

PEER-REVIEWED

The toxicity of iron, an essential element

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Iron is the most abundant trace mineral in the body and is an essential element in most biological systems.^{1,2} It is likely that iron was essential for developing aerobic life on Earth.³ But iron is toxic to cells in excessive amounts. Acute iron poisoning is common and potentially lethal in dogs, cats, and many other animals. Iron is also a leading cause of unintentional poisoning deaths in children less than 6 years old.

Normal iron content and storage

About 70% of the iron in mammals is found in hemoglobin, and about 5% to 10% is found in myoglobin. When bound to normal hemoglobin and myoglobin, iron is in the ferrous (Fe^{2+}) form.^{1,2,4} Up to 25% of iron in the body is in the ferric (Fe^{3+}) form and is stored in hemosiderin, ferritin, and transferrin in the liver, spleen, and bone marrow.^{1,2,5} Ferric iron is used in iron-containing enzymes, such as peroxidase, catalase, and cytochrome-c.

Sources

One reason iron toxicosis is such an important problem is that the general public is often unaware of the potential toxicity of products that are considered natural and necessary for our health.⁶

Another reason is that many pharmaceutical preparations contain iron. Multivitamins containing iron are readily

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TABLE 1 Iron Salts and the Percentage of Elemental Iron*

Form of Iron	Elemental Iron (%)
Ferric hydroxide	63
Ferrous carbonate (anhydrous)	48
Ferric phosphate	37
Ferrous sulfate (anhydrous)	37
Ferric chloride	34
Ferrous fumarate	33
Ferric pyrophosphate	30
Ferrous lactate	24
Ferrous sulfate (hydrate)	20
Peptonized iron	17
Ferroglycine sulfate	16
Ferric ammonium citrate	15
Ferrous gluconate	12
Ferrocholate	12

*Source: References 1-3.

available. Many are brightly colored and sugarcoated, making them attractive to animals and small children. In addition, several iron supplements are available over the counter. Another frequent source of iron overdose in pets is prenatal vitamins. Many prescription prenatal vitamins contain more than 60 mg of elemental iron in each pill, so animals can develop severe iron toxicosis even if only a few tablets are ingested.

Numerous other products contain iron, including one-time-use heating pads. Iron can also be found in fertilizers and pesticides and in the soil.^{1,2,4}

Iron is also used in injectable products and is bound to proteins in supplements (chelated iron) to treat iron deficiencies in animals. There are several forms of injectable iron (iron dextran, iron dextrin, iron sorbitol, ferric ammonium citrate) and several chelated forms of iron. Chelated iron is almost as effective in treating iron deficiencies as other

salts are but is about a fourth as toxic.^{1,2,4} Product labels do not always indicate if the iron is chelated. Most products that contain iron have it in a salt form. *Table 1* lists several iron salts and the percentage of elemental iron in each.

Iron absorption

Iron absorption is a two-step process. First, iron ions are absorbed from the intestinal lumen into mucosal cells. Ferrous iron is better absorbed than ferric iron because ferric iron precipitates out of solution at around pH 7 or under normal physiologic conditions.⁷ However, both forms can be absorbed if they are ionized.^{1,2,5} Because iron must be ionized to be absorbed, metallic iron and iron oxide (rust) are not generally of concern when they are ingested.^{1,2}

Most iron absorption occurs in the duodenum and upper jejunum, but in animals with iron toxicosis, the iron seems to be well-absorbed along all parts of the intestinal tract.^{1,2,5,6} A diet high in sugar and vitamin C increases iron absorption, while a high-phosphate diet reduces iron absorption.^{1,2,4,5} But in acute overdoses, the iron seems to be absorbed in a passive, concentration-dependent fashion, similar to how most other metals are absorbed.

Second, iron is transferred to ferritin or into circulation bound to transferrin proteins. Transferrin is an alpha₁-globulin produced in the liver.^{1,2,7} Complexed with transferrin, iron is distributed to other iron storage locations in the body. A unique feature of iron metabolism is the almost complete absence of iron excretion. Any iron lost from hemoglobin degradation is rapidly bound to transferrin and transported to the bone marrow for the resynthesis of he-

signs. When the amount of elemental iron ingested is greater than 60 mg/kg, serious clinical signs can develop.² In all animals, oral doses between 100 and 200 mg/kg are potentially lethal.^{2,4}

Clinical signs

Iron toxicosis manifests clinically in four stages. The first stage occurs in the six hours after an iron overdose. It is marked primarily by gastrointestinal effects, such as vomiting, diarrhea, and gastrointestinal bleeding.^{2,4,6} The greatest mucosal damage occurs on an empty stomach. Most animals with mild to moderate iron toxicosis do not progress beyond this stage.⁵

