HEAVY METALS
Larissa I. Velez and Ellen J. O'Connell

IRON

Iron, which is essential to the function of hemoglobin, myoglobin, many cytochromes, and many catalytic enzymes, can be extremely toxic when levels are elevated after an overdose or from accumulation in disease states.[1] The acute ingestion of iron is especially hazardous to children. Ingestions of pediatric multivitamin formulations are the most common iron exposures. These occur in children younger than 6 years and are minimally toxic. Life-threatening toxicity is associated with ingestion of potent adult preparations, such as prenatal vitamins. Serious iron ingestions in adults are usually associated with suicide attempts.[2]

Principles of Disease

Pharmacology

Under normal conditions, approximately 10% of ingested iron is absorbed from the intestine and subsequently bound to transferrin, using only 15 to 35% of the iron-binding capacity of transferrin. Normal serum iron levels range from 50 to 150 µg/dL. The total iron-binding capacity (TIBC), a crude measure of the ability of serum proteins—including transferrin—to bind iron, ranges from 300 to 400 µg/dL. It is higher than the serum iron level because of a low degree of saturation. When iron levels rise after a significant iron overdose, transferrin becomes saturated so that excess iron circulates as free, unbound iron in the serum. This unbound iron is directly toxic to target organs.

In assessment of the severity of an iron exposure, it is important to refer to the amount of elemental iron ingested because the toxicity of an iron compound depends on the amount of elemental iron it contains (Table 157-1). Different formulations of iron salts contain different percentages of elemental iron. The total amount of elemental iron ingested can be approximated by multiplying the estimated number of tablets by the fraction of elemental iron contained in the tablet. Manufacturers are also required to list the amount of elemental iron per tablet. Ingestions of less than 20 mg/kg of elemental iron usually cause no symptoms. Ingestion of 20 to 60 mg/kg results in mild to moderate symptoms, and ingestion of more than 60 mg/kg may lead to severe morbidity and mortality. Although the dose of elemental iron associated with 50% mortality (LD_{50}) is 200 to 250 mg/kg, doses as small as 130 mg of elemental iron have been lethal in children.[3] Newer forms of iron are carbonyl iron and iron polysaccharide; both are non-ionic and associated with lower toxicity. Neither form is directly corrosive, and the conversion to the iron ion, which is responsible for toxicity, is very slow. There are no reported cases of serious toxicity or death from the ingestion of these compounds.[4,5]

Pathophysiology

Iron has two distinct toxic effects: (1) it causes direct caustic injury to the gastrointestinal mucosa, and (2) it impairs cellular metabolism, primarily of the heart, liver, and central nervous system (CNS). The caustic effects of iron on the gut cause the initial symptoms of vomiting, diarrhea, and abdominal pain. Hemorrhagic necrosis of gastric or intestinal mucosa can lead to bleeding, perforation, and peritonitis.[3] Unbound (free) iron moves into cells and localizes near the mitochondrial cristae, resulting in uncoupling of oxidative phosphorylation and impairment of adenosine triphosphate synthesis. Cell membranes are injured by free radical–mediated lipid peroxidation.[3,6]

Iron increases capillary permeability and both arteriolar dilation and venodilation, resulting in hypotension. Direct myocardial toxicity decreases cardiac output. Hydration of the iron molecule creates an excess of unbuffered protons, worsening metabolic acidosis.[3] These effects, combined with severe gastrointestinal fluid losses, can lead to shock, cardiovascular collapse, and death.[3]

Clinical Features

The clinical effects of acute iron poisoning occur in five stages. Not every patient goes through every phase. Phase I reflects the corrosive effects of iron on the gut. Vomiting occurs within 80 minutes of ingestion in more than 90% of symptomatic cases. Diarrhea, which can be bloody, soon follows. Phase II represents an apparent (but not complete) recovery that lasts less than 24 hours but can extend up to 2 days. Most patients recover after this point. Phase III is characterized by the recurrence of gastrointestinal symptoms, severe lethargy or coma, anion gap metabolic acidosis, leukocytosis, coagulopathy, renal failure, and cardiovascular collapse. Serum iron levels may have fallen to normal during this phase because of distribution of iron into the tissues. Metabolic derangements due to iron poisoning include hypoglycemia, leukocytosis, and severe lactic acidosis from hypoperfusion and interference with cellular respiration. Early coagulation defects are probably related to direct effects of iron on vitamin K–dependent clotting factors.[7] Later coagulation defects are due to hepatic failure. Hypoglycemia and elevations of bilirubin and aspartate and alanine transaminases are other markers of hepatotoxicity. Phase IV, characterized by fulminant hepatic failure, occurs 2 to 5 days after ingestion. This is relatively rare, appears to be dose related, and is usually fatal.[8] Phase V represents the consequences of healing of the injured gastrointestinal mucosa. It is characterized by pyloric or proximal bowel scarring, which is sometimes associated with obstruction.

Table 157-1	Common Iron Preparations	
COMPOUND	**PERCENTAGE OF ELEMENTAL IRON**
Ferrous sulfate	20
Ferrous fumarate	33
Ferrous gluconate	12
Ferric pyrophosphate	30
Ferrocholinate	14
Ferroglycine sulfate	16
Ferrous sulfate, dried	33
Ferrous carbonate, anhydrous	38
Carbonyl iron	100
Iron polysaccharide	46

Table 157-2	Toxicity of Iron by Amount Ingested and Peak Serum Levels	
ELEMENTAL IRON (mg/kg)	**PEAK SERUM IRON LEVEL (µG/DL)**	**TOXICITY**
<20	50-150	None
20-40	150-300	Mild
40-60	300-500	Moderate
>60	>500	Severe

Figure 157-1. Radiopaque iron tablets *(arrow)* seen on abdominal radiograph. (From Craig SA: Radiology. In Ford MD, Delaney KA, Ling LJ, Erickson T [eds]: Clinical Toxicology. Philadelphia, WB Saunders, 2001, p 62.)

