

**Medical management and treatment of rodenticides –  
It's not just Vitamin K1 anymore!**



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As fall approaches, veterinary clinics will be seeing more accidental rodenticide poisonings. Think you know how to treat that dog that just ingested a green or blue block of rodenticide? Well, before reaching for your bottle of Vitamin K1, make sure you identify the correct active ingredient! New mandates by the EPA (effective 2011) were created that will reduce the availability of long-acting anticoagulants (LAAC); instead, bromethalin and cholecalciferol may become more prevalent in the future. So, before you reach for that Vitamin K1, read on!

### **RODENTICIDES**

One of the most common mistakes seen in the field of veterinary toxicology is assuming that every green or blue block of rat or mouse poison is a long-acting anticoagulant (LAAC) rodenticide. The active ingredient of a rodenticide *cannot* be identified based on physical appearance (e.g., color, shape, size, etc.). When in doubt, the EPA-Reg. number or active ingredient (and concentration) must be properly identified to ensure appropriate treatment and management of rodenticide toxicoses. Several different classes of rodenticides exist, including those that contain bromethalin, zinc phosphide, and cholecalciferol (Vitamin D<sub>3</sub>).

### **BROMETHALIN**

Bromethalin, a neurotoxic rodenticide, is marketed under several common brand names of Assault®, Tomcat Mole Killer®, Talpirid®, Real Kill®, Clout®, Fastrac®, Vengeance®, etc. Bromethalin is *not* an anticoagulant rodenticide and should *not* be treated with Vitamin K<sub>1</sub> as an antidote. Bromethalin works by uncoupling oxidative phosphorylation in the brain and liver mitochondria.<sup>1</sup> This results in decreased ATP production, which affects sodium and potassium pumps; as a result, lipid peroxidation occurs, resulting in sodium accumulation within the cell.<sup>1</sup> Edema of the central nervous system (CNS) may result.<sup>1</sup>

In dogs, the LD<sub>50</sub> of bromethalin is 2.38-3.65 mg/kg, with a minimum lethal dose being 2.5 mg/kg.<sup>1</sup> Cats are more sensitive to the effects of bromethalin, and the LD<sub>50</sub> is significantly lower (0.54 mg/kg).<sup>1</sup> Clinical signs are dose-dependent, and the onset of clinical signs depends on the amount ingested. Typically, with acute ingestion, signs may be seen within 2-24 hours.<sup>1</sup> Clinical signs of CNS stimulation or depression, abnormal behavior, ataxia, hyperesthesia, seizures, and coma may be seen.<sup>1</sup> Other common signs include paresis, hind limb paralysis, anisocoria, nystagmus, changes in the pupillary light reflex, and tremors may also be seen. Treatment includes early decontamination, prevention of cerebral edema, and symptomatic supportive care. With recent ingestion in an asymptomatic patient, the use of decontamination (e.g., emesis induction, activated charcoal) is warranted. As bromethalin undergoes enterohepatic recirculation, the use of multiple doses of activated charcoal (without a cathartic) can be administered q 6 hours for 24 hours. Patients should be monitored for signs of neurotoxicity. The use of IV fluid therapy, oxygen support, head elevation, mannitol (to decrease cerebral edema), anticonvulsant therapy, and thermoregulation is warranted if clinical signs develop. The prognosis varies depending on the amount ingested and the severity of clinical signs. If persistent seizures or paralytic syndrome is seen, the prognosis is poorer.

### **PHOSPHIDES**

Phosphide rodenticides have been used since the 1930's and are still readily available on the market.<sup>2</sup> Aluminum phosphide is a pelleted product used as a fumigant in grain storage silos, while the more common zinc phosphide is labeled for use in control of rats, mice, ground squirrels, prairie dogs, voles, nutria, muskrats, feral rabbits, and gophers.<sup>2</sup> Zinc phosphide, a crystalline, grey powder, is available in 2-10% concentrations as grain or sugar-based baits in a powder, pellet, tablet, or paste formulation.<sup>2</sup> Trade names of some of the commercially available zinc phosphide products include: Gopha-Rid, Gopher Bait II, Rodenticide AG, This is the Way, Prozap, Hopkins, and Sweeney's Poison Peanuts Mole.<sup>2</sup> Formulations of phosphides have a unique, distinctive odor similar to rotten fish, garlic, or acetylene.<sup>2</sup> You should care about this type of rodenticide because it is potentially poisonous to you, your pet owner, and your staff too!

