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. 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). 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.

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. 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. 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. Bromethalin excretion is primarily in the bile, and prevention of enterohepatic recirculation along with supportive care are the mainstays of treatment.

Uncoupling of oxidative phosphorylation results in decreased adenosine triphosphate concentrations and eventual failure of
adrenosine 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. 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. 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 approxi-
mately 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 intrave-
nously 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. The only intervention between the pre-lipid
serum sample and the post-lipid serum sample was the adminis-
tration 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. 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.
ingestion. 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. 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. 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.

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. If emesis is induced within 10 min of ingestion, only 75% of the toxin may be returned. Gastric lavage is no longer recommended due to weak evidence of efficacy.

Use of activated charcoal has been recommended with bromethalin ingestion, as it has significant enterohepatic recirculation. 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). 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.

ILEs have been used with increasing frequency to treat acute systemic toxicities involving both local anesthetics and other lipophilic, non-anesthetic drugs. The most common form of ILE is 20% Intralipid 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. 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.” 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. 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. 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.

REFERENCES


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