The second stage occurs six to 24 hours after the overdose. This is referred to as a *latent period*, a period of apparent clinical recovery. In animals with severe iron toxicosis, this recovery period is transient and soon progresses to the third stage.²

The third stage of iron toxicosis occurs about 12 to 96 hours after the initial clinical signs develop. This stage is marked by lethargy, a recurrence of gastrointestinal signs, metabolic acidosis, shock, hypotension, tachycardia, cardiovascular collapse, coagulation deficits, hepatic necrosis, and possibly death.^{2,5,6}

The fourth stage, which may occur two to six weeks after the iron overdose,^{2,5} is when animals that had gastrointestinal ulcerations and survived are healing. As these ulcerations heal, scarring occurs and strictures may develop. Even animals that had only gastrointestinal irritation in the first stage of iron toxicosis are at risk of developing strictures.²

Other abnormalities noted when iron overdoses occur are dehydration, hypovolemia, anemia, evidence of hepatic necrosis (elevated alanine transaminase and aspartate transaminase activities), and liver failure (hypoglycemia, hyperammonemia).^{2,5} In addition, iron toxicosis causes coagulation disturbances that are related to thrombocytopenia, hypoprothrombinemia, and impaired clotting

factor synthesis.⁵ In people, the presence of hyperglycemia and leukocytosis often indicates a serum iron concentration of greater than 30 µg/dl.² Finally, iron toxicosis results in several central nervous system signs. Often these signs result from effects on other cellular processes. For example, metabolic acidosis and hepatotoxicity can lead to other signs such as lethargy and hepatic encephalopathy.⁵ Other central nervous system signs that occur are comas, seizures, and tremors.^{1,2,5}

Diagnosis

Testing an animal's serum iron concentration is the best method to confirm iron poisoning. It is also beneficial to measure total iron-binding capacity, although neither test alone is sufficient to determine whether treatment is needed. Most human hospitals offer serum iron concentration and total iron-binding capacity testing, but not all veterinary clinical pathology laboratories do.

Since the normal serum iron concentration and normal total iron-binding capacity can vary from animal to animal, it is best to measure both and correlate the test results with clinical observations. Serum iron concentrations can change dramatically during the first few hours after ingestion, so repeat the serum iron test four to six hours after initial measurement. When the serum iron concentration exceeds the total iron-binding capacity or the serum iron concentration is greater than 500 µg/dl, severe systemic effects can be expected. Normal serum iron-binding capacity is usually about 25% to 30% saturated.² Every laboratory is different, but an example of how the serum iron concentration and total iron-binding capacity results are reported is $Fe = 134 \mu\text{g/dl}$ and total iron-binding capacity = $436 \mu\text{g/dl}$, or $134/436 \times 100 = 30.7\%$ saturated.

Obtaining multiple blood samples to test serum iron concentrations may be indicated, especially when the total

iron dose is unknown or the animal is symptomatic. An abdominal radiographic examination can be useful to identify metallic objects since iron tablets are radiopaque.^{2,5}

