Intravenous Lipid Emulsion Therapy for the Management of Toxicities in Dogs and Cats

Introduction

The first report of the use of intravenous lipid emulsion (ILE) therapy was in 2006, in a human experiencing cardiac arrest secondary to bupivacaine toxicosis[1]. Since that time, ILE therapy has been utilized in a wide range of toxicosis. The direct impact of ILE in management of toxicosis is at time, unclear, as published case reports usually only reflect positive outcomes, and the independent impact of ILE is difficult to prove in a patient receiving concurrent therapies as part of their illness management[1,2]. The aim of this short review is to examine the scientific data on ILE in the management of toxicosis in dogs and cats, and to outline sound recommendations on its use, based on available understanding.

Mechanism of Action:

Broadly, the effects that ILE infusion has on toxicosis include either scavenging or non-scavenging mechanisms of action[1-4].

Scavenging mechanism:

Following intravenous administration of ILE, the high lipid concentration within the plasma scavenges xenobiotic (foreign chemicals) molecules from target tissues, including the heart, muscles, CNS etc., and shuttles them to tissues where they are either stored (skeletal muscle, adipose tissue); metabolised (liver) or excreted (kidney).

Lipid solubility, as well as the degree of xenobiotic ionization appear to be the most important factors in determining the effectiveness of the lipid shuttle scavenging system.

Non-scavenging mechanism:

Non-scavenging mechanisms of ILE activity are numerous and include blood pressure maintenance via alteration in nitric oxide signaling, direct cardiotonic effects, and a post-conditioning effect that minimises reperfusion injury[1].

Other documented non-scavenging mechanisms studied in bupivacaine toxicity include

- Calcium-mediated positive inotropism theory[2]
    - Because fatty acids can increase calcium concentrations in cardiac myocytes, lipids may cause an increase in inotropy that overcomes the cardiac depressive effects of certain intoxications e.g. calcium-channel toxicities
- Free fatty acid energy theory[2]
    - Myocardial cells obtain 80-90% of their energy from free fatty acids
    - Intravenous lipid overwhelms bupivacaine inhibition of carnitine exchange, and augments mitochondrial fatty acid metabolism, increasing ATP stores and myocardial energy available for cardiac myocytes to recover from myocardial depressant effects of local anaesthetic toxicity.

Formulation:

20% lipid emulsion (Intralipid) is recommended. 30# lipid emulsions are available and may be preferred in severe cardiotoxicity in cases of local anaesthesia toxicity[1].

Dosage:

Note that the following dosing regimes are stated using 20% lipid emulsion formulations[1,2.]

- Bolus: 1.5 ml/kg IV over 2-3 minutes. The is usually followed by a continuous infusion
- Continuous infusion: 0.025 ml/kg/minute (1.5 ml/kg/hr) for 30-120 minutes
- Repeat doses:
    - Blood test at 4-6 hrs. following completion of continuous infusion.
        - If no lipaemia is observed, and the patient is still clinically unwell because of toxicosis, the bolus and/or the infusion dose may be repeated
        - If lipaemia present, withhold treatment; retest for lipaemia q 2 hrs.
        - Repeat dose only if lipaemia has resolved
- Maximum dose: 8 ml/kg/24hrs

Clinical Uses:

Numerous case reports, case series, and a few clinical trials have been published in recent years, evaluating the response to administration of ILE in a range of toxicosis[5]. A brief summary of these is provided in the table below:

Toxicant	Response to Therapy	Additional Recommendations
Amlodipine[6]	Variable response	Adjunctive therapy recommendation only
Amphetamine/methamphetamines[6,7]	Moderate response	Useful adjunctive therapy
Baclofen[8]	Good response. May require multiple doses	Recommended for most cases, particularly those with severe symptoms
Bromethalin[6,9]	Variable response from poor to good	Adjunctive therapy recommendation only
Carprofen[10]	Good response	Potentially beneficial as adjunctive therapy
Cocaine[11]	Good response	Potentially beneficial as adjunctive therapy
Diltiazem[12]	Good response when combined with high dose insulin (canine case report)	May be useful in severely affected patients
Ibuprofen[13]	Improvement in neurological status	Useful especially if neurological signs present
Lidocaine, bupivacaine[14]	Good response	Recommended for cases with CNS or cardiovascular symptoms
Loperamide[15]	Positive response	Use naloxone initially; second line treatment with ILE only in refractory cases
Macrocyclic lactones (ivermectin, milbemycin, moxidectin etc.)[1,2,16-21]	Good response observed; poor response in dogs with ABCB1-delta mutation	Useful treatment. Dogs with ABCB1-delta gene mutations may not respond
Marijuana[22]	Good response	Use for severely affected patients is likely justified; mild symptoms probably don't require ILE
Naproxen[23]	Insufficient data	Insufficient data to recommend
Organophosphates[1,5]	Poor response	No evidence to support use of ILE at this time
Permethrins[24-26]	Moderate to good improvement in most cases	Adjunctive therapy recommendation
Phenobarbital[1,2]	Mild to moderate response	Consider in severely affected patients
Tremorgenic mycotoxins[27]	96% positive response	Consider in severely affected patients refractory to methocarbamol and benzodiazepines

