ADVANCES IN TOXICOLOGY: THE USE OF INTRA-LIPID THERAPY & HIGH-DEXTROSE INSULIN THERAPY

Justine A. Lee, DVM, DACVECC
Pet Poison Helpline, Minneapolis, MN

INTRODUCTION

The use of intravenous lipid emulsion (ILE) or intravenous fat emulsion (IFE) has been well utilized in both human and veterinary medicine for decades as part of component therapy in the form of either total (TPN) or partial parenteral nutrition (PPN). More recently, the use of IFE has been utilized as an antidote for fat-soluble drug toxicity, particularly with local anesthesia overdoses in human medicine (i.e., bupivacaine),[1-4] where acute cardiopulmonary arrest has occurred. Numerous published case reports and experimental studies describe the beneficial use of IFE in the treatment of patients intoxicated with other drugs, including verapamil,[5] bupoprion, lamotrigine,[6] quetiapine, sertraline, calcium-channel blockers, and beta-blockers. Recently, IFE has been utilized in veterinary medicine also for cases of toxicity caused by administration or ingestion of lipid-soluble compounds including:

- Local anesthetics (i.e., bupivacaine, lidocaine)
- Clomipramine,[7] tricyclic antidepressants (TCA)
- Propranolol[8]
- Buproprion (i.e., Wellbutrin®, Zyban®) and others
- Muscle relaxants (i.e., baclofen, flexeril)
- Macrocyclic lactones (i.e., moxidectin, ivermectin)[9-11]

The exact mechanism of action by which IFE acts as an antidote and helps augments conventional resuscitation efforts is unknown. Currently, four potential hypotheses on how IFE is effective with fat-soluble toxicities include:

1. Providing myocytes energy substrates, thereby augmenting cardiac performance
2. Restoration of myocardial function by increasing intracellular calcium concentration
3. Acting as a "lipid sink" by sequestration of lipophilic compounds into the newly created lipid compartment within the intravascular space (a lipid or pharmacological sink). With this "lipid sink" hypotheses, compartmentalization of the drug into the lipid phase results in lesser free drug concentration available to tissues.
4. Increasing the overall fatty acid pool, which then overcomes bupivacaine inhibition of mitochondrial fatty acid metabolism.

Human and animal data

Extensive human literature exists on this topic, and the attendees are referred to the references listed below. As for veterinary medicine, there have not been any recent, prospective clinical trials evaluating the use of IFE; however, there is extensive animal literature on the use of IFE in *experimental* studies,[12,13] showing benefit for the following drugs: bupivacaine, propranolol, thiopental, verapamil, beta-blockers, clomipramine, and chlorpromazine. Recently, individual clinical case reports documenting the use of IFE in veterinary medicine been published (i.e., moxidectin);[10] however, blood levels for the toxic agent were not evaluated. Based on human literature and clinical response to therapy, the use of IFE has been recommended as a standard of care by both Pet Poison Helpline and the ASPCA Animal Poison Control for fat-soluble toxicities, particularly in severe, life-threatening overdoses with baclofen and ivermectin. There are anecdotal reports of the successful use of IFE with ivermectin, baclofen, and lidocaine toxicity in small animal veterinary medicine. Despite the paucity of data in veterinary medicine, clinical outcome with IFE has been successful.

Dosing

When using IFE therapy, it is important that veterinarians be aware of the different lipid emulsion formulations that are currently available in the market. Intravenous lipid emulsion is readily available at most human health care facilities and at veterinary emergency or specialty referral hospitals (where it may be used as part of PPN or TPN therapy). Currently, a commercially available antidote is available - LipidRescue 20%. More information can be found at: http://lipidrescue.squarespace.com. This product is specifically marketed as an antidote for toxicities in human medicine. Other IFE sources are readily available through veterinary suppliers (i.e., Baxter) as both a 10 and 20% solution. Currently, dose recommendations for IFE are extrapolated from human medicine and are listed below:

20% solution IFE dosing: Administer 1.5 ml/kg IV bloused over 1 minute, followed by 0.25 ml/kg/min for 30-60 minutes. The initial bolus could be repeated 1-2 times if no response to the initial bolus is obtained, with a goal to not exceed 8 ml/kg/day.

That said, this dose has been exceeded in clinical recommendations by Pet Poison Helpline without ill effect. A current retrospective case series evaluating the use of IFE by Pet Poison Helpline may hopefully clarify what therapeutic doses can be safely used.

