Case Report

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Moxidectin toxicosis in a puppy successfully treated with intravenous lipids

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Abstract

Objective – To describe successful treatment of canine moxidectin toxicosis with the novel therapy of IV lipid administration.

Case Summary – A 16-week-old female Jack Russell Terrier was presented with acute onset of seizures followed by paralysis and coma shortly following suspected exposure to an equine formulation of moxidectin. Moxidectin toxicity was later confirmed. Initial therapy consisted of diazepam, glycopyrrolate, and IV fluids. Mechanical ventilation and supportive nursing care were provided as needed. An emulsion of 20% soybean oil in water, commonly used as the fat component of parenteral nutrition, was administered intravenously as a bolus of 2 mL/kg followed by 4 mL/kg/h for 4 hours beginning 10 hours after exposure and was administered again at a rate of 0.5 mL/kg/min for 30 minutes beginning 25.5 hours post-exposure. Mild improvement was seen after the first dose, and dramatic improvement was noted within 30 minutes of the second dose. The puppy's neurologic status returned to normal within 6 hours of the second administration, with no relapses.

Unique Information Provided – IV lipid therapy is a novel treatment approach for moxidectin toxicity. Its use is supported by recent research and case studies involving IV lipid administration for bupivacaine and other fat-soluble toxins. Lipid administration appeared to reverse the signs of toxicity and may prove to be a highly effective therapy for moxidectin and other fat-soluble toxins.

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Introduction

Moxidectin is a macrocyclic lactone parasiticide, used in veterinary medicine for canine heartworm prophylaxis and large animal endoparasitism. Canine moxidectin toxicity is frequently due to massive ingestion through exposure to equine formulations of moxidectin (20,000 µg/mL), as in the present case, or feces from livestock treated with moxidectin.[a] Clinical signs are vomiting, ataxia, tremor progressing to seizures, and in severe cases, respiratory paralysis. Current therapeutic recommendations consist of supportive care, including nutritional and ventilator support in those cases with respiratory paralysis. Within the last 6 years, 107 cases of canine moxidectin exposure, excluding exposure to products licensed for dogs, have been reported to the American Society for the Prevention of Cruelty to Animals Animal Poison Control Center. This likely underestimates the prevalence, as many cases are not reported. Only a handful of case reports describing canine moxidectin toxicity are published.[1–4]

Case Report

A 16-week-old female Jack Russell Terrier puppy weighing 3.2 kg was presented for management of suspected moxidectin toxicity. Her relevant medical history included a recent 30-day course of ivermectin (1.0 mg, PO, q 24 h) intended for prevention of demodicosis. The puppy also recently had brief contact with several horses who had received treatment with a 2% moxidectin parasiticide.[b] Forty-five minutes after the suspected exposure, the puppy vomited a large volume of stomach contents, became ataxic, and developed

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tremors. Within several minutes she developed generalized tonic-clonic seizure activity and was immediately transported to the local veterinary clinic.

On arrival at the primary care clinic, the puppy was seizing. Her recorded vital signs at presentation were temperature, 38.7°C (101.7°F); heart rate, 130/min; and blood pressure, 148/129 mm Hg. Her respiratory sounds were described as raspy. A 22-Ga IV catheter was placed in the right cephalic vein, through which diazepam[c] (2.5 mg) was administered. The diazepam was effective at stopping the tonic-clonic movements, but the puppy became comatose. IV 0.9% sodium chloride (16 mL/h) was administered. Over the following 45 minutes, the puppy's heart rate decreased to 95/min and blood pressure dropped to 102/34 mm Hg. Glycopyrrolate[d] (0.01 mg/kg, IV) was administered and the developing bradycardia resolved. Results from a biochemistry profile and CBC were within reference intervals for the age and species. The puppy was transferred to a tertiary care facility.

