Lead and Zinc Intoxication in Companion Birds

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Abstract: *Although the toxicity of lead and zinc to birds is widely recognized by veterinarians and bird owners, these metals are frequently found in the environments of pet and aviary birds, and intoxications are common. Clinical signs exhibited by intoxicated birds are often nonspecific, which makes early diagnosis difficult. Fortunately, lead and zinc analyses of whole blood and serum or plasma, respectively, are readily available and inexpensive; elevated concentrations can confirm intoxication. Once diagnosed, intoxication can be effectively treated by (1) preventing further exposure, (2) administering chelating drugs, and (3) providing symptomatic and supportive care.*

At a Glance

Metal intoxication is routinely diagnosed in companion birds, although the diagnosis can present a major challenge to the avian practitioner. Companion birds are intelligent, inquisitive, playful animals with a tendency to explore objects with their beak and tongue. They are especially fond of metallic objects, resulting in an increased risk for metal intoxication. Lead and zinc are the metals that most commonly result in clinical disease that requires a specific diagnostic workup and intensive treatment.

Recognition of the toxicity of lead to pet and aviary birds and its subsequent elimination from their environment has likely decreased the incidence of exposure to this metal, although intoxications still occur regularly. However, little information is available to judge the actual incidence of lead intoxication in pet and aviary birds. In one retrospective study over a 5-year period (1987 to 1992) in Boston, 85 cases of lead intoxication were diagnosed in small companion animals.[1] Dogs were the most frequently affected species (n = 53), followed by birds (n = 20; species were not given). The authors noted a steady decline of cases across species, including birds, over the period of the study. In contrast, a search of our diagnostic laboratory database did not show a decline in lead intoxication in psittacines between 1995 and 2005. During this period, an average of 13 cases were diagnosed per year. Recently, several cases submitted to the toxicology laboratory of the California Animal Health and Food Safety Laboratory System involved accidental exposure to atypical lead sources. In one case, an aviary in a large zoo was contaminated with lead from welding activities outside the exhibit, causing intoxication in a group of black parrots.[a]

Over the past 10 to 20 years, an upsurge in zinc poisoning, especially in psittacines, has been attributed to the more common use of galvanized metal for cages and aviaries. This has led to zinc intoxication being called *new wire disease*.[2,3] The increased number of documented zinc intoxications may also reflect pet bird owners' and veterinarians' increased awareness of the risks associated with exposure to galvanized metal. Unfortunately, there is a relative paucity of information in the veterinary and human medical literature regarding the treatment of zinc toxicosis.

Lead

Potential Sources of Exposure

Lead is used in an impressive array of products, from industrial items (e.g., tank linings, radiation shielding) to common consumer products such as paint pigments, inks, ammunition, solder, linoleum, wine bottle foil, lubricants, bearings, ceramics, plastics, electronic devices, fishing gear, jewelry, and small toys.[4,5] Wrappers used for imported candy have been found to

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[a]Personal communication, Dr. Jacqueline Jencek, San Francisco Zoo, 2006.

be printed with lead-contaminated inks.[6] Lead-contaminated soil can also be a source of intoxication for birds.[7,8] However, the most common sources of lead exposure for pet and aviary birds kept in home or cage environments are paint (either from direct ingestion of lead-based paint flakes or secondary to paint dust contaminating the environment) and small, lead-containing household objects.

Because lead is toxic to children and waterfowl, several former uses for lead have been eliminated or curtailed (e.g., paint, gasoline, shot). Lead has not intentionally been added to most paint since 1978, although it has been estimated by the Centers for Disease Control and Prevention that 74% of privately owned US homes built before 1980 still contain hazardous quantities of lead paint.[9] Thus, birds kept in older homes have an increased risk of lead exposure from paint.

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Toxicity

Few studies have determined the acute or chronic toxicity of lead in pet birds. Factors that influence the risk for lead intoxication include the amount and form of lead ingested, species exposed, dietary factors, size of ingested lead particles, and amount of grit in the ventriculus.[5] The duration of retention of lead particles in the GI tract varies among individuals within a given species and between species; birds that rapidly eliminate lead particles are less likely to be intoxicated.[10] Bird species that regurgitate indigestible parts of their diet, such as raptors, are less likely to be intoxicated by lead because they more efficiently remove lead from their ventriculus.[11]

Diets low in protein and calcium increase the toxicity of lead.[12] One study examined the toxicity of a single size 7½ (2.41-mm) lead shot to cowbirds. Three of 10 dosed birds on a natural diet containing wild bird seed and cracked corn died within 24 hours, whereas none of the birds fed a pelleted commercial diet died.[10]

Given the number of variables that can affect the toxicity of lead, the availability of precise toxic or lethal doses is limited. A chronic cumulative lead dose of 2 mg/kg/day is reported to be toxic for ducks.[13]

