Bromethalin and Beyond: Interesting Current Events

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In 2008, the USEPA decided to issue new rules regarding the availability and use of ten rodenticides: first generation anticoagulant rodenticides (FGAR) warfarin, diphacinone, and chlorophacinone; second generation anticoagulant rodenticides (SAR) brodifacoum, bromodiolone, difenacoum, and difethialone; and the non-anticoagulant rodenticides bromethalin, cholecalciferol, and zinc phosphide. The rules were instituted following an assessment of the effects of these compounds on human and animal health. One commonly voiced concern with restrictions on use of SGAR is that pets will be more likely to ingest FGAR or non-anticoagulant rodenticides such as bromethalin. Generally speaking, non-anticoagulant rodenticide intoxicated pets will present a greater diagnostic and treatment challenge than anticoagulant rodenticide intoxicated animals. Also, cats are much more sensitive to non-anticoagulant rodenticides such as bromethalin than they are to FGAR or SGAR. Thus, more intoxicated cats are likely to be seen as these alternatives are increasingly used.

Bromethalin

Bromethalin is a potent neurotoxin. It is available for use in residential settings and is sold under several trade names. Most commonly, bromethalin is marketed as a 0.01% formulation (2.84 mg active ingredient per ounce of bait) for consumer use and must be sold in block form. Bromethalin LD_{50}s for dogs and cats are reported to be 2.38 to 5.6 mg/kg and 0.4 to 0.71 mg/kg, respectively. Dosages as low as 0.95 mg/kg and 0.24 mg/kg have been associated with clinical signs in dogs and cats, respectively.

Toxicity is primarily due to the metabolite, desmethyl bromethalin. The onset of clinical signs can be rapid or delayed depending upon the dose ingested. Animals ingesting a large dose can exhibit acute onset of severe muscle tremors, hyperesthesia, hyperexcitability, seizures (can be induced by external stimuli), and hyperthermia. Death is most often due to respiratory failure. Clinical signs associated with moderate ingestions can be somewhat delayed in onset. Signs include rear limb paralysis, ataxia, paddling, hyperthermia, muscle tremors, hyperexcitability, inability to vocalize, loss of tactile sensation, extensor rigidity, seizures, and death within 2 to 4 days. Onset of clinical signs associated with low, but still toxic, doses can be delayed for several days and progress over 1 to 2 weeks post exposure. Signs can include lethargy, depression, emesis, tremors, ataxia, inability to vocalize, paralysis, lateral recumbency, coma, and death. The most common presentation with low dose exposure is hindlimb ataxia and paresis secondary to decreased hindlimb proprioception. There are usually no significant alterations of serum biochemistry parameters.

In the absence of a history of ingestion, a diagnosis of bromethalin intoxication can be difficult due to variability of clinical signs that are dose dependent, a large number of other toxic etiologies, no suggestive routine laboratory changes, and lack of availability of tests to confirm exposure antemortem. There is only one laboratory in the United States that offers routine testing for bromethalin and desmethyl bromethalin (California Animal Health and Food Safety Laboratory System). A postmortem diagnosis, in the absence of a history of exposure, requires demonstration of characteristic lesions within the central nervous system and detection of the parent or metabolite in samples such as fat.

There is no specific antidote for bromethalin intoxication. One key to successful management is early decontamination to prevent absorption. However, the effectiveness of inducing emesis beyond one hour post ingestion is questionable. The administration of activated charcoal (AC) should be done as soon as possible after ingestion. Since bromethalin undergoes significant enterohepatic recirculation, administration of AC might still be useful long after ingestion. It has been suggested that AC should be given every 4 to 6 hours for a minimum of 2 to 3 days. In symptomatic animals, treatment for cerebral edema and increased intracranial pressure is typically needed. The current standard of care recommends the use of mannitol to control cerebral edema. Side effects of administration of mannitol include hypernatremia, pulmonary edema, and dehydration. Supportive care includes good nursing care, padded bedding, frequent turning, and nutritional support since many patients are non-ambulatory and anorectic. Even with moderate ingestions, symptoms in intoxicated animals might take several weeks to resolve and subtle signs of neurologic dysfunction can persist. The prognosis is poor for animals showing severe clinical signs such as paralysis and/or coma.