Vital signs on admission to the tertiary care hospital, approximately 5 hours after the suspected toxin exposure, were heart rate, 60/min; respiratory rate, 40/min with shallow thoracic excursions; rectal temperature, 38.2°C (100.8°F); oscillometric blood pressure,[e] 118/77 mm Hg: and SpO_2,[f] 88%. The puppy was flaccid and unresponsive to noxious stimuli. Pupils were mid sized, symmetric, and light responsive. Bilateral palpebral reflexes were present. A lead II ECG indicated sinus bradycardia, marked sinus arrhythmia, and spiked *T*-waves (Figure 1). Venous pH was 7.127, PCO_2 was 72.3 mm Hg, and PO_2 was 39.0 mm Hg. Lactate was 3.7 mmol/L (reference interval 1.1–2.0 mmol/L), and glucose was 7.4 mmol/L (133 mg/dL) (reference interval 3.6–7.0 mmol/L [65–126 mg/dL]). Sodium, potassium, chloride, and ionized calcium were within reference intervals.[g]

Initial treatment consisted of tracheal intubation, positive pressure ventilation with 100% oxygen using an anesthesia ventilator,[h] and atropine[i] (0.04 mg/kg, IV). Activated charcoal[j] (15 mL) was administered by orogastric tube. IV fluids[k] (30 mL/h) were also initiated. The puppy was admitted to the intensive care unit and monitored closely for the next several hours. She remained ventilator dependent, as determined by monitoring respiratory excursions, SpO_2, and arterial blood-gas analysis when ventilator weaning was attempted. When ventilated manually with an AMBU bag[l] on room air (FiO_2 21%), arterial pH was 7.469, PCO_2 was 34.9 mm Hg, and PO_2 was 97.0 mm Hg. Atropine was given as needed to treat bradycardia. External warming[m] was provided to maintain normothermia.

Approximately 10 hours after suspected toxin exposure, and 5.5 hours after admission to the tertiary care hospital, a bolus of an emulsion of 20% soybean oil in water[n] (6.5 mL) (commonly used as the fat component of parenteral nutrition) was administered through the peripheral catheter. This was followed by an infusion of 12 mL/h for 4 hours. Within 2 hours of initiation of lipid therapy, the puppy's respiratory effort improved sufficiently to allow discontinuation of mechanical ventilation but not extubation. With endotracheal oxygen insufflation of 3 L/min, arterial pH was 7.207, PCO_2 66.5 mm Hg, and PO_2 386 mm Hg. She developed periocular muscle twitching but remained unconscious.

Eleven hours after initiation of lipid therapy, and approximately 20 hours after suspected toxin exposure, the puppy began to swallow and was extubated. Oxygen (0.5 L/min) was provided with a nasal oxygen catheter. Her twitching gradually increased in intensity and frequency, and tactile stimulation precipitated tonic-clonic muscle activity. The puppy remained laterally recumbent.

Twenty-five hours after suspected toxin exposure, another bolus dose of lipid emulsion (48 mL, IV, over 30 min) was administered. Immediately following administration of this second dose of lipid emulsion, an IV infusion of diazepam (0.3 mg/kg/h, CRI) was initiated to treat the suspected seizure activity. Within 30 minutes of finishing the second dose of lipid emulsion the puppy was ambulatory, albeit ataxic, and was attempting to chew off her bandages. Oxygen supplementation was discontinued 2 hours after the second dose of lipid emulsion as SpO_2 remained at 98% on room air, and respiratory excursions visibly improved. Her behavior normalized over the next 3–4 hours. Within 6 hours of the second dose of lipid emulsion, the puppy ate well, and then slept normally for the next several hours. She was rousable from sleep. The diazepam infusion was discontinued within 3 hours of initiation.

Blood submitted for a CBC 48 hours after admission showed no abnormalities, and a full biochemical profile showed mild elevation of CK (518 U/L; reference interval, 5–235 U/L), and decreased urea (1.6 mmol/L

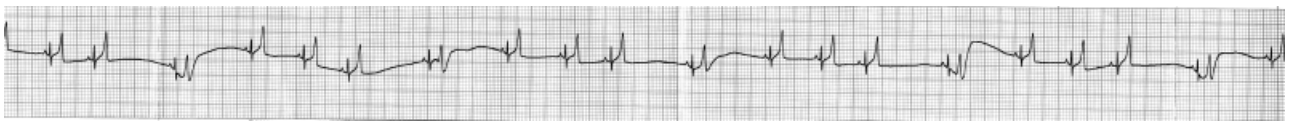

Figure 1: ECG on admission. Paper speed 25 mm/s, heart rate 61/min.