The toxic dose of zinc phosphide in dogs is approximately 20-40 mg/kg, but up to 300 mg/kg on empty stomachs.<sup>3</sup> With zinc phosphide, the administration of food (e.g., bread, milk, etc.) is contraindicated, as it may potentially release gastric acid, promoting hydrolysis and further production of phosphine gas.<sup>3</sup>

Phosphide rodenticides result in the production of phosphine gas. When zinc phosphide combines with gastric acid or moisture (or the presence of food!), liberated phosphine gas is rapidly absorbed across gastric mucosa and distributed systemically, where it exerts its toxic effect. Phosphine gas is considered a corrosive and a direct irritant to the gastrointestinal tract (GIT). Clinical signs can be seen within 15 minutes to 4 hours; death has been reported within 3-48 hours.<sup>3</sup> Clinical signs include severe gastrointestinal (GI) signs (e.g., vomiting, bloat, abdominal pain, hematemesis, melena, etc.), CNS signs (e.g., tremoring, seizuring, death), and rarely, cardiopulmonary signs (e.g., pulmonary edema, tachypnea, pleural effusion, etc.) or organ dysfunction.<sup>3</sup>

Zinc phosphide also carries a public health risk. Emesis – whether intentionally induced or occurring due to clinical signs – can result in poisoning to the pet owner or the veterinary professional secondary to exposure of phosphine gas. Clinical signs of nausea and difficulty breathing have been reported in humans exposed. To minimize these risks, emesis induction should always be performed in a well ventilated area (e.g., opening the car window if the patient vomits or inducing emesis outside or in a well-ventilated area). Pet owners should be appropriately educated on the toxic gas exposure to themselves also. Pet owners should be informed *not* to feed their pet to prevent further production of phosphine gas. In addition, the administration of an antacid (e.g., aluminum hydroxide) prior to emesis induction may help decrease the presence of phosphine gas. With recent ingestion in an asymptomatic patient, the use of emesis induction (following antacid administration) and one dose of activated charcoal with a cathartic is warranted to minimize toxic effects of zinc phosphide. Symptomatic supportive care, including anti-emetic therapy, IV fluid therapy, gastric protectants, and analgesics are warranted.

### **CHOLECALCIFEROL**

Cholecalciferol, the chemical name for vitamin D<sub>3</sub>, is one of the most deadly – and costly – rodenticides to pets. Ingestion of toxic levels of cholecalciferol can result in severe hypercalcemia and hyperphosphatemia, with secondary acute renal failure (ARF) developing as a result of dystrophic mineralization to the soft tissue and kidneys. Common sources of Vitamin D<sub>3</sub> include over-the-counter (OTC) or prescription vitamins (typically found in a calcium/Vitamin D<sub>3</sub> combination), psoriasis creams (in the form of calcipotriene), and rodenticides. With cholecalciferol-containing rodenticides, only a tiny amount of rodenticide needs to be ingested before clinical toxicosis occurs due to a very narrow margin of safety within these products. In dogs, cholecalciferol has an LD<sub>50</sub> of 85 mg/kg (based on the rodenticide concentration of 0.075%).<sup>4</sup> Doses of Vitamin D<sub>3</sub> > 0.1-0.5 mg/kg can result in clinical signs and hypercalcemia, respectively.<sup>4</sup>

Typically, clinical signs often do not develop for 1-3 days until the patient has already developed clinical signs of ARF.<sup>4</sup> That said, renal failure can occur within 12-36 hours following toxic ingestion. Clinical signs and clinicopathologic findings include increased thirst and urination, weakness, lethargy, anorexia, vomiting, generalized malaise, uremic halitosis, dehydration, hypercalcemia, hyperphosphatemia, azotemia, melena, hemorrhagic diarrhea, and death.<sup>4</sup>

Aggressive treatment must be initiated with cholecalciferol toxicosis, due to the narrow margin of safety. Decontamination should include emesis induction, if ingestion was recent and the patient is asymptomatic. As cholecalciferol undergoes enterohepatic recirculation, the administration of multiple doses of activated charcoal (without a cathartic) is warranted q 6 hours X 24 hours. Additional treatment includes the aggressive use of IV fluid therapy to promote calciuresis (e.g., 0.9% NaCl), calcium monitoring, gastrointestinal support (e.g., anti-emetics, H<sub>2</sub> blockers, sucralfate, phosphate binders, etc.), and the use of medications to increase calciuresis (e.g., prednisone, furosemide) and prevent hypercalcemia (e.g., pamidronate, calcitonin). Treatment is often expensive, and requires hospitalization for an extended period of time. Most patients are continued on oral furosemide and prednisone for weeks, following discharge from the hospital. Frequent monitoring of renal function and electrolytes is imperative. Calcium, phosphorous, BUN, creatinine, and ionized calcium should be evaluated every 12-24 hours while hospitalized, and then every 2-3 days thereafter for the next 2-4 weeks. This will allow one to assess the ability to titrate the prednisone and furosemide therapy, and to ensure that the patient does not develop secondary ARF [or potentially chronic renal failure (CRF)]. Even with aggressive treatment, CRF may be a secondary sequela.