Currently, when IFE is utilized for nutritional support, general guidelines are to not exceed 2 g/kg/day. However, some veterinary nutritionists utilize 20% IFE for sole PPN replacement by providing 100% of the resting energy requirement (RER) as lipid for short-term therapy (1-2 days). This would readily exceed the 2g/kg/day requirement. Therefore, based on the variability in dose of IFE used for PPN, the use of IFE in an acute setting for toxicity likely can exceed the current human recommendations. A comparison of doses for IFE and PPN are demonstrated below, and are designed to help indicate the variability in dosing:

General RER calculations:
Dog: 15 kcal/lb of dog; Cat: 20 kcal/lb of cat
20% IFE has 2 kcal/ml; 10% IFE has 1 kcal/ml; 20% solution = 200 mg/ml = 1g/5 mls

Using a 20% solution of IFE (osmolality 280 mOsm/L) to meet 100% of the RER, one can calculate the amount of lipid to administer:
Patient RER/2 = X mls of 20% IFE

Example:
11 lb cat
RER: 20 kcal X 11 lbs = 220 kcal/day
To meet 100% of the RER via 20% IFE (2 kcal/ml) = 110 ml/day
Lipid dose: **110 ml/day** = 4.6 ml/hour

Current human maximum recommendation of IFE: 8 ml/kg/day
11 lb cat = **40 ml/day**

Some nutritionalists recommend not to exceed: 2 g/kg/day
Cat: 2 g/kg/day X 5 kgs = 10 g/day = **50 ml/day**

Based on the variability in dosing, it is likely that IFE administration in the acute toxicology setting can warrant current increased dosing regimens to:

- Consider *additional* doses of 1.5 ml/kg IV over 30 min q. 4-6 hours X 24-36 hours until clinical signs resolve (based on clinical judgment) or
- Maintaining a CRI of 0.5 ml/kg/hour until clinical signs resolve.

Concurrent recommendations include the use of drug levels (serum or plasma) to evaluate the response to IFE therapy. This will aid in data collection for future retrospective study analysis. Time frames for drug levels include: time 0 (at the time of presentation to the health care facility), 30 minutes after administration of IFE, 1 hour post, 6, hours post, 12 hours post, and 24 hours post.

Side effects and potential complications of IFE administration
Deleterious effects from IFE are rare, and the benefits must out way the risks of use. Deleterious effects may be caused directly by the emulsion (egg-based, anaphylactoid reaction) or due to contamination of the infusate. Risks of microbial contamination and sepsis from IFE exist, as they do with the administration of TPN or PPN, but this rarely occurs when IFE is infused as a sole agent. Other known reported side effects seen in human medicine include: pulmonary toxicity, bacterial contamination, thrombophlebitis, fat embolism, hyperlipidemia, pancreatitis, immunosuppression, and hypersensitivity. Generally, IFE is well tolerated in the acute setting. In veterinary medicine, the side effects and known potential complications are likely similar, albeit more difficult to diagnose. Without the use of ventilation:perfusion scans, contrast-enhanced computerized tomography, etc., fat embolism is likely difficult to diagnose.

Patients should be carefully monitored during administration of IFE, particularly within the first 20 minutes, due to potential risks of acute, adverse “colloid reaction” or pyrogenic reactions. While rare (<1%), these reactions resemble anaphylactoid reaction and may include nausea, vomiting, fever, dyspnea and cyanosis. Another complicating factor with the use of IFE is “fat overload syndrome.” This may be due to administration of large amounts of IFE, which then overwhelm the endogenous lipid clearance mechanisms. In human medicine, IFE administrate rates above 0.11g/kg/hr can be associated with fat complications. Clinical signs of “fat overload syndrome” in human medicine include hyperlipidemia, hepatomegaly, icterus, splenomegaly, fat embolism, thrombocytopenia, hemolysis, and prolonged clotting times. There is very little veterinary information on “fat overload syndrome.” That said, severe lipemia has been seen in veterinary patients administered IFE. Severe hyperlipidemia may be easily detected on clinicopathologic testing (hematocrit tubes), and may affect total solid monitoring.

The potential use of heparin therapy (75-250 units/kg SQ q. 6) can be considered in cases where severe hyperlipidemia is present. However, as heparin infusion increases intralipid clearance, its effect on IFE therapy in the face of toxicity is unknown at this time. Partial thromboplastin time (PTT) should be carefully monitored prior to the use of heparin to ensure the patient is not already coagulopathic. If PTT exceeds 2-2.5X normal, the use of heparin should be either lowered (75 units/kg SQ q. 6-8) or discontinued. Currently, unless the patient is at risk for pancreatitis (i.e., Shetland sheepdog, miniature schnauzer, Yorkshire terrier, obesity, etc.), heparin therapy is not recommended with acute toxicosis and IFE treatment unless clinical signs or advanced diagnostics indicate otherwise, due to its unknown effect on the “lipid sink” hypothesis of IFE.

