Iron Toxicosis

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Iron, a heavy metal, is the most abundant trace mineral in the body.[1-3] Although iron is essential for the transport of oxygen, the presence of excess iron in the blood can lead to iron toxicosis. The most common cause of iron overdose is accidental ingestion of iron-containing compounds; however, iatrogenic overdose via injection of agents to treat iron deficiency (e.g., iron dextran complex) is possible.[4,5] Iron-containing items that animals may accidentally ingest include multivitamins, birth control pills, fertilizers, hand and foot warmers, heat patches or wraps, some slug and snail baits, and oxygen absorber sachets.[6-9]

PATHOPHYSIOLOGY

Iron can exist in two ionic states—ferrous (Fe^{2+}) and ferric (Fe^{3+})—within the body.[1,3] Although ferrous iron is more readily absorbed by the body, both forms can be absorbed if they are ionized.[1,2] Metallic iron and iron oxide (i.e., rust) do not readily ionize; therefore, these forms are typically not problematic if ingested.[1,6]

After iron is ionized, most of it is absorbed by mucosal cells in the duodenum and upper jejunum.[1,2] However, in cases of overdose, the entire intestinal tract may absorb iron.[1] Absorption is also increased in the presence of vitamin C.[1,3] The iron is then transported across cell membranes to the blood, where it binds to transferrin, which is the primary iron transport molecule.[1,4,6] Transferrin is produced in the liver and is normally 25% to 30% saturated with iron.[3,4] Most iron is transported by transferrin to the bone marrow for the production of hemoglobin.[1,3] The body absorbs 2% to 15% of ingested iron, but only 0.01% is eliminated daily;[1,3,5] the remainder is bound to ferritin, an iron storage protein, and is stored in the liver, spleen, and bone marrow.[1,3,5]

When iron toxicosis occurs, transferrin becomes saturated so that the total serum iron (SI) concentration exceeds the transferrin iron-binding capacity; therefore, the amount of free circulating iron in the blood increases.[1,6] This free iron enters cells of the liver, heart, and brain, where it binds to cell membranes and stimulates lipid peroxidation, in which free radicals remove electrons from the lipid in cell membranes, resulting in cell damage.[1,2,6,9]

The development of toxicosis also depends on the amount of iron already in the body.[1] Animals that have a large amount of stored iron may develop signs of toxicosis even when the level of iron ingested causes no problems in other animals.[1]

TOXICOSIS AND CLINICAL SIGNS

Toxicosis is not expected in healthy dogs and cats that ingest <20 mg/kg of elemental iron.[1,6,9] Ingestion of 20 to 60 mg/kg of elemental iron may cause toxicosis with mild gastrointestinal (GI) signs.[1,6,9] Ingestion of >60 mg/kg of elemental iron is considered potentially serious and may result in GI hemorrhage as well as metabolic

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acidosis and elevated liver enzyme values.[1,4,6,9] Death may result if an animal ingests 100 to 200 mg/kg of elemental iron and does not receive treatment.[1,6,9] TABLE 1 lists the elemental iron content of commonly ingested iron salts; BOX 1 describes how to calculate the amount of elemental iron ingested.

Toxicosis can be characterized as peracute, subacute, or chronic.[4,5,8] In peracute toxicosis, such as that occurring after an iron injection, clinical signs develop within minutes to a few hours after exposure.[4,5,8] Signs are similar to those of an anaphylactic reaction and may include hypovolemic shock followed by sudden death as a result of vascular collapse.[4,5,8] At the injection site, the skin may be discolored and edema may develop.[4,8]

Subacute toxicosis, such as that occurring after oral ingestion, can be grouped into four phases.[1,2,6-8] During the first phase, signs develop up to 6 hours after exposure

TABLE 1 Iron Salts and Their Elemental Iron Content[3,4,a]

IRON SALT	ELEMENTAL IRON (%)
Ferrocholinate	12
Ferrous gluconate	12
Ferric ammonium citrate	15
Ferroglycine sulfate	16
Peptonized iron	17
Ferrous sulfate (hydrate)	20
Ferrous lactate	24
Ferric pyrophosphate	30
Ferrous fumarate	33
Ferric chloride	34
Ferrous sulfate (anhydrous)	37
Ferric phosphate	37
Ferrous carbonate (anhydrous)	48
Ferric hydroxide	63

[a] Williams RJ. Biomineralization: iron and the origins of life. *Nature* 1990;343:213-214.

