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SCOPE OF ILE (INTRAVENOUS LIPID EMULSION) AS AN ANTIDOTE IN VETERINARY CLINICAL PRACTICE

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ABSTRACT

Intravenous lipid emulsion (ILE) is a mixture of long chain fatty acids or medium chain fatty acids or a combination of both that was first formulated for intravenous administration to supply necessary fatty acids and a dense source of calories for patients on parenteral nutrition (PN). The available formulations contain alternative sources of fatty acids, such as medium-chain triglyceride oils, olive, fish, and soybean oils. Lipid emulsion as a rescue agent for intentional and inadvertent overdoses of liphophilic substances has created a new therapeutic window for the drugs that do not have any specific antidote in the market. The use of ILE therapy is nowadays used a new antidote for the treatment of toxicity of liphophilic pharmaceutical agents.

Keywords: Antidote, Emulsion, Liphophilic, Toxicity

INTRODUCTION

Lipid emulsions are sterile mini-emulsions (0.4–0.5 mm) of oil in water having a turbid (white) appearance, meant for intravenous use (Robben and Dijkman, 2017). The oil phase consists of neutral long-chain triglycerides (LCTs), or a mixture of medium-chain triglycerides (MCTs) and long-chain triglycerides, derived from unsaturated plant fatty acids like soya bean oil (Intralipid, Fresenius Kabi AB, Uppsala, Sweden). Newer products are also introduced in the market containing olive, fish, safflower, and coconut (MCT) oil. Most common formulations used are with the concentrations of 10-30 percent. Intravenous lipid emulsions are an energy-dense source of calories and supply various essential fatty acids that are not synthesized endogenously in the patients. Initially, intravenous lipid emulsions are used in parenteral nutrition admixtures as a source of calorie and an energy substrate in the patients especially with intestinal

failure who cannot absorb nutrition through enteral route. It was first clinically used in humans for the treatment of local anesthetic systemic toxicity (LAST) in 2006. It is also effective as a drug delivery vehicle for the drugs that are poorly water soluble (propofol).

Components of injectable lipid emulsion

The intravenous lipid emulsions broadly consist of 3 components:

A. Lipid phase-Include LCTs or MCTs or a mixture of both.

B. Emulsifiers- Emulsions are thermo-dynamically unstable and they undergo physical changes like aggregation, creaming, and droplet formation etc., over time. Emulsifiers help to keep emulsions stable by lowering the interfacial tension and providing adequate surface charge for droplet to droplet repulsion. Tween 80, isopropyl alcohol, glycerol are commonly used emulsifiers (Rossi and Leroux, 2006).

C. Aqueous Phase- used to add antioxidants, tonicity modifiers, and preservatives etc.

Formulation Process

Ingredients that are water soluble and those that are oil soluble are dissolved in the aqueous and oil phases, respectively. Emulsifiers can be added in either oil or aqueous phase. Both phases are adequately heated and stirred to dissolve the ingredients properly. To form a homogeneously dispersed coarse emulsion, the lipid phase is mixed to the aqueous phase under controlled temperature and agitated by high-shear mixers (Hansrani *et al*., 1983; Floyd, 1999). To further reduce the droplet size and form a fine emulsion, the coarse emulsion is homogenised using a microfluidizer or a high-pressure homogenizer at appropriate combination of pressure, temperature, and number of cycles (Washington and Davis, 1988; Innocente *et al*., 2009). The fine emulsion thus formed is then packed in USP type I glass containers. Optimum size of developed emulsion should be 500 nm. It should be frozen and the desired storage temperature is less than 25ºC.

Mechanisms of Action

The exact mechanism of action is currently unknown. According to the current theories it is assumed to be associated with improvement of cardiac performance and a 'lipid sink' effect. The theory behind ILE therapy is that a) it improves cardiac performance by supplying free fatty acids (FFA) to the myocardium, which is the preferred substrate and b) "lipid sink" mechanism which involves the creation of an expanded lipid phase within the plasma that sequester various lipophilic compounds and reduce their effective concentration at

the target tissues.

A. Improved myocardial performance

ILE therapy improves cardiac function by two ways, first by direct effect of lipids on the myocardium and second, by reversal of cardiovascular dysfunction caused by the specific toxicant. The potential direct effects include an increase in intracellular calcium, utilization of free fatty acids as an energy source by the myocardium, α-adrenergic receptor mediated increased vasopressor effect, and the reduction of insulin and nitrous oxide induced vasodilatation by ILE.

B. Drug sequestration or 'lipid sink' theory

A drug is said to be liphophilic nature if it has log P>1 and log P denotes logarithmic ratio of concentrations of a solute between the two solvents. This mechanism is also known as the lipid or pharmacological 'sink'. An expanded lipid phase is created by lipid emulsion infusion, and the resultant equilibrium cause migration of toxic drugs such as local anaesthetics away from high-concentration locations such as the heart or brain to the "lipid sink" (Rothschild *et al*., 2010).

Biological fate of injectable lipid emulsions

Intravenous lipid emulsions are either metabolised like endogenous chylomicrons or eliminated by mononuclear phagocyte systems, such as kupffer cells and splenic macrophages (Rossi and Leroux, 2006). Half life of ILE is 3 to 6 minutes. LD50 of ILE is 67 ml/kg bwt.

Indications

- In local anaesthetic toxicity at onset of neurological or cardiovascular symptoms (Weinberg *et al*., 2011)
- If the toxicant is resistant to conventional advanced cardiovascular life support agents and there is no known alternate antidote (Robben and Dijkman, 2017)
- Lipophilic toxicant causes hemodynamic compromise and the conventional resuscitation protocols fail (Fernandez *et al*., 2011)

Tissue perfusion and oxygenation must be maximised prior to ILE administration. Conventional therapy should be used if an effective therapy or

antidote has already been established in veterinary toxicology above ILE therapy due to the unknown effects of ILE administration.

Table 1. Common drug toxicities reported to be treated with intravenous lipid emulsion

Compound	Type
Amitriptyline	Tricyclic antidepressant
Parathion	OP pesticide
Diazinon	OP pesticide
Bupivacaine	Local anesthetic
Sulfur mustard	CWA, blister
Malathion	OP pesticide
VX	CWA, nerve
Diazo-	OP pesticide, active metabolite of diazinon
Paraoxon	OP pesticide, active metabolite of parathion
Mepivacaine	Local anaesthetic
Soman (GD)	CWA, nerve
Sarin (GB)	CWA, nerve
Atenolol	Beta blocker
Glyphosate	OP herbicide
Propranolol	Beta blocker
Clomipramine	Tricyclic antidepressant
Verapamil	Calcium-channel blocker
Chlorpromazine	Phenothiazine
Nifedipine	Calcium-channel blocker
Thiopental	Short- acting barbiturate
Ivermectin	Macrocytic lactone

Dosage recommendations

No single recommended dosing strategy is available in veterinary medicine so far (Benavides and Babyak, 2019). The dose recommendations for 20 per cent ILE is-1.5 mL/kg, IV, bolus over 1 min, followed by a continuous rate of infusion of 0.25 mL/kg/min, IV, for 30–60 min. If progressive hypotension is noticed, CRI rate of administration can be further increased to 0.5 mL/kg/min, IV. In non-responsive patients, additional intermittent bolus can be given slowly up to 7 ml/kg, every 3-5 min, and a total of 3 bolus can be given (Fernandez *et al*., 2011). If multiple doses are to be given, serial serum evaluation should be done for lipemia. If serum is not lipemic, the bolus and CRI dosing may be repeated, but not to exceed 24 h (Gwaltney and Meadows, 2012). The infusion should be discontinued, if no improvement is noticed following three total doses. In some human protocols, continued intermittent bolus dosing of 1.5mL/kg every 4–6 hours until clinical signs improve is advocated (not to exceed 24 h). The recommended upper limit for 20 per cent ILE is 10mL/kg/day (El Bahri, 2016).

Commercial availability

A. Soybean-Oil Lipid Emulsions- consist of 50 per cent omega-6 fatty acids (linoleic acid), 25 per cent of omega-9 (oleic acid) and ~10 per cent of omega-3 fatty acids (α-linolenic acid). Eg. **Intralipid®** and **Nutrilipid®**

B. Fish-Oil Lipid Emulsion

Eg.**Omegaven®**- most recently approved lipid emulsion, contains negligible amounts of essential fatty-acids, linoleic and α-linolenic acid.

C. Mixed-Oil Lipid Emulsions

Eg. **Clinolipid®** and **Smoflipid®** (newest mixed-oil emulsion)

Reported potential adverse effects

- **Microbial contamination** of the lipid product due to inappropriate handling or nonsterile technique resulting in local or systemic infection, venous irritation and subsequent thrombophlebitis (Robben and Dijkman, 2016).
- **Allergic or anaphylactoid reactions** to the product or its components, such as the egg phospholipid or the soybean oil components, rarely occur (Fernandez *et al*., 2011).
- **Volume overload**
- **Fat overload syndrome**, if rate of administration is greater than 0.11 g/kg/h (Fernandez *et al*., 2011)
- **Neurologic complications and adverse changes in pulmonary function** in septic patients and those with acute respiratory distress syndrome (Fernandez *et al*., 2011)
- **Hypertriglyceridemia and lipemia**
- **Hemolysis** (Gwaltney-Brant and Meadows, 2012)
- **Local swelling and pain due to** extravasation of lipid emulsions **(**Bates *et al*., 2013)
- **Interference with laboratory and blood gas analysis** (Ozcan and Weinberg, 2011)

CONCLUSION

In veterinary medicine, the use of ILE to treat local anaesthetic or other lipophilic medication toxicity is still in its early stages, and its potential is unclear. This newer 'antidote' should be used prudently on the basis of lipophilic nature of the drug. The stronger a drug's affinity for lipids, the more likely it is to be reversed by ILE therapy. Before adopting this therapy, conventional resuscitation strategies should be exhausted, and the possible adverse effects of ILE should be thoroughly assessed. To determine an effective and safe dose of ILE therapy more research is needed both in veterinary and human fields.

REFERENCES

Bates, N., Chatterton, J., Robbins, C., Wells, K., Hughes, J., Stone, M. and Campbell, A., 2013. Lipid infusion in the management of poisoning: a report of 6 canine cases. *Vet Rec.* **172**: 339-339.

Benavides, K., and Babyak, J. 2019. Lipid rescue therapy. In: Drobatz, K.J, Hopper, K, Rozanski, E, Silverstein,

D.C. (ed.). *Text Journal of Small Animal Emergency Medicine.* New Jersey, NJ: John Wiley and Sons. p. 831–834.

El Bahri, IV, L. 2016. Role of IV lipid emulsion antidote. *Vet. Times.* **46**: 9-10.

Fernandez, A.L., Lee, J.A., Rahilly, L., Hovda, L., Brutlag, A.G. and Engebretsen, K. 2011. The use of intravenous lipid emulsion as an antidote in veterinary toxicology. *J Vet Emerg Crit Care*. **21**: 309-320.

Floyd, A.G. 1999. Top ten considerations in the development of parenteral emulsions. *Pharm Sci Technol Today.* **2**: 134–43.

Gwaltney-Brant, S and Meadows, I. 2012. Use of intravenous lipid emulsions for treating certain poisoning cases in small animals. *Vet. Clin. North Am. Small. Anim. Pract*. **42** : 251–62.

Hansrani, P.K., Davis, S.S. and Groves, M.J. 1983. The preparation and properties of sterile intravenous emulsions. *J. Parenter. Sci. Technol*. **37**: 145–50.

Innocente, N., Biasutti, M., Venir, E., Spaziani, M. and Marchesini, G. 2009. Effect of high-pressure homogenization on droplet size distribution and rheological properties of ice cream mixes. *J. Dairy. Sci.* **92**: 1864–75

Ozcan, M.S. and Weinberg G. 2011. Update on the use of lipid emulsions in local anesthetic systemic toxicity. *Int Anesthesiol Clin.* **49** :91–103.

Robben, J.H. and Dijkman, M.A. 2017. Lipid therapy for intoxications. *Vet Clin North Am Small Anim Pract*. **47**: 435-50.

Rossi, J. and Leroux, J.C. 2006. Principles in the development of intravenous lipid emulsions. In: Wasan, K.M. (ed.) *Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery*. New York: Wiley; p. 88–123.

Rothschild, L., Bern, S., Oswald, S. and Weinberg, G. 2010. Intravenous lipid emulsion in clinical toxicology. *Scand. J. Trauma. Resusc. Emerg. Med.* **18**: 1-8.

Washington, C., and Davis, S.S. 1988. The production of parenteral feeding emulsions by Microfluidizer. *Int. J. Pharm.* **44**: 169–76

Weinberg G.L., Di Gregorio G., Ripper R., Kelly K., Massad M., Edelman L., Schwartz D., Shah N., Zheng S. and Feinstein D.L. 2011. Resuscitation with lipid versus epinephrine in a rat model of bupivacaine overdose. *Anesthesiology*. **108:** 907-913.