Kinetics

The bioavailability of ingested lead depends on its form and, to a lesser extent, the physiologic state of the animal (e.g., age). Elemental lead is less bioavailable than inorganic lead salts (e.g., lead acetate) or organic lead (e.g., tetraethyl lead). Elemental lead is relatively insoluble in hard, basic water but is more soluble in acidic water. Therefore, elemental lead is more soluble and relatively more bioavailable in the acidic fluids of the proventriculus or ventriculus of birds.[11] Lead is actively transported across the GI tract through the same transport mechanism used for calcium absorption.[9] This absorption mechanism explains the greater bioavailability of lead in immature, rapidly growing animals with an increased need for calcium compared with adult animals. Irrespective of its form, ingested lead is mostly excreted in the feces without being absorbed.

Approximately 90% of absorbed lead is contained in red blood cells; small amounts are bound to albumin or found in plasma as free lead. Within red blood cells, lead is associated with the cell membrane, hemoglobin, and possibly other cell components.[14] Lead is widely distributed in soft tissue, and bone serves as a long-term storage site. The half-life of lead is multiphasic because of its redistribution within various compartments of the body.[13] For example, the half-life of lead in whole blood is approximately 35 days, whereas in brain tissue, it is approximately 2 years. Lead can persist in bone for years. Enhanced bone remodeling associated with egg laying or dietary calcium:phosphorus abnormalities can increase the release of sequestered lead into the blood and cause adverse effects. Normal

QuickNotes

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bone turnover does not result in a clinically significant release of lead. Absorbed lead can be eliminated via sloughing of renal tubular epithelial cells or in bile or pancreatic secretions.[13]

Pathophysiology

Metal ions play many diverse roles in biologic systems. They serve as charge carriers, intermediaries in catalyzed reactions, and structural elements in the maintenance of protein conformation. Disruption of these functions can affect metal transport, energy metabolism, apoptosis, ionic conduction, cell adhesion, inter- and intracellular signaling, diverse enzymatic processes, protein maturation, and genetic regulation.[15] Lead damages cells primarily through its ability to substitute for several metal ions, especially calcium and zinc, at their binding sites.[15] Lead produces oxidative damage to lipids and proteins as a result of iron release, disruption of antioxidant mechanisms, and direct oxidative damage.[15–17]

The neurotoxicity of lead is most likely due to such diverse mechanisms as lipid peroxidation; excitotoxicity (i.e., cell damage secondary to receptor overstimulation by excitatory neurotransmitters such as glutamate); alterations in neurotransmitter synthesis, storage, and release; alterations in expression and functioning of receptors, such as glutamate and N-methyl-D-aspartate receptors; interference with mitochondrial metabolism and second messenger systems; and damage to astroglia and oligodendroglia.[15]

The mechanism by which lead reduces GI motility is not entirely clear, but it does not appear to be related to an effect on peripheral nerves or calcium flux. Lead-induced GI relaxation may be due to stimulation of adenylate cyclase activity, resulting in increased intracellular cAMP.[18]

Lead causes anemia by increasing erythrocyte fragility, delaying erythrocyte maturation, and inhibiting heme synthesis. Heme synthesis is impaired as a result of inhibition of amin-

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olevulinic acid synthetase, δ-aminolevulinic acid dehydratase (ALAD), coproporphyrinogen decarboxylase, and ferrochelatase.[19]

Clinical Signs of Intoxication

The clinical signs of lead intoxication are primarily related to the effects of lead on the nervous, GI, hematopoietic, and renal systems. The signs vary depending on whether the intoxication is acute or chronic, which, in turn, depends on the amount and form of lead ingested over time. Chronic intoxication is more likely in pet birds as a result of repeated exposure to a source of lead or the slow degradation and release of lead from ingested lead objects. However, death can be acute without premonitory signs.[20] Signs of intoxication can be nonspecific and limited to regurgitation, anorexia, weakness, and weight loss.

Signs related to nervous system impairment include lethargy, wing droop, leg paresis or paralysis, changes in phonation, head tilt, ataxia, blindness, circling, head tremors, and seizures.[11,20] GI signs include regurgitation and decreased motility of the upper GI tract (esophagus, proventriculus, and ventriculus) resulting in impaction and greenish diarrhea that stains feathers around the vent.[11,20] Signs related to hematopoietic impairment can include weakness. Lead causes renal tubular necrosis and renal nephrosis resulting in polyuria, proteinuria, and hematuria.[5] The severity of clinical signs does not always correlate with whole blood lead concentration.

