Intravenous Lipid Emulsion Therapy for Bromethalin Toxicity in a Dog

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ABSTRACT

Bromethalin is a central nervous system toxin currently incorporated into several different rodenticides. In 2008, the EPA requested that manufacturers phase out second-generation anticoagulant rodenticides. In response, manufacturers began to increase production of bromethalin-based rodenticides. It is likely that pet exposure to bromethalin will increase in the future. Bromethalin has no known antidote and tends to deposit in fat. Intravenous lipid emulsions (ILEs) are being used with increasing frequency in both human and veterinary medicine to treat numerous acute systemic toxicities. A 4 yr old spayed female Pit bull terrier was presented following witnessed ingestion of bromethalin rodenticide by the owners. Decontamination was unsuccessful and ILE was started. Serum was frozen at −80°C before and 1 hr after completion of ILE. In rats, the half-life of desmethylbromethalin, the toxic metabolite, has been reported at 5.6 days and 6 days, and it is likely to be similar in dogs. The only intervention between the pre-lipid serum sample and the post-lipid serum sample was the administration of ILE, and the serum desmethylbromethalin levels were reduced by 75% (from 4 ppb to 1 ppb) during this time. To the authors' knowledge, this is the first report describing treatment of bromethalin ingestion with ILE. (*J Am Anim Hosp Assoc* 2016; 52:265–268. DOI 10.5326/JAAHA-MS-6396)

Introduction

Bromethalin (2,4-dinitro-N-methyl-N-[2,4,6-tribromophenyl]-6-[trifluoromethyl] benzenamine) is a central nervous system toxin that is currently incorporated into several different rodenticides. In 2008, the EPA requested that manufacturers phase out second-generation (longer-acting) anticoagulant rodenticides. The goal was to have the phase-out completed by 2011. In response, many manufacturers began to increase production of bromethalin-based rodenticides, and the new regulations have considerably increased sales of over-the-counter bromethalin products.[1] It is likely that pet exposure to this rodenticide will increase in the future, and there have been multiple warnings to this effect on the American Society for the Prevention of Cruelty to Animals (ASPCA) toxicology website (www.aspca.org/pet-care/animal-poison-control) and the National Poison Control Center blogs (www.petpoisonhelpline.com).[2] Due to the concern about accidental ingestion by children and pets, some countries, such as Canada, have placed regulations on methods of baiting with bromethalin.[3]

Bromethalin is a rapidly acting toxin with no known antidote. Metabolism of bromethalin has been studied in rats, and it has been shown that peak plasma concentrations of the metabolite, desmethylbromethalin, occur within 4 h after ingestion.[4] Hepatic metabolism converts bromethalin to the more toxic metabolite, desmethylbromethalin, rapidly. Its principal mechanism of action is to uncouple mitochondrial oxidative phosphorylation, and it reaches its highest concentration in body fat.[5] The oral lethal dose 50 in dogs has been reported to be 3.7 mg/kg, but it is possible that individual dogs could develop clinical signs following exposure to just one-tenth of the oral lethal does 50.[6,7] Bromethalin excretion is primarily in the bile, and prevention of enterohepatic recirculation along with supportive care are the mainstays of treatment.[4]

Uncoupling of oxidative phosphorylation results in decreased adenosine triphosphate concentrations and eventual failure of

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ASPCA (American Society for the Prevention of Cruelty to Animals); ILE (intravenous lipid emulsions)

adenosine triphosphate-dependent cell membrane pumps. With sodium unable to be excreted, water enters and cells swell, leading to central nervous system edema. Increased cerebral lipid peroxidation also occurs, most likely as a result of increased reactive oxygen species.[4] Clinical signs include seizures, ataxia, hyperesthesia, coma, and death. With no known antidote, treatment consists of decontamination (emesis, activated charcoal) and supportive care, and the prognosis is poor for dogs that develop toxicity.