Precautions and Adverse Reactions[1,2]

Side effect and adverse reactions to ILE therapy are infrequent but have been reported. A summary of reported adverse effects is listed below:

- Anaphylactoid reaction
- Bacterial contamination of solution
    - Sterile preparation and administration technique should be used
    - Discard unused solutions after 24 hrs.
- Pulmonary lipid emboli
    - Reported in human paediatric patients receiving ILE therapy
- Lipaemia
    - If lipaemia is present in blood tests following treatment, subsequent doses should be delayed until serum is non-lipaemic, recommended to ostensibly reduce risk of pancreatitis that has been observed in humans and veterinary patients following ILE therapy
- Poor response to treatment
    - Do not administer more than 3 doses if no significant response is seen
- Non-selective binding of therapeutic agents
    - ILE may bind to antidotes or supportive medications e.g. benzodiazepine medications used to control seizures, and may worsen symptoms of toxicity as a result
    - Discontinue use if deterioration of patient status is observed
- Reappearance of clinical signs
    - Most notably in toxicosis caused by agents with long half-lives. Repeated ILE infusions may be required in such cases
- Immune compromise in septic patients
- Volume overload (especially with repeated doses)
- Fat over load syndrome
    - Due to excessive volumes or high administration rates, or administered to patients with reduced lipid clearance rates (liver disease etc.)
    - Leads to
        - Hyperlipidaemia
        - Fat embolism – lungs, brain
        - Hepatomegaly
        - Icterus
        - Splenomegaly
        - Thrombocytopaenia
        - Increased clotting times
        - Haemolysis

Pharmacodynamics and Excretion[4]:

ILE has the following clearance properties from circulation:

- Skeletal muscle: 47%
- Splanchnic viscera: 25%
- Myocardium: 14%
- Subcutaneous tissues: 13%

Conclusion:

The use of ILE in small animal toxicology has led to improved clinical outcomes in a wide range of toxicities, including from compounds with both highly lipophilic properties, to those that are less lipophilic as well. Evidence to date involves mostly small cohorts of patients, or case reports, however, which does give rise to equivocal or uncertain recommendations for some of these agents. The hope is for more prospective control-based studies in future, so that our knowledge of the effects of ILE on various toxicities becomes more objective. In the meantime, it appears that ILE is a reasonably safe, useful adjunctive therapy to consider where we have published evidence of efficacy to date.

References:

1. Gwaltney-Brant, Sharon, and Irina Meadows. "Intravenous lipid emulsions in veterinary clinical toxicology." *Veterinary Clinics: Small Animal Practice* 48, no. 6 (2018): 933-942.

2. Fernandez, Alberto L., Justine A. Lee, Louisa Rahilly, Lynn Hovda, Ahna G. Brutlag, and Kristin Engebretsen. "The use of intravenous lipid emulsion as an antidote in veterinary toxicology." *Journal of Veterinary Emergency and Critical Care* 21, no. 4 (2011): 309-320.

3. Ozcan, Mehmet S., and Guy Weinberg. "Intravenous lipid emulsion for the treatment of drug toxicity." *Journal of intensive care medicine* 29, no. 2 (2014): 59-70.

4. Rothschild, Leelach, Sarah Bern, Sarah Oswald, and Guy Weinberg. "Intravenous lipid emulsion in clinical toxicology." *Scandinavian journal of trauma, resuscitation and emergency medicine* 18, no. 1 (2010): 1-8.

5. Cave, Grant, and Martyn Harvey. "Intravenous lipid emulsion as antidote beyond local anesthetic toxicity: a systematic review." *Academic Emergency Medicine* 16, no. 9 (2009): 815-824.

6. Becker, Michael D., and Brian C. Young. "Treatment of severe lipophilic intoxications with intravenous lipid emulsion: a case series (2011–2014)." *Veterinary Medicine: Research and Reports* 8 (2017): 77.

7. Harris, Stephanie, Maureen A. McMichael, Roy Harmon, and Dawn Boothe. "Case Report: Successful Intravenous Lipid Emulsion Therapy for Canine Amphetamine Toxicosis." *Frontiers in Veterinary Science* 9 (2022).

8. Butler, Jarrod. "Successful treatment of baclofen overdose with intravenous lipid emulsion." *Veterinary Medicine* 109, no. 1 (2014): 7-12.

9. Heggem-Perry, Brittany, Maureen McMichael, Mauria O'Brien, and Clara Moran. "Intravenous lipid emulsion therapy for bromethalin toxicity in a dog." *Journal of the American Animal Hospital Association* 52, no. 4 (2016): 265-268.