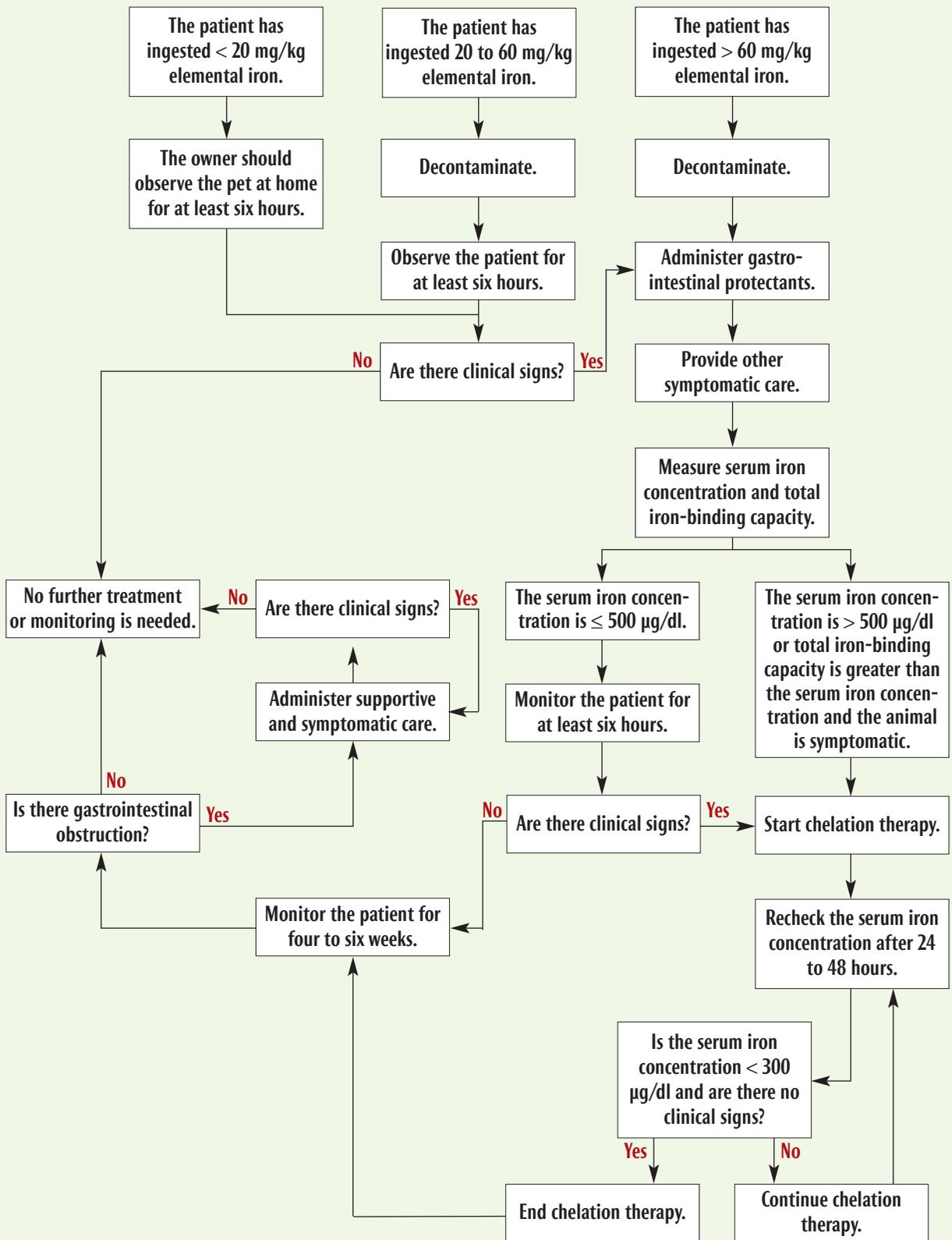
Treatment

A protocol for treating iron toxicosis is described in *Figure 1*. Animals that have recently ingested large doses of iron will benefit from gastrointestinal decontamination. In animals that can vomit, induce emesis with 3% hydrogen peroxide (1 to 5 ml/kg orally), apomorphine hydrochloride (0.03 mg/kg intravenously, 0.04 mg/kg intramuscularly), or other appropriate emetics.⁸ Gastric lavage can be performed on anesthetized animals, although it may not be effective if large pills are involved or if the pills adhere to gastric mucosa. Place a cuffed endotracheal tube to prevent aspiration of lavage material.² In a recent study, activated charcoal adsorbed ferrous sulfate solution at a pH environment consistent with that of the duodenum.⁹ It has been suggested that iron can be precipitated to a nonabsorbable form in the digestive tract by using sodium phosphate, sodium bicarbonate, or magnesium hydroxide; however, the clinical significance of this therapy is questionable.^{2,4,6}

Restoring fluids, electrolytes, and acid-base balance is essential to successfully treating iron toxicosis. Fluids are also needed to prevent hypovolemic shock. Administer fluids based on the animal's maintenance and replacement needs.² Monitor electrolytes, and correct any abnormalities. Administering gastrointestinal protectants such as sucralfate, cimetidine, misoprostol, or other inhibitors of gastric acid secretion may also be helpful.^{2,10}

Chelation therapy is indicated in animals at risk of or showing clinical signs of severe iron toxicosis. This includes animals that ingest more than 60 mg/kg of elemental iron, animals that have a total iron-binding capacity that is greater

Management of Iron Toxicosis



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Zeniquin[®] (marbofloxacin)

Tablets
For oral use in dogs and cats only
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Federal law prohibits the extralabel use of this drug in food-producing animals.

DESCRIPTION: Marbofloxacin is a synthetic broad-spectrum antibacterial agent from the fluoroquinolone class of chemotherapeutic agents.

INDICATIONS: ZENQUIN (marbofloxacin) tablets are indicated for the treatment of infections in dogs and cats associated with bacteria susceptible to marbofloxacin.

EFFECTIVENESS CONFIRMATION: Clinical effectiveness was confirmed in bacterial skin and soft-tissue infections in dogs and cats and urinary tract infections (pyelitis) in dogs associated with bacteria susceptible to marbofloxacin.

DOSEAGE AND ADMINISTRATION: The recommended dosage for oral administration to dogs and cats is 1.25 mg marbofloxacin per lb of body weight, once daily, but the dosage may be safely increased to 2.5 mg/lb.

For the treatment of skin and soft-tissue infections, ZENQUIN tablets should be given for 2-3 days beyond the cessation of clinical signs for a maximum of 30 days. For the treatment of urinary tract infections, ZENQUIN tablets should be administered for at least 10 days. If no improvement is noted within 5 days, the diagnosis should be re-evaluated and a different course of therapy considered.