Clinical Pathology

In cases of chronic exposure, a microcytic, hypochromic, regenerative anemia may be present. Characteristic changes noted in mammalian intoxication, such as basophilic stippling and cytoplasmic vacuolization of red blood cells, are generally not noted in birds.[5] Serum lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and creatine phosphokinase (CPK) activities and uric acid concentrations can be elevated.[5,20]

*Quick*Notes

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Pathology

Acute lead intoxication may not cause gross lesions. Splenomegaly can occur secondary to increased removal of damaged erythrocytes.[5] Weight loss, air sacculitis, renal or visceral gout, pale musculature or viscera consistent with anemia, and muscle and fat atrophy have been reported.[11,21] In raptor species, bile stasis consistently occurs and is associated with an engorged gallbladder; viscous, dark-green bile; a greenish appearance to the liver; and bile-stained gastric and intestinal mucosa.[11]

Histopathologic lesions can include myocardial necrosis associated with fibrinoid necrosis of arterioles, hepatocellular necrosis, renal tubular necrosis (with or without characteristic intranuclear inclusion bodies in renal tubular cells), brain edema, peripheral nerve degeneration, and necrosis of ventriculus muscles.[11,13] Hemosiderosis is a common histopathologic finding in some avian species.[16] This may be secondary to intravascular hemolysis or impairment of heme synthesis.[16,20]

Diagnosis

As mentioned, the clinical signs associated with lead intoxication can be nonspecific, making diagnosis difficult. Radiographs may identify metallic objects in the GI tract. However, the absence of metal densities does not rule out metal exposure because the lead may have come from an object that was passed or a nonradiodense form. Diagnosis of lead exposure or intoxication is most directly made by measurement of lead in whole blood samples. Serum and plasma are not appropriate samples for lead analysis because lead associates with red blood cells.

Lead analyses are widely available through veterinary diagnostic laboratories. Fortunately, small sample sizes can be used; blood samples as small as 20 μL are often suitable. In general, any anticoagulant, including EDTA, can be used to prevent samples from clotting, although there may be exceptions to this rule. It is best to consult the laboratory conducting the testing before sample collection. Whole blood lead concentrations consistent with lead exposure or intoxication are generally 0.20 ppm (20 μg/dL) or greater. There are no "normal" background blood lead concentrations in pet birds. ALAD activity, blood zinc protoporphyrin concentrations, and free erythrocyte protoporphyrin concentrations are good biomarkers of lead exposure, but these tests are not widely available.

Postmortem diagnosis depends on a history of compatible clinical signs, detection of metallic particles or other forms of lead in the GI tract, and measurement of liver or kidney lead concentrations. Reported diagnostic liver or kidney concentrations vary, but values of 4 ppm wet weight or greater in either tissue are likely to be significant. There can be significant differences in liver and kidney tissue concentrations in the same bird; consequently, it is often advisable to test both organs.

Case Management

Decontamination approaches include the use of emollient laxatives such as mineral oil, bulk laxatives such as psyllium, or cathartics such as sodium sulfate to promote movement through the GI tract.[5] In theory, sulfate can bind free lead to form an insoluble and, therefore, unabsorbable lead salt.[21] However, use of sodium sulfate in combination with chelators such as calcium disodium EDTA (CaNa$_2$EDTA) or succimer has not been shown to be more effective than using a chelator alone.[21] Administration of three to five pieces of grit of a size appropriate for the bird species affected has been reported to aid in the passage of metal objects from the ventriculus.[20]

Early removal of lead objects in the upper GI tract should be strongly considered because retention of objects is common. Nineteen of 25 cockatiels (72%) given two #12 lead shot to induce lead intoxication retained at least one pellet for 19 days, and 11 of 25 (44%) retained at least one pellet for 26 days.[21] Saline lavage has been successful in removing lead particles from the proventriculus or ventriculus of lead-intoxicated birds.[4,22,23] Endoscopy can be used to remove lead particles entrapped in proventricular or ventricular folds.[23] Proventriculotomy may be necessary if other removal attempts fail. Unfortunately, the removal of small lead fragments using such techniques can be difficult and incomplete.

Chelation Therapy

The mainstay of treatment for lead intoxication is chelation therapy. Several chelators can effectively bind lead, including CaNa$_2$EDTA, succimer, D-penicillamine, and British anti-

Lewisite. CaNa$_2$EDTA and succimer are currently the chelators of choice, although no veterinary-approved forms are available.

There is evidence in mammals that the efficacy of chelation is improved when thiamine or antioxidants (e.g., ascorbic acid) are used in conjunction with chelators.[24–26] This has not been investigated in birds.

