

The use of intravenous lipid emulsion as an antidote in veterinary toxicology

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Abstract

Objective – To review the use of IV lipid emulsion (ILE) for the treatment of toxicities related to fat-soluble agents; evaluate current human and veterinary literature; and to provide proposed guidelines for the use of this emerging therapy in veterinary medicine and toxicology.

Data Sources – Human and veterinary medical literature.

Human Data Synthesis – Human data are composed mostly of case reports describing the response to treatment with ILE as variant from mild improvement to complete resolution of clinical signs, which is suspected to be due to the variability of lipid solubility of the drugs. The use of ILE therapy has been advocated as an antidote in cases of local anesthetic and other lipophilic drug toxicoses, particularly in the face of cardiopulmonary arrest and unsuccessful cardiopulmonary cerebral resuscitation.

Veterinary Data Synthesis – The use of ILE therapy in veterinary medicine has recently been advocated by animal poison control centers for toxicoses associated with fat-soluble agents, but there are only few clinical reports documenting successful use of this therapy. Evidence for the use of ILE in both human and veterinary medicine is composed primarily from experimental animal data.

Conclusions – The use of ILE appears to be a safe therapy for the poisoned animal patient, but is warranted only with certain toxicoses. Adverse events associated with ILE in veterinary medicine are rare and anecdotal. Standard resuscitation protocols should be exhausted before considering this therapy and the potential side effects should be evaluated before administration of ILE as a potential antidote in cases of lipophilic drug toxicoses. Further research is warranted.

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Introduction

Intravenous lipid emulsion (ILE), also referred to as IV fat emulsions (IFE), have been reported as an antidote in cases of local anesthetic (LA) and other lipophilic drug toxicosis. Toxicoses which have been reported as potentially responsive to treatment with lipid emulsions include bupivacaine,^{1–9} clomipramine,^{10–12} verapamil,^{13–16}

bupropion,¹⁷ mepivacaine,¹⁸ ropivacaine,¹⁹ haloperidol,²⁰ quetiapine,²¹ doxepin,²² carvedilol,²³ carbamazepine,⁶ flecainide,⁶ hydrochloroquine,⁶ amlodipine,²⁴ propranolol,²⁵ and moxidectin.²⁶ The purposes of this review are to evaluate current literature and pertinent information available regarding the subject of ILE therapy in toxicology, to provide the clinician with an understanding of the proposed mechanisms of action, and to provide some proposed guidelines for the use of this emerging therapy in veterinary medicine.

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History

Studies in the 1970s and 1980s evaluated the effects of ILE in the pharmacokinetics of chlorpromazine and cyclosporine in rabbits^{27,28} and phenytoin in rats.²⁹ In 1998, Weinberg et al¹ demonstrated that infusion of a lipid emulsion shifts the dose–response of bupivacaine–

induced cardiac arrest in rats, indicating the potential beneficial effects of ILE in the treatment of LA toxicosis. This seminal study triggered a series of experimental studies and case reports exploring the effects of ILE administration in instances of LA toxicosis. Since then, the experimental evaluation of ILE as a treatment for other lipophilic drug-induced toxicoses has lagged behind.

However, a series of human and veterinary case reports have been published recently and propose the potential benefits of ILE in instances of neurologic or cardiac toxicoses associated with other drugs in addition to LA.^{17,18,21–24,26,30–32} In human medicine, the use of ILE is generally reserved for severe toxicosis and life-threatening conditions (eg, cardiopulmonary arrest [CPA], nonresponsive hypotension) and when conventional therapies have failed to improve physiological parameters. This perhaps differs from the approach undertaken in veterinary medicine, where administration of ILE is generally initiated earlier in the course of therapy in symptomatic patients. The use of ILE in veterinary medicine is warranted for toxicities associated with a high morbidity, particularly where traditional therapies (including ventilator management) have failed or are cost prohibitive. In both human and veterinary medicine, ILE therapy is generally considered relatively safe. Response to ILE therapy ranges from mild improvement to complete resolution of clinical signs associated with toxicosis. The variation in response is thought to be related to the lipid solubility of the toxin in question.

Formulations

The clinical use of lipid emulsions as part of a parenteral nutrition (PN) formulation began during the 1960s with the production of soybean-oil-based formulations. Later, additional lipid formulations containing olive oil, fish oil, safflower oil, and medium-chain triglycerides (MCT) were produced. In addition to PN, lipid emulsions are also used as a vehicle for drug delivery (eg, propofol).³³ Currently, the most commonly reported ILE used in the treatment of a lipophilic drug toxicosis is Intralipid 20%,^a which is a soybean-oil-based emulsion of long-chain triglycerides (LCT). A recent case report demonstrated the successful use of a mixed 20% emulsion containing equal amounts of MCT and LCT in the treatment of mepivacaine toxicosis in a human patient.¹⁸

Soybean-oil-based emulsions are the most frequently utilized emulsions in PN and in the treatment of lipophilic drug toxicoses.³⁴ The fatty acids (FA) contained in soybean oil emulsions include linoleic, oleic, palmitic, linolenic, and stearic acids.³⁵ The FA component is classified based on the length of the carbon chain,

degree of saturation, and by the position of the first double bond starting from the methyl end.³³

Pharmaceutical IV lipid formulations can be categorized in 3 main groups based on their mean droplet size (MDS): macro (MDS > 1.0 μm), mini (MDS < 1.0 μm), and micro (MDS < 0.1 μm) emulsions. Macro- and mini-emulsions require energy for their formulation and have a turbid appearance, which is not present in micro-emulsions. Micro-emulsions are thermodynamically stable and their formation occurs spontaneously. These emulsions are created by forcing a mixture of water, an emulsifier, and the selected oils through small apertures. By repeating this process multiple times, the shearing forces applied to the mixture create a submicron lipid droplet emulsion.³⁵ The injectable lipid emulsions used in PN and in the treatment of lipophilic drug toxicoses are classified as mini-emulsions, while other IV formulations fit into various categories.