DRUG INTERACTIONS: Compounds (e.g., succinylate, anilids, and mineral supplements) containing chelating and irritant cations (e.g., iron, aluminum, calcium, magnesium, and zinc) can interfere with the absorption of quinolones which may result in a decrease in product bioavailability. Therefore, the concurrent oral administration of quinolones with foods, supplements, or other preparations containing these compounds should be avoided.

CONTRAINDICATIONS: Marbofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested, the dog being particularly sensitive to this side effect. Marbofloxacin is contraindicated in immature dogs during the rapid growth phase (small adult medium breeds up to 8 months of age, large breeds up to 12 months of age, and giant breeds up to 18 months of age). Marbofloxacin is contraindicated in cats under 12 months of age. Marbofloxacin is contraindicated in dogs and cats known to be hypersensitive to quinolones.

PRECAUTIONS: Quinolones should be used with caution in animals with known or suspected central nervous system (CNS) disorders. In such animals, a seizure may occur, in rare instances, have been associated with CNS disorders which may lead to convulsive seizures. Quinolones have been shown to produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. The use of fluoroquinolones in cats has been reported to adversely affect the retina. Such products should be used with caution in cats. The safety of marbofloxacin in animals used for breeding purposes, pregnant, or lactating has not been demonstrated.

HUMAN WARNINGS: For use in animals only. Keep out of reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation persists following proper dermal exposure. Irritation may occur in a history of hypersensitivity to fluoroquinolones should avoid this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight.

ADVERSE REACTIONS: The following clinical signs were reported during the course of clinical field studies in dogs receiving marbofloxacin at dosages up to 2.5 mg/lb/day: decreased or loss of appetite (5.4%), decreased activity (4.4%), and vomiting (2.9%). The following signs were reported in less than 1% of cases in dogs: increased thirst, soft stool/diarrhea, behavioral changes, shivering/shaking/tremors, and alopecia. One dog which had a seizure the day before study enrollment experienced a seizure while on marbofloxacin therapy.

The following clinical signs were reported during clinical field studies in cats receiving 1.25 mg/lb/day: diarrhea (2.1%) and soft stool (1.4%). Vomiting was reported in less than 1% of cases in cats.

HOW SUPPLIED: Marbofloxacin is supplied in 25 mg, 50 mg, 100 mg, and 200 mg scored, coated tablets.

STORAGE CONDITIONS: Store below 30°C (86°F).

For a copy of the Material Safety Data Sheet (MSDS) call 1-800-733-5500. To report adverse reactions call Pfizer Animal Health at 1-800-352-5225.

NADA #141-151, Approved by FDA

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Toxicology Brief

continued

than the serum iron concentration, or animals that have a serum iron concentration greater than 500 µg/dl. Deferoxamine mesylate (Desferal—Novartis Pharmaceuticals), the chelator of choice for excessive iron in the body, is the only chelator available that seems to be effective at reducing serum iron concentrations. The recommended dosage of deferoxamine is 40 mg/kg given intramuscularly every four to eight hours. Alternatively, give deferoxamine as a continuous infusion at the rate of 15 mg/kg/hr. Continue chelation therapy until the serum iron concentrations decrease below 300 µg/dl and the clinical signs resolve. Often, iron toxicosis requires two or three days of chelation therapy.^{2,4,5} Deferoxamine causes reddish-colored urine, which indicates free iron is being excreted. In people, deferoxamine therapy is continued until the urine color returns to normal.⁶ Deferoxamine has not been reported to cause iron deficiency.

Calcium EDTA has also been used to reduce serum iron concentrations but has not been shown to reduce mortality in cases of acute iron poisoning. An experimental iron chelator, N, N'-bis(2-hydroxybenzyl) ethylenediamine-N, N'-diacetic acid monosodium salt (NaHBED), has been used to successfully treat iron overdoses in dogs and monkeys and was shown to be about twice as effective as deferoxamine and with fewer side effects.¹¹ If NaHBED is approved for use in people, it may also become an alternative iron chelator for animals.

Monitoring and prognosis

Monitor all treated animals for four to six weeks for evidence of gastrointestinal obstruction.² Once signs of iron toxicosis have developed, the prognosis is guarded.

Severe iron poisoning requires a lot of time and effort to treat effectively. Thus, treatment can become costly. In addition, it is often difficult to obtain

deferoxamine. If the serum iron concentration exceeds 500 µg/dl and a chelator is unavailable, the prognosis is poor.

Prevention is the best treatment for iron toxicosis. Teaching owners about the dangers of iron toxicosis and the importance of keeping all medications, multivitamins, and iron supplements out of reach of animals will help avoid serious injury.

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