Lipid Therapy for Intoxications

Joris Henricus Robben, DVM, PhD[a,*], Marieke Annet Dijkman, PhD[b]

KEYWORDS

• Poisoning • Toxin • Lipid • Fat • Emulsion • Intralipid • ILE
• Lipid resuscitation therapy

KEY POINTS

- Intravenous lipid emulsion (ILE) is a promising treatment modality for poisonings with lipophilic agents, especially in situations whereby patients already have developed serious clinical signs as a result of the poisoning.
- Scientific evidence on mechanisms of action, such as the lipid sink/shuttle and the cardiovascular effects of ILE therapy, is increasing; but much remains to be elucidated.
- Current dosing protocols are derived from protocols used for the treatment of local anesthetic systemic toxicity in man; although they seem safe and represent a cost-effective therapeutic intervention, it remains obscure if these are the optimal dosing protocols.
- The veterinary literature on the efficacy of ILE therapy consists primarily of case reports and case series that limit interpretation as they represent low-quality evidence; they should be evaluated with caution.

INTRODUCTION

The use of intravenous lipid emulsions (ILEs) in human clinical toxicology has become common practice as a life-saving treatment of local anesthetic–induced cardiotoxicity. Weinberg and colleagues[1] first reported its potential as a treatment option in toxicology in 1998. It was first clinically used in humans for the treatment of local anesthetic systemic toxicity (LAST) in 2006,[2,3] followed by its first use in other lipophilic drug poisonings in 2008.[4] In recent years several position papers on ILE therapy have been published by medical organizations, such as the American and British/Irish societies of anesthesiology and the American Medical College of Toxicology.[5–7] Since

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[a] Intensive Care Unit, Department of Clinical Sciences of Companion Animals, Faculty of Veterinary Medicine, Utrecht University, PO Box 80.154, Utrecht NL-3584 CM, The Netherlands; [b] Dutch Poisons Information Center, Division of Anesthesiology, Intensive Care and Emergency Medicine, University Medical Center Utrecht, Heidelberglaan 100, P.O. Box 85500, 3508 GA Utrecht, The Netherlands
* Corresponding author.
E-mail address: j.h.robben@uu.nl

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the introduction of ILE for the treatment of lipophilic drug toxicity, the interest in veterinary medicine has rapidly increased. The popularity of this treatment modality has been fed by the dramatic clinical improvement in reported clinical cases, the relative simplicity, low risks and low cost of its use, as well as the limited options that exist for the treatment of animals with certain poisonings. The use of ILE has been extensively discussed by Fernandez and colleagues[8] in 2011 and addressed previously in this journal in 2012.[9] This review discusses current information from the latest literature regarding the subject of ILE therapy in toxicology. Based on this information, insight in the possibilities for and efficacy of ILE therapy is provided.

MECHANISM OF ACTION

How lipid resuscitation works in systemic toxicity after intravenous administration of local anesthetics has been extensively investigated. The mechanisms of action are still not fully understood but include a dynamic scavenging component and direct cardiovascular effects.[10]

Scavenging/Partitioning Effect: from Lipid Sink to Lipid Shuttle

The original mechanistic hypothesis proposed by Weinberg and colleagues[1] in 1998 was that intravenous infusion of liposomes provides a compartment for lipophilic drugs in the circulation to partition into, making them unavailable to act on their target organs. This concept is known as the lipid sink (**Fig. 1**).

With improved understanding of lipid resuscitation, intravenous liposomes are viewed as a lipid shuttle or a capture/release mechanism to move a drug around and not a sink that captures and isolates the drug.[10] An intravenous lipid compartment transiently sequesters the drug, accelerating its movement from drug-susceptible organs, such as brain and heart, to organs that can store (muscle, adipose), detoxify (liver), and excrete (kidney, bladder) the drug. In this respect, metabolism of exogenous lipid is thought to be similar to chylomicrons.

There is support for a lipid sink/shuttle mechanism by in vitro, ex vivo, and in vivo studies. Transient increase followed by a subsequent decrease in the blood concentration of lipophilic drugs after ILE treatment have been reported in experimental animals as well as in human and veterinary case reports. Ivermectin plasma concentration increased substantially after administration of ILE to a border collie and a Shetland pony, followed by a decrease in plasma concentration when compared with baseline.[11–13] Confirmation of liposome partitioning does not necessarily translate into an improvement in clinical signs of intoxication in vivo. For example, decrease in target organ drug concentration may be insufficient to lead to clinical improvement; it might not be the drug itself but its metabolites that are responsible for the clinical effect, or the detoxification and excretion pathways may become saturated. In veterinary toxicology, this may play a role in ivermectin-intoxicated dogs with the ABCB-1Δ gene mutation.[14]

Direct Cardiovascular Effects or Nonscavenging Mechanisms

Lipid emulsions have a direct effect on myocardial cells improving cardiac output. The underlying mechanisms by which ILE therapy exerts this effect have not been fully elucidated.[15] The volume of the ILE bolus is definitely a factor, whereas other contributors are unclear. Several candidates for contributors have been suggested, with the calcium and fatty acid hypotheses being the two most popular. There is still conflicting experimental evidence whether fatty acids increase Ca^{2+} influx in the myocardial cells to produce a positive inotropic effect because inhibition of the Ca^{2+} influx also has been demonstrated. According to the fatty acid hypothesis, the infusion of ILE may