[4.5 mg/dL]; reference interval, 3.0–10.0 mmol/L [8.4–28 mg/dL]). Serum samples taken within 30 minutes of the second dose of lipid infusion were positive for moxidectin (463 ppb) and negative for ivermectin.[o]

The puppy had no relapse of neurologic signs and was discharged to her owners 2 days following admission. Her owners noted her behavior following hospital discharge was completely normal. A follow-up CBC and biochemical profile 9 days after toxin ingestion were within reference intervals.

Discussion

The broad-spectrum antiparasitic activity of macrocyclic lactone drugs has revolutionized parasitic control in human and veterinary medicine.[5] Moxidectin, a milbemycin, and ivermectin, an avermectin, are macrocyclic lactones. Milbemycins and avermectins are lipophilic molecules produced from *Streptomyces* spp. and share structural and physicochemical properties. Macrocyclic lactones bind to glutamate-gated chloride channels expressed on nematode neurons and pharyngeal muscle cells. Once bound and activated, these chloride channels open slowly but irreversibly, resulting in prolonged hyperpolarization or depolarization of the neuron or muscle cell.[6] Rapid paralysis and inability to feed result in death of the parasite.[6]

Mammalian neurotoxicity is likely caused by binding to postsynaptic λ-amino-butyric-acid (GABA)-gated chloride channels within the CNS, causing hyperpolarization and blockade of neuronal impulse transmission.[7,8] P-glycoprotein (P-gp), a large transmembrane transporter protein present on the luminal membrane of capillary endothelial cells at the blood-brain barrier, actively limits penetration of avermectins into the brain, preventing neurotoxicity at therapeutic doses.[9] A subpopulation of Collies and related dog breeds exhibit increased sensitivity to the neurotoxic effects of ivermectin, due to a homozygous exonic deletion in the P-gp encoding gene, causing absence of the P-gp transporter.[10] Moxidectin is reported to have a wider safety margin than ivermectin in these breeds,[11] however, severe moxidectin toxicity in a Collie dog has been described.[1] Oral moxidectin doses of 90 μg/kg were tolerated without clinical signs in a group of ivermectin-sensitive Collies.[11] Beagles remained asymptomatic following the administration of 1130 μg/kg/d for 1 year.[p] The clinical signs associated with moxidectin and ivermectin toxicity include vomiting, ataxia, progressive weakness, tremor, and seizures. Time to peak plasma levels (T_{max}) for moxidectin is 2.0 ± 1.0 hours after ingestion.[12] The clinical course in affected dogs is dependent on the dose ingested and typically recovery is measured in days to weeks.[1–3,13] Current treatment recommendations are supportive nursing care including ventilatory and nutritional support as needed. Picrotoxin, a GABA antagonist, appeared to facilitate recovery in 1 case of ivermectin toxicity,[14] but precipitated seizures. Consequently, its use in the treatment of ivermectin toxicity has not been further investigated or recommended. Physostigmine, an anticholinesterase agent, will produce very transient clinical improvement but is not a direct antagonist of ivermectin and is associated with adverse effects of salivation, lacrimation, urination, defecation, and seizures. Although used in an attempt to control tremors and hyperactivity in the current case, benzodiazepines may actually be contraindicated because of their GABA-enhancing properties.[15]

The unique feature of this case is the IV use of a lipid emulsion for moxidectin intoxication, which appeared to dramatically abbreviate the course of recovery. We utilized an emulsion of 20% soybean oil in water that is frequently used as the fat component of parenteral nutrition. Its use in the treatment of moxidectin toxicity has not been described previously.

The use of lipid emulsions as therapy for toxicosis originates from research investigating the metabolic effects of bupivacaine in humans. Researchers found that pretreating rats with a lipid soybean oil emulsion resulted in marked resistance to the adverse cardiac effects of bupivacaine infusion.[16] Lipid administration after a rapid bolus of a toxic bupivacaine dose dramatically improved survival.[16] Infusion of lipid to anesthetized dogs immediately following administration of 10 mg/kg bupivacaine resulted in rapid recovery of normal ECG and blood pressure, compared with control dogs who uniformly died despite aggressive resuscitative efforts.[16] Furthermore, lipid administration given 10 minutes after injection of the same dose of bupivacaine and routine resuscitative efforts including cardiac massage also resulted in complete recovery of normal hemodynamics in all 6 treated dogs, compared with death in the 6 control subjects.[16] Consequently, it has been suggested that lipid infusion may be therapeutic in treating local anesthetic toxicity. Recent published case reports documented dramatic recoveries in humans suffering from cardiovascular collapse caused by local anesthetics[17–19] and buproprion, an aminoketone antidepressant.[20]

