Rodenticides & Regulations

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DCS Seminar
December 4, 2015

Learning Objectives:

- Understand the new EPA regulations concerning rodenticides
- Understand how these regulations will affect practicing veterinarians.
- Know common anticoagulant rodenticides.
- Know other common types of rodenticides, MOA, clinical signs, treatment, and prognosis
    - Bromethalin
    - Cholecalciferol
    - Zinc phosphide
- Know which is likely to expose the client and veterinary professional to toxic gas.

Introduction: Anticoagulant rodenticides have been marketed since the late 1940s, when warfarin was developed by the Wisconsin Alumni Research Foundation. Because warfarin required multiple feedings, and resistance was developing in some rodent populations, other anticoagulants were developed and marketed. The first generation of new anticoagulant rodenticides, called the indandiones, include predominantly diphacinone and chlorophacinone. Later, second generation compounds were developed, including brodifacoum, bromadiolone, and difethialone, and others. These compounds were more effective because they were more potent, (only a single exposure needed,) and longer acting. Unfortunately, the extended tissue half-life of these products has been associated with bioaccumulation and biomagnification in animals that consume rodents. About half of the raptors in New York and most of the wild felids and foxes in California have detectable tissue concentrations of anticoagulant rodenticides. Often more than one is present, and they can have additive effects. Though there have been reports of clinical coagulopathies in exposed wild predators, other clinical problems have been linked to anticoagulant rodenticides as well.

Another common rodenticide is bromethalin, a neurotoxin which increases intracranial pressure and causes demyelination. Cholecalciferol is a vitamin D_3 analog which causes metastatic mineralization. Zinc phosphide is a rapid-acting rodenticide which, after ingestion, produces phosphine, a gas that prevents oxygen utilization by tissues and can harm people and animals in the vicinity of the victim.

US EPA Regulations: Because of the wildlife-related problems, as well as the risks rodenticides pose to children and pets, the United States Environmental Protection Association has put regulations into effect concerning anticoagulant rodenticides. These regulations state that all rodenticides must be placed in bait stations and cannot be set out as loose pellets, packets, or blocks. The three types of bait stations are:

- Tier 1: Indoor/outdoor, child and dog resistant, weather resistant.
- Tier 2: Indoor only, child and dog resistant, not weather resistant.
- Tier 3: Indoor only, child resistant, not dog resistant.

Additional regulations can be broken down into household use regulations and agricultural/commercial use regulations.

Household products can include warfarin, chlorophacinone, and diphacinone, as well as non-anticoagulant products such as bromethalin and cholecalciferol. These products must be sold with bait stations and packages must not contain more than a pound of bait. Products no longer regulated for household use include: brodifacoum, bromadiolone, difethialone, and difenacoum.

Agricultural and commercial products must be used in bait stations but can be sold in bulk containers holding at least 4 lbs for first generation anticoagulants and non-anticoagulants and 8 to 16 lbs for second-generation products. These bulk containers are considered impractical for household use.

Several drawbacks are apparent. One major drawback of this new legislation is the continued use of long-acting rodenticides in rural areas. A problem for the practicing veterinarian is that while some bait stations are dog-resistant, they may not be dog proof. Another problem is that increased regulation of anticoagulant rodenticides is likely to lead to increased use of other types of products. Anticoagulant rodenticide poisoning can be treated using vitamin K1 as an antidote, but most of the other rodenticide products have no specific antidotes and can be complicated and difficult to manage.

Anticoagulant rodenticides: Warfarin, the first anticoagulant rodenticide, is infrequently used. Warfarin has an LD_{50} of more than 10 mg/kg for dogs and baits contain 0.025% active ingredient, so the median lethal dose for bait is > 40 g/kg, which is > 0.36 kg bait (0.8 lbs) for a 20 lb dog.

Diphacinone has an LD_{50} for dogs between 3 and 8 mg/kg and is sold as 0.005% bait, so the median lethal dose is equivalent to 60 to 160 g bait/kg. The lower end of this

range would be about 540g (a little more than a pound) of bait for a 20 lb dog. Chlorophacinone is also sold as 0.005% bait and diphacinone and chlorophacinone have longer half-lives than warfarin, though those half-lives have not been reported.