Diagnostic Strategies

The presence of gastrointestinal symptoms suggests a potentially serious ingestion, whereas their absence is reassuring.[5] A serum iron level measured at its peak, 3 to 5 hours after ingestion, is the most useful laboratory test to evaluate the potential severity of an iron overdose. Sustained-release or enteric-coated preparations may have erratic absorption, so a second level 6 to 8 hours after ingestion should also be checked. Peak serum iron levels below 350 µg/dL are generally associated with minimal toxicity; 350 to 500 µg/dL, with moderate toxicity; and above 500 µg/dL, with potentially severe toxicity (Table 157-2).[5] Because iron is rapidly cleared from the serum and deposited in the liver, the level of iron after a substantial ingestion may be deceptively low if it is measured after its peak. TIBC is a crude test and is not useful to gauge the severity of iron poisoning.[9]

When serum iron levels are not immediately available, elevations of the serum glucose level above 150 mg/dL and leukocyte count above 15,000 are 100% specific for prediction of serum iron levels of more than 300 µg/mL. However, a sensitivity of only 50% limits their sole use as indicators of toxicity.[10]

Most tablets that contain a significant amount of elemental iron are radiopaque, although a false-negative radiograph may occur with chewable, liquid, and completely dissolved iron compounds. The presence of tablets on a radiograph correlates with the severity of the ingestion (Fig. 157-1).[11,12] Repeated radiographs can also demonstrate the efficacy of gastrointestinal decontamination efforts.

Management

Gastric Emptying

Decontamination may prevent absorption of additional iron from the gastrointestinal tract and can be performed concomitantly with interventions that address drug that has already been absorbed (see later section on deferoxamine). Activated charcoal does not bind iron, and neither gastric lavage nor ipecac effectively removes large numbers of pills. Iron tablets clump together as their outer coatings dissolve, often forming large pharmacobezoars. Whole-bowel irrigation is generally the preferred method of decontamination for significant iron ingestions.[13] This recommendation is supported by the position statement of the American Academy of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists; it is based on case reports and the lack of effective alternative decontamination techniques for this potentially deadly toxin.[14]

For significant ingestions (>20 mg/kg of elemental iron), especially when tablets are identified on the abdominal radiograph, whole-bowel irrigation with a polyethylene glycol–electrolyte lavage solution (PEG-ELS; CoLyte, NuLytely, or GoLytely) should be initiated.[14] The solution is either taken orally or, more often, administered through a small nasogastric tube.[15] The usual rate of administration of PEG-ELS is 20 to 40 mL/kg/hr in young children and 1.5 to 2 L/hr in teenagers or adults, continued until the rectal effluent is clear and there is no radiographic evidence of pill fragments. This technique has been used in children, adolescents, and pregnant women without serious complications or electrolyte disturbances.[13,16,17] Common side effects include nausea, vomiting, abdominal cramping, and bloating. Whole-bowel irrigation is contraindicated in the presence of bowel obstruction, perforation, or ileus.[14]

Hemodialysis and hemoperfusion are not effective in the removal of iron because of its large volume of distribution. Early exchange transfusions have been recommended for severely symptomatic patients with serum iron levels exceeding 1000 µg/dL.[18,19]

Deferoxamine

Deferoxamine chelates iron to form the water-soluble compound ferrioxamine, which is renally excreted and can be dialyzed;

100 mg will chelate 9.35 mg of elemental iron.[3] Deferoxamine may also limit the entrance of iron into the cell and chelate intracellular iron. Because of its short half-life, it is administered as a continuous infusion at 15 mg/kg/hr for up to 24 hours.[20] The maximum rate of administration is 35 mg/kg/hr. Rapid administration of deferoxamine can lead to hypotension, which resolves by reducing the initial rate of the infusion and slowly increasing it to the desired rate. Pregnancy is not a contraindication to deferoxamine.[4,21,22] However, the pre-pregnancy weight should be used to calculate the dose. Deferoxamine can falsely lower serum iron levels, so measurements should be taken before its administration.[23]

The presence of ferrioxamine turns the urine a "vin rosé" color, which reflects the excretion of chelated iron. The deferoxamine challenge test, which relied on detection of this color change, has been used to detect the presence of free iron in the serum. However, the color change is difficult to detect, especially when the urine is dilute, with false-negative results even in cases of serious poisoning.[24]

Deferoxamine has been associated with acute respiratory distress syndrome and also with *Yersinia* sepsis. The pulmonary complications are usually related to high-dose deferoxamine for durations longer than 24 hours.[20] The presence of fever and sepsis in a patient who has recently been treated for iron poisoning should prompt suspicion for *Yersinia* sepsis.[25,26]

Disposition

The asymptomatic patient who is reliably known to have ingested less than 20 mg/kg of elemental iron and has a normal abdominal radiograph can be observed without further therapy. The patient can be discharged if he or she remains asymptomatic after 6 hours of observation.[5]

The patient who has ingested more than 20 mg/kg of elemental iron or has pills visible on an abdominal radiograph should receive whole-bowel irrigation.[23] Follow-up abdominal radiographs can verify adequate gastrointestinal decontamination. The serum iron concentration should be checked 3 to 5 hours after ingestion. A second iron level 6 to 8 hours after ingestion should be decreasing. If peak levels are less than 300 μg/dL and are not rising and the patient is asymptomatic during 6 hours of observation, the patient can be discharged home. Moderate gastrointestinal toxicity can be expected with peak levels of 300 to 500 μg/dL. Deferoxamine should be used if these patients have symptoms of systemic toxicity evidenced by metabolic acidosis, repetitive vomiting, toxic appearance, lethargy, hypotension, or signs of shock. Patients with a serum iron level above 500 μg/dL require chelation with deferoxamine regardless of symptoms.[4] If serum iron levels are not available, a normal serum glucose level and leukocyte count suggest a low iron level; if there are no signs or symptoms of toxicity during the 6-hour postingestion period and the abdominal radiographs do not show pills in the gastrointestinal tract, the patient can be sent home.

Patients with large ingestions demonstrated by abdominal radiographs should be treated with whole-bowel irrigation until subsequent radiographs show a clean gastrointestinal tract.

LEAD

Lead poisoning is a disease of industrialization and has become the most common environmental toxicologic problem in the United States.[27] Most exposures are from inhalation of lead dust or fumes or ingestion of contaminated substances, such as paint chips. Less often, it results from direct skin contact with organic lead compounds or from retained bullets in or near joints.[28] Approximately 3 to 4 million children (1 in 20) in the United States have toxic blood lead levels (BLLs), defined currently as levels exceeding 10 μg/dL.[29] Although the addition of lead to household paint and gasoline was banned in the United States in the 1970s, residual lead-based paint is still found in 30 million homes.[29] Other sources of toxic lead ingestions include curtain weights, buckshot, fishing weights, lead-contaminated soil or water, bootleg whiskey ("moonshine"), food or beverages stored or prepared in lead-soldered cans, lead-glazed pottery, and lead crystal decanters.[30] Herbal and folk remedies, toys, and numerous products imported from Asia and Mexico can also contain dangerous amounts of lead.[31,32] This has resulted in multiple drug and toy recalls in the United States. Lead found in buckshot can cause toxic effects in those who eat wild game.[33]

Children typically present to the emergency department (1) after an ingestion of lead, (2) symptomatic with a possible exposure history, or (3) referred for management of an elevated BLL. Lead toxicity in adults most often results from inhalational exposure in the workplace as well as from hobbies and related activities. It is estimated that more than 3 million workers in the United States are at risk for toxic lead exposure in industries such as lead smelting, battery manufacture, radiator repair, bridge and ship construction or demolition, soldering or welding, cable or tin can production, stained glass manufacture, lead-glazed or crystal pottery making, glass production, firing range operation, and lead-based paint abatement. Hobbies at risk include making glazed pottery, target shooting at indoor firing ranges, soldering lead, smelting lead in the preparation of buckshot and fishing sinkers, repairing cars or boats, and remodeling homes. Lead toxicity should be considered in adults with compatible symptoms associated with these exposures.

Principles of Disease

Pharmacology

Lead is generally poorly absorbed from the gastrointestinal tract, but its absorption is highest in malnourished children (approximately 40%) and in pregnant women. Although 90 to 95% of lead is stored in cortical bone and teeth, it is also found in the brain, liver, and kidneys. Approximately 75% of the absorbed lead is eliminated by the kidneys; the remainder is excreted through the skin, hair, sweat, nails, and gastrointestinal tract.

Pathophysiology

There is no known physiologic need for lead. Lead binds to sulfhydryl groups and other ligands and interferes with critical enzymatic reactions.[12] Its toxic effects are most prominent in the hematopoietic, neurologic, and renal systems.[34]

Anemia, the classic manifestation of hematopoietic toxicity, may be either normochromic or hypochromic. The severity of the anemia correlates directly with the BLL. Inhibition of heme biosynthesis results in the accumulation of heme precursors, such as D-aminolevulinic acid and protoporphyrin. In the peripheral nervous system, segmental demyelination and degeneration of motor axons result in peripheral neuropathies. Wristdrop and footdrop are characteristic of adult lead poisoning. Lead toxicity also causes a host of neuropsychiatric disorders. In children, elevated BLL is associated with decreased intelligence (IQ) scores, hyperactivity, decreased attention span, overaggressive behavior, learning disabilities, and criminal behavior.[35-38] It has also been associated with subclinical sensorineural hearing loss.[39] Lead nephropathy is characterized by fibrosis in the proximal tubules, with relative sparing of the glomeruli. Hyperuricemic gout ("saturnine gout") can result from increased reuptake of uric acid by the tubular cells.[40] Lead poisoning also correlates with hypertension.[41] Adults and children with severe acute toxicity may present

with lead encephalopathy associated with increased capillary permeability and cerebral edema.[42,43]

Clinical Features

Symptoms of chronic, mild lead poisoning are slow in onset and nonspecific. The diagnosis is suspected by obtaining an accurate and comprehensive history of exposure to lead.

Acute exposure to lead can result in symptomatic poisoning. "Lead colic" is characterized by cramping abdominal pain with nausea, vomiting, constipation, and, occasionally, diarrhea.[43] Other characteristic symptoms and signs of acute toxicity include fatigue, anemia, peripheral neuropathy, renal impairment, and hepatic and CNS dysfunction. The CNS toxicity may be manifested as mild headache or personality changes to full-blown encephalopathy with coma, convulsions, and papilledema. Permanent neurologic and behavioral sequelae may occur.

Diagnostic Strategies

Although capillary lead levels correlate well with BLLs, the most informative biomarker is a BLL.[44-46] The Centers for Disease Control and Prevention has defined a chronic BLL of more than 10 µg/dL as toxic for a child. Acute exposure can result in levels above 100 µg/dL (Table 157-3). Other ancillary data include findings on complete blood cell count, serum glucose level, blood urea nitrogen and creatinine concentrations, electrolyte levels, and urinalysis. A peripheral smear may show basophilic stippling. Markers of hepatic injury may be elevated after acute exposure. Because lead-containing paints and objects are radiopaque when lead is present in sufficient quantities, radiographs can confirm acute ingestion and also monitor the effectiveness of whole-bowel irrigation. In cases of altered mental status, seizures, or coma, a computed tomography scan of the head will show cerebral edema associated with acute lead encephalopathy and rule out other causes of these symptoms. In children, plain radiographs of the wrist and knees may show increased metaphyseal activity manifested as "lead bands" or "lead lines" that are characteristic of chronic exposures.

Table 157-3	Serum Lead Levels and Symptoms	
	SYMPTOMS	
LEVEL (µg/dL)	Adults	Children
10	None	Decreased IQ Decreased hearing Decreased growth
20	Increased protoporphyrin No symptoms	Decreased nerve conduction velocity Increased protoporphyrin
30	Increased blood pressure Decreased hearing	Decreased vitamin D metabolism
40	Peripheral neuropathies Nephropathy Infertility (men)	Decreased hemoglobin synthesis
50	Decreased hemoglobin synthesis	Lead colic
70	Anemia	Anemia Encephalopathy Nephropathy
100	Encephalopathy	Death

Management

Acute Lead Encephalopathy

Acute lead encephalopathy can be rapidly fatal. The initial goals in management are identification and treatment of all life-threatening conditions, followed by prevention of further exposure to lead, minimization of ingested lead absorption, enhancement of its elimination, and prevention or reversal of pathologic cell changes. Standard measures to control cerebral edema, including intubation and neurosurgical consultation for invasive monitoring of intracranial pressure, are indicated. When a severe poisoning is associated with recent ingestion or if radiopacities are seen on the radiograph, decontamination with whole-bowel irrigation should be considered.[47,48] This intervention has not been prospectively studied but has been successful in case reports.[14] Activated charcoal does not adsorb lead and should not be used.

Chelation Therapy

The use of chelation in cases of acute lead poisoning is guided by the patient's clinical status and the BLL. Any patient with a BLL above 70 µg/dL or with signs suggestive of encephalopathy will require admission for parenteral chelation therapy. For these seriously poisoned patients, dimercaprol (or British anti-Lewisite [BAL]) should be the first chelator given. The dosage for treatment of lead encephalopathy is 75 mg/m² deep intramuscular injection every 4 hours for 5 days for children or 4 mg/kg every 4 hours for adults. Dimercaprol forms complexes that undergo both renal and biliary excretion. Adverse reactions to dimercaprol include nausea, vomiting, urticaria, pyrexia, hypertension, and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.[49] Because dimercaprol is diluted in peanut oil, it is contraindicated in patients allergic to peanuts.[49] Dimercaprol is followed by calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$), a highly effective lead chelator. Because of concerns that the chelated lead can cross the blood-brain barrier and worsen encephalopathy, the first dose of $CaNa_2EDTA$ is administered with the second dose of dimercaprol. The dosage of $CaNa_2EDTA$ for patients with acute lead encephalopathy is 1500 mg/m²/day (approximately 50-75 mg/kg/day) given by continuous intravenous infusion. Adverse reactions include renal tubular injury and chelation of other metals, especially iron and zinc. $CaNa_2EDTA$ should be given only with adequate urine flow or with hemodialysis in the patient with renal failure.[50] It is important that $CaNa_2EDTA$ not be confused with sodium EDTA. The administration of sodium EDTA has been associated with hypocalcemia and death from arrhythmias.[51]

The need for parenteral chelation therapy in asymptomatic or minimally symptomatic children is guided by the BLL. A BLL of more than 69 µg/dL is an indication for hospitalization and parenteral chelation therapy. For less seriously poisoned patients, the dosage of $CaNa_2EDTA$ is 50 mg/kg/day or 1000 mg/m²/day, given in two to four divided doses for up to 5 days.

Serum lead levels of 45 to 69 µg/dL in patients without vomiting or CNS symptoms can be managed in the outpatient setting with oral succimer (2,3-dimercaptosuccinic acid [DMSA]; Chemet). The initial dose of DMSA is 10 mg/kg every 8 hours for 5 days, then 10 mg/kg every 12 hours for 14 days. The most common adverse reactions include nausea, vomiting, diarrhea, and transient elevations in liver transaminase levels. Although DMSA has been approved only for children, it is effective and also used for adults.[44,52,53] Oral D-penicillamine is less efficacious than succimer and has more adverse reactions; it should be used only in patients who do not tolerate succimer. The usual oral dose of

Table 157-4 **Chelators**

CHELATOR	DOSE	INDICATIONS	CONTRAINDICATIONS
Deferoxamine	15 mg/kg/hr up to 24 hr (titrate up slowly because of hypotension)	Iron level >500 g/dL or systemic symptoms	
Dimercaprol (British anti-Lewisite, BAL)	Lead encephalopathy: 75 mg/m² deep intramuscular (IM) injection every 4 hr for 5 days in children or 4 mg/kg every 4 hr for adults Arsenic (severe): no established regimen; consider 3 mg/kg IM every 4 hr for 48 hr, then twice daily for 7-10 days Mercury: 5 mg/kg IM first, then 2.5 mg/kg every 12-24 hr	Lead level >70 g/dL or encephalopathy Arsenic: symptomatic patient with known exposure Mercury: inorganic	Peanut allergy Organic mercury poisoning
CaNa₂EDTA	1500 mg/m²/day continuous intravenous infusion 50 mg/kg/day or 1000 mg/m²/day in 2-4 divided doses for up to 5 days if less severe symptoms	Lead: given after first dose of BAL for blood lead level above 70 g/dL or encephalopathy	
Succimer (DMSA)	10 mg/kg q8h × 5 days, then q12h for 14 days	Lead level of 45-69 g/dL Arsenic: if tolerated orally for subacute and chronic toxicity Mercury: acute and chronic	
D-Penicillamine	25 mg/kg q6h × 5 days	Lead level of 45-69 g/dL, succimer not tolerated Arsenic: only if BAL and DMSA are unavailable Mercury: if BAL and DMSA are unavailable or not tolerated	Penicillin allergy
DMPS (investigational)	5 mg/kg/dose IM q6-8h day 1, q8-12h day 2, q12-24h day 3 and until 24-hr urine is <50 µg/L	Lead (chronic) Arsenic Mercury	

Note: Indications for chelation and dosing regimens may change. Consult with a toxicologist or poison control center for the most up-to-date recommendations.

D-penicillamine is 25 mg/kg every 6 hours for 5 days. Penicillin allergy is a contraindication to the use of D-penicillamine. Another oral chelator is 2,3-dimercapto-1-propanesulfonic acid (DMPS), which, like succimer, is similar to BAL. At this time, it is experimental, although it can be considered in chronic lead poisoning.[54,55] Table 157-4 summarizes available chelating agents with indications and doses.

Evidence indicates no need for chelation for children with a BLL lower than 45 µg/dL.[43] A BLL between 20 and 44 µg/dL in a patient who is asymptomatic or minimally symptomatic requires a medical and environmental evaluation. Children with lead levels of 10 to 19 µg/dL require family counseling about the symptoms and sources of lead exposure and careful follow-up, with frequent screening of BLLs. The key to management of chronic lead toxicity is the identification and reduction of sources of primary exposure, which can often be arranged with the local public health department. Any patient treated on an outpatient basis should be discharged to a lead-free environment.

The treatment of adults with chronic poisoning is based primarily on symptoms and is less aggressive than treatment of children with the same BLL. If gastrointestinal symptoms or CNS problems are present, hospitalization with parenteral chelation therapy is indicated. In the asymptomatic adult or the adult with only mild clinical problems, the only intervention needed is cessation of exposure. According to the Occupational Safety and Health Administration lead standard, workers with serum lead levels above 50 µg/dL should be removed from work.

Pregnant women should be treated in accordance with adult treatment guidelines. Lead does cross the placenta and may accumulate in the fetus, and the newborn may require chelation as well.

Disposition

Patients who have ingested a single lead foreign body (e.g., fishing sinker) will usually pass it harmlessly.[56] If the foreign body remains in the gastrointestinal tract after 2 weeks, removal should be considered to prevent systemic lead toxicity. Gunshot victims with too many lead buckshot pellets to remove may be at risk for elevated BLL and require follow-up lead levels. Asymptomatic children and adults should be counseled on how to avoid further exposure and have a repeated BLL checked in 2 weeks to ensure decreasing levels.

Patients who are significantly symptomatic with CNS symptoms after an acute lead exposure and children with a BLL of 69 µg/dL or higher require hospitalization and chelation therapy. Patients discharged home with oral chelation therapy should not return to a contaminated environment. The health department should conduct an environmental assessment so that the primary source of lead exposure can be identified and further exposure prevented. Follow-up should be arranged with an experienced pediatrician, toxicologist, or occupational medicine physician.[57]

ARSENIC

Arsenic, a tasteless, odorless substance that looks like sugar, has an infamous history as an agent of homicide. Arsenic has also been implicated in many epidemic poisonings. Currently, arsenic exposure is primarily environmental and occupational. It is found in smelters and electric power plants that burn arsenic-rich coal. It is used in industry as a wood preservative and in the production of glass and microcircuits. Inorganic arsenicals are also used in rodenticides, fungicides, insecticides, paint, and tanning agents and as defoliants in the cotton industry. Arsenic is still used for medicinal purposes in the treatment of trypanosomiasis,

amebiasis, and leukemia. It has also been found as a contaminant in herbal remedies and drugs such as opium.[58] There are widespread reports of chronic poisoning associated with arsenic-contaminated drinking water in underdeveloped countries.[59] Arsenic poisoning should be suspected if compatible symptoms occur with the use of these products or these possible exposures.

Principles of Disease

Pharmacology

Arsenic has no metabolic or biologic function. The elemental metal (As) is poorly water soluble and is considered nontoxic. Of the two inorganic forms, trivalent arsenite (As^{3+}) is highly lipid soluble and is 5 to 10 times more toxic than the pentavalent arsenate (As^{5+}) form. The more toxic trivalent arsenite form has a lower gastrointestinal absorption but is well absorbed by the skin. The pentavalent arsenate form, although less toxic, is water soluble and readily absorbed from the gastrointestinal tract. Absorbed arsenic is bound by hemoglobin, leukocytes, and plasma proteins. It is cleared from the intravascular compartment within 24 hours and concentrates in the liver, kidneys, spleen, lungs, and gastrointestinal tract. Arsenic crosses the placenta and can also accumulate in the fetus. Its affinity for sulfhydryl groups in keratin makes arsenic detectable in the hair, skin, and nails.[60] Arsine (AsH_3), a colorless and almost odorless gas, is extremely toxic.[61] It is immediately lethal at 250 ppm.

The excretion of arsenic and its metabolites occurs mainly through the kidneys.

Pathophysiology

Arsenic binds avidly to sulfhydryl groups, inhibiting critical enzymes such as lactate dehydrogenase and glyceraldehyde-3-phosphate dehydrogenase, a critical step in glycolysis. It also disrupts oxidative phosphorylation by replacing phosphorus in the formation of high-energy phosphate bonds (arsenolysis).[59] Arsine causes massive hemolysis, but the exact mechanism for this is poorly understood.[62,63]

Clinical Features

Acute exposure to arsine gas is characterized by severe hemolysis that is also associated with renal tubular injury. Gastrointestinal symptoms are common, and CNS and liver dysfunction can occur; the mortality rate is 25 to 30%.[64] Exchange transfusions and plasma exchange have been used to remove arsine, which is tightly bound to the erythrocytes.[64] Urinary alkalinization can be used to decrease renal deposition of hemoglobin and subsequent renal failure.

Acute gastrointestinal effects (nausea, vomiting, abdominal pain, and diarrhea) predominate as the initial manifestations of acute exposure to arsenic salts.[65,66] These symptoms can be so severe as to be manifested with hematemesis and hematochezia. Within 30 to 60 minutes of exposure, patients complain of a metallic or garlicky taste. The patient can also have encephalopathy with seizures and coma, respiratory failure associated with acute respiratory distress syndrome, and dysrhythmias associated with cardiac conduction disturbances.[67-69] In cases of severe poisoning, cardiovascular collapse and death ensue.[70] Less common complications include hepatitis, rhabdomyolysis, hemolytic anemia, renal failure, unilateral facial nerve palsy, pancreatitis, pericarditis, pleuritis, and fetal demise (Box 157-1).[66] The early arsenic poisoning syndrome may be misdiagnosed as gastroenteritis or sepsis.

Weeks to months after the initial symptoms, chronic effects of arsenic poisoning appear, including characteristic lines in the nails

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Box 157-1 Acute Effects of Arsenic Poisoning

Gastrointestinal
Violent gastroenteritis; hematemesis or hematochezia
Jaundice
Pancreatitis
Dysphagia
Hepatomegaly

Cardiovascular
Third spacing with shock
Sinus or ventricular tachycardia
Prolonged QT interval, ST depression, T wave inversion
Torsades de pointes
Pericarditis

Respiratory
Respiratory failure
Acute respiratory distress syndrome
Pulmonary edema
Pneumonia

Renal
Proteinuria
Hematuria
Oliguria
Renal failure

Neurologic
Headache
Drowsiness
Delirium
Coma
Encephalopathy
Seizures

(Mees lines), painful sensorimotor neuropathy, and hyperkeratosis of the palms and soles. Arsenic poisoning should also be considered in any patient with a history of severe or recurrent gastroenteritis or abdominal pain and unexplained dermatologic lesions associated with peripheral neuropathy. Finally, arsenic is a known human carcinogen.

Diagnostic Strategies

Normal arsenic levels are 5 µg/L or less in blood or less than 50 µg/day in a 24-hour urine collection, which is the best way to diagnose the poisoning. Any urine level above 100 µg/day or 50 µg/L necessitates treatment. A spot urine sample may be falsely low because urinary excretion of arsenic is intermittent. Seafood contains arsenobetaine, which can increase urinary arsenic excretion to as high as 1700 µg/L.[71] Arsenobetaine, however, does not result in arsenic toxicity. For this reason, patients should refrain from eating seafood, specifically shellfish, before testing, or the laboratory should be asked to speciate the type of arsenic measured.[72]

Other laboratory results may suggest arsenic poisoning in the right clinical setting. Anemia, leukocytosis or leukopenia, and erythrocyte basophilic stippling are seen in the complete blood cell count. The results of renal function tests may be abnormal, demonstrating proteinuria, hematuria, and pyuria. The alanine transaminase, aspartate transaminase, and bilirubin levels may be elevated. In cases of chronic arsenic poisoning, the serum and urine arsenic levels may be undetectable, whereas hair and nail specimens can confirm the diagnosis.

Arsenic in the gastrointestinal tract is radiopaque and can appear on a radiograph, although sensitivity is limited by its rapid absorption and the ensuing gastroenteritis.

Management

The initial management should address life-threatening conditions with supportive management of shock, dysrhythmias, and seizures. Activated charcoal does not adsorb arsenic and is of no value. Although there is no evidence for improved outcomes, orogastric lavage or whole-bowel irrigation should be considered for recent (<1 hour) ingestions or if radiopaque material is visualized on an abdominal radiograph. This recommendation is based on two case reports demonstrating clearance of radiopaque material on the abdominal radiographs of patients who had ingested arsenic. There are no studies demonstrating clinical efficacy of this intervention. Hemodialysis removes arsenic in the setting of acute renal failure.[69] Exchange transfusions or plasma exchange can be considered early after an arsine exposure.[64]

With a known history of exposure in a symptomatic patient, chelation should start as early as possible without waiting for laboratory confirmation of the arsenic levels, which may take some time. Intramuscular dimercaprol is the preferred chelator in patients who are critically ill as described for lead poisoning. DMSA is a water-soluble analogue of dimercaprol that can be given orally.[72,73] The use of DMSA is often limited by the violent gastroenteritis resulting from arsenic poisoning. D-Penicillamine has a high side effect profile, and its ability to chelate arsenic is inferior to that of dimercaprol and DMSA. Therefore, it should be used only when *both* dimercaprol and DMSA are unavailable. All patients receiving chelation for acute arsenic toxicity should be admitted. Chelation is not useful for arsine exposures. Workers should modify their habits to avoid further absorption, and repeated monthly 24-hour urine collections can follow arsenic excretion.

Table 157-4 summarizes available chelating agents with indications and doses.

MERCURY

Mercury is a silver-white metal, familiar to most as the only metal that is liquid at room temperature. It has a long history of medicinal uses as an antiparasitic, a diuretic, a cathartic, an antiseptic, and a preservative in many vaccines. Significant poisoning in the home has occurred when relatively small amounts of spilled mercury, such as that contained in a sphygmomanometer, were aerosolized by vacuuming (which should be avoided) or when mercury was heated on the kitchen stove to extract gold from ore.[74,75] Various other sources of mercury have also been implicated in intoxication. Because of many industrial uses that include the manufacture of fluorescent lights, batteries, polyvinyl chloride, and latex paint, mercury is a common pollutant of air and water. This has led to restrictions in the consumption of fish caught in many local waters, especially by pregnant women and children.[76,77]

Principles of Disease

Pharmacology

The most familiar form of mercury is elemental or metallic mercury, also known as quicksilver. A common route of exposure to elemental mercury is the inhalation of volatilized vapor.[78] Aspiration of elemental mercury and intentional subcutaneous and intravenous injections also cause poisoning.[79] After inhalation, 74% of the metallic mercury is retained in the lungs. This can result in severe pneumonitis and acute respiratory distress syndrome.[80] Aspiration of elemental mercury results in primary pulmonary toxicity in addition to CNS and renal toxicities.[81] Elemental mercury is not absorbed by the gastrointestinal tract, so ingestion does not normally lead to systemic toxicity unless it becomes trapped in diverticula. Mercury is absorbed through the skin at 1% of the rate of inhaled mercury and is not a concern.

Inorganic mercury salts have two different valences, Hg^{1+} (*mercurous*) and Hg^{2+} (*mercuric*). Ingestion of either salt leads to significant gastrointestinal and renal toxicity.

The organic mercury compounds are categorized as either short chain (*alkyl*) or long chain (*aryl*). The major route of exposure to this type of mercury is through ingestion, but these compounds are also readily absorbed through the skin. These organic forms classically result in delayed neurotoxicity with prominent ataxia, tremor, dysarthria, and tunnel vision.[76,82]

Pathophysiology

Mercury has no known physiologic role. Mercury binds covalently to sulfhydryl groups, disturbing multiple cellular enzyme functions. Nephrotoxicity results from both direct damage and an immune reaction in the kidney.[74] Inorganic salts have a direct corrosive effect on the gastrointestinal tract with third spacing and hemorrhage. Skin changes associated with mercury poisoning are also caused by an immune reaction. Mercury increases catecholamine levels by inhibition of catechol-*O*-methyltransferase, resulting in hypertension and tachycardia.[83,84] Atrophy of the cerebellum, postcentral gyri, and calcarine areas of the brain correlates with the symptoms of ataxia and sensory and visual field disturbances.[85]

Clinical Features

The clinical manifestations of mercury poisoning depend on the acuity of the exposure, the route of exposure, and the chemical form of mercury. Inhalation of elemental mercury vapor results in the rapid onset of shortness of breath, fever, and chills that progress to pneumonitis and respiratory distress.[75,80,86] Aspiration of liquid metallic mercury during medical procedures results in the rapid onset of tracheobronchial hemorrhage.

Acute ingestion of inorganic salts typically causes a corrosive gastroenteritis with third spacing and hemorrhage. Patients may have a metallic taste in the mouth and a grayish discoloration of the mucous membranes. Massive fluid loss results in shock and acute tubular necrosis. The manifestations of subacute or chronic inorganic mercury poisoning are neurologic (e.g., neurasthenia and erethism), renal (ranging from proteinuria to the nephrotic syndrome), and gastrointestinal (e.g., metallic taste, gingivostomatitis, loose teeth sensation, burning sensation in mouth, hypersalivation, and nausea).[74,87]

Exposure to organic mercury compounds is not associated with acute toxicity. Neurologic symptoms develop during weeks to months. The neurologic and teratogenic effects of chronic exposure to methylmercury were well illustrated by the tragic poisoning of the population of Minamata, Japan, by eating of fish caught in mercury-polluted water. Slowly progressive fatal CNS injury was described after a minor topical exposure to dimethylmercury in a laboratory researcher (Table 157-5).[76,82,88]

Diagnostic Strategies

Measurement of 24-hour urine mercury levels is the most helpful test in confirming exposure and monitoring the effectiveness of chelation. For organic mercury compounds, which undergo little urinary excretion, serum levels should be used to confirm the diagnosis. "Normal" mercury levels are considered to be less than 10 μg/L in the blood or less than 20 μg/L in the urine. Blood levels above 35 μg/L and urine levels above 150 μg/L require intervention. No information is available on chelation at levels between 20 and 150 μg/L. Fish can be contaminated with mercury, especially larger fish and those from certain bodies of water known by state

