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Clinical Report

Intralipid Emulsion Therapy for the Treatment of Suspected Toxicity in 2 Avian Species

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Abstract: Intravenous lipid emulsion (ILE) therapy has shown promise as a treatment option for a variety of lipophilic toxins. Two birds presented for suspected ingestion of a toxic substance. A blue-and-gold macaw (*Ara ararauna*) presented after chewing a block of bromethalin rodenticide without overt clinical signs at the time of presentation. Additionally, a free-ranging bald eagle (*Haliaeetus leucocephalus*) was found weak and depressed near a municipal landfill after presumptive ingestion of pentobarbital. Both birds were treated with ILE therapy for potential intoxication without any adverse events. The macaw was clinically normal after 3 days of hospitalization and at a 1-week reevaluation. The eagle was transferred to a rehabilitation center after markedly improved mentation and strength and was released 7 days later. Clinicians should consider ILE therapy for the treatment of lipophilic toxicities; however, monitoring is recommended for persistent lipemia and other adverse effects that have been reported in the veterinary literature.

Key words: bromethalin, intralipid, pentobarbital, avian, blue-and-gold macaw, *Ara ararauna*, bald eagle, *Haliaeetus leucocephalus*

CLINICAL REPORT

Case 1

A 4-year-old, intact male, blue-and-gold macaw (*Ara ararauna*) was presented for suspected ingestion of bromethalin-based rodenticide (Tomcat All-Weather Rodent Blocks, Motomco, Madison, WI, USA). An entire rodenticide brick was found broken into pieces after the bird had been unsupervised for several hours; however, the owners could not estimate the amount of the rodenticide brick that was missing. The bird had no prior medical history and was reportedly healthy before this incident. On presentation, the bird was bright and alert, in good body condition (5/9 body condition score, body weight 1.02 kg), and had no overt physiological abnormalities. Basic decontamination treatment was initiated with the administration of activated charcoal without additional sorbitol (30 mL/kg PO, every 2 hours overnight and then intermittently during hospitalization, for a total of 11 doses; ToxiBan Suspension, Vet-A-Mix, Shenandoah, IA, USA) and fluid therapy (60 mL/kg SC, q12h, 3 treatments; lactated Ringer's solution, Hospira, Lake Forest, IL, USA). The bird was monitored overnight for inappropriate neurological status and seizures. Neurological examination performed the next morning found no overt abnormalities.

Although clinically significant toxicity was not evident, treatment with intravenous lipid emulsion

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(ILE) was recommended because of the severe and lethal consequences of bromethalin toxicity reported in psittacine species.[1,2] The bird was sedated with midazolam (2 mg/kg intranasal; midazolam hydrochloride injection, West-Ward [now Hikma], Eatontown, NJ, USA) and butorphanol (1 mg/kg IM; Torbugesic, Pfizer, New York, NY, USA) before anesthetic induction with isoflurane (2% by mask; Fluriso, MWI Veterinary Supply Co, Boise, ID, USA) in oxygen (2 L/min) and then maintained by mask with isoflurane (2–3%) in a 2 L/min flow of oxygen. A 24-g intravenous catheter was placed in the right medial metatarsal vein, and an infusion of ILE (loading dose of 1.5 mL/kg over 20 minutes, followed by 23 mL/kg per hour IV for 60 minutes; Intralipid 20%, Baxter Healthcare Corporation, Deerfield, IL, USA) was administered; dosing was extrapolated from previous treatment recommendations for dogs.[3] An avian restraint collar (Veterinary Specialty Products, Overland Park, KS, USA) was used to prohibit removal of the intravenous catheter. Serum lipemia was monitored by collecting serial hematocrits from the jugular vein and was evident immediately and 2 hours posttreatment but was no longer present thereafter. Plasma and fecal samples were collected ~1 hour before treatment and immediately after treatment and later submitted for analysis of bromethalin and desmethyl-bromethalin concentrations.

Subcutaneous fluid therapy with lactated Ringer's solution was continued for an additional 24 hours after the intravenous catheter was removed, and the bird was maintained in hospital for an additional 48 hours for monitoring. The bird remained alert, active, and neurologically appropriate throughout the course of observation. No additional ILE was administered after the initial treatment. After discharge, the bird returned 5 days later for reexamination. At that time, the owner reported the bird had been reluctant to fly at home and experienced a single episode of imbalance but otherwise was doing well and appeared to have returned to normal. Additional samples of plasma and feces were acquired at that time to measure bromethalin concentrations.