Brodifacoum, a common second-generation anticoagulant rodenticide has an LD_{50} for dogs of about 0.2 mg/kg, and is sold as 0.005% bait, so the median lethal dose for bait is about 4 g/kg, or 36 g of bait for a 20 lb dog. Two Fig Newtons = 31g, for comparison. Brodifacoum has a 6 day plasma half-life, but the half-life in the liver is around 180 days, thus it can be causing its clinical effect long after the parent compound is undetectable in the blood.

Bromadiolone is another commonly used second-generation anticoagulant rodenticide with a median lethal dose around 0.5 mg/kg, equivalent to 10 g bait/kg for 0.005% bait. A 20 lb dog would need to consume about 90g of bait, so a little more than half the weight of dog food in a small can. The plasma half-life is similar to that of brodifacoum.

Difethialone is another second-generation anticoagulant rodenticide seen frequently in the area. The LD_{50} dose for dogs is about 4 mg/kg, but the bait is usually 0.0025% active ingredient. The approximate LD_{50} for the bait, then, is around 160 g/kg, nearly 1.5 kg for a 20 lb dog. Like brodifacoum and bromadiolone, difethialone remains in the liver long after it is no longer detectable in blood.

Diagnosis is based on history of exposure and the presence of coagulopathy. Anticoagulant rodenticides competitively inhibit vitamin K epoxide reductase, the enzyme needed for recycling vitamin K, which is a cofactor for production of prothrombin (factor II) and coagulation factors VII, IX, and X. These factors can no longer be produced, but because existing factors degrade relatively slowly, coagulopathy doesn't develop right away. The shortest half-life is for factor VII in dogs, about 6 hours. Based on this half-life, factor VII is about 97% depleted 30 hours after the rodenticide is absorbed. This is why clinical signs are usually delayed for at least a couple of days.

Because factor VII is needed for the extrinsic arm of the coagulation cascade, the prothrombin time (PT) is usually elevated in 32-48 hours. The activated partial thromboplastin time (aPTT) becomes prolonged later. No increase in fibrin degradation products is expected, nor is the platelet count affected unless due to consumption.

Dogs and cats poisoned with anticoagulant rodenticide can present in a variety of ways, depending on where the bleeding occurs. They can rapidly bleed out into the abdomen or thorax, or hemorrhage within the closed space of the calvarium or joints. Or they can

present with subcutaneous or external hemorrhage, or bleed into the gastrointestinal tract. If a dog is thought to have ingested more than 0.02 mg/kg of a second-generation rodenticide, treatment is indicated even before clinical signs become evident.

The vital element for management of anticoagulant rodenticide toxicosis is vitamin K1 (phytonadione). Vitamin K1 is best given orally for at least one week in the case of warfarin, and at least 4 weeks in the case of other anticoagulant rodenticides. Forty-eight hours after cessation of therapy PT is retested and, if elevated, vitamin K1 dosing is started again.

If the animal presents soon after ingestion of anticoagulant bait, vomiting can be induced followed by instillation of activated charcoal. These patients can be put on vitamin K1 therapy as directed above, or have PT values checked in 48 hours to determine if they are likely to have absorbed enough anticoagulant to produce clinical signs. If exposure is not known, but clinical signs are present, a careful history can be helpful. If the PT is significantly prolonged, the patient should be treated in the same manner as a clinically affected animal. Treatment of clinically affected animals could require replacement of clotting factors or whole blood, with other symptomatic and supportive therapies based on your clinical judgement. Prognosis with timely and aggressive therapy prior to clinical hemorrhage is excellent. Animals presenting with evidence of hemorrhage have a more guarded prognosis but, again, this is dependent on the site of the bleeding. Client compliance, extended vitamin K1 therapy, and monitoring are, in any case, critical. The consequences of abbreviated therapy can be dire.

Bromethalin: Bromethalin baits look like anticoagulant baits, but the mechanism of action is completely different. The LD_{50} for bromethalin is about 2 mg/kg for dogs, but cats are sensitive at doses less than 1 mg/kg. Baits are 0.01% active ingredient, therefore, the median lethal dose of bait for a dog is below 20 g/kg (about 180 g for a 20 lb dog, equal to about half of a large can of dog food), and less than 10 g/kg for a cat (about 45 g, equivalent to about half of a can of Fancy Feast). The plasma half-life is about 6 days, so relay poisoning is possible.