CaNa$_2$EDTA

To avoid calcium chelation and resulting hypocalcemia, only the calcium salt of EDTA should be used.[21,27] However, there are three significant disadvantages to the use of CaNa$_2$EDTA. First, it is potentially nephrotoxic,[20] although nephrotoxicity may be due to the metal chelate and not to CaNa$_2$EDTA itself.[28] Also, renal function may already be impaired in lead-intoxicated birds. Unfortunately, the incidence of CaNa$_2$EDTA-associated nephrotoxicity in birds is unknown. Second, CaNa$_2$EDTA must be administered parenterally because oral administration enhances the absorption of lead from the GI tract. However, repeated IM injections in birds can cause significant pain and muscle damage. Third, CaNa$_2$EDTA chelates important endogenous minerals such as zinc.

CaNa$_2$EDTA can be administered in doses of 10 to 40 mg/kg IM or SC bid.[5,20,21] Prolonged use is generally interrupted by intervals of no therapy to avoid adverse effects. The recommended protocol is a 5- to 10-day treatment period followed by a 3- to 5-day "rest" period to allow for a redistribution of tissue and fluid lead concentrations.[29] Assessment of blood lead concentrations at the end of each rest period should dictate the length of chelation therapy. These follow-up tests should not be conducted before the end of the rest period because earlier assessment may not allow sufficient time for remaining lead to redistribute in the body. The goal is to chelate for the minimum amount of time necessary to resolve the intoxication (based on a decline in blood lead to an undetectable concentration). However, 40 mg/kg CaNa$_2$EDTA given IM bid for 21 consecutive days was not associated with adverse effects in experimentally intoxicated cockatiels.[21] The subacute toxicities of CaNa$_2$EDTA

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and succimer were evaluated in experimentally intoxicated domestic pigeons.[30] Doses of CaNa$_2$EDTA up to 270 mg/kg bid (route of administration not indicated) for 15 days were not lethal, although increases in uric acid and AST, LDH, and CPK activities compared with prechelation and control bird (receiving no CaNa$_2$EDTA) values were noted. Due to the potential nephrotoxicity of CaNa$_2$EDTA, periodic assessment of renal function during chelation therapy is recommended.

Neurologic signs may initially worsen in birds treated with CaNa$_2$EDTA.[30] Theoretically, this could be due to CaNa$_2$EDTA-induced mobilization of lead from bone. Thus, birds with chronic lead exposure and potentially higher bone lead concentrations may be more likely to be affected than acutely intoxicated birds. However, this has not been shown experimentally.

Succimer

Succimer (dimercaptosuccinic acid, DMSA) is a newer chelating agent that has several advantages over CaNa$_2$EDTA. It can be given orally, does not increase elimination of other essential minerals, and is not nephrotoxic. However, oral administration can be a disadvantage in a regurgitating bird. Succimer is more effective than CaNa$_2$EDTA at removing lead from soft tissues,[21] and it decreases lead concentrations in the central nervous system more rapidly than CaNa$_2$EDTA.[13] Succimer can be given at 20 to 40 mg/kg bid without adverse effects, although 80 mg/kg bid for 26 days was lethal to a significant percentage of cockatiels in one experimental study.[21] This dose was less toxic in birds with lead intoxication compared with nonintoxicated controls. Unfortunately, days to death were not reported in this study. In contrast, succimer at doses up to 270 mg/kg bid for 15 days was not associated with significant adverse effects in experimentally intoxicated domestic pigeons.[30] The only change noted was an initial increase in uric acid that plateaued by day 3 of dosing.

Succimer should be given orally by gavage or other direct means (i.e., via syringe), although it has been effective when sprinkled on food.[27] As with CaNa$_2$EDTA use, the total length of treatment should be based on clinical

Quick**Notes**

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improvement and determination of blood lead concentrations. The dosage of succimer in birds should not exceed 40 mg/kg PO q12h. Doses as low as 10 mg/kg PO have been suggested as effective.[31] Unfortunately, an optimal dosing protocol has not been determined for birds. Whole blood lead concentration should be determined after a course of chelation to assess the need for additional therapy. If the concentration is still elevated, another course of therapy is indicated. As with CaNa$_2$EDTA, 3 to 5 days should be allowed for the remaining lead to redistribute to obtain an accurate assessment of lead status.

Clinical improvement is likely to be more rapid (within 24 hours) after succimer administration than after CaNa$_2$EDTA.[30] Combining CaNa$_2$EDTA and succimer does not appear to be more efficacious than administering CaNa$_2$EDTA or succimer alone, based on an experimental model of intoxication in cockatiels.[21] **TABLE 1** compares the advantages and disadvantages of CaNa$_2$EDTA and succimer.