Once all samples were collected, feces and plasma at pretreatment (18–24 hours of potential exposure), at posttreatment (immediately after treatment), and when the bird was reexamined (7 days after potential exposure) were transported to the University of Georgia Infectious Diseases Laboratory (Athens, GA, USA) to measure bromethalin and desmethyl-bromethalin concentrations.[1] All samples were below the limits of detection for both bromethalin and desmethyl-bromethalin (<0.01 μg/g), except for the pretreatment fecal sample that had a bromethalin concentration of 0.04 μg/g.

Case 2

An adult (>5 years old, on the basis of morphological traits), free-ranging, intact male (presumed by size), bald eagle (*Haliaeetus leucocephalus*) was presented for evaluation of generalized weakness. The bird was found near a municipal landfill that was reported to accept euthanatized carcasses. When examined, the bird was in sternal recumbency but able to stand, reactive to stimuli, underconditioned (body condition score 2/5, 3.31 kg), mildly tachycardic (250 beats per minute), and had feather lice. Stabilization was initiated with lactated Ringer's solution (50 mL/kg SC), and the bird was housed in an incubator at 40% oxygen.

Over the next 5 hours, the clinical signs progressed with declining mentation and activity level. The bird was briefly anesthetized with isoflurane (5% by facemask) at an unknown oxygen flow rate and then maintained by facemask with isoflurane (2.5–3%) for phlebotomy for hematologic diagnostic testing and intravenous catheter placement (20 g) in the medial metatarsal vein. A complete blood count (CBC) and serum biochemistry panel were within normal reference ranges. Blood lead concentration (LeadCare II, Meridian Bioscience, Cincinnati, OH, USA) was too low to read (<3.3 μg/dL). The remaining serum was frozen at –80°C for future toxicological testing. On the basis of presenting clinical signs, normal CBC and serum biochemistry panel, and location bird was found, pentobarbital relay toxicosis (PRT) was highly suspected.

To treat the presumed PRT, ILE (1.5 mL/kg IV loading dose over 5 minutes followed by 15 mL/kg per hour IV over 60 minutes) was administered according to ILE treatment information published on dogs.[3] Serum lipemia was not assessed immediately after treatment to reduce handling, and the animal appeared clinically unchanged after the ILE infusion. Thereafter, the bird was treated with lactated Ringer's solution (140 mL/kg per day IV). The following morning (16 hours later), the eagle remained quiet, but mentation was improved, and the animal was more alert and responsive and had removed its catheter. Because of the significant improvement in mentation and behavior, no additional treatments were administered, and the catheter was not replaced.

The bird was anesthetized 16 hours post-ILE administration as previously described for whole body radiographic images and serum evaluation for lipemia. No abnormalities were noted in the radiographic images, including no evidence of trauma or heavy metal ingestion, and the serum was not lipemic. After an uneventful recovery from anesthesia, the bird was stable for transfer to a licensed wildlife rehabilitator for additional monitoring. The clinical signs continued to improve, and the bird showed no evidence of renarcotization. The eagle was released after 7 days in rehabilitation.

After the recovery and release of the eagle, the pretreatment serum was tested for pentobarbital concentrations (Veterinary Forensic Sciences Laboratory, University of Florida, Gainesville, FL, USA). The serum sample was analyzed with a barbiturate group enzyme-linked immunosorbent assay (ELISA) kit (product 130619, Neogen Corporation, Lexington, KY, USA). Drug-free bald eagle whole blood and a commercially prepared drug standard for pentobarbital (Cerilliant Corporation, Round Rock, TX, USA) were used to prepare positive and negative control samples. Equipment used for standard and sample preparation included pipettes (Fisher Scientific, Waltham, MA, USA) with disposable tips and Eppendorf tubes (Eppendorf, Hauppauge, NY, USA). The manufacturer's instructions were followed, and a 1:5 dilution of serum with the enzyme immunoassay buffer included in the kit was made and loaded onto the microplate reader (BioTek, Winooski, VT, USA). Optical density was measured at 450 nm, and the cut off was established at 75% above the average optical density of the blanks. The serum sample was analyzed along with matrix-matched negative and positive controls. The serum showed a positive reaction for barbiturates, and the positive and negative controls correctly identified positive and negative reactions, respectively.

DISCUSSION

In this case series, the use of ILE in 2 avian species for the management of toxin ingestion is described. In case 1, ILE was initiated before onset of clinical signs of suspected and later confirmed bromethalin ingestion. In case 2, ILE was administered for suspected and later confirmed PRT. Both birds survived the toxicity and treatment and did not experience any detrimental effects during or after ILE therapy.