Bromethalin inhibits oxidative phosphorylation and the effect seems to be restricted to myelin producing cells. Since oxidative phosphorylation is needed for ATP production, and ATP is needed for sodium/potassium ion pumps involved in cellular osmoregulation, water moves into the myelin cells of the central nervous system. If the animal ingested a high dose of bromethalin, this happens quickly, causing a rapid increase in intracranial pressure. This commonly happens in cats, due to their sensitivity to bromethalin, but it can also occur in dogs. If the dose is smaller, myelin

degeneration is progressive, leading to conduction disturbances. This occurs most commonly in dogs. Diagnosis is based on history and clinical signs. Tissues or baits can be analyzed at some diagnostic toxicology laboratories, and postmortem lesions are usually evident.

Acute clinical signs of cerebral edema can occur within 24 hours. Animals present with hyperesthesia, vocalizations suggesting pain, tremors, seizures, and secondary hyperthermia. The prognosis for these animals is grave. Mannitol and corticosteroids have been ineffective at treating the cerebral edema caused by bromethalin. Diazepam, levetiracetam, or other anticonvulsants can help control seizures.

Animals that ingested lower doses can present 72 hours post-exposure with vomiting and anorexia. Demyelination causes hind limb paresis progressing to paralysis with loss of deep pain and hyperreflexia. Prognosis is good to guarded with supportive care, but dogs can die of respiratory failure. There is no specific therapy for demyelinating injury.

Cholecalciferol: Cholecalciferol is a vitamin D3 analog. The toxic dose in dogs is about 2 mg/kg and the lethal dose is about 10 mg/kg. Baits are not visibly distinguishable from other types of rodenticides, and contain 0.075% D3. Therefore, the median lethal bait dose is about 13 g/kg, or 117 g for a 20 lb dog, but clinical signs can occur if the dog ingests as little as 24 g of bait (similar to 2 Oreo cookies).

Cholecalciferol is required for health. It is metabolized first by the liver to 25-hydroxycholecalciferol, and then by the kidneys to 1,25-dihydroxycholecalciferol (calcitriol) which is about 100 times more biologically active than the parent compound. Calcitriol acts to increase calcium absorption from the intestine, promote osteoclasis, and decrease renal calcium excretion. High doses of cholecalciferol lead to remarkable increases in circulating calcium and phosphorus, which leads to metastatic mineralization. The predominant organ of concern is the kidney.

Diagnosis of cholecalciferol poisoning is based on history of exposure and elevated serum calcium and phosphorus concentrations. The phosphorus increases within about 12 hours and can be over 8 mg/dL. If the product of the calcium and phosphorus concentration is greater than 60, metastatic mineralization is likely ([Ca]X[P] > 60). The BUN and creatinine can be elevated and isosthenuria can occur within 24 hours of exposure due to renal mineralization. Acute kidney injury (AKI) can lead to vomiting, sometimes bloody, and melena. Clinical signs of hypercalcemia include arrhythmia and hypertension.

Treatment of cholecalciferol poisoning can be challenging, time intensive, and expensive. Detoxification soon after exposure is recommended. Emetics within four hours of exposure (the patient will be asymptomatic at this point) is followed by four days of monitoring. Since vitamin D is fat soluble, intravenous lipid infusion has been suggested by some. Serum chemistry is repeated every 12 hours for about 4 days to monitor calcium, phosphorus, and renal function. If the calcium and phosphorus concentrations become elevated, forced diuresis is needed. Use saline at twice maintenance to enhance calciuresis. Many patient with require more aggressive therapy with furosemide and/or prednisone. If serum calcium cannot be controlled by diuresis, the first choice for therapy is pamidronate (bisphosphonate). One dose is usually sufficient but the dose can be repeated in 7 days if needed. If pamidronate is not available, salmon calcitonin can be attempted, but it is not reliably effective. Regardless of the treatment options used, the animal should be put on a low vitamin D diet and perhaps kept out of sunlight. Symptomatic therapy can include gastroprotectants and antiemetics, as well as diazepam if needed to control seizures. Oral phosphate binders such as aluminum hydroxide can be used if needed for elevated phosphorus. The patient will need daily monitoring for a week, serum chemistry every other day for the following 2 weeks, and again one month post-exposure.