Cholecalciferol

Cholecalciferol (vitamin D_3) products designed for rodent control contain 0.075%active ingredient (0.75 mg per kg of bait). A reported dog oral LD_{50} value for cholecalciferol of 88 mg/kg is misleading, since oral doses as low as 0.1 to 0.5 mg/kg have been associated with clinical signs and lethality has been reported at doses as low as 2.0 mg/kg. Cats are considered more resistant than dogs, but signs of intoxication have occurred at dosages as low as 0.1 mg/kg. Young animals are more sensitive than adults.

Calcitriol (active metabolite of cholecalciferol) increases renal tubular reabsorption of calcium, calcium release from bone, and intestinal absorption of calcium, while decreasing parathyroid hormone synthesis. These actions result in unregulated increases in

serum/plasma calcium and phosphorus concentrations. When the calcium X phosphorus product exceeds 60 mg/dl, metastatic tissue calcification of soft tissues occurs. Tissue calcification is most pronounced in the kidneys, intima of large vessels, myocardium, and the gastrointestinal tract. Hypercalcemia itself has multiple adverse consequences including altering membrane permeability, decreasing cell energy production, altering calcium pumps, depressing vasopressin's influence on renal tubules, and inducing cell necrosis.

Pathophysiologic effects include acute renal tubular necrosis, gastrointestinal stasis, increased gastric acid secretion, and decreased skeletal muscle and neural tissue responses. Signs can be delayed for 8 to 12 hours post-ingestion due to the metabolism to calcitriol. The severity of presenting signs is a function of the degree of hypercalcemia and the rate of its occurrence. Signs include polyuria, polydipsia, dehydration, gastrointestinal hemorrhage, anorexia, lethargy, abdominal pain, hematemesis, melena, emesis, and diarrhea. Bradycardia and seizures can occur.

Consistent abnormal laboratory values in intoxicated animals include hyperphosphatemia, hypercalcemia, elevated blood urea nitrogen, and elevated creatinine. The Ca X P product is 60 or above (puppies and kittens can have normal Ca X P products > 60). Hyperphosphatemia preceeds hypercalcemia. Demonstrating increased serum concentrations of calcifediol and calcitriol, along with decreased parathyroid hormone is useful, but few veterinary laboratories offer routine testing for these metabolites. Radiographic evidence of soft tissue mineralization might be present. Postmortem diagnosis relies on the presence of widespread tissue calcification along with demonstration of high tissue concentrations of cholecalciferol metabolites.

If an animal is known to have recently ingested cholecalciferol, induction of emesis is warranted (within 1 to 1.5 hours of ingestion). Since cholecalciferol undergoes extensive enterohepatic recirculation, appropriate decontamination includes multiple doses of activated charcoal. Cholestryramine has also been recommended as an adsorbent. In an asymptomatic patient, serial assessment of serum phosphorus, calcium, blood urea nitrogen, and creatinine is recommended every 12 hours for a minimum of 4 days. In symptomatic animals, lowering of serum calcium concentrations by removing excess calcium and decreasing calcium release by bone is critical. Administration of normal saline is necessary to correct dehydration and to promote Ca elimination by limiting renal calcium uptake. This often necessitates prolonged fluid administration which can cause hypokalemia and hypomagnesemia. Therefore, monitoring electrolyte concentrations and urine output is important. Furosemide, a diuretic, helps lower calcium by inhibiting Ca uptake in the ascending loop of Henle. Administration of the corticosteroid prednisolone helps to reduce bone resorption, increase calcium excretion, and decreases intestinal calcium uptake. Effective pharmacologic action takes up to 7 days and its efficacy in reducing serum Ca concentrations is uncertain. Calcitonin has been used to lower serum Ca, but its effects are transient and often only effective for a few days. Given the long-half lives of cholecalciferol and its metabolites, the use of calcitonin is problematic. An alternative approach is to use a bisphosphonate such as pamidronate disodium. These drugs inhibit release of calcium from bone. Although expensive, the use of a bisphosphonate might preclude the need for prolonged hospitalization and IV fluid administration. Phosphate binders such as aluminum hydroxide gel given orally are recommended to be given until Ca and P concentrations stabilize. Once serum calcium concentrations return to normal (typically up to a week), IV fluid administration is slowly decreased while closely monitoring Ca concentrations. One suggested scheme involves monitoring Ca concentrations daily for 4 days after stopping fluids, twice a week for a subsequent two weeks, and then weekly for two weeks (total of 10 times). Symptomatic care might also be required (e.g., antiemetics and GI protectants). The overall prognosis is fair if treatment is instituted prior to soft tissue calcification. If mineralization has occurred the prognosis is much graver. The degree of mineralization and renal impairment are related to the prognosis. Medical management is involved, prolonged, and expensive.