Supportive Care

Symptomatic and supportive care is also critical. Seizure control should be attempted using diazepam at 0.5 to 1.0 mg/kg given IM two to three times daily or as needed. Midazolam at 0.1 mg/kg IM controlled seizures in an intoxicated double yellow-headed Amazon parrot.[5] If diarrhea is present, hydration and electrolyte status must be monitored and treated appropriately. Administration of B-complex vitamins and assisted alimentation should also be considered. Fluid support is critical to maintain urine output and to replace increased losses following the use of a cathartic; lactated Ringer's solution can be given subcutaneously.

Zinc
Potential Sources of Exposure

Metallic zinc is commonly used to galvanize metals such as iron and steel to provide a

> Sources of zinc in documented avian zinc toxicoses include galvanized wire and cage bars, zinc-contaminated drinking water, pennies minted after 1982, cage coatings, cage accessories, hardware, and metallic toys.

*Quick***Notes**

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protective coating. Until 1982, pennies consisted mainly of copper (95%) with a small amount of zinc (4%), but the copper-clad pennies minted after 1982 contain 97% zinc and 2.5% copper.[32] Sources of zinc in documented avian zinc toxicoses include galvanized wire[3] and cage bars,[33] zinc-contaminated drinking water,[34] pennies minted after 1982,[35,36] cage coatings,[37] cage accessories, hardware, and metallic toys.[38] Zinc poisoning associated with zinc-coated food containers has been reported in humans but not in birds.[39] Additionally, zinc is found in soil and may be present in high enough concentrations to result in avian poisonings. Zinc is also used in a variety of medical formulations, pigments, wood preservatives, insecticides, and rubber, but toxic exposure to any of these sources has not been reported in birds.

Toxicity

Zinc is an essential metal, and animals and humans regulate zinc effectively. Mammals can tolerate dietary loadings greater than 100 times the minimum recommended daily zinc requirement.[40] Dietary zinc requirements for pet birds have not been established, but most diets for companion birds contain between 70 and 110 ppm (mg/kg) of zinc. Research to establish zinc requirements in birds has focused on chickens and turkeys. For example, the dietary zinc requirement of young broilers is approximately 35 to 40 ppm (mg/kg).[41]

If dietary exposure is excessive and homeostatic mechanisms fail, zinc toxicity can occur. Zinc toxicosis has been reported in numerous animal species, including dogs,[42] calves,[43] chickens,[44] and humans.[39,45] Definite data on the toxicity of zinc in companion birds are lacking, although limited information is available for certain species. In chicks, dietary concentrations of greater than 2200 ppm (mg/kg) zinc are considered toxic.[46] Likewise, in one study, liver zinc concentrations in mal-

TABLE 1 Comparison of CaNa$_2$EDTA and Succimer for the Treatment of Lead and Zinc Intoxications

	CaNa$_2$EDTA	Succimer
Trade names and formulations	Calcium Disodium Versenate (3M); 200 mg/mL	Chemet (Sanofi-Synthelabo); 100-mg capsules
Routes of administration	▸ Slow IV infusion; IM or SC injection ▸ Dilution with saline or 5% dextrose needed if given IV	Oral
Advantages	▸ Rapid absorption ▸ Can chelate lead and zinc	▸ Oral administration ▸ Not nephrotoxic ▸ Does not chelate essential minerals such as manganese and copper ▸ More rapid clinical improvement in lead intoxication ▸ More effective at removing lead from soft tissues
Disadvantages	▸ Need for repeated IM or SC injections ▸ Pain at injection site ▸ Potential nephrotoxicity; need to monitor renal function regularly ▸ Chelation of essential minerals such as zinc, manganese, and copper with long-term use ▸ Potential to worsen central nervous system signs as a result of lead redistribution	▸ Less effective chelation of zinc; efficacy uncertain in zinc intoxication ▸ Regurgitation noted in cockatiels ▸ Potentially narrow margin of safety
Recommended dosage	10 to 40 mg/kg bid; 5- to 10-day treatment intervals interspersed with 3- to 5-day rest periods	20 to 40 mg/kg bid; rest period not essential, but periodic reassessment of lead and zinc concentration is recommended
Toxicity	Doses of up to 270 mg/kg bid for 15 days caused increases in AST, LDH, CPK, and uric acid in domestic pigeons but no other abnormalities[30]	▸ 80 mg/kg bid caused death in cockatiels[21] ▸ 270 mg/kg bid not lethal for domestic pigeons (some increase in uric acid)[30]

AST = aspartate aminotransferase, *CPK* = creatine phosphokinase, *LDH* = lactate dehydrogeriase

lards reached toxic levels when dietary zinc exceeded 3000 ppm (mg/kg).[47] In another study, oral exposure to 16 mg of zinc over a 2-week period resulted in 50% mortality in cockatiels, but even as little as 2 mg of zinc per week proved lethal in some birds.[37] Reported cases of naturally occurring zinc poisoning in birds involved ducks,[36] a Nicobar pigeon,[48] a gray-headed chachalaca,[49] macaws,[33,38,50] lovebirds,[3] and Amazon parrots.[34]

