ABSTRACT: Cases of zinc toxicosis in domestic animals are often characterized by specific clinical and laboratory findings but are often misdiagnosed as cases of autoimmune hemolytic anemia. This article reviews the pathophysiology of zinc toxicosis in small animals and highlights key diagnostic and treatment facts. Early diagnosis and treatment of zinc toxicosis can result in a favorable outcome in small animal patients.

Zinc is a ubiquitous trace metal that exists in many forms in nature. It can be found in everything from foodstuffs to snake venom. Zinc plays an essential role in many biologic processes, including carbohydrate metabolism and protein synthesis. It is responsible for the proper functioning of over 70 metalloenzymes, including alkaline phosphatase, carbonic anhydrase, carboxypeptidase, and various dehydrogenases.

Common sources of zinc in the environment may include batteries, wood preservatives, paints, zinc-oxide creams, zippers on clothing and luggage, board-game pieces, herbal supplements, the coating on some galvanized cookware, and screws or nuts used to secure the lids on pet carriers. Zinc phosphide rodenticides are not a significant source of zinc but are toxic nonetheless, likely due to the phosphine that is released on ingestion. One of the most well-known sources of zinc that has caused zinc toxicosis following ingestion in both humans and animals is the U.S. Lincoln penny.

The metallic form of zinc is essentially nonreactive. However, inhalation of zinc fumes or dust results in chemical pneumonitis (referred to as metal fume fever in humans), and ingestion of some forms of zinc causes formation of highly toxic and corrosive soluble zinc salts in the acidic environment of the stomach. Zinc toxicity has been well documented in humans and has been reported in ferrets, sheep, cattle, dogs, horses, pigs, birds, and various species of wildlife. The number of cases of zinc toxicosis in the veterinary literature is biased toward dogs, possibly because of a higher degree of indiscriminate eating behavior.

PHARMACOKINETICS

The absorption of zinc is influenced by many factors. Specifically, on inges-
The History of Zinc in the Penny

The history of the composition of the penny over the past century provides insight into the role of this coin as a potentially toxic source of zinc. From 1909 through 1942, the penny was composed (by weight) of 95% copper, 4% zinc, and 1% impurities (mostly lead and iron). In 1943, copper resources were needed for ammunition during World War II, so the U.S. Treasury Department issued a zinc-coated steel cent. From 1944 to 1946, pennies were manufactured from spent shell casings and consisted roughly of 95% copper, 4% zinc, and 1% impurities. In 1962, some of the impurities were removed and the zinc content of the cent was increased to 5%. In 1983, the rising cost of copper prompted the U.S. government to reformulate the penny. Some of the pennies minted during 1983 and all pennies minted after 1983 contain a zinc alloy core covered by a pure copper plating. These copper-clad pennies are approximately 96% zinc, 2.5% copper, and 1.5% impurities (lead, iron, and aluminum).

Absorption of the metallic form of zinc, the low pH of the gastric environment promotes the formation of soluble zinc salts, which are absorbed from the duodenum. When absorbed, approximately one third of the zinc in blood is bound tightly to protein, specifically albumin and β2-macroglobulin. Zinc is then rapidly distributed to various tissues throughout the body. In both humans and animals, zinc accumulates in many tissues; the liver, kidneys, prostate, muscles, bones, and pancreas accumulate some of the highest concentrations. Zinc is primarily excreted through the feces, with pancreatic secretions accounting for one quarter of the total amount excreted. Excretion through urine, bile, and saliva occurs to a lesser extent.

TOXIC EFFECTS

The median lethal dose \( (LD_{50}) \) of zinc salts in animals is approximately 100 mg/kg, and diets containing dietary zinc levels in excess of 2000 ppm can cause chronic zinc toxicosis in many domestic species. Zinc salts have direct irritant and corrosive effects on tissue. The effects are most severe when the gastric mucosa ulcerates secondary to the presence of chronic gastric zinc foreign bodies. Zinc also has the ability to interfere with the normal metabolism of other ions (e.g., copper, cadmium, calcium, iron) and thus alter normal metabolic pathways in various tissues throughout the body. The mechanisms by which zinc exerts these toxic effects are not completely understood.