The mechanism by which lipids rescue patients from bupivacaine toxicity is not completely understood. Under aerobic conditions, fatty acids are the preferred fuel for oxidative metabolism by cardiac myocytes. Bupivacaine inhibits carnitine acylcarnitine translocase, a key enzyme of mitochondrial fatty acid metabolism.[21] It has been suggested that lipid infusion may increase intracellular fatty acid sufficiently to overcome the inhibi-

tion of carnitine acylcarnitine translocase.[16] An alternate proposal is through a *lipid sink* mechanism where offending drug is removed from the affected tissues by partitioning into a plasma lipid phase created by the infusion. This hypothesis is bolstered by recent reports describing the successful use of lipid infusions in the treatment of intoxication by drugs that differ from bupivacaine in their mechanism of action. IV lipid therapy has been used successfully in the treatment of buproprion and lamogitrine toxicity.[20] In rabbits, lipid therapy has been successful in treatment of clomipramine toxicity.[22] Buproprion, clomipramine, and bupivacaine share very high lipid solubility. The lipid/aqueous partition coefficient of bupivacaine is log *P* 3.64.[23] Moxidectin, with log *P* 4.1,[24] is yet more lipid soluble. Thus, the IV lipid may work by creating a large lipid pool, thereby removing the toxin from nervous system receptors into the lipid-rich plasma from where it is eventually excreted.

The temporal relationship between the lipid administration and the puppy's recovery suggests a causal association. Two hours following the initiation of a bolus of 2 mL/kg and a slow infusion of 4 mL/kg/h, the puppy was weaned from mechanical ventilation. Over the next several hours, the swallow reflex returned, but she remained recumbent, nasal-oxygen dependent and developed seizure-like myoclonic activity. The second dose of lipid was given at a faster rate, and within 30 minutes, the puppy became sternal and soon thereafter was ambulatory. She had full neurologic recovery within 6 hours of the second lipid dose, approximately 32 hours after exposure.

Lipid administration for moxidectin toxicity is uncharted territory. The initial lipid dose was loosely based on therapeutic recommendations for bupivacaine toxicity in humans of a 1.5 mL/kg bolus followed, if necessary, by a continuous infusion of 0.25 mL/kg/min for 30–60 minutes. In this case, the total 1-hour dose of an infusion of 0.25 mL/kg/min was administered over 4 hours rather than 1 hour, for fear of adverse consequences from unorthodox rapid administration of a large lipid volume. The second, generous lipid dose of a continuous infusion of 0.5 mL/kg/min for 30 minutes was given when the patient had improved but remained severely affected clinically and was at risk of euthanasia due to owner financial constraints. This large volume given over 30 minutes appeared to reverse signs of toxicity almost immediately.

The course of this puppy's recovery was remarkably short in contrast to a Collie intoxicated with moxidectin that required mechanical ventilation for 6 days and continued to be lethargic 10 days after exposure.[1] Another case report documented 2 confirmed canine moxidectin toxicoses. A 2-year-old Weimeraner presented with clinical signs of ataxia, tremors, and hyperesthesia but no respiratory dysfunction, and required 3 days for resolution of signs.[2] A 5-year-old Labrador Retriever presented with ataxia and mild partial seizures, did not need oxygen or ventilatory support, and recovered normal neurologic function 5 days post-exposure.[2] Moxidectin toxicity in a 6-year-old Labrador Retriever caused severe clinical signs of hypothermia, bradycardia, and paralysis, similar to this case presentation. The dog died within 3 days without the benefit of mechanical ventilation and intensive care.[3] A more recent case report describes a 10-month-old Border Collie with onset of seizures within 3 hours and coma within 6.5 hours of ingestion of an unknown dose of moxidectin. Ventilatory support was provided; the patient was extubated 36 hours after toxin exposure, and was able to walk with mild ataxia 58 hours after ingestion.[4]

The puppy reported here displayed rapid onset of severe neurologic dysfunction that quickly devolved into respiratory muscle paralysis, suggesting the ingestion of a large quantity of moxidectin. A recovery period of days to weeks with prolonged ventilator support was expected. Pharmacokinetic data also predicted a long convalescence as the terminal elimination half-life of moxidectin in the dog is 25.9 days.[12] The puppy's rapid and complete recovery from clinical signs of toxicity suggests lipid therapy hastened recovery.