High-dose insulin (HDI) therapy
The use of HDI therapy (with regular insulin CRIs) has been recently advocated for the use of beta-blocker toxicity in both human and veterinary medicine to increase inotropy and treatment of hypoperfusion. Beta-blocker toxicity results in severe hypotension, bradycardia, cardiovascular collapse, shock, and death. Treatment traditionally includes fluid resuscitation, atropine, temporary

pacemaker therapy, vasopressors, and inotropes.[14] Unfortunately, catecholamine vasopressors are often ineffective as they work on the same cell membrane receptors that are affected by beta-blockers.[14] Temporary cardiac pacemaker therapy and glucagon (which has inotropic properties) have previously been used in veterinary medicine,[15,16] but have been recently found to be less effective than the use of HDI therapy.[14] Glucagon was thought to reverse beta-blocker toxicity due to its ability to increase intracellular cAMP via a non-catecholamine receptor on the cell wall, thereby increasing myocardial cAMP.[14] Unfortunately, the effects of glucagon are variable, and fail as a single agent for the treatment of beta-blocker toxicity; currently, it is no longer considered the antidote for beta-blocker overdose. Other vasopressors have been evaluated for beta-blocker toxicity, including epinephrine and vasopressin. Holger et al evaluated the use of HDI at the dosing of 2 regular units/kg/hour, up to 10 units/kg/hour, compared to vasopressin (V) with epinephrine (E) (vasopressin 0.0028 units/kg/minute up to 0.014 units/kg/minute; epinephrine 10 mcg/kg/min up to 50 mcg/kg/minute) in a porcine model of beta-blocker toxicity.[14] In this study, glucose was concurrently administered in the HDI group when hypoglycemia < 60 mg/dL occurred.[14] Overall, all V/E pigs died with 90 minutes, while all HDI pigs survived. In the HDI group, cardiac output (CO) increased with the use of insulin therapy, while MAP, SBP, and systemic vascular resistance (SVR) all trended slightly downward. In the V/E group, CO dropped until death, while MAP, SBP, and SVR rose dramatically until 30-60 minutes, followed by an abrupt drop and then death. Overall, the use of HDI was superior to V/E in treating beta-blocker toxicity, and HDI was display marked inotropic properties when compared to the use of other vasopressors.[14] The attendees are referred to the references for further details about beta-blocker toxicity.

The exact mechanism of how HDI therapy works is unclear and currently unknown, and does not appear to be from a direct vasopressor effect. Rather, HDI's effectiveness may be due to insulin's ionotropic effects which increase perfusion by increasing cardiac output. While HDI does not increase SVR directly (thereby, no active increases in SBP or MAP are seen), clinical improvement in tissue perfusion is thought to occur with HDI. In addition, HDI helps promote aerobic metabolism in the myocardium,[14] and appears to promote the uptake and utilization of carbohydrates as an energy source. Insulin also prevents ischemic-reperfusion injury during shock states, and prevents apoptosis. Other hypotheses on how insulin works with beta-blocker toxicity is by enhancing glucose transport to the myocardium during the toxic state, improving intracellular calcium homeostasis by enhancing calcium channels, and stimulating catecholamine release.[14] HDI is also thought to enhance cardiac contractility and cardiac output.

Unfortunately, there is a paucity of veterinary literature evaluating the use of HDI in small animal medicine. Extrapolating from human medicine, currently, HDI treatment recommendations for toxicity cases include:

1) Central line placement for ease of patient care and blood glucose (BG) monitoring.
2) Check BG. Administer 0.5 ml/kg 50% dextrose IV if BG is <100 mg/dL for dog or < 200mg/dL for cat.
3) Administer regular insulin at 1 unit (U)/kg IV bolus, followed immediately with a CRI IV infusion of regular insulin at 2 units/kg/hr.
4) The regular insulin infusion can be increased 2 units/kg/hr every 10 minutes up to a maximum dose of 10 units/kg/hr.
5) Due to the HDI, carefully BG monitoring is imperative every 10 minutes while adjusting insulin dosing. Aggressive dextrose supplementation (typically > 5% dextrose CRI, IV) must be supplemented via the central line. Once insulin dosing has stabilized, the BG should continued to be monitored every 30-60 minutes.
6) Due to the intracellular shifting of potassium with insulin therapy, potassium levels should be frequently monitored every hour. Aggressive potassium supplementation should be utilized to maintain potassium within the low therapeutic range (3 mmol/L). Administer potassium chloride if $K^+ \leq 3.0$ mmol/L.
7) Once beta blocker toxicity has resolved, the regular insulin CRI should be slowly decreased by 1-2 units/kg/hr. Both potassium and dextrose supplementation will likely need to be continued for up to 24 hours, and careful monitoring should still be maintained. Likewise, frequent calcium levels should be monitored as the insulin CRI is decreased.

CONCLUSION

The use of newer modalities in veterinary toxicity may dramatically improve the overall outcome in toxicities that have been previously associated with a high morbidity, mortality, and cost (i.e., baclofen, ivermectin, etc.). The extra-label use of these new modalities should be judiciously used. Appropriate case selection is imperative.

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