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Topical Review

Bromethalin

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A B S T R A C T

Bromethalin is a potent neurotoxin capable of inducing fatal cerebral edema in companion animals. Bromethalin decreases adenosine triphosphate production resulting in cerebral edema. Toxicosis can be seen in cats and dogs with oral exposures as low as 0.3 and 2.5 mg/kg, respectively. High doses produce severe muscle tremors, hyperthermia, seizures, and death within a couple hours postingestion. The usual presentation after moderate to low exposure develops over 12-24 hours with progressive ataxia, paresis, and hindlimb paralysis. Central nervous system depression continues to semicoma or coma. Diagnosis is based upon history of exposure, development of progressive appropriate clinical signs and chemical confirmation in tissues. Treatment relies heavily upon early emesis induction and prolonged decontamination with pulse dosing of activated charcoal. There is no specific antidote; attempts to control cerebral edema with diuretics and corticosteroids have met with limited success. Significant supportive care is usually required, often including seizure management, nutritional support, and defense against decubital ulceration. Prognosis is guarded to poor.

Introduction

Bromethalin was discovered in the mid-1970s and was rapidly incorporated into a variety of rodenticides.[1] Chemical structure is 2,4-dinitro-N-methyl-N-[2,4,6-tribromophenyl]-6-[trifluoromethyl] benzenamine.

New Environmental Protection Agency regulations for rodenticide use in the United States came into effect in 2011. The Environmental Protection Agency was concerned that over 14,000 rodenticide exposures in children less than 5 years of age were reported annually to the Poison Control system in the United States, coupled with significant number of reports of poisoning in companion animals, nontarget wildlife and relay or secondary toxicosis in predators and scavengers. The risk mitigation decision was made to ban residential use of second generation anticoagulant rodenticides, also known as single-feeding anticoagulant rodenticides. Those products targeted for removal from the over-the-counter market include as the active ingredients brodifacoum, bromadiolone, difethialone, and difenacoum. There are other requirements regarding allowable quantities of toxin, acceptable form of toxin (e.g., no pellets and blocks only) coupled with specific bait station configurations. These new regulations have considerably increased the sales of over-the-counter bromethalin products. The danger is that many anticoagulatant rodenticides have similar names and bromethalin may be confused as such instead of the potent neurotoxin it is.

Bromethalin rodenticides are readily available for over-the-counter purchase by the public for residential use. This toxin is the active ingredient in a variety of products (Table 1). Bromethalin cannot be distinguished from other rodenticide baits by appearance or color.

Bromethalin is usually marketed as a 0.01% formulation (2.84-mg bromethalin per ounce of bait) for consumers and by law must be in a block form.

Toxic Dose

Bromethalin has a Lethal Dose 50% (LD_{50}) of 2.38-5.6 mg/kg in dogs and 0.4-0.71 mg/kg in cats.[2,3] The guinea pig bromethalin LD_{50} is 1000 mg/kg, this is due to the relative inability to metabolize the parent compound to the more toxic metabolite desmethyl bromethalin.[4] Deaths have been reported with oral bromethalin exposures as low as 0.95-1.05 mg/kg in dogs. Clinical signs may manifest following exposures as low as 10% of the LD_{50}. Clinical signs of bromethalin toxicosis have been exhibited in cats with oral doses as low as 0.24 mg/kg. Relay toxicosis has never been demonstrated experimentally.

Toxicokinetics

In the rat model, bromethalin has a relatively rapid intestinal uptake with peak plasma concentrations occurring within 4 hours postingestion with an absorption half-life of 2.7 hours.[4] Metabolism occurs rapidly by hepatic mixed-function oxygenases via N-demethylation to its metabolite desmethyl bromethalin.[4] Plasma half-life of bromethalin is approximately 6 days indicating slow elimination. Both bromethalin and its metabolite are widely distributed in all body tissues, with highest concentrations occurring in fat.[5] Bromethalin is primarily excreted by the bile by enterohepatic circulation, with less than 3% renally excreted. Enterohepatic reabsorption occurs with cycling between the bile and reuptake from the intestinal tract.