Intravenous lipid emulsions (ILEs) are being used with increasing frequency in both human and veterinary medicine to treat acute systemic toxicities ranging from large doses of local anesthetic drugs to other lipophilic drug poisonings.[8–10] Lipids have been shown to reverse the cardiotoxic effects of local anesthetic overdose as well as overdose of other medications such as beta blockers, calcium channel blockers, parasiticides, herbicides, and a variety of psychotropic agents.

This report describes the use of ILE to treat bromethalin ingestion in a dog.

Case Report

A 4 yr old spayed female Pit bull terrier weighing 33 kg was presented to the University of Illinois veterinary teaching hospital 3 h after witnessed ingestion of bromethalin rodenticide by the owners. The owners believed that the dog ate one brick of rat bait that contained 0.01% bromethalin. Each brick weighed approximately 28.5 g (1 oz) and contained 2.85 mg of bromethalin. The owner administered hydrogen peroxide by mouth per instructions by the ASPCA Poison Control Center, but this failed to induce emesis. It was at this time that the owner elected to bring the dog to the emergency room.

While in the hospital, the dog had a single bowel movement in which flecks of green material resembling rodenticide could be seen. Therefore, it was determined that the dog had likely consumed additional rodenticide prior to the witnessed event. After speaking with ASPCA Poison Control, it was determined that 2 oz of the bait would reach the low end of the toxic dose for this dog, and it was assumed that the patient had consumed at least this amount. The owners later reported that it was possible that two blocks of rodenticide were missing from their yard.

Upon presentation, the dog was bright, alert, responsive, and aggressive. She had a temperature of 104.3°F, a pulse of 126 beats per min, and a respiratory rate of 44 breaths per min. The reminder of the physical examination was unremarkable. Initial blood work revealed an elevated lactate at 5.4 mmol/L (0.44–2.93) and decreased potassium at 3.5 mmol/L (3.7–4.91). The packed cell volume was 60% and total solid concentration was 7.4 g/dL. Serum was frozen at −80°F for desmethylbromethalin levels.

Intravenous apomorphine at 0.03 mg/kg was administered twice and failed to produce emesis both times. An intravenous catheter was placed and ILE was administered at 1.5 ml/kg given over the first 20 min followed by 0.38 ml/kg/min for 60 min. Serum was obtained for desmethylbromethalin levels 1 h following administration of the intravenous lipids and was immediately frozen at −80°F until analysis. After the second sample was collected, isotonic crystalloids were started at 5 ml/kg/h intravenously and were continued throughout the night. Activated charcoal was administered by mouth at 7.3 ml/kg every 6 h.

The dog was kept hospitalized with supportive care for 24 h, during which no neurologic abnormalities were noted. After 24 h, the owner elected to take the patient home for continued monitoring because of financial reasons. The owner reported the dog was acting normally at a 2 wk follow-up call.

The pre-lipid and post-lipid serum samples were submitted to the California Animal Health and Safety Laboratory System, University of California—Davis, Davis, California, for analysis of desmethylbromethalin concentrations. The reporting limit for desmethylbromethalin in the pre-lipid sample was 4.0 ppb. The reporting limit for the desmethylbromethalin in the post-lipid sample was 1.0 ppb.

Discussion

To the authors' knowledge, this is the first report describing treatment of bromethalin ingestion with ILE. Although the actual ingested dose is unknown, it is likely to have been a minimum of two bricks, or 5.7 g. The reported half-life of desmethylbromethalin in rats has been reported at 5.6 days and 6 days, and it is likely to be similar in dogs.[1,4] The only intervention between the pre-lipid serum sample and the post-lipid serum sample was the administration of ILE, and the serum desmethylbromethalin levels were reduced by 75% (from 4 ppb to 1 ppb) during this time. It is therefore likely that the ILE was responsible for the rapid and significant decrease in the desmethylbromethalin levels.