Of interest in this case is this patient's prior month-long daily exposure to ivermectin, the last dose of which was administered the morning of moxidectin ingestion. The terminal elimination half-life of ivermectin is 80 ± 29.8 hours,[12] suggesting some tissue concentration of ivermectin was likely present, although plasma levels were not detected. This discrepancy may be due in part to the large volume of distribution of ivermectin, the relatively low doses used, or both, such that plasma levels fell beneath the detection limit of the assay. Ivermectin is both a potent substrate and inhibitor of P-gp.[25] Possibly, saturation or inhibition of blood-brain barrier P-gp with ivermectin enhanced CNS penetration of moxidectin. Ivermectin toxicity in the dog has been well documented, and presents with similar clinical signs. Lipid therapy may be beneficial in ivermectin toxicity as it is also lipophilic.

Lipid emulsions have a long track record of safety as part of parenteral nutrition where they are used as a much slower constant infusion. Bolus administration of large quantities of lipids such as those recommended for the treatment of drug toxicity have not been assessed for safety. No noted detrimental adverse effects have been noted in any human case report,[17–20] and this puppy exhibited no clinically appreciated adverse events following the administration of the lipid emul-

sion. While the induction of pancreatitis or creation of a fat embolism are theoretical concerns associated with lipid therapy, in the absence of any current, identified adverse reactions, it seems reasonable to consider lipid therapy when the alternative is death or euthanasia.

Lipid administration for treatment of fat-soluble toxins holds exciting therapeutic promise in human and veterinary medicine. A noncommercial, educational website (http://www.lipidrescue.org) dedicated to the dissemination of information and fostering discussion on lipid administration has been established by the principal original researcher.[16] There has been a call in the human anesthesia literature to strongly consider lipid administration in recalcitrant cases of local anesthetic toxicity and to have lipids readily available where local anesthetics are administered.[26] Current dosage recommendations for bupivacaine toxicity in humans, based on the previously noted animal studies, are bolus administration of 1.5 mL/kg Intralipid[n] (other product formulations of lipid emulsion have not been reported, so the use of Intralipid is favored), followed by an infusion of 0.25 mL/kg/min for 30–60 minutes.[16] The authors note, however, that much remains to be learned regarding optimal dosing schedules and lipid formulation for bupivacaine toxicity. The role of lipid in treatment of non-bupivacaine toxicities presents further unanswered questions. The findings in this case are promising; however, the contribution of lipid therapy to this puppy's recovery must remain speculative. The temporal association between lipid therapy and recovery, considered in the context of published animal laboratory studies and human case reports, presents a compelling argument for the therapeutic benefit of lipid administration in this case of moxidectin toxicity. Measurement of serum toxin levels before and after lipid administration in future cases may be of help in documenting evidence to substantiate or refute the lipid-sink hypothesis.

Footnotes

[a] Animal Poison Control Center of the American Society for Prevention of Cruelty to Animals, University of Illinois: Personal communication, 2007.
[b] Quest Gel, Wyeth Animal Health, Guelph, ON, Canada.
[c] Diazepam, Sandoz Canada, Boucherville, QC, Canada.
[d] Glycopyrrolate, Sandoz Canada.
[e] Cardell 9401, Sharn Veterinary Inc, Tampa, FL.
[f] Model 512, Novametrix Medical Systems Inc, Wallingford, CT.
[g] ABL 715, Radiometer, Copenhagen, Denmark.
[h] V725000 SAV 2500 Small Animal Ventilation, Smiths Medical PM Inc, Waukesha, WI.
[i] Atropine sulfate, Bimeda-MTC Animal Health Inc, Cambridge, ON, Canada.
[j] Charcodote, Pharmascience Inc, Montreal, QC, Canada.
[k] Plasmalyte A, Baxter Canada, Alliston, ON, Canada.
[l] CPR Bag, Mercury Medical, Clearwater, FL.
[m] Warm Touch Patient Warming System, Nellcor, Boulder, CO.
[n] Intralipid, for Baxter Pharmaceuticals by Fresenius Kabi, Uppsala, Sweden.
[o] California Animal Health & Food Safety Laboratory System, Davis, CA.
[p] Proheart, Fort Dodge Animal Health, Overland Park, KS.

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