Mechanism of Toxicity

Bioactivation is important in the development of toxicity of bromethalin. This is evidenced by the relative resistance to toxicity in species unable to metabolize bromethalin to desmethyl bromethalin (e.g., guinea pigs with an LD_{50} 1000 mg/kg).[4] The proposed mechanism for toxicity is the uncoupling of mitochondrial oxidative phosphorylation.[4] This results in reduction of adenosine triphosphate synthesis resulting in less energy available to maintain Na^+/K^+ pumps due to weakened ion gradients. The net effect is loss of oncotic control and retention of water causing edema of the myelin sheath and subsequent separation of the myelin lamellae causing dramatic increases in intracranial and cerebrospinal fluid (CSF) pressures.

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Table 1
Some commercial bromethalin-containing rodenticides

Assault
Fastrac
Gladiator
Rampage
Tomcat
Trounce
Vengeance

Bromethalin is also responsible for increased cerebral lipid peroxidation.[6]

Clinical Signs

The primary target organ for bromethalin toxicity is the central nervous system (CNS). Onset of clinical signs usually begins approximately 10 hours postingestion with a range of 2-14 hours. Generally, the earlier the onset of clinical signs the higher the dose ingested. As with most poisonings the presenting clinical signs are dependent upon amount of toxin ingested, time since ingestion, and stage of intoxication. Patients with very large exposures exhibit an acute onset of clinical signs with the onset of severe muscle tremors, hyperesthesia, hyperexcitablity, hyperthermia, and seizures (focal motor or generalized or both) which can be induced by external stimuli.[2,3] The primary cause of death is respiratory paralysis.

Patients with moderate exposures to bromethalin manifest clinical signs consistent with cerebral edema and myelin sheath abnormalities. The onset of these clinical signs may be somewhat delayed and may include paralysis of rear limbs, ataxia, paddling, hyperthermia, muscle tremors, hyperexcitiblity, occasionally a loss of vocalization, loss of tactile sensation, forelimb extensor rigidity, seizures, and death within 2-4 days.[2,3,7] Rear limb ataxia progresses to diminished deep pain responses, upper motor neuron bladder paralysis, and patellar hyperreflexia.

Lower dose exposure patients may take several days for the onset of clinical signs that can progress over 1-2 weeks post-exposure.[2,3] CNS depression usually occurs in patients exhibiting hindlimb ataxia and can progress to coma. Clinical signs may include lethargy, depression, vomiting, tremors, ataxia, loss of voice, paralysis, lateral recumbency, coma, and death.

The most common presentation is hindlimb ataxia and paresis secondary to decreased hindlimb proprioception. Gastrointestinal signs can occur including vomiting, anorexia, and occasionally in cats abdominal distention from enlarged bowel loops.

Minimum Database

There are usually no significant alterations in laboratory serum biochemistries. CSF analysis is normal in spite of elevated CSF pressure.[3,4]

Confirmatory Test

Diagnosis of bromethalin toxicosis relies upon a history of exposure to a potentially toxic quantity of toxin and development of appropriate clinical signs. Chemical detection is possible, contact the diagnostic lab for testing recommendations, turnaround time may be an issue relative to the individual case at hand.[5,8,9]

Postmortem diagnosis may be inferred by histologic examination of diffuse white matter vacuolization in CNS tissue samples.[10]

Treatment

There is no specific antidote for bromethalin. Symptomatic and supportive care is the mainstay of treatment. Therefore, the key to successful management is early decontamination and efforts to prevent gastrointestinal absorption.