Intravenous lipid emulsion therapy has become an increasingly used treatment for the management of lipophilic toxins in veterinary patients. First evaluated for its use as a treatment for local anesthetic toxicity,[4] it has since been reported for the treatment of toxicities associated with lipophilic compounds in humans, dogs, cats, chelonians, and wild birds.[3–7] Case-controlled studies on efficacy and dosing are limited, and administration is anecdotally based on human medicine.[5] The doses employed in this case series differed slightly because the patients were presented to different institutions, highlighting the anecdotal nature of available dosing information.

The mechanism of action of ILE is not completely understood. The most widely accepted mechanistic theory is the "lipid sink theory," wherein ILE, as lipid droplets, exists as a discrete hydrophobic phase in the bloodstream that attracts lipophilic agents, including toxins,[4,5] and sequester the toxins and redistribute them from critical organ tissues into the vascular system.[4,5] Toxins successfully treated with ILE in the canine and feline literature include local anesthetics, permethrin, ivermectin, moxidectin, baclofen, naproxen, ibuprofen, marijuana (*Cannabis sativa*), and bromethalin, among others.[3,5] Both bromethalin and pentobarbital are lipophilic compounds; therefore, ILE therapy was pursued to reduce the toxic effect of these agents.[8,9] Although reports of the use of ILE in nondomestic species are few, the compound has been found to be efficacious for the treatment for brevetoxicosis caused by lipophilic brevotoxins in yellow-bellied slider turtles (*Trachemys scripta scripta*) and double-crested cormorants (*Phalacrocorax auritus*), where treated animals had higher rates of survival compared with controls.[6,7] Clinicians treating a wide range of suspected toxicities from lipophilic toxins should consider ILE therapy to manage future cases.

Bromethalin [*N*-methyl-2,4-dinitro-*N*-(2,4,6-tribromophenyl)-6-(trifluoromethyl)-benzenamine] and its primary metabolite desmethyl-bromethalin are strong uncouplers of oxidative phosphorylation. This results in intramyelin accumulation, leading to long nerve demyelination and intramyelin cerebral edema. The net result of bromethalin toxicity is cerebral and spinal edema and increased cerebral spinal fluid pressure, leading to neurologic dysfunction.[9,10] Hepatic bioconversion alters bromethalin to the more lethal metabolite, desmethyl-bromethalin, and both achieve high concentrations in fat and fat-laden tissues.[9] Although toxicity is known in a variety of mammalian species, controlled studies are lacking in avian

species. Two reports of bromethalin intoxication causing neuropathic effects in feral conures (*Psittacara* species) describe inconsistent concentrations of bromethalin and metabolites in the plasma, tissues, and feces.[1,2] These findings suggest that bromethalin and desmethyl-bromethalin metabolism are not well understood in these species. Severe neurological clinical signs were evident in the conures with bromethalin fecal concentrations as low as 0.8 μg/g.[1] Neurological clinical signs reported in the intoxicated conures included paraparesis, ataxia, dysphagia, and tetraparesis. Given the diffuse central nervous system distribution of the pathological changes, it would be expected that any neurologic sign ranging from mild to severe and from any central neurolocalization could be expected in an intoxicated bird.[2] Bromethalin has no direct antidote, although because of its lipophilic nature, ILE can be used as a potential treatment of this toxin.[9]

The macaw in this case series was treated with ILE according to the known exposure to a bromethalin-containing rodenticide and had bromethalin concentrations measured after treatment. The only sample from this bird that had quantifiable bromethalin was the pretreatment fecal sample (0.04 μg/g), indicating exposure; however, this did not correspond to changes in mentation or neurological status. In comparison, a feral conure with exposure to bromethalin that developed vacuolar degeneration of cerebellar white matter had bromethalin fecal concentrations of 4.06 μg/g and desmethyl-bromethalin fecal concentrations below the limit of detection.[1] In the published reports of intoxicated conures, liver, brain, and fat tissues did show elevated bromethalin and the demethylated metabolite weeks to months after initial presentation.[1] Rats have been shown to have an incredibly slow elimination of plasma bromethalin, with a plasma half-life of 6 days.[9]

Given that the positive fecal sample from the blue-and-gold macaw in case 1 was collected 18–24 hours after exposure, it is likely that the bromethalin in the feces represented biliary excretion. It is unknown why the plasma samples did not have quantifiable bromethalin or associated metabolite detection, but it may have been because of differences in metabolism in this species. Because of the delay in time needed for shipping and testing samples, as well as concern for the development of severe irreversible neurologic sequelae, treatment with ILE was initiated on the blue-and-gold macaw without initial confirmation of bromethalin concentrations. Whether ILE administration was the reason the bird did not develop clinical signs of toxicity or whether the amount of bromethalin exposure was so limited that the bird never would have developed overt neurological signs is unknown. Nevertheless, ILE therapy was safely administered, did not cause any appreciable adverse side effects, was easily administered, and, given the potential severe sequelae of toxicosis, should be considered in future cases of bromethalin exposure.