The safety of an ILE is determined by globule size distribution. Lipid emulsions become potentially unsafe for administration when the lipid fat droplets coalesce with each other, forming large globules that separate from the aqueous phase. Droplets > 1 μm are phagocytized by the reticuloendothelial activation system, increasing the risk of microvascular embolization and a secondary inflammatory response.³⁶ For this reason, independent of the final concentration of the emulsion, the MDS should not exceed 500 nm, the volume-weighted percentage of fat should not exceed 0.05% of the total dispersed phase, and the free FA concentration should be ≤ 0.07 mEq/g.

Commercially available ILE (Table 1) contain an excess of emulsifier, which aggregate to form molecules called liposomes, which are typically smaller than

Table 1: Commercially available intravenous lipid emulsion (ILE)

Product	Manufacturer	Oil source
Intralipid ^a	Fresenius Kabi, Uppsala, Sweden	Soybean (100%)
Liposyn III	Hospira, Lake Forest, IL, USA	Soybean (100%)
Lipoven	Fresenius Kabi, Uppsala, Sweden	Soybean (100%)
Lipofundin-MCT	B. Braun, Melsungen, Germany	Coconut (50%), soybean (50%)
Structolipid	Fresenius Kabi, Uppsala, Sweden	Coconut (36%), soybean (64%)
Omegaven	Fresenius Kabi, Uppsala, Sweden	Fish (100%)
Lipoplus	B. Braun, Melsungen, Germany	Coconut (50%), soybean (40%), fish (10%)
Clinoleic	Baxter, Deerfield, IL, USA	Olive (80%), soybean (20%)
SMOFLipid	Fresenius Kabi, Uppsala, Sweden	Coconut (30%), soybean (30%), olive (25%), fish (15%)

80 nm in diameter. This aggregation affects the liposome content of the formulation; for example, the liposome content is higher in a 10% emulsion than in a 30% emulsion, resulting in a higher emulsifier to oil ratio. The higher the liposome content, the more catabolism of liposomes occurs, resulting in the formation of lipoprotein-X (LP-X). Lipoprotein-X is resistant to lipolysis and remains stable in circulation.³³ Intravascular accumulation of LP-X can result in hypercholesterolemia. The oil concentration of the emulsion, the rate of administration, and the length of therapy with ILE all directly result in accumulation of liposomes and therefore cholesterol. The lower the oil concentration, the higher the potential for hypercholesterolemia. When ILE are used in PN, it is recommended that products with higher concentrations (eg, >20%) be administered at slower infusion rates.³³ This contrasts the use of ILE as a therapy for lipophilic drug toxicosis, as relatively large volumes are infused over shorter periods of time. However, the total amount of lipid infused per 24 hours in toxicological applications are still lower than the maximal amount recommended for PN administration. The rapid administration of ILE is currently recommended in the poisoned patient in an attempt to rapidly increase energy production, to alter the kinetics of the toxin, or to rapidly create a 'lipid sink' compartment within the intravascular space.

Physical and chemical stresses can decrease the shelf life and safety of ILE. The manufacturer's instructions for handling and storage must be followed to minimize external variables that can accelerate the destabilization process of ILE. In addition, the United States Pharmacopeia (USP) has established that, regardless of the use, the pH of ILE must be kept between 6.0 and 9.0 for the shelf life of the product. Because of hydrolysis of the triglycerides into free fatty acids (FFA), the pH of an emulsion decreases from an initial pH of 9.0 to 6.0 by the end of the shelf life. Specific indications for storage vary depending on the manufacturer, type of emulsion, and packaging. When using these products, strict aseptic techniques are imperative to prevent risk of bacterial contamination of the ILE, resulting in potential bacteremia, but also destabilization of the emulsion.³⁵ The unused portion of the ILE used should be stored protected, under refrigeration (2–8°C), and discarded after 24 hours. If prolonged therapy (>24 h) is required, a new bag or vial must be used. As commercially available ILE preparations are isotonic, they can be safely administered through a peripheral IV catheter.

Reported Adverse Effects

Adverse effects of ILE are uncommon but may be caused by 1 of 2 events: contamination of the lipid

product or direct reaction to the emulsion. Contamination is of particular concern for nutrient-rich products such as lipid emulsions. Microbial contamination of the lipid product can occur following inappropriate handling or nonsterile technique and may result in local or systemic infection and venous irritation, with subsequent thrombophlebitis. Introduction of microbial organisms and particulate material is more likely to occur when lipid emulsions are used as a component of PN; however, this rarely occurs when ILE is infused alone.³⁷ Adverse effects of ILE may also be due to direct reaction to the emulsion, which results in an acute adverse pyrogenic reaction or 'colloid reaction'.³⁷ While rare (occurring in fewer than 1% of human cases), clinical reactions include 'anaphylactoid-like signs' which can occur within 20 minutes of administration. Signs include fever, nausea, vomiting, dyspnea, tachypnea, cyanosis, arrhythmias, hypotension, and cardiovascular collapse.^{35,37} Allergic reactions to the egg phospholipid or the soybean oