LIPID THERAPY FOR SELECTED TOXINS

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KEY POINTS:

- Intravenous lipid emulsion (IVLE) therapy has shown recent promise in veterinary medicine for the treatment of several common poisonings such as ivermectin, permethrin (cats), local anesthetics and baclofen, among others.
- Few placebo-controlled studies exist for veterinary patients. Evidence for efficacy has been primarily anecdotal and based on case reports thus far.
- Dosing protocol is 1.5ml/kg of 20% IVLE solution IV as a bolus, followed by 0.25ml/kg/min for 1-2 hours.

INTRODUCTION:

The use of intravenous lipid emulsions (IVLE) has received much recent attention as potential antidote for a variety of lipophilic drug intoxications in veterinary medicine. Several case reports have shown promise, but to date few placebo-controlled studies have been performed. Potential toxicants that may respond to IVLE therapy include local anesthetics (such as lidocaine and bupivacaine), permethrin, muscle relaxers (such as baclofen), some anti-depressants, and avermectin parasiticides such as ivermectin.

The original study by Weinberg et al in 2006, demonstrated that IVLE administered to rats increased survival after bupivacaine-induced cardiac arrest. A follow-up study using a canine model showed that IVLE administration increased survival in bupivacaine overdose. A normal sinus rhythm was established after 5 minutes in all dogs that were given IVLE, while no dogs receiving saline placebo survived.

Subsequent studies in rabbits, mice, and dogs also showed that IVLE improved resuscitative efforts and survival in verapamil, propranolol, and clomipramine intoxications compared to standard resuscitative interventions alone.

Two clinical case reports exist in the veterinary literature. One involves moxidectin toxicity and the successful use of IVLE. In this case report, a puppy was exposed to moxidectin, and shortly thereafter developed vomiting, ataxia, seizures and tremors. Seizure activity was treated with intravenous diazepam but the patient became comatose, requiring mechanical ventilation. IVLE therapy was initiated 10 hours post exposure, and within 2 hours of initiation of IVLE therapy the patient's condition improved to the point that he was able to be extubated. The patient was discharged 2 days after admission with no further neurological signs. The second report concerns a 5 year-old cat given a SQ overdose of lidocaine who made a complete recovery after an IV lipid infusion.

MECHANISM OF ACTION:

The precise mechanism of IVLE therapy as an antidote has not been firmly established, however there are several mechanisms that have been proposed by investigators. One hypothesis suggests the possibility of a "lipid sink" in which lipid emulsions provide a separate plasma compartment for lipophilic agents to partition into. Another hypothesis is that administration of free fatty acids may augment cardiac performance in cardiotoxic drug overdoses by enhancing ATP production by mitochondria. Under normal conditions, fatty acids are the preferred myocardial metabolic substrate. If fatty acid transport is impaired due to cardiotoxic drug overdose (as is seen in local anesthetic overdose), the administration of lipid emulsions may provide enough fatty acids to improve myocardial metabolism and restore function.

IVLE are typically used as a dense source of calories in parenteral nutrition admixtures for either partial or total parenteral nutrition (PPN/TPN). They are also used as a drug delivery vehicle for drugs which are poorly water soluble, most notably, propofol. The most common brand used for IVLE therapy of toxicities is Intralipid® manufactured by Baxter Pharmaceuticals (Deerfield, IL). Other brands used in this technique are Liposyn (Hospira Pharmaceuticals, Lake Forest, IL) and Medialipid® (B Braun Pharmaceuticals, Germany).

IVLE are composed of medium chain triglycerides, long chain triglycerides, or a combination of both. The most common IVLE is a soybean oil in water formulation that has been stabilized by an egg phospholipid emulsifier. The soybean oil is used as a source of essential fatty acids linolenate and linoleate. The most common formulations used clinically are in concentrations of 10-30%. The toxicity of IVLE (600-900 mOsm/l) allows administration through small peripheral veins, although administration through a central catheter with its tip in the vena cava is preferred if possible. The toxicity of IVLE differs from total parenteral nutrition (TPN) solutions (osmolality 1000-3000 mOsm/l) which limits infusion of TPN to central catheters only.

Most of the adverse effects associated with IVLE are associated with long term administration and impairments in plasma clearance of the solution. Toxicity has not been documented for one time, rapid infusions as are used in IVLE therapy.
for toxicities. The most common reported adverse events in humans are hypersensitivity reactions to the egg stabilizer and thrombophlebitis at the catheter site.