Prior to ILE therapy, the macaw in case 1 had decontamination attempted with the administration of activated charcoal. Charcoal has the ability to bind toxins in the gastrointestinal tract, whether originating from primary ingestion or enterohepatic circulation, and has been used in other cases of bromethalin intoxication.[9] Despite the benefits of its use, administration of this product can have serious side effects, most notably the development of hypernatremia, which has been reported in 6% of human cases postadministration.[11] The veterinary literature has no such data. The macaw in this report was eating and drinking during treatment and was administered fluid therapy during the first 36 hours of hospitalization to support hydration. Sodium concentrations were not evaluated at any time during the macaw's hospital stay. However, clinicians using activated charcoal should consider the potential of hypernatremia and contemplate the judicious use of fluid therapy and serial monitoring of plasma sodium concentrations.

Pentobarbital, a Drug Enforcement Agency class II controlled substance, is a drug within the barbiturate class of sedative-hypnotic drugs and a γ-aminobutyric acid receptor agonist.[12] Ingestion of pentobarbital results in central nervous system depression.[13] Sodium pentobarbital is a commonly used euthanasia solution for animals in the United States. Unfortunately, euthanized animals are occasionally ingested by scavenging animals, including raptorial birds, carnivores, and companion animals. Most commonly, birds of prey have been reported to feed on the carcasses of improperly handled euthanized animals. Multiple bald eagles have been reported to die after feeding on a cat and a cow that were improperly disposed of after euthanized.[14–17] In a retrospective review regarding pentobarbital toxicity in animals, 131 different events of PRT were reported, and a total of 432 animals died because of intoxication.[18] In that report, affected bird species included bald eagles, golden eagles (*Aquila chrysaetos*), and griffon vultures (*Gyps fulvus*). Clinical signs reported in birds with PRT ranged from depression and weakness to death.[15–18]

The eagle presented in this report was found down in proximity to a site where euthanized large animal carcasses are commonly disposed of; thus, a presumptive diagnosis of PRT was determined. Analysis of pretreatment serum was positive for barbiturates by a commercially available barbiturate group ELISA kit. In published reports and the experience of the authors (K.A.K., A.A.), birds with PRT can recover with supportive care over a period of several days.[17,18] The eagle in this report had ILE therapy initiated after the presumptive diagnosis of PRT and within a day of presentation. Subsequently, the eagle experienced significant improvement in mentation and neurologic status. Ultimately, this bird was transferred to a rehabilitation center and successfully released back into its natural habitat. The rapid clinical improvement in the eagle supports a positive effect of the ILE; however, it is unknown whether this eagle would have made a full recovery with supportive measures only. Consequently, ILE therapy should be considered in cases of presumptive or confirmed PRT, when available.

Therapy with ILE has been associated with rare adverse events, including lipemia, corneal lipidosis, and acute respiratory distress syndrome.[4,19,20] In metabolic studies on king penguin (*Aptenodytes patagonicus*) chicks experimentally infused with ILE, no clinical abnormalities were reported post-infusion. The only biochemical parameters evaluated in that study were triglycerides, fatty acids, and glucose concentrations, which were transiently elevated but returned to baseline 3 hours post-infusion.[21] Although lipemic plasma posttreatment has been reported, this finding is rarely persistent.[4,5] Transient lipemia is typically not concerning in itself; however, it can interfere with laboratory evaluation of some blood chemistry values.[4,5] Prolonged lipemia has the potential to lead to concerning sequelae, including vascular events; therefore, it is recommended to avoid repeated ILE dosing if lipemia is present. Additionally, because ILE solution is a nutrient-rich solution, microbial contamination is a concern and requires appropriate handling and sterile techniques.[4,5]

In prior reports of administration of ILE in chelonians and cormorants, no deleterious effects were reported in either study.[6,7] Neither the macaw nor the eagle in this case series experienced any obvious adverse effects from the ILE therapy. The macaw was screened for lipemia and only had lipemia present in the immediate posttreatment period. A blood sample collected 16 hours post-ILE administration in the eagle was not lipemic, indicating no persistent lipemia in this individual. Despite the favorable outcome in the birds in this report, clinicians that use ILE therapy should be aware of the potentially serious complications.

This case series presents 2 cases of initially suspected and then confirmed toxicity in avian species that were then administered ILE. Both cases resulted in good outcomes with no evidence of adverse side effects associated with ILE administration. Intravenous lipid emulsion therapy has the potential to be a useful treatment in avian species for management of toxicosis caused by lipophilic agents.

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