemental iron, and most chewable and liquid formulations will not be radiographically visible at all, so x-ray imaging is not a very sensitive test.⁵

Deferoxamine challenge via intramuscular injection is no longer recommended to test for iron ingestion. Deferoxamine binds to free iron to form ferrioxamine, which is (again theoretically) excreted in the urine to give it a brick orange discoloration or the classic “vin rosé” appearance. However, there have been multiple cases in which a deferoxamine challenge produced no urine discoloration despite toxic serum iron concentrations.⁶

THERAPEUTIC CONSIDERATIONS

There are no consensus guidelines for the management of acute iron toxicity, the use of whole bowel irrigation, deferoxamine therapy, or observation and discharge versus admission, but the following are some recommendations based on the current evidence.

If an asymptomatic patient has ingested less than 20 mg/kg of elemental iron according to the history, observation is sufficient and discharge is appropriate if there is no change in the patient's condition after 6 hours.⁴

If the patient has ingested more than 20 mg/kg of elemental iron, has visible pills on x-ray, or shows signs of mild toxicity, whole bowel irrigation is recommended. Keeping in mind that peak iron concentrations typically occur 3 to 5 hours after ingestion, but may be delayed in sustained-release or enteric-coated formulations, the serum iron level should be checked initially and again 6 to 8 hours after the ingestion reportedly occurred to ensure decreasing levels.⁴ If peak serum iron levels are less than 300 µg/dL, and the patient remains asymptomatic after 6 hours of observation, he or she may be discharged. If peak levels are greater than 500 µg/dL, or the patient shows any signs of systemic toxicity, deferoxamine therapy should be initiated.⁴

Whole bowel irrigation is done by using a polyethylene glycol electrolyte lavage solution. Irrigation should be administered at 1.5 to 2 L/h in adults, 20 to 40 mL/kg/h for children, and should be continued until the rectal effluent is clear.⁴

As previously noted, deferoxamine is a chelating agent that binds to iron to form ferrioxamine, a nontoxic compound that is renally excreted. Its optimal dosing and route of administration have not been established, but continuous intravenous infusion at an initial dose of 15 mg/kg/h

is typically recommended over the intramuscular route in severe toxicity, particularly for those in circulatory shock.⁷ For those not in shock, however, the FDA recommends administering deferoxamine intramuscularly.

The correct duration of deferoxamine therapy has not been well established either, since its efficacy cannot be reliably assessed by following serum iron concentrations.

Some sources have recommended using resolution of clinical symptoms such as metabolic acidosis as the therapeutic end point. Typically, deferoxamine is given over about 24 hours.² However, it is recommended that dosing

and duration decisions be made in consultation with a medical toxicologist or a regional poison control center. Major adverse effects include hypotension, which can be controlled with adequate hydration and adjustments to the infusion rate, and adult respiratory distress syndrome, which typically occurs after more than 32 hours of continuous infusion.²

There is no role for gastric lavage, activated charcoal, hemodialysis, or hemoperfusion in the treatment of acute iron toxicity.⁴ □

>>FAST TRACK<<

If an asymptomatic patient has ingested less than 20 mg/kg of elemental iron according to the history, observation is sufficient and discharge is appropriate if there is no change in the patient's condition after 6 hours.

REFERENCES

1. Watson WA, Litovitz TL, Rodgers GC Jr, et al. 2004 Annual report of the American Association of Poison Control Centers toxic exposure surveillance system. *Am J Emerg Med.* 2005;23(5):589-666.
2. Liebelt LL, Kronfol R. Acute iron intoxication. UpToDate.com. <http://www.uptodateonline.com/patients/content/topic.do?topicKey=~a8nJ1gFQ5I2CT>. Updated September 8, 2008. Accessed April 20, 2009.
3. Juurlink DN, Tenenbein M, Koren G, Redelmeier, DA. Iron poisoning in young children: association with the birth of a sibling. *CMAJ.* 2003;168(12):1539-1542.
4. Velez LI, Delaney KA. Heavy metals: iron, lead, arsenic and mercury. In: Marx JA, Hockberger RS, Walls RM, et al., eds. *Rosen's Emergency Medicine Concepts and Clinical Practice.* 6th ed. Philadelphia, Pennsylvania: Mosby; 2006: 2418-2451.
5. Everson GW, Oudjhane K, Young LW, Krenzelok EP. Effectiveness of abdominal radiographs in visualizing chewable iron supplements following overdose. *Am J Emerg Med.* 1989;7(5):459-463.
6. Fine JS. Iron poisoning. *Curr Probl Pediatr.* 2000;30(3):71-90.
7. Tenenbein M. Iron. In: Ford MD, Delaney KA, Ling LJ, et al., eds. *Clinical Toxicology.* 1st ed. Philadelphia, Pennsylvania: WB Saunders; 2001: 305.