Table 157-5	Mercury Intoxication Syndromes
TYPE OF MERCURY AND ROUTE OF EXPOSURE	**SIGNS AND SYMPTOMS**
Inhalation of metallic mercury	Hypoxemia, dyspnea, chest tightness Fever, chills Burning in mouth and throat Nausea, vomiting, bloody diarrhea Renal tubular necrosis
Aspiration of metallic mercury	Aspiration pneumonitis, ARDS
Subacute or chronic inhalation of metallic mercury	Metal fume fever Neuropsychiatric symptoms Renal dysfunction Skin changes
Ingestion of inorganic mercury salts	Severe hemorrhagic gastroenteritis, shock, hypovolemia, third spacing Acute tubular necrosis in 24 hr, with albuminuria and hematuria
Subacute or chronic inhalation of inorganic mercury	Neurasthenia, erethism, acrodynia
Organomercury exposure (methyl-, diethyl-)	Delayed neurologic problems (ataxia, tremor, dysarthria), visual field constriction, hearing loss, spasticity, hyper-reflexia

ARDS, acute respiratory distress syndrome.

health departments to be most polluted. Individuals eating these locally caught fish will have elevated mercury levels. Metallic mercury is radiopaque on plain radiographs, which can be ordered in cases of injection or ingestion of metallic mercury.[79]

Management

Initial management in the acutely poisoned patient is supportive. Gastric lavage with protein-containing solutions (e.g., milk and egg whites) has been suggested; however, no data exist to support this practice, and it is not recommended. Similarly, whole-bowel irrigation or any other gastric decontamination is without evidence of benefit. Charcoal adsorbs very little mercury and is not recommended unless another serious coingestant is suspected. Ingested metallic mercury is generally harmless unless its passage is impaired by entrapment in a diverticulum or the appendix.[89]

For acute inhalational exposures, the patient should be removed from the source and supportive management provided. There is no role for prophylactic antibiotics or steroids. Suction and postural drainage are indicated in cases of acute aspiration of metallic mercury. Self-injection of metallic mercury often requires surgical débridement of infiltrated tissue.[79]

Help in the management of mercury spills can be obtained from the local hazardous materials team and the local health department.[78] Information on handling of mercury spills or compact fluorescent light bulb breakage can also be found at the Environmental Protection Agency websites at www.epa.gov/hg/spills/index.htm and www.epa.gov/cfl/cflcleanup.html, respectively. Sand or mercury decontamination kits that contain calcium polysulfide, which converts mercury to mercuric sulfide, should be used for elemental mercury spills. Absorbable surfaces such as carpets should be removed. Attempts to remove mercury by vacuuming should be avoided as this can volatilize the mercury and precipitate acute inhalational toxicity. Small spills, such as the contents of a home thermometer or a fluorescent bulb (amount = 30 mL or two tablespoons), can be scooped up with a stiff card or aspirated into a dropper placed onto a damp paper towel, sealed in a plastic bag, and disposed of as hazardous waste. Mercury placed in household trash is incinerated, is spread as an airborne

contaminant, contributes to soil and water pollution, and ultimately accumulates in the food chain.

Chelation Therapy

Chelating agents have thiol groups that compete with the enzyme sulfhydryl groups that bind mercury. BAL is used for clinically significant acute inorganic mercury intoxication. Because it increases brain mercury levels in patients with methylmercury poisoning, BAL is contraindicated for patients poisoned with organic mercury compounds.[90] Although DMSA is not currently approved by the U.S. Food and Drug Administration for this indication, it is used for both acute and chronic mercury poisoning and may be the best chelator for methylmercury. D-Penicillamine is also used but should be administered only after thorough gastrointestinal decontamination because mercury absorption from the intestinal lumen is enhanced by the penicillamines. DMPS may also be considered if other options are unavailable or contraindicated. Table 157-4 summarizes available chelating agents with indications and doses.

Disposition

In general, in cases of acute intoxication, the most toxic forms are the inorganic mercurials. Suicidal patients with such ingestions require decontamination and admission for supportive treatment. Patients who self-inject metallic mercury often need admission for surgical débridement. Patients with signs of neurotoxicity from an organomercurial also need admission. Most asymptomatic individuals and fish eaters should abstain from eating locally caught fish and can be observed closely with monthly urine testing as outpatients.

KEY CONCEPTS

- Acute ingestion of the salts of most metals causes severe gastrointestinal pain and emesis.
- Chelation with acute iron ingestion is guided by symptoms and at least two serum iron levels measured between 3 and 8 hours after ingestion.
- Patients with symptomatic acute lead exposures require immediate chelation. Asymptomatic or minimally symptomatic children with elevated BLLs require close follow-up and possible outpatient (oral) chelation. Parenteral chelation is indicated in children with BLLs above 69 μg/dL.
- Patients with a possible chronic heavy metal exposure and compatible symptoms should have further investigation to eliminate exposure and close follow-up testing.
- There is no evidence, beyond case reports, supporting gastric lavage and whole-bowel irrigation in any heavy metal toxicity case. Whole-bowel irrigation should be considered primarily if unabsorbed metal is present, as evidenced by abdominal radiographs.
- Activated charcoal has no role in decontamination of heavy metals.
- The recommendations for chelation are variable, and these patients should be treated under the guidance of a clinical toxicologist whenever possible.

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