The most common clinically recognized effect of zinc toxicosis is anemia (usually hemolytic), which is believed to be caused by the inhibition of normal red blood cell (RBC) production and function. It is known that zinc interferes with iron and copper metabolism, thereby directly affecting hematopoiesis. Also, it has been suggested that RBC fragility may be influenced as a consequence of zinc toxicosis. Although the exact mechanisms for this have not been fully elucidated, it has been hypothesized that zinc toxicosis results in RBC hemolysis through direct inhibition of RBC enzymes, direct
damage to RBC membranes, or hapten-induced immune destruction. These effects may be species specific. In addition, a scenario has been proposed in which zinc may indirectly promote RBC damage through the inhibition of enzymes that normally protect RBCs from oxidative damage, notably glutathione reductase or enzymes of the hexose monophosphate shunt. This may help explain the presence of Heinz body anemia in some cases of zinc toxicosis.

**CLINICAL SIGNS**

Clinical signs of zinc toxicosis can vary based on the duration and amount of exposure. Typically, initial signs include anorexia and vomiting, followed by lethargy, diarrhea, and dark red or brown urine (secondary to hemoglobinuria). The primary presenting complaint is often port wine–colored urine. Halitosis can also be present as a consequence of the corrosive effect of chronic gastric zinc foreign bodies. Signs of advanced zinc toxicosis can include pale membranes, icterus, lameness, polyuria, polydipsia, exophthalmia, and seizures. Cardiac murmurs may also be present due to anemia.

**LABORATORY FINDINGS**

**Blood Work and Urinalysis**

Changes on serum chemistry, CBC, and urinalysis often correlate with the damage that zinc causes to various organ systems. Some of these changes are the result of biochemical pathway alterations within the RBCs. Prehepatic bilirubinemia from acute intravascular hemolysis causes an increase in unconjugated bilirubin, leading to icterus. Anemia, hemoglobinemia, and hemoglobinuria also occur as a result of hemolysis. Hemoglobinemia precedes hemoglobinuria and causes the serum to be discolored pink or brown. Centrifuging the urine will differentiate between hemoglobinuria and hematuria because the discoloration of the urine will not spin out in the case of hemoglobinuria.

Elevated levels of alkaline phosphatase and transaminases can result from hepatocellular damage, and increased amylase and lipase can be induced by the resultant pancreatitis and pancreatic necrosis. As seen in various types of heavy metal intoxications, elevations in blood urea nitrogen, creatinine, amylase, and urine protein can occur as a consequence of renal tubular epithelial necrosis and glomerular damage. Tubular epithelial cell necrosis can occur secondary to intratubular obstruction by heme pigments or as a result of direct toxic damage of zinc to tubular epithelial cells. Casts may also be present in the urine.

A hemogram often reveals a regenerative hemolytic anemia highlighted by polychromasia, anisocytosis, reticulocytosis, spherocytes, nucleated RBCs, target cells, Heinz bodies, and basophilic stippling (also seen in cases of chronic lead toxicosis). A leukogram may show neutrophilic leukocytosis for a variety of reasons, including physiologic stress, pancreatitis, hepatocellular changes, and regenerative bone marrow. Monocytosis may also be present.

As part of the discussion on hematologic changes in cases of zinc toxicosis, a note should be made regarding the use of the direct antiglobulin test, also known as the direct Coombs' test, to rule out a primary autoimmune disorder. In this test, specific antiglobulin is used to detect antibodies or complement attached to RBC membranes as a result of a primary autoimmune disorder or a secondary immune-mediated process. The medical literature reminds us that the hematologic similarities between autoimmune disorders and zinc toxicosis can contribute to the misdiagnosis of a primary autoimmune disorder and may lead to the inappropriate use of immunosuppressive drugs. The assumption that primary autoimmune disease can be eliminated by the direct Coombs' test is inaccurate. Considering how the test works, zinc toxicosis can cause a positive outcome in the absence of a primary autoimmune disorder. This may occur due to nonspecific adsorption of serum proteins to the damaged RBCs in zinc-toxic patients. Also, it may be possible for zinc to interact with RBC surface proteins and induce an immune response by altering the antigenic determinants on those RBCs. Thus zinc toxicosis can induce an immune-mediated hemolytic anemia that is not a primary autoimmune disorder requiring immunosuppressive therapy. Positive direct antiglobulin test results, therefore, do not necessarily indicate the presence of a primary autoimmune disorder and the need for immunosuppressive drugs.