Following ingestion of bromethalin, hepatic metabolism converts it to the more toxic metabolite desmethylbromethalin, and this is then excreted in the bile by enterohepatic circulation, with renal excretion being less than 3%. Reuptake from the bile and intestinal tract causes enterohepatic reabsorption to occur.[1] Due to bromethalin and its metabolite primarily being deposited in fat, the lipophilic nature of bromethalin would make it an ideal toxin to be treated with intravenous lipid therapy.[11]

Desmethylbromethalin primarily acts on the central nervous system and can cause onset of clinical signs within 2–14 h post

ingestion.[1] Patients with high dose exposures can show acute onset of clinical signs such as muscle tremors, hyperesthesia, hyperthermia, and seizures, with the eventual final cause of death being respiratory paralysis.[6] In moderate dose exposures, clinical signs may be somewhat delayed and may include paralysis of the rear limbs, ataxia, muscle tremors, hyperthermia, paddling, seizures, and death within 2–4 days.[6] With lower dose exposures, patients may exhibit clinical signs that progress over 1–2 wk and may include lethargy, depression, vomiting, tremors, ataxia, paralysis, coma, and possible death.[6]

It has been mentioned that there is no specific antidote for bromethalin, and supportive care is the mainstay of therapy. Early decontamination and treatment to prevent gastrointestinal absorption and enterohepatic recirculation are suggested; however, decontamination is not always possible, as in this case. Due to bromethalin's rapid absorption, it is also recommended that patients who have ingested bromethalin more than 1.5 h prior to presentation should not have emesis induced.[1] If emesis is induced within 10 min of ingestion, only 75% of the toxin may be returned.[1] Gastric lavage is no longer recommended due to weak evidence of efficacy.[12]

Use of activated charcoal has been recommended with bromethalin ingestion, as it has significant enterohepatic recirculation.[1] However, the slow elimination of desmethylbromethalin creates the need to have low doses administered frequently for an extended period of time (1 mg/kg every 4–6 h for 2–3 days).[11] Diuresis with intravenous fluids is typically attempted in cases of bromethalin toxicosis but is usually of limited benefit, as only 3% of the toxin is cleared by kidneys.[1]

ILEs have been used with increasing frequency to treat acute systemic toxicities involving both local anesthetics and other lipophilic, non-anesthetic drugs.[8–10] The most common form of ILE is 20% Intralipid[a] emulsion. This product is made up of 20% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, water, and sodium hydroxide. Reviews of recent case reports and uses of ILEs have been recently published in both human and veterinary medicine.[13–15] Several mechanisms of action have been suggested for the improved clinical outcome seen following administration of ILEs. The most widely accepted theory is based on the idea of a "lipid sink."[16,17] The increased lipid concentration introduced into the plasma is thought to create a new pharmacokinetic equilibrium that converts the drug from the tissue to the aqueous plasma phase and then to the lipid phase. Lipophilic substances will therefore be attracted to the high concentration of fat, and a concentration gradient forms between the tissue and blood, causing the drug to move away from fat deposits within the body. As a result, we hypothesized that the lipophilic nature of bromethalin would allow the ILE to exert the same "lipid sink" effect, thereby decreasing the amount of circulating active toxin. The lipid phase is then thought to be eliminated through the biliary system.

While limited, ILE use in veterinary medicine has proven to result in very few side effects.[18,19] However, it should be noted that some reports of complications with ILE use in human medicine have been reported, such as hypertriglyceridemia, pancreatitis, and acute lung injury. Most commonly, lipemia resulted in interference with laboratory testing.[20] Patients receiving ILE should be monitored for hemodynamic changes and pancreatitis.

Conclusion

The laboratory results demonstrated a dramatic reduction in serum desmethylbromethalin concentrations secondary to ILE administration. We hypothesize that the ILE hastened the removal of the desmethylbromethalin by first attracting it to the lipid compartment and then eliminating it via the biliary system. The lipophilic nature of bromethalin makes it an excellent candidate for this treatment, and this is the only report of an intervention that has rapidly reduced the circulating levels of bromethalin, to the authors' knowledge. ILEs offer a potentially attractive option for the treatment of bromethalin toxicity, and this treatment should be considered in such cases.

FOOTNOTE

[a] Intralipid 20% solution; Hospira Inc., Lake Forest, IL

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