**INDICATIONS:**

*Local anesthetics:* Local anesthetics act directly on nerve cells to block their ability to transmit impulses down their axons. Local anesthetics act on the voltage dependent sodium channels which exist in all neurons. Because termination of local anesthetic action ultimately depends on movement of the drug into the systemic circulation, side effects and toxicity can result from the blockade of impulse propagation in excitable organs and tissues as well as from accidental intravenous injection. Depression of cortical inhibitory neurons, without the balancing depression of excitatory nerves, may result in the tremor and restlessness and culminate in seizures, coma and respiratory failure. Local anesthetics can also potentially have adverse effects on the cardiac pacemaker activity, electrical excitability, conduction and cardiac contractile forces. Among the local anesthetics in current use, bupivicaine is considered to be the most cardiotoxic. Cats are particularly sensitive to local anesthetic overdose as compared to dogs.

*Calcium channel blockers:* Calcium channel blockers (CCB) are used to treat cardiac arrhythmias, systemic hypertension and hypertrophic cardiomyopathy. CCB act on voltage-gated transmembrane channels in vascular smooth muscles, nonvascular smooth muscle, and non-contractile tissue. Blockage of the L-type channels in vascular smooth muscle causes relaxation of vascular smooth muscle, and blockage of channels within cardiac tissue causes negative inotropic and chronotropic effects. These particular agents may exert profound effects on the cardiovascular system at therapeutic doses as well as with overdoses.

The most common clinical signs seen with CCB overdose include hypotension, brady- or tachycardia, seizures, and pulmonary edema. Treatment usually is aimed at early and aggressive decontamination and supportive care with intravenous calcium, supportive care and vasoactive substances. More serious intoxications may required tranvenous pacing or placement of a temporary pacemaker.

*Avermectin parasiticides:* Ivermectin and moxidectin are commonly used parasiticides with action against a wide variety of nematodes and arthropods. The mechanism of action is through binding to ion channels in peripheral nerves that are not present in mammals. The avermectins appear to have a very wide safety margin in mammals due to the blood brain barrier, which does not permit entry into the CNS in most breeds. Certain canine breeds, including Collies and Collie-derived breeds are prone to avermectin toxicity due to the presence of a genetic mutation that allows CNS entry of these compounds. Additionally, large overdoses can penetrate the CNS in any breed of dog. Clinical signs of avermectin intoxication include depression, mydriasis, blindness, weakness, recumbency, ataxia, and coma. Treatment is usually symptomatic and supportive with more serious cases requiring mechanical ventilation. Recovery with standard therapy can take several days to weeks; several anecdotal reports of IVLE therapy in cases of avermectin parasiticide overdose have shown dramatic and rapid resolution of symptoms.

**Anecdotal intoxications**

There have been many anecdotal reports of the use of IVLE in other toxicities encountered in veterinary medicine including:

- Baclofen
- Permethrin
- Loperamide (Immodium©)
- Bupropion
- Sertraline.

Of these, permethrin toxicosis holds great potential for shortening the hospital stay and decreasing the sometimes significant expense and morbidity/mortality seen with this condition in cats.

**DOSE AND TECHNIQUE:**

Information from the developer of the technique suggests the following supplies be on hand for IVLE therapy:

- 500ml 20% Intralipid®
- IV tubing
- 3 60mL syringes
- several 18-gauge needles
- a printout of the LipidRescue© instructions.

The standard dosing protocol using the 20% formulation of IVLE is **1.5 ml/kg over 5-15 minutes then 0.25 ml/kg/min over 1-2 hours.** This dose can be repeated in several hours if clinical signs of toxicity return. Prior to repeating the dose, a
peripheral blood sample should be evaluated for evidence of lipemia; additional doses should not be given if serum is lipemic. As the IVLE suspension is susceptible to bacterial overgrowth, aseptic technique is required.

Consultation with a professional poison control agency, such as the National Animal Poison Control Center or the Pet Poison Helpline can be helpful with general toxin management and specific instructions for IVLE therapy. Other supportive measures such as IV fluid therapy, oxygen therapy, mechanical ventilation, standard toxin decontamination and seizure control may also be indicated depending on the nature of the toxin.

REFERENCES
5. Harvey, Cave. Intralipid Infusion Ameliorates Propanolol-Induced Hypotension in Rabbits. Journal of Medical Toxicology 2008; 4(2): 71-75

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