### **LONG-ACTING ANTICOAGULANTS (LAAC)**

First and second generation LAAC anticoagulants result in inhibition of Vitamin K epoxide reductase, resulting in inactivation of clotting factors II, VII, IX, and X. First generation rodenticides (e.g., warfarin, pindone)<sup>5</sup> have been largely replaced by more potent second generation anticoagulants (e.g., brodifacoum, bromadiolone, diphacinone, chlorophacinone, etc.).<sup>5</sup> Second generation LAACs are more recently developed and are generally considered to be more toxic with a longer duration of action (requiring a longer duration of treatment compared to first generation anticoagulants).<sup>5</sup> Each individual LAAC varies in the margin of safety and LD<sub>50</sub>. Some have very narrow margins of safety (e.g., brodifacoum), while some have very wide margins of safety (e.g., bromadiolone). When in doubt, the toxic dose should be calculated, or Pet Poison Helpline contacted to determine if a toxic dose has been ingested. Finally, keep in mind that species differences exist; cats are much more resistant to the affects of LAAC as compared to dogs.

Canine LD <sub>50</sub>	Feline LD <sub>50</sub>
Difethialone: 4 mg/kg	> 16 mg/kg
Brodifacoum: 0.25-4 mg/kg	25 mg/kg
Bromadiolone: 11-20 mg/kg	> 25 mg/kg
Diphacinone: 3-7.5 mg/kg	> 15 mg/kg

When a toxic ingestion of LAAC has occurred, prolongation in coagulation factors [prothrombin (PT) or activated partial thromboplastin time (aPTT)] is not seen for 36-48 hours, as based on the half-life of factor VII. Clinical signs typically do not develop for 3-5 days. Clinical signs are due to clotting factor depletion, resulting in generalized hemorrhage. The most common clinical signs include lethargy, exercise intolerance, inappetence, pallor, dyspnea, coughing, hemoptysis, etc. Hemoabdomen, hemothorax, pericardial effusion may also occur. Rarer clinical signs include gingival bleeding, epistaxis, ecchymoses, petechia, hematuria, bleeding into the subcutaneous space or joint space, and melena.<sup>5</sup>

Errors are often made by veterinary professionals when it comes to the medical management of LAAC rodenticides. While it is often appropriate to decontaminate a patient with emesis induction and activated charcoal administration, with non-toxic ingestions (based on the LD<sub>10</sub>), this is often unnecessary (unless the patient is neonatal, geriatric, has an underlying hepatopathy, or has previously ingested a LAAC before). Next, the administration of a “one-time,” parenteral injection of vitamin K<sub>1</sub> at the time of decontamination is unnecessary and potentially detrimental. First, vitamin K<sub>1</sub> is faster absorbed *orally* than parenterally (particularly with a fatty meal). Another reason why the “one-time shot” should be avoided is because it will skew point-of-care, accurate blood results of the PT test. As factor VII has the shortest half-life, PT will be the first blood test to be prolonged with LAAC ingestion; however, this prolongation of the PT will not normally occur until approximately 36-48 hours post-LAAC ingestion. Testing prior to this time is unnecessary (unless the patient has been chronically ingesting a LAAC over several days), as the PT will be normal prior to 36-48 hours. By administering a “one-time shot” of Vitamin K<sub>1</sub> therapy, the patient’s PT will be falsely normal at 48 hours, and instead, the patient will be coagulopathic days later (3-5 days, instead of 2 days). Normally, clinical signs of acute, LAAC toxicosis typically occur at 3-5 days post-ingestion. With a “one-time shot,” the patient will bleed out at 5-7 days instead of 3-5 days!

When treating LAAC rodenticides, two considerations for treatments should be utilized.

- 1) With an acute, one-time ingestion of a LAAC, one can decontaminate and check a PT 48 hours post-initial ingestion. If the PT is prolonged at 48 hours, 3-4 weeks of Vitamin K<sub>1</sub> therapy should be initiated (3-5 mg/kg PO, divided SID-BID X 4 weeks). A recheck PT should be performed 48 hours after the last dose; if prolonged, an additional 2 weeks of therapy is indicated, with another PT performed 48 hours after the last dose OR
- 2) With an acute one-time ingestion of a LAAC, one can just prophylactically treat with Vitamin K<sub>1</sub> therapy, particularly if the patient is young, debilitated, geriatric, or has underlying liver pathology. Treatment includes Vitamin K<sub>1</sub> therapy (3-5 mg/kg PO, divided SID-BID X 4 weeks), with a recheck PT being performed 48 hours after the last dose; if prolonged, an additional 2 weeks of therapy is indicated, with another PT performed 48 hours after the last dose.

#### **Clinical application:**

1. You don’t typically need to bother testing the patient’s PT while they are on chronic Vitamin K<sub>1</sub> administration – it will be normal while on therapy (unless the owner is not appropriately administering it)!

2. In dogs ingesting LAACs chronically, there is the risk of potential accumulation within the body. Any “second” exposure should be prophylactically treated with oral Vitamin K<sub>1</sub> therapy for the appropriate duration of time.
3. Vitamin K<sub>1</sub> should not be administered intramuscularly (IM) or IV. If you suspect a patient is coagulopathic, administer into a vascular muscle bed (IM) can result in a large hematoma within the muscle. Also, intravenous administration of Vitamin K<sub>1</sub> can result in anaphylactic shock. Rather, critically ill, actively bleeding dogs should be stabilized with frozen plasma (FP) or fresh frozen plasma (FFP) concurrently.

#### **REFERENCES**

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