Zinc phosphide

Zinc phosphide is labeled for use for control of rats, mice, voles, ground squirrels, prairie dogs, nutria, muskrats, feral rabbits, and gophers. It is a grey crystalline powder that is available in 2% or 10% concentrations as grain- or sugar-based baits in powder, pellet, paste, or tablet formulations. A minimum toxic or lethal dose for dogs or cats has not been reported. In one unpublished trial, a dog dosed with 40 mg/kg zinc phosphide died following acute convulsive activity approximately 8 hours post-dosing. Toxicity is likely influenced by whether a dog has been fasted or not; fasted dogs are less sensitive based upon rather limited data. Toxicity is due to the liberation of phosphine gas which is produced by hydrolysis of zinc phosphide in a moist or acid environment.

In dogs, early and protracted vomiting, followed by abdominal pain and distention are commonly reported signs. Lethargy, coma, seizures, and sudden death are other reported signs. In one retrospective study in dogs, the most commonly noted signs in descending order of frequency were vomiting, generalized lethargy, depression, dullness, weakness, diarrhea, tremors, agitation, restlessness, seizures, lateral recumbency, abdominal pain, and death. The multiplicity of signs is consistent with multi-organ system involvement following intoxication. The onset of clinical signs can be rapid (vomiting can occur within 15 to 60 minutes), although in rare cases the onset can be delayed from 4 to 18 hours. A number of non-specific clinical pathologic changes are associated with intoxication including hypo- or hyperglycemia, elevated serum liver enzyme activity, hypo- or hyperbilirubinemia, azotemia, electrolyte abnormalities, metabolic acidosis, thrombocytopenia, and disseminated intravascular coagulation. A diagnosis relies on a history of exposure, consistent clinical signs and/or detection of phosphine gas stomach contents.

Although many dogs ingesting zinc phosphide do not develop clinical signs, those that do require intensive treatment in a veterinary hospital. Intravenous fluids or synthetic colloids, pressor agents such as dopamine, and sodium bicarbonate are often needed to treat circulatory shock and metabolic acidosis. Oxygen supplementation is recommended for all cases. Benzodiazepines and/or methocarbamol are indicated for animals that are seizuring or experiencing skeletal muscle tremors, respectively. Close monitoring for and correction of electrolyte abnormalities is indicated. Other therapeutic interventions might include atropine sulfate, n-acetylcysteine, melatonin, medications for pain, and GI mucosal protectants. Perhaps the important point to make is that symptomatic animals require close monitoring and possible treatment for multiple organ system dysfunction.

In one study in dogs, the median time from exposure to poison center call initiation by the pet owner or veterinarian had a significant effect on survival rate. Thus, early decontamination and initiation of symptomatic and supportive care will improve the prognosis. One published case series (N = 362 cases) indicated that ~ 60% of dogs that ingested zinc phosphide did not develop clinical signs. However, another case series summary in which case outcome was available, 171 of 297 dogs died or were euthanized. Dogs which remain asymptomatic for longer than 8 to 12 hours after exposure have a favorable prognosis, as do dogs that initially vomit but otherwise remain asymptomatic for 12 to 24 hours. When moderate to severe multi-organ system occurs within the first few hours of exposure, the prognosis is guarded.

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