Kinetics

In chickens, zinc is absorbed in the proventriculus and small intestine.[51] The rate of absorption depends on the amount and form of zinc.[52] Once absorbed, zinc is distributed to sites such as the pancreas, liver, kidneys, bones, muscles, brain, retinas, intestinal mucosa, and skin, where it binds to metallothionein, especially in the pancreas, liver, kidneys, intestinal mucosa, and brain. Metallothionein is a low-molecular-weight, cysteine-rich protein that has potent metal-binding capabilities.[53] Zinc has a high binding affinity for metallothionein, which may play an integral role in zinc metabolism.[54] The major route of excretion is via biliary, pancreatic, and gastroduodenal secretions into feces.

Pathophysiology

Zinc is present in more than 200 metalloenzymes and thousands of protein domains.[55] It is essential for bone formation, immune function, keratogenesis, reproduction, growth, vision, wound healing, brain development, normal functioning of the central nervous system, and many other physiologic processes.[56–58]

Major pathophysiologic mechanisms of zinc are attributed to direct and indirect toxic effects on the GI tract, liver, kidneys, pancreas, red blood cells, and brain, but many of the specific underlying mechanisms have not been established. In acute cases of zinc poisoning, local corrosive effects may occur in the GI tract, followed by damage to the liver, kidneys, and pancreas. Zinc has been shown to cause acute pancreatic, hepatic, and renal failure in birds.

In birds, a major concern is chronic zinc toxicosis with resulting anemia. The toxic effects of zinc leading to hemolytic anemia have recently been investigated in mallards.[59] Excess zinc is thought to result in a functional iron deficiency leading to reduced heme synthesis and erythropoiesis. The interaction between zinc and iron may therefore play a major role in the development of anemia in birds overexposed to zinc. In addition, zinc limits copper availability[46] and decreases tissue copper and ceruloplasmin concentrations. Decreased ceruloplasmin concentrations can result in lower availability of iron for hemoglobin synthesis.[59]

Overall, tissue hypoxia can lead to tissue damage in the pancreas, liver, kidneys, and brain. Recently, zinc toxicity has been associated with brain damage that is most likely due to a combination of hypoxic and direct toxic effects.[60]

Clinical Signs of Intoxication

Clinical signs of zinc intoxication in birds are varied and nonspecific. They include lethargy, anorexia, regurgitation, polyuria, polydipsia, hematuria, hematochezia, pallor, dark or bright green diarrhea, foul-smelling feces, paresis, seizures, and sudden death.[33–35,37–59] Zinc toxicosis was associated with sudden death in 7 of 21 psittacine birds evaluated in one study.[61] Therefore, any acute death in a companion bird should be evaluated for possible zinc poisoning. Zinc exposure has been suggested as a cause of feather picking, but there is no evidence to link the two.

Pathology

Common findings on gross examination of birds that have died from zinc toxicosis include greenish, mucoid feces in the ileum, colon, or cloaca and muscle wasting, especially of the pectoral muscles. Occasionally, the liver or kidneys are slightly enlarged. No other consistent lesions are usually noted on gross examination.

In zinc-intoxicated birds, microscopic changes are found in the pancreas, liver, kidneys, and GI tract. Experimental studies and case reports have indicated that the pancreas is the major target organ of zinc toxicity in birds. Histologic and ultrastructural pancreatic lesions include disruption of the normal zymogen granules, atrophy of acinar cells, loss of normal architecture, necrotizing pancreatitis, the presence of hyaline bodies and other electron-dense debris, cellular atrophy and necrosis of individual acinar cells, and interstitial fibrosis.[36,61,62] The pancreatic islets are spared.

Liver lesions vary from hepatic biliary retention and hemosiderosis to multifocal, necrotizing hepatitis.[37,61] Lesions in the kidneys include varying degrees of acute tubular necrosis, occasionally with secondary renal or visceral gout, and moderate interstitial nephritis in addition to nephrosis.[61] GI lesions include intestinal hemorrhage, hemorrhagic enteritis, hemorrhagic ventriculitis, ventricular koilin degeneration, and, in one case, cloacitis.[61]

> When submitting samples for zinc concentration, special care must be taken to avoid contact with rubber products that can be a source of zinc (e.g., rubber-topped tubes) and hemolysis.

Diagnosis

Diagnosis involves a careful history, correlating exposure to items made of zinc with expected clinical signs, a thorough physical examination, radiography, measurement of serum or plasma and tissue zinc concentrations, and blood smear evaluation. The absence of radiographically evident metal densities in the GI tract does not rule out zinc toxicosis in the differential diagnosis because some particles might not be dense enough to appear. A necropsy with complete histologic evaluation should be performed on all birds that have died of a potential metal toxicosis.

In live birds showing clinical signs suggestive of zinc poisoning, serum and plasma samples are considered suitable for zinc determination.[63] For most laboratories, sample volumes of 50 to 100 μL are sufficient for analysis. Special care must be taken to avoid contact with rubber products that can be a source of zinc (e.g., rubber-topped tubes)[64] and hemolysis, which may also increase zinc concentrations. Additionally, zinc concentrations in plasma collected from psittacines show significant diurnal variation, with the highest concentrations detected in morning samples.[65] For most psittacines, the average, physiologic, nontoxic zinc concentration in serum or plasma is at or below 2 ppm (0.2 mg/dL). Cockatoos and eclectus parrots tend to have higher physiologic concentrations of zinc in serum and plasma, with acceptable nontoxic concentrations of up to 3.5 ppm (0.35 mg/dL) for cockatoos and up to 2.5 ppm (0.25 mg/dL) for eclectus parrots.[61] An

assessment of erythrocyte morphology can aid in the diagnosis of zinc poisoning in birds. Observed abnormalities include a greater number of immature red blood cells, hypochromasia, poikilocytosis, and nuclear abnormalities, such as fusiform, elongated, and irregular nuclei.[59]

Postmortem evaluations include gross and histologic examinations along with the determination of zinc concentrations in fresh liver samples. Most companion birds have acceptable liver zinc concentrations of 30 to 70 ppm (mg/kg) wet weight,[61] and liver zinc concentrations of up to 100 ppm (mg/kg) expressed as wet weight are considered nontoxic. Once liver zinc concentrations exceed 100 ppm,[34] zinc poisoning may be present and careful histologic evaluation is necessary for a definitive diagnosis.

Case Management

Unless the patient is severely affected, clinical signs may resolve with supportive care once the source of zinc is removed from the digestive tract or from the bird's environment.[34,36] Removal of metal objects from the upper GI tract can be accomplished with lavage, endoscopy, or surgery or with the use of emollient laxatives or cathartics.[5] In dogs, it has been shown that plasma zinc concentrations decline relatively rapidly once further zinc absorption is prevented.[66] In a puppy with zinc toxicosis caused by ingestion of four pennies, the serum zinc concentration decreased from 28.8 ppm to 16.8 ppm within 24 hours after surgical removal of the pennies. On day 14 after surgery, the serum zinc concentration had dropped to 3.2 ppm with only supportive care. Thus, preventing further absorption of zinc should be the primary goal of therapy and, along with supportive care, may be sufficient for the management of zinc toxicosis.

Removing the source of zinc in a timely manner or in its entirety is not always possible. The limitation of endoscopy is that only larger particles can be removed, while small

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particles may not be visible. In this situation, and in birds showing severe clinical signs, chelation therapy is an important component of treatment for zinc toxicosis.

Chelation Therapy

A variety of parenteral chelating agents are reported to be effective for chelating zinc. The advantages of $CaNa_2EDTA$ include its affinity for zinc[67] and the fact that it reaches therapeutic systemic levels rapidly. $CaNa_2EDTA$ therapy may be indicated to enhance removal of zinc in fragile patients for which anesthesia for endoscopy or surgery is too risky. Chelation therapy with $CaNa_2EDTA$ can be commenced while the bird's condition is stabilized. $CaNa_2EDTA$ must be administered intramuscularly, subcutaneously, or intravenously, as it is poorly absorbed from the GI tract. The recommended dose of $CaNa_2EDTA$ is 40 mg/kg IM q12h for 5 days.[21] While $CaNa_2EDTA$ is a relatively safe agent, renal and GI toxicity may result from long-term therapy.[68] In addition, a series of $CaNa_2EDTA$ chelation therapy sessions may remove essential minerals, such as iron or copper.[69] These effects can have undesirable clinical consequences, especially in birds that are deficient in these elements before chelation treatment. Thus, it is critical to monitor essential minerals in birds receiving $CaNa_2EDTA$ to prevent deficiencies.

Succimer is another heavy metal chelator that may be a suitable alternative to $CaNa_2EDTA$. Use of succimer is relatively new to veterinary medicine,[21] although it has been used for decades in human medicine for the treatment of industrial heavy metal toxicosis and childhood lead toxicosis.[70] Compared with other chelators, succimer is fairly specific for lead, mercury, and arsenic.[71] In mice, succimer is less effective than $CaNa_2EDTA$ but more effective than D-penicillamine for the treatment of zinc toxicosis.[72] The chief advantage of succimer over $CaNa_2EDTA$ is that it can be given orally. However, oral administration can be a disadvantage in a regurgitating bird.

The efficacy and safety of succimer for the treatment of zinc toxicosis has not been investigated in birds. A study in cockatiels with lead toxicosis demonstrated that succimer has a relatively narrow margin of safety (see lead chelation therapy section for details). The most common side effect of succimer therapy in cockatiels was regurgitation. Therefore, based on limited information, the dosage of succimer in birds should not exceed 40 mg/kg PO q12h. While succimer is usually given for 10 days, the length of treatment should be based on clinical improvement and determination of serum zinc concentrations.

Supportive Care

Symptomatic and supportive care is as critical for a bird with zinc toxicosis as it is for a bird with lead intoxication. Hydration and electrolyte status must be monitored regularly and treated appropriately. Lactated Ringer's solution can be given for fluid support. Seizures can be controlled with diazepam (0.5 to 1.0 mg/kg IV or IM) or midazolam (0.1 mg/kg IM).[5] Administration of B-complex vitamins and assisted alimentation should also be considered.

Prevention of Lead and Zinc Intoxication in Companion Birds

The best method of preventing lead or zinc intoxication is to recognize potential sources of exposure and eliminate them from the environment. Most reputable bird cage and toy manufacturers avoid the use of lead and zinc in their products. However, there is always the potential for products to contain toxic metals. Owners of pet birds should inspect their bird's complete environment, carefully evaluate cage and toy materials, and remove materials that may contain lead or zinc. Questionable materials should be tested by a veterinary toxicology laboratory before they are given to birds.

Conclusion

Companion birds continue to be exposed to lead and zinc from their environment, and intoxications are frequently reported. Because of the nonspecific clinical signs associated with lead and zinc intoxication, a comprehensive diagnostic workup is required to establish an accurate diagnosis. Lead and zinc analyses are routinely available at veterinary toxicology laboratories, and results are often available within hours of sample submission. Once a diagnosis is reached, treatment should be initiated as quickly as possible. An important part of treatment is prevention of recurrence. Owners should be advised about the risk of hazardous materials in the birds' environment. C

*Quick**Notes***

The best method of preventing lead or zinc intoxication is to recognize potential sources of exposure and eliminate them from the environment.

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1. Lead toxicity in birds is influenced by all of the following except the
a. form of lead ingested.
b. bird's diet.
c. quantity of grit in the ventriculus.
d. length of the bird's small intestine.

2. Which statement regarding the kinetics of absorbed lead is incorrect?
a. Lead is actively absorbed from the GI tract.
b. Lead in the blood is primarily associated with red blood cells and not plasma.
c. Bone serves as a long-term storage depot for lead.
d. Once absorbed, lead has a half-life of approximately 2 weeks.

3. Which organ or system is not a primary target for lead damage?
a. central nervous system
b. liver
c. hematopoetic system
d. GI system

4. Which statement is true regarding the diagnosis of lead intoxication in birds?
a. Basophilic stippling is a common finding on blood smears from intoxicated birds.
b. Gross and microscopic postmortem lesions are pathognomonic for lead intoxication.

c. Measurement of lead in whole blood samples is critical for a diagnosis of lead intoxication.
d. Measurement of lead in feathers is a useful way to assess lead exposure.

5. Which intervention is not generally indicated when treating a lead-intoxicated bird?
a. remove lead objects that remain in the GI tract at the time of presentation
b. initiate chelation therapy with either succimer or CaNa$_2$EDTA
c. control seizures using benzodiazepines such as diazepam or midazolam
d. administer blood transfusions to correct nonregenerative anemia

6. What is the most common source for zinc poisoning in birds?
a. wood preservatives
b. zinc-coated food containers
c. galvanized cage material
d. pennies minted before 1982

7. Acute zinc poisoning in birds does not result in
a. anemia.
b. corrosive effects in the GI tract.
c. pancreatic damage.
d. liver damage.

8. Which statement is true regarding the diagnosis of zinc intoxication in birds?
a. There is no need to handle serum or plasma samples with special care when evaluating zinc concentrations.
b. Nontoxic serum and plasma zinc concentrations are the same for all psittacines.
c. Zinc concentrations in plasma are highest in morning samples.
d. Toxic zinc concentrations have not been established for birds.

9. Which mechanism is known to contribute to the development of anemia in birds with chronic zinc intoxication?
a. Excess zinc decreases copper availability, leading to decreased ceruloplasmin concentrations.
b. Zinc inhibits heme synthesis by interfering with ALAD.
c. Zinc increases erythrocyte fragility.
d. Zinc delays erythrocyte maturation.

10. Which statement is true with regard to the use of succimer in birds?
a. Succimer must be given IV or IM.
b. Succimer is given orally.
c. Succimer is nephrotoxic.
d. Succimer is not recommended as a chelator for metal toxicoses.