10. Chumbler, Nathan S., Julie C. Schildt, Diane I. Mawby, and Mark G. Papich. "Use of intravenous lipid therapy in a cat with carprofen overdose." *Clinical Case Reports* 8, no. 4 (2020): 653-657.

11. Royle, Kirsty, and Carsten Bandt. "Intravenous lipid emulsion to treat suspected cocaine toxicosis in a dog." *The Canadian Veterinary Journal* 61, no. 1 (2020): 49.

12. Maton, Barbara L., Erin E. Simmonds, Justine A. Lee, and Amy J. Alwood. "The use of high-dose insulin therapy and intravenous lipid emulsion to treat severe, refractory diltiazem toxicosis in a dog." *Journal of Veterinary Emergency and Critical Care* 23, no. 3 (2013): 321-327.

13. Bolfer, Luiz, Maureen McMichael, Thandeka R. Ngwenyama, and Mauria A. O'Brien. "Treatment of ibuprofen toxicosis in a dog with IV lipid emulsion." *Journal of the American Animal Hospital Association* 50, no. 2 (2014): 136-140.

14. O'Brien, Taylor Q., Stuart C. Clark-Price, Erika E. Evans, Renata Di Fazio, and Maureen A. McMichael. "Infusion of a lipid emulsion to treat lidocaine intoxication in a cat." *Journal of the American Veterinary Medical Association* 237, no. 12 (2010): 1455-1458.

15. Long, Whitney M., Virginia B. Sinnott, Kiko Bracker, and Danielle Thomas. "Use of 20% intravenous lipid emulsion for the treatment of loperamide toxicosis in a Collie homozygous for the ABCB1-1Δ mutation." *Journal of Veterinary Emergency and Critical Care* 27, no. 3 (2017): 357-361.

16. Clarke, Dana L., Justine A. Lee, Lisa A. Murphy, and Erica L. Reineke. "Use of intravenous lipid emulsion to treat ivermectin toxicosis in a Border Collie." *Journal of the American Veterinary Medical Association* 239, no. 10 (2011): 1328-1333.

17. Epstein, Steven E., and Steven R. Hollingsworth. "Ivermectin-induced blindness treated with intravenous lipid therapy in a dog." *Journal of Veterinary Emergency and Critical Care* 23, no. 1 (2013): 58-62.

18. Wright, Heather M., Annie V. Chen, Patricia A. Talcott, Robert H. Poppenga, and Katrina L. Mealey. "Intravenous fat emulsion as treatment for ivermectin toxicosis in three dogs homozygous for the ABCB 1–1Δ gene mutation." *Journal of Veterinary Emergency and Critical Care* 21, no. 6 (2011): 666-672.

19. Kidwell, James H., Gareth J. Buckley, Ashley E. Allen, and Carsten Bandt. "Use of IV lipid emulsion for treatment of ivermectin toxicosis in a cat." *Journal of the American Animal Hospital Association* 50, no. 1 (2014): 59-61.

20. Crandell, Dawn E., and Guy L. Weinberg. "Moxidectin toxicosis in a puppy successfully treated with intravenous lipids." *Journal of Veterinary Emergency and Critical Care* 19, no. 2 (2009): 181-186.

21. Bates, N., J. Chatterton, C. Robbins, K. Wells, J. Hughes, M. Stone, and A. Campbell. "Lipid infusion in the management of poisoning: a report of 6 canine cases." *Veterinary Record* 172, no. 13 (2013): 339-339.

22. Williams, Keysa, Raegan J. Wells, and Mary Kay McLean. "Suspected synthetic cannabinoid toxicosis in a dog." *Journal of veterinary emergency and critical care* 25, no. 6 (2015): 739-744.

23. Herring, Jennifer M., Maureen A. McMichael, Raffaella Corsi, and Virginie Wurlod. "Intravenous lipid emulsion therapy in three cases of canine naproxen overdose." *Journal of Veterinary Emergency and Critical Care* 25, no. 5 (2015): 672-678.

24. Kopke, Matthew A., and Ivayla D. Yozova. "Management of presumptive canine permethrin toxicosis using intravenous lipid emulsion as an adjunctive therapy." *Veterinary Record Case Reports* 8, no. 2 (2020): e001041.

25. Ceccherini, G., Francesca Perondi, I. Lippi, G. Grazia, and Veronica Marchetti. "Intravenous lipid emulsion and dexmedetomidine for treatment of feline permethrin intoxication: a report from 4 cases." *Open veterinary journal* 5, no. 2 (2015): 113-121.

26. Kaplan, Amy, and Megan Whelan. "The use of IV lipid emulsion for lipophilic drug toxicities." *Journal of the American Animal Hospital Association* 48, no. 4 (2012): 221-227.

27. Kormpou, Foteini, Aoife O'Sullivan, Laura Troth, and Sophie Adamantos. "Use of intravenous lipid emulsion in dogs with suspected tremorgenic mycotoxicosis: 53 cases." *Veterinary Evidence* 3, no. 2 (2018).