Zinc Phosphide: Zinc phosphide is a grey-black powder that is sold as pelleted bait or mixed with grain. Products usually contain 0.5 to 10% zinc phosphide. The lethal dose of zinc phosphide in a dog is about 40 mg/kg, so for bait with 10% zinc phosphide, the lethal dose is about 0.4 g bait/kg, or 3.6 g for a 20 lb dog, about half the weight of a Hershey's kiss. If the bait is 1%, the lethal dose for the above dog would be 36 g, so about 3 Oreo cookies' worth. Commercial zinc phosphide products usually contain an emetic. This likely saves a lot of dogs, but causes a unique problem for the veterinarian and client. Zinc phosphide reacts with acid (pH ≤ 4.0) to produce phosphine gas. Once ingested and exposed to stomach acid, the phosphine gas produced has rapid systemic absorption. It can cause pulmonary edema early. Phosphine inhibits the cytochrome c oxidase needed for electron transport in mitochondria, so cells can no longer undergo aerobic respiration. Metabolically active tissues rapidly become hypoxic.

Clinical signs can occur within 15 minutes, but it takes longer if the animal ingests bait on an empty stomach. About 2/3rds of dogs that ingest zinc phosphide will vomit due to the emetic, but the vomitus will continue to release phosphine gas. ***If the odor of phosphine gas (acetylene, garlic, or spoiled fish) is detectable, people are at risk!*** Vomit can also contain blood and be associated with abdominal pain. Many dogs become obtunded and a few undergo other neurologic signs such as tremors or seizures. Diagnosis is based on history and clinical signs and can be supported by the

odor of vomitus—though you *really* do not want to be breathing it. Dogs can have metabolic acidosis due to anaerobic respiration, as well as hypocalcemia and hypomagnesemia. If organ damage occurs, elevated BUN can usually be detected within a couple of days and liver enzymes within 2 weeks.

Treatment for zinc phosphide toxicosis must be undertaken in a well-ventilated area! According to the CDC, between 2006 and 2011, four veterinary clinics had to be evacuated due to phosphine gas. **Do not give the patient food**, as this will enhance gastric acid secretion and, therefore, phosphine production. Liquid antacid solutions such as sodium bicarbonate, calcium carbonate, and magnesium hydroxide can be helpful to keep the gastric pH low. Emetics can be attempted if the patient does not vomit on their own, but this is risky due to the potential clinical signs. Gastric lavage is also risky because there can be mucosal damage, but if attempted, an antacid solution should be instilled. Activated charcoal has been recommended. Because oxidative damage due to anaerobic respiration causes much of the organ damage, *N*-acetylcysteine or vitamin C PO have been suggested. Other supportive and symptomatic care can include use of gastroprotectants, seizure control, and respiratory support for pulmonary edema. The prognosis with early treatment is good, one paper reported 98% survival in dogs.

Summary: EPA regulations on anticoagulant rodenticides have become stricter because of the problem of bioaccumulation in wildlife. Currently, anticoagulant rodenticides must be used in bait stations and *some* of the long-acting anticoagulants are no longer available for household use. They are, however, still available in bulk for agricultural and commercial users. Anticoagulant rodenticide ingestion is relatively easy to treat with vitamin K1 and has an excellent prognosis if caught early and with the proper duration of therapy. Unfortunately, other types of rodenticides can require prolonged treatment, such as cholecalciferol. While no antidote is present for bromethalin, most animals survive due to the low concentration of active ingredient in bait. Most animals also survive zinc phosphide poisoning, but the poisoned patient can expose owners and veterinary professionals to highly toxic phosphine gas.

Drug doses:

Activated Charcoal PO 1 to 4 g/kg (dissolve 1 g ac/5g water)

Aluminum hydroxide PO 30 to 90 mg/kg/day

Apomorphine as an emetic intraconjunctival tablet for dogs, rinse after vomiting, or injectable 0.03 mg/kg IV

Diazepam IV 0.5 mg/kg for dogs, 0.25 to 0.5 mg/kg for cats

Furosemide IV 2-4 mg/kg

Levetiracetam IV 20-30 mg/kg for dogs & cats, can be repeated

Milk of magnesia PO 5 to 15 mL

Pamidronate IV 1.3 to 2 mg/kg given slowly

Prednisone PO 0.5 mg/kg 2 times/day

Salmon Calcitonin SC 4 to 6 IU/kg every 12 hours until [Ca] < 12.5 mg/dL

Vitamin K1 PO 2.5 to 5 mg/kg/day, 1 week (warfarin) 4 weeks (other anticoagulants)
*Retest PT 48 after last dose

Xylazine as an emetic for cats 0.44 mg/kg