

Lipid Therapy: Magic Milk?

Tina Wismer, DVM, DABVT, DABT
ASPCA Animal Poison Control Center
Urbana, IL

History

The use of lipid emulsions to treat toxicoses has really taken off in the past five years in both human and veterinary medicine. Lipid emulsions have been historically given intravenously to patients who were unable to get enough fat in their diet. In 1998, Weinberg *et al* demonstrated that an infusion of lipid emulsion protects against cardiac arrest secondary to a bupivacaine (local anesthetic) overdose in rats. This paper led to the idea that lipids may potentially be used to treat many other toxins.

Mechanism of action

The exact mechanism of action is unknown, but there are three theories. The first is the 'lipid sink' theory. In this theory lipophilic drugs are redistributed (bound) in the expanded plasma lipid volume and this decreases free (active) drug levels. The second theory is that because fatty acids can increase calcium concentrations in cardiomyocytes, lipids may cause an increase in inotropy that overcomes the depressive effects of the intoxication. The third theory is that local anesthetics inhibit carnitine acyltransferase, which is needed to transport fatty acids across myocardial mitochondrial membranes for oxidative phosphorylation. Lipids may overcome the decreased fatty acid transport via mass action or an unknown mechanism. All three of these theories may work for local anesthetic overdoses, but theory one is the prevailing thought for lipids working on non-local anesthetic intoxicants.

It is thought that after administration, the lipids are cleared from the blood by striated muscle, viscera, myocardium and subcutaneous tissues. The lipids are metabolized into free fatty acids and glycerol. What happens to the toxin is unknown.

Formulations and dosing

The lipid emulsion of choice for treating toxicoses is the 20% solution. This may be given through a peripheral catheter (no central line is needed). Veterinary dosing guidelines are taken from the human literature and are considered extra-label. Dosing is a 1.5 mL/kg initial IV bolus. In humans this is given very quickly (over 1 minute) as many of these patients are in asystole. The bolus is followed by a constant rate infusion (CRI) of 0.25 mL/kg/min for 30-60 minutes. The CRI can be repeated in 4-6 hours if no lipemia is present and the animal is still symptomatic. A total limit of 8 mL/kg/d has been suggested in the human literature.

When to use?

In human medicine, use of lipids is reserved for severe toxicoses and life threatening conditions after conventional therapies have failed. In veterinary medicine as we have no 'standardized protocols' to follow lipids have been tried more frequently.

The published human papers are mainly case reports. Lipids have been used successfully in local anesthetic (bupivacaine, mepivacaine, ropivacaine), beta-blockers (propranolol, carvedilol), calcium channel blockers (verapamil, amlodipine) bupropion, haloperidol, quetiapine, carbamazepine (anticonvulsant), hydrochloroquine (antimalarial), flecainide (class Ic antiarrhythmic), thiopentone and serotonergic drug (sertraline, doxepin) overdoses.

Theoretically, lipids will work best on more lipid soluble toxins. Studies in laboratory animals have confirmed the efficacy of lipid emulsions for treating local anesthetics, chlorpromazine, cyclosporine, clomipramine and verapamil. Papers published in the veterinary literature include using lipids to treat moxidectin toxicosis in a puppy, lidocaine intoxication in a cat and ivermectin toxicosis in a cat.

The use of lipids unfortunately has not been shown to be effective in all cases of lipophilic drug toxicosis. In the human literature there have been failures when treating verapamil, amlodipine and tricyclic antidepressants. The veterinary literature also has a case report where lipids were unhelpful in treating ivermectin toxicosis in a group of ABCB1-1 mutant status dogs (MDR-1). Anecdotal, using lipids to treat baclofen intoxication in dogs sometimes works well and other times has no effect. In both of these situations the toxin can easily cross the blood-brain barrier (drug itself or genetic defect). It is possible that once these drugs are in the CNS, lipids will not help.

Adverse effects

Adverse effects of lipids are uncommon but have been reported. Bacterial contamination of the product can occur as the emulsion is nutrient rich. Make sure sterile technique is followed. A bag should only be used for 24 hours and then discarded. The unused portion between doses should be stored in the refrigerator and still discarded after 24 hours.

Rarely, an animal can have a reaction to the emulsion, which can cause an anaphylactoid-like reaction within 20 minutes of administration. Allergic reactions to the egg or soybean oil content can also occur. Side effects can include lipemia, hypertriglyceridemia, immunosuppression (immune cell dysfunction), hemolysis (oxidative damage), phlebitis, thrombosis, and

hepatic lipidosis. It is unknown if dogs have a higher risk of pancreatitis and seizures secondary to hypertriglyceridemia in these situations.

Fat overload syndrome is delayed and is caused by excessive volumes or high administration rates overwhelming the endogenous lipid clearance mechanisms. Fat overload syndrome is associated with hyperlipidemia, fat embolism, hepatomegaly, splenomegaly, thrombocytopenia, jaundice, increased clotting times and hemolysis.

Lipids can also bind antidotes or other therapies that are being used to treat the patient. This can cause a worsening of the clinical condition.

Conclusions

The use of lipids to treat intoxications appears to be a safe therapy, but more research is needed. If there is an effective therapy or antidote available, then the traditional therapy is recommended. If the toxin is lipid soluble and traditional therapies have failed or are too expensive, then using lipids is an option. The more lipophilic the toxin, the better the lipids may work. Some animals will experience complete resolution of their signs, while others may have no or minimal improvement. Appropriate supportive care is still needed in these patients. Fortunately, adverse events are rare.

Suggested readings

Crandell DE, Weinberg GL. Moxidectin toxicosis in a puppy successfully treated with intravenous lipids. *J Vet Emerg Crit Care* 2009;19:181–186.

Fernandez AL, Lee JA, Rahilly L, Hovda L, Brutlag AG, Engebretsen K. The use of intravenous lipid emulsion as an antidote in veterinary toxicology. *J Vet Emerg Crit Care* 2011; 21(4): 309–320.

O'Brien TQ, Clark-Price SC, Evans EE, Di Fazio R, McMichael MA. Infusion of a lipid emulsion to treat lidocaine intoxication in a cat. *J Am Vet Med Assoc* 2010;237:1455–1458.

Weinberg G, Vadeboncouer T, Ramaraju GA, et al. Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. *Anesthesiology*. 1998;88:1071-1075.

Wright HM, Chen AV, Talcott PA, Poppenga RH, Mealey KL. Intravenous fat emulsion as treatment for ivermectin toxicosis in three dogs homozygous for the ABCB1–1Δ gene mutation. *J Vet Emerg Crit Care* 2011; 21(6): 666–672.