Additional consequences of zinc toxicosis include alterations in both the coagulation cascade and cardiac conduction. Prolongation of blood coagulation profiles, including prothrombin time and activated partial thromboplastin time, may be the result of either direct or indirect effects of zinc on specific coagulation factors and/or the synthesis of these factors by the liver. Possible mechanisms to explain the cardiac arrhythmias include a direct effect of zinc or free hemoglobin on the myocardium, the release of inflammatory mediators (e.g., tumor necrosis factor) from an inflamed pancreas, or myocardial hypoxia secondary to anemia.
Histopathologic findings in cases of zinc toxicosis have included acute hepatocellular centrolobular necrosis with hemosiderosis and vacuolar degeneration, pancreatic duct necrosis with fibrosis and interlobular fat necrosis, gastrointestinal (GI) hyperemia and serositis, alveolar edema, and mineralization of both alveolar septa and tracheal cartilage (secondary to renal tubular epithelial necrosis). 10,12,13,18

DIAGNOSIS
Radiographic identification of radiodense material in the intestinal tract (especially the stomach; Figures 1 and 2) should raise a very strong suspicion of zinc toxicosis in animals exhibiting any of the clinical signs previously discussed. Also, since animals that ingest pennies are at risk for ingesting other foreign material, thoracic and pharyngeal films should be considered to evaluate the entire GI tract for evidence of other foreign bodies that may need to be addressed.

A definitive diagnosis of zinc poisoning can be made by documenting elevated levels of zinc in tissue, specifically blood. Serum zinc levels are reliable and readily quantifiable using atomic absorption spectrophotometry. The normal serum zinc level in dogs and cats is 0.7 to 2 µg/ml. 15 Techniques to measure zinc levels from saliva and hair have not been fully validated in domestic animals. Also, measuring zinc concentrations in urine may not provide an accurate measure of toxicity since the elimination of zinc via that route is variable and often minimal.

It is important to note that tubes and syringes free of trace elements should preferably be used for sampling because the grommets on older plastic syringes and the rubber stoppers on certain blood collection tubes may contain zinc stearate in their lubricants. 23 Some silicon-coated tubes may also leach zinc. 28 Ideally, serum samples should be submitted in royal blue–top trace element tubes, although some laboratories accept serum in green-top heparinized tubes, which are commonly found in veterinary facilities. Your diagnostic laboratory can provide further information regarding proper blood collection and handling, particularly in reference to exotic species.

Other causes of hemolytic anemia to be ruled out include tick-borne disease (Babesia canis, Ehrlichia canis), primary (autoimmune) and secondary immune-mediated disorders, acetaminophen toxicity, mothball toxicity (naphthalene and paradichlorobenzene), allium toxicity (chive, garlic, leek, onion, shallot), toxicity from other metals (lead, copper) or drugs (especially sulfa-containing compounds, cephalosporins, methimazole), hypophosphatemia, neoplasia (hemangiosarcoma, lymphosarcoma, malignant histiocytosis), splenic torsion, infectious disease (hemobartonellosis, heartworm disease, leptospirosis, feline leukemia virus infection), phosphofructokinase deficiency, and pyruvate-kinase deficiency.

TREATMENT
Successful treatment of zinc toxicosis relies on removal of the source as early as possible. This often requires surgical or endoscopic retrieval of the foreign metal. Stabilization before administering anesthesia is essential. It is important to remember that activated...
charcoal does not bind zinc in appreciable amounts to justify its use as an effective method of decontamination. Also, although the induction of emesis to remove gastric zinc foreign bodies may occasionally be successful, this should be carefully considered, particularly in cases of chronic zinc intoxication. Because many animals with zinc toxicity have already vomited before presentation, inducing emesis may not be a realistic method of decontamination. Also, because zinc foreign bodies are corrosive and adhere to the gastric mucosa, additional vomiting may not be productive and may even exacerbate existing gastritis and/or potentially predispose the animal to gastric perforation.