BOX 1 Calculating Ingested Iron

Most products that contain iron include it as a salt compound. To calculate the amount of iron ingested, it is important to determine the amount of elemental iron (i.e., the amount of iron without a salt compound). TABLE 1 lists various iron salts and the percentage of elemental iron in each salt. For example, if a cat has ingested 10 tablets, each containing 32.5 mg of ferrous fumarate, the calculations would be performed as follows:

1. To calculate the total amount of ferrous fumarate ingested, multiply 10 by 32.5, which equals 325 mg of ferrous fumarate.
2. To calculate the amount of elemental iron ingested, multiply 325 by 0.33 (the factor that represents the percentage of elemental iron in ferrous fumarate; see TABLE 1), which equals 107 mg of elemental iron.
3. To calculate the amount of iron ingested per kilogram of body weight, divide 107 by the animal's weight in kilograms.

and include lethargy and bloody vomiting and diarrhea caused by GI hemorrhage.[1,2,6-8] In the second phase, which develops within 6 to 24 hours after exposure, the patient's condition appears to improve.[1,2,6-8] During the third phase, about 12 to 96 hours after exposure, GI signs recur, along with depression, shock, hypotension, tachycardia, cardiovascular collapse, metabolic acidosis, coagulopathy, liver failure, or even death.[1,2,6-8] Acute renal failure secondary to shock may also develop.[1,7,8] Animals that survive this phase may enter a fourth phase 2 to 6 weeks after exposure.[1,2,7,8] In this phase, gastric obstruction may develop secondary to gastric or pyloric stenosis.[1,2,6-8]

Chronic toxicosis occurs when iron is repeatedly ingested at low levels that individually do not have adverse effects. Long-term iron exposures may lead to the development of hemochromatosis, a pathologic accumulation of iron in the tissues that can cause organ damage, often resulting in fibrosis.[2,5]

DIAGNOSIS

If a patient has ingested an iron salt–containing substance in amounts sufficient to cause toxicosis, the veterinary staff should observe the patient's clinical signs and measure the SI level and total iron-binding capacity (TIBC).[1,6] Testing an animal's SI level is the best method of confirming a tentative diagnosis of iron toxicosis and may be performed at most human hospitals if needed.[1,2,6] The SI test measures bound and free SI, whereas the TIBC test assesses the total amount of iron that the transferrin can bind.[1] SI testing should be conducted within a few hours of ingestion to obtain a baseline level[1,6] and then repeated 4 to 6 hours after the first assays as SI levels may vary widely within the first few hours after ingestion.[1,6] Normal ranges for SI and TIBC vary from animal to animal and the type of laboratory test used.[1,2] Veterinary technicians should check the range of the specific test to determine whether results are abnormal. Toxicosis can be confirmed if the SI value is greater than the TIBC value.[1,2,7]

If a patient has ingested radiopaque iron-containing tablets, it may be useful to obtain abdominal radiographs within a few hours of ingestion.[1,4,7] Radiographs should be repeated after GI decontamination.[8]

TREATMENT

If an animal has ingested <20 mg/kg of elemental iron, the veterinary staff should observe the patient and provide treatment based on clinical signs.[1] Animals that remain asymptomatic for 6 to 8 hours are unlikely to develop clinical signs.[2] A single oral dose of magnesium hydroxide or calcium carbonate tablets may reduce iron absorption by 30% to 40%[10] and can be administered to asymptomatic animals.[1,4,6-8]

TECHPOINT

Veterinary technicians should educate owners about the signs of iron toxicosis and instruct them to keep iron-containing products away from pets.

If an animal has ingested >20 mg/kg of elemental iron, GI decontamination through induced vomiting with 3% hydrogen peroxide or apomorphine should be considered up to 1 to 2 hours after ingestion, unless the animal is already vomiting.[1] Activated charcoal is not indicated because it does not bind well to iron.[6-9] In animals that are already vomiting, emesis can be managed with antiemetics (such as maropitant or ondansetron).[7,8] GI protectants such as sucralfate, along with an H_2 blocker (such as famotidine, cimetidine, or ranitidine) or a proton pump inhibitor, such as omeprazole, may be administered.[1,2,7-9] Intravenous fluid support—which helps manage shock and hypotension—can be offered.[1,2,7,8] Gastric lavage can be performed when emesis is contraindicated or when pill bezoars are identified.[7-9] Emergency gastrotomy may be indicated if lavage fails to remove pills adhered to the stomach wall or bezoars.[2,5,7] A complete blood cell count and chemistry profile should be obtained to assess liver and kidney function, coagulation, dehydration, leukocytosis, and hyperglycemia.[1,2,6-9] Electrolyte level and acid–base status should also be monitored in patients exhibiting clinical signs.[1,2,7,8] Supportive care should be provided as needed.

When the SI value is greater than the TIBC value or is above 300 to 500 mcg/dL, excess iron must be removed from the blood.[1,2,4,6-8] The drug of choice for this purpose is deferoxamine mesylate, an iron chelator.[1,2,4,6-8] This agent is best given within the first 24 hours after exposure, at a rate of 40 mg/kg IM q4–8h or 15 mg/kg/h IV.[1,2,6-9] Deferoxamine is excreted primarily by the kidneys and can cause hypotension[2,4,6,8] or cardiac arrhythmias.[2,6,7,9] It should be infused slowly, and care must be taken when administering it to animals that are in shock or have renal insufficiency.[2,5] Administering ascorbic acid after the gut has been cleared of iron increases the effectiveness of the drug.[2,8] Use of deferoxamine mesylate causes the urine to become reddish-brown if SI is elevated.[1,4] Treatment is usually continued until the urine is no longer discolored, clinical signs start to resolve, or the SI value is <300 mcg/dL.[1,2,4,7,8]

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