Upon initial presentation, if the ingestion occurred within the last hour, emesis should be induced. Attempts at emesis induction should occur expeditiously because of rapid uptake of the toxin. However, if the patient is already presenting with clinical signs consistent with CNS depression emesis should not be attempted as the risk of aspiration is significant. Patients exposed greater than 1.5 hours before presentation should not have emesis induced as the effectiveness of this decontamination technique is poor at this time and onset of other therapies will be delayed. An hour postingestion, unless the block of toxin is still intact, the probability of removing significant toxin is poor. Even in the best of circumstances with early (within 10 minutes) emesis induction the maximum return is 75% of toxin. Emetics routinely administered in dogs include intramuscular administration of apomorphine at 0.04 mg/kg or peroral administration of 3% hydrogen peroxide at 1 mL/kg. In exposed cats, peroral administration of 3% hydrogen peroxide at 1 mL/kg or intramuscular or subcutaneous administration of xylazine at 0.4-1.1 mg/kg has been used successfully.

Gastric lavage is no longer recommended in human medicine for decontamination as evidence for its efficacy is weak.[11]

Bromethalin has significant enterohepatic recirculation (as much as 25%), which is an indication for the use of activated charcoal. The usual dose of activated charcoal is 1-4 g/kg, there is no evidence that added cathartics improve clinical outcomes in treating toxicities. This may be particularly true in bromethalin cases where intestinal ileus has been described. If a cathartic is administered do not use magnesium sulfate as it could add to the CNS depression. Owing to the slow elimination of bromethalin subsequent lower doses of activated charcoal should be administered every 4-6 hours at 1 g/kg for a minimum of 2-3 days.[3,12]

There is some risk of hypernatremia after activated-charcoal administration, usually in smaller patients ingesting a toxin which causes high sodium levels or those patients with underlying renal dysfunction. Attempting to mitigate this risk many animals on a pulse-dose activated-charcoal regime are placed on intravenous (IV) fluid therapy. IV fluids can be used in bromethalin-intoxicated patients but with caution as they may increase cerebral edema. IV fluids are of limited benefit in aiding bromethalin clearance as only 3% is cleared by the kidneys.

Monitor and treat for cerebral edema and elevated intracranial pressure. In rat studies constant rate infusions of mannitol or furosemide or dexamethasone reduced CSF pressure but these effects were transient as once the infusion stopped the pressures returned.[3,4,12,13] Despite the treatment failures observed with mannitol and dexamethasone in research dogs and cats, the use of a hyperosmotic agent such as mannitol (250 mg/kg, administered every 6 hours IV) is still indicated for the control of bromethalin-induced cerebral edema.[13] Mannitol side effects can include hypernatremia (remember hypernatremia can be an issue with activated charcoal as well), pulmonary edema, and dehydration. The best approach to prevent or manage the dehydration is frequent oral administration of water. Dehydrated animals are at risk of rebound cerebral and pulmonary edema when IV rehydration is attempted as evidenced by a deterioration of neurologic clinical signs.

Hyperosmolar agents can be avoided with the administration of furosemide (1 mg/kg, IV every 4-6 hours) rather than mannitol

thereby preventing risk of rebound edema, hypernatremia, and significant alterations in serum osmolarity. Patients can benefit with the addition of IV dexamethasone (2 mg/kg, every 6 hours) with either diuretic, however the effects of all are transient and disappear once administration of the drug is ceased.

Severe trembling or seizures may be controlled with either diazepam (1-2 mg/kg, IV as needed) or phenobarbital to control seizures (5-15 mg/kg, IV as needed).

Supportive care should include quality nursing care, padded bedding, frequent turning, and nutritional support as many victims are anorexic.

Prognosis

Some animals may recover from bromethalin toxicosis. In mild poisoning cases, overt clinical signs usually resolve within several weeks of ingestion, although subtle signs of neurologic dysfunction may persist. Animals with the more severe clinical signs, including coma or paralysis, generally have a grave prognosis.[13]

Differential Diagnosis

Differential diagnosis should consist of most neurologic syndromes including lead, ethylene glycol, organophosphates, strychnine, methaldehyde, zinc phosphide, monosodium fluoroacetate (1080), and tremogenic mycotoxins.[13]

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