On presentation, animals should be assessed and treated for their anemia accordingly. Supplemental oxygen may be needed based on clinical signs (weak pulse, tachycardia, pale mucous membranes, prolonged capillary refill time, decreased PaO₂). Packed RBC transfusions (10 ml/kg) after blood typing (and cross-matching if necessary) may be indicated to treat cases of severe anemia. Oxyglobin® (Biopure; 15 ml/kg in dogs; 2 to 5 ml/kg in cats; give slowly without exceeding 10 ml/kg/hr) can be used as an alternative to packed RBCs. Fresh-frozen plasma (10 ml/kg) should be considered for animals with evidence of acute pancreatitis and/or a coagulopathy (petechiation, prothrombin time/activated partial thromboplastin time prolonged more than 25%) that can occur secondary to zinc toxicity. Fresh-frozen plasma provides clotting factors for coagulopathic animals and acute-phase proteins to bind and inactivate the damaging proteases that are released into circulation from the pancreas in animals with acute pancreatitis secondary to zinc intoxication. Because pancreatitis can precipitate coagulopathies, animals with pancreatitis or a coagulopathy can be given fresh-frozen plasma incubated with heparin (75 U/kg) to promote antithrombin III activity in an attempt to minimize hypercoagulation. In cases with severe anemia and concomitant pancreatitis and/or coagulopathy, whole blood (10 ml/kg) can be administered instead of packed RBCs and fresh-frozen plasma.

Diuresis with a balanced crystalloid solution (NaCl, lactated Ringer’s solution) is indicated to address dehydration, prevent hemoglobinuric nephrosis, and promote renal excretion of zinc. A twice-maintenance fluid rate (approximately 130 ml/kg/day) should be considered. When possible, echocardiography is indicated to document that an existing heart murmur is the result of anemia and not primary cardiac disease. Thoracic radiographs can also be taken to look for the presence of primary cardiac disease (cardiomegaly, pulmonary edema, pleural effusion, enlarged pulmonary vasculature).

The use of H₂ blockers to reduce gastric acid output is indicated to decrease the release of zinc salts in cases with gastric zinc foreign bodies. Sucralfate (1000 mg tid for dogs over 20 kg, 500 mg tid for dogs under 20 kg, and 250 mg tid for cats) may also be beneficial in coating areas of gastric ulceration.

Phenothiazines, such as chlorpromazine (0.2 to 0.5 mg/kg IM q6–8h) and prochlorperazine (0.13 mg/kg IM q6–8h), can be used to help suppress vomiting. The use of metoclopramide as an antiemetic should be used judiciously, particularly if there is suspicion of GI obstruction (metoclopramide is dosed at 0.1 to 0.5 mg/kg IV/IM/SC tid or 1 to 2 mg/kg/day constant-rate infusion).

There has been debate over whether chelation therapy is necessary in cases of zinc toxicity. Although animals may recover from zinc intoxication following only supportive care and removal of the source, chelation therapy may enhance elimination of the toxic metal from the body. Compounds used to attempt to chelate zinc include calcium disodium ethylenediaminetetraacetate (CaEDTA), d-penicillamine, and dimercaprol (British antilewisite). Succimer (dimercaptosuccinic acid) is not an effective chelator of zinc but will appropriately chelate lead, mercury, and arsenic. Certain precautions should be taken when initiating certain chelation protocols, particularly in compromised animals. For example, crystalloid support should be provided during treatment with chelators (particularly CaEDTA).
and dimercaprol) to minimize any potential toxic effects of the chelating agents on the kidneys. Also, there is question as to whether chelators can be detrimental because of their ability to bind essential metals other than zinc in the body. This has led to debate over the appropriate duration of chelation therapy. Clearly, the benefits of adding a chelator need to be weighed against possible deleterious effects. CaEDTA is the most commonly used chelating agent and is dosed at 100 mg/kg SC (diluted) divided into four doses per day. In small animals, dosages for D-penicillamine and dimercaprol have not been specifically validated for cases of zinc toxicosis, but suggestions include 110 mg/kg/day for 7 to 14 days and 3 to 6 mg/kg tid for 3 to 5 days, respectively. Although the most appropriate duration of chelation therapy is unclear, it is reasonable to continue until serum zinc levels are normal or near normal.

Finally, complete treatment of any case of zinc exposure must include elimination of the environmental exposure.

MONITORING

Monitoring in cases of zinc toxicosis should include heart rate, respiratory rate, temperature, electrocardiogram results, blood pressure results, hematocrit results, reticulocyte count, electrolyte levels, serum chemistries (including blood urea nitrogen, creatinine, and lipase), urine-specific gravity, urine protein:creatinine ratio (to monitor for protein-losing nephropathy secondary to renal tubular epithelial necrosis and glomerular damage), and zinc level. It is prudent to consider monitoring the serum zinc level during therapy (as well as several days after) for potential mobilization of zinc deposits from various tissues.

SUMMARY

Zinc toxicosis is not uncommon in domestic animals. If diagnosed early and treated aggressively, the prognosis is often favorable. The direct antiglobulin test (direct Coombs’ test) is not reliable in ruling out primary autoimmune hemolytic anemia in cases of zinc toxicosis. Early removal of the source of zinc is essential, and chelation therapy can be carefully considered to help eliminate excess zinc from the body. Elimination of the environmental exposure is important in preventing recurrence.

REFERENCES


ARTICLE #5 CE TEST

The article you have read qualifies for 1.5 contact hours of Continuing Education Credit from the Auburn University College of Veterinary Medicine. Choose the best answer to each of the following questions; then mark your answers on the postage-paid envelope inserted in *Compendium*.

1. The main route of zinc excretion is through  
   a. feces. c. tears.  
   b. urine. d. saliva.

2. Potential sources of zinc in the environment include  
   a. screws used to secure the lids on pet carriers.  
   b. pennies minted during 1943 and after 1982.  
   c. board-game pieces.  
   d. all of the above.

3. The LD$_{50}$ of zinc in most domestic species is _____ mg/kg.  
   a. 50  
   b. 100  
   c. 200  
   d. none of the above

4. Histopathologic findings in cases of zinc toxicosis in animals include  
   a. hepatocellular necrosis.  
   b. pancreatic duct necrosis.  
   c. a and b  
   d. none of the above.

5. Which statement regarding zinc toxicosis is true?  
   b. Cardiac arrhythmias are not a finding in animals.  
   c. The direct antiglobulin test (direct Coombs’ test) uses antiglobulin to detect antibodies or complement on leukocytes.  
   d. Methods of sample collection and submission can influence measurement of serum zinc levels.

6. Which of the following is not an effective chelator of zinc?  
   a. British antilewisite  
   b. dimercaptosuccinic acid  
   c. D-penicillamine  
   d. CaEDTA

7. Which clinical sign can characterize the early phase of zinc toxicosis?  
   a. vomiting  
   b. anorexia  
   c. lethargy  
   d. all of the above

8. Which statement regarding zinc toxicity is false?  
   a. Intravascular hemolysis can occur in cases of zinc toxicosis.  
   b. The direct antiglobulin test (direct Coombs’ test) reliably rules out autoimmune hemolytic anemia in cases of suspected zinc toxicosis.  
   c. Zinc intoxication has been reported in humans, domestic animals, and wildlife.  
   d. H$_2$ blockers help decrease the release of zinc salts from gastric zinc foreign bodies.

9. The mechanism of RBC lysis secondary to zinc toxicosis  
   a. has not been fully elucidated.  
   b. is explained only by direct damage to RBC membranes.  
   c. has been proven to be the same for all species.  
   d. occurs exclusively in the extravascular space.

10. Successful decontamination in cases with gastric zinc foreign bodies should include  
    a. multiple-dose activated charcoal.  
    b. induction of vomiting until the gastric foreign body is retrieved.  
    c. surgical or endoscopic removal once the patient is stabilized.  
    d. none of the above.