PEER-REVIEWED

Bromethalin: The other rodenticide

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While most veterinarians are familiar with anticoagulant and cholecalciferol rodent baits, many are unfamiliar with bromethalin-containing baits. Because its name resembles that of the anticoagulant baits bromadiolone and brodifacoum, bromethalin is often mistaken for another anticoagulant bait. Actually, it differs from anticoagulant rodenticides in both its mode of action and treatment.

Available since 1985 to kill rodents resistant to anticoagulants,[1,2] bromethalin (N-methyl-2,4-dinitro-N-[2,4,6-tribromophenyl]-6-[trifluoromethyl] benzenamine) is marketed in a 0.01% formulation (2.84 mg of bromethalin per ounce of bait) and comes in bait pellets, bars, and place packs.[2] Bromethalin baits cannot be distinguished from other rodent baits by color or appearance alone.[3]

Signs of bromethalin toxicosis are most pronounced in the central nervous system.

Toxicity

In dogs, the oral LD_{50} for bromethalin in baits is about 2.38 to 5.6 mg/kg, and the reported minimum lethal dose is 2.5 mg/kg.[1] In experimental studies, doses below 1.5 mg/kg were not associated with clinical signs.[1] However, according to ASPCA Animal Poison Control Center (APCC) case records, deaths have been reported in dogs ingesting bromethalin at doses as low as 0.95 to 1.05 mg/kg (ASPCA APCC Database: Unpublished data, 1998-2000).

Cats are much more sensitive to bromethalin than dogs. Based on experimental studies, in cats the LD_{50} for bait formulations is about 0.54 mg/kg, the minimum lethal dose is 0.45 mg/kg, and 0.75 mg/kg is uniformly fatal.[4] Based on cases reported to the ASPCA APCC, however, cats have shown signs after ingesting doses of bromethalin as low as 0.24 mg/kg (ASPCA APCC Database: Unpublished data, 1998-2000).

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Metabolism

Toxicokinetic information on bromethalin has largely been derived from experimental studies in rats. After ingestion, bromethalin is rapidly absorbed; plasma concentrations peak in about four hours.[3] After absorption, bromethalin undergoes N-demethylation in the liver, forming desmethylbromethalin, which is thought to be bromethalin's major toxic metabolite.[3] (Guinea pigs do not perform effective N-demethylation of bromethalin, and their oral LD_{50} for bromethalin is more than 1 g/kg, while their oral LD_{50} for desmethylbromethalin is 7.5 mg/kg, which is similar to the LD_{50} for bromethalin in other species.) The body slowly eliminates bromethalin; bromethalin's plasma half-life in rats is about six days.[2,5] Excretion occurs mainly in bile, and enterohepatic recirculation is suspected.[3]

Bromethalin's mechanism of action is the uncoupling of oxidative phosphorylation, which leads to decreased cellular ATP production and failure of the Na^+,K^+-ATPase pumps. As a result, cells lose their ability to maintain osmotic control, sodium is retained intracellularly, and the cells swell with water. In vitro studies show that bromethalin and its metabolite are potent uncouplers of oxidative phosphorylation, with desmethylbromethalin being about two to three times more potent than bromethalin.[5] Signs of bromethalin toxicosis are most pronounced in the central nervous system (CNS) because cerebral and spinal cord edema elevates cerebrospinal fluid (CSF) pressures and leads to neurologic dysfunction.[1]

Clinical signs

Bromethalin toxicosis in dogs manifests as either a paralytic or convulsant syndrome. Dogs ingesting less

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than the LD_{50} but more than the minimum toxic dose develop signs of a paralytic syndrome one to four days after ingestion, beginning with hindlimb weakness and ataxia. As the syndrome progresses, depression, tremors, hyperreflexive hindlimb paralysis, loss of deep pain, and decreased conscious proprioception may develop. Other signs include vomiting, anorexia, nystagmus, anisocoria, opisthotonos, Schiff-Sherrington syndrome, seizures, and coma. The signs may progress for one or two weeks. Death may be due to respiratory failure. Signs may take several weeks to resolve in animals recovering from bromethalin poisoning.[1]

Dogs ingesting doses exceeding the LD_{50} exhibit a convulsant syndrome. The onset of signs generally occurs four to 36 hours after ingestion and includes hyperexcitability, hyperthermia, tremors, and focal and generalized motor seizures that may be sound- or light-induced.[1]

Cats appear to develop the paralytic syndrome regardless of the dose ingested. In addition to the signs seen in dogs, cats may show abdominal distention due to ileus and an inability to urinate as well as increased urethral tone indicative of upper motor neuron bladder paralysis. In the final phases of

the toxicosis, cats may show a decerebrate posture.[4]

Diagnosis

Without a history of bait ingestion, it may be difficult to diagnose bromethalin toxicosis because there are no pathognomonic clinical laboratory abnormalities in dogs or cats.[1,4] A postmortem diagnosis can be made by finding characteristic CNS lesions and bromethalin in body tissues. Microscopically, CNS changes include mild to moderate cerebral edema and white-matter spongiosis from widespread myelin vacuolization. There is no evidence of inflammation.[5-7] Changes occur in the optic nerves but not in the peripheral nervous system.[3,6,7] The highest concentrations of bromethalin are found in fat, the liver, the kidneys, and the brain.[6]

Differential diagnoses for the convulsant presentation of a bromethalin toxicosis may include infectious CNS diseases such as rabies as well as metaldehyde, strychnine, zinc phosphide, and ethylene glycol intoxication. Differential diagnoses for the paralytic presentation are spinal cord or CNS trauma, neoplasia, intervertebral disk disease, rabies, ionophore (*e.g.* monensin) toxicosis, and coonhound paralysis (idiopathic polyradiculoneuritis).

TABLE 1 The ASPCA APCC's Decontamination Recommendations for Bromethalin Ingestion

Time Since Exposure	Dose Ingested*	Action
	Dogs	
< 4 hours	0.1–0.49 mg/kg	Emesis or one dose of activated charcoal
> 4 hours	0.1–0.49 mg/kg	One dose of activated charcoal
< 4 hours	0.5–0.75 mg/kg	Emesis and three doses of activated charcoal over 24 hours
> 4 hours	0.5–0.75 mg/kg	Three doses of activated charcoal over 24 hours
< 4 hours	> 0.75 mg/kg	Emesis and three doses of activated charcoal a day for 48 hours
> 4 hours	> 0.75 mg/kg	Three doses of activated charcoal a day for 48 hours
	Cats	
< 4 hours	0.05–0.1 mg/kg	Emesis or one dose of activated charcoal
> 4 hours	0.05–0.1 mg/kg	One dose of activated charcoal
< 4 hours	0.1–0.3 mg/kg	Emesis and three doses of activated charcoal over 24 hours
> 4 hours	0.1–0.3 mg/kg	Three doses of activated charcoal over 24 hours
< 4 hours	> 0.3 mg/kg	Emesis and three doses of activated charcoal a day for 48 hours
> 4 hours	> 0.3 mg/kg	Three doses of activated charcoal a day for 48 hours

*Note: 1 oz 0.01% bromethalin bait contains 2.84 mg of bromethalin.

Treatment and prognosis

The best treatment for bromethalin ingestion is early, aggressive decontamination. Emesis or gastric lavage to reduce the ingested dose may be the most useful treatment. But emesis should not be induced in symptomatic animals. Multiple doses of activated charcoal, even hours after ingestion, have been suggested because bromethalin and its metabolite appear to undergo enterohepatic recirculation.[8] While this regimen may delay the onset and reduce the magnitude of signs in dogs, multiple doses of activated charcoal may not be as beneficial in cats.[4] The ASPCA APCC's recommendation to induce emesis or administer activated charcoal is based on the potential dose ingested and time since ingestion (*Table 1*). If you are not sure how much was ingested, treat at the most aggressive level.

Since the signs of bromethalin intoxication result from cerebral edema and elevated CSF pressure, treatment with corticosteroids and osmotic agents intended to reduce cerebral edema would seem to be indicated. Initial studies in rats showed that corticosteroids and osmotic agents help treat bromethalin-induced cerebral edema.[5] Unfortunately, the clinical

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use of these agents in dogs and cats has proved ineffective. In dogs, these agents may initially lower the CSF pressure, but stopping treatment returns CSF pressure to pretreatment levels quickly. Further, the use of these agents has little effect on the progression of signs.[8] In cats, no effect on the onset or progression of signs was seen with these treatments.[4] The failure of treatments intended to reduce cerebral edema may be due to the accumulation of fluid within myelin sheaths since it may be more difficult to mobilize the edema from these locations.[3]

One study indicated that *Gingko biloba* might effectively treat bromethalin-induced cerebral edema. Rats given 100 mg/kg of a commercial *G. biloba* preparation at the same time that they were given bromethalin exhibited significantly less cerebral edema than the untreated controls.[9] However, since these rats were euthanized about 48 hours after dosing, the treatment's long-term efficacy and its potential usefulness after the onset of signs are unknown.

Once signs of a bromethalin toxicosis appear, offer symptomatic and supportive treatment, including seizure control, nutritional support, and basic nursing care for recumbent animals. Mild signs such as hindlimb weakness may resolve with time. Animals with paralysis or seizures generally have a poor to grave prognosis for survival.[3,4,8]

Conclusion

Bromethalin ingestion can cause potentially life-threatening signs in dogs and cats. Prompt, aggressive decontamination remains the most effective treatment. Management of any rodenticide toxicosis depends on the type and amount of bait ingested. Because a rodenticide's active ingredient cannot be determined from the bait's physical appearance, veterinary staff should identify an ingested rodenticide from the package's label to ensure proper treatment. Instruct clients to bring the product's package to the veterinary clinic along with their pets.

REFERENCES

1. Dorman, D.C. *et al.*: Bromethalin toxicosis in the dog. Part I: Clinical effects. *JAAHA 26* (6):589-594; 1991.
2. *Reregistration Eligibility Decision (RED): Rodenticide Cluster.* U.S. Environmental Protection Agency, Washington, D.C., 1998.
3. Dorman, D.C.: Bromethalin. *Small Animal Toxicology* (M.E. Peterson; P.A. Talcott, eds.). W.B. Saunders, Philadelphia, Pa., 2001; pp 435-444.
4. Dorman, D.C. *et al.*: Bromethalin neurotoxicosis in the cat. *Prog. Vet. Neurol. 1* (2):189-196; 1990.
5. van Lier, R.B.L.; Cherry, L.D.: The toxicity and mechanism of action of bromethalin: A new single-feeding rodenticide. *Fundam. Appl. Toxicol. 11* (4):664-672; 1988.
6. Dorman, D.C. *et al.*: Diagnosis of bromethalin toxicosis in the dog. *J. Vet. Diagn. Invest. 2* (2):123-128; 1990.
7. Dorman, D.C. *et al.*: Neuropathologic findings of bromethalin toxicosis in the cat. *Vet. Pathol. 29* (2):139-144; 1992.
8. Dorman, D.C. *et al.*: Bromethalin toxicosis in the dog. Part II: Selected treatments for the toxic syndrome. *JAAHA 26* (6):595-598; 1991.
9. Dorman, D.C. *et al.*: Effects of an extract of *Gingko biloba* on bromethalin-induced cerebral lipid peroxidation and edema in rats. *AJVR 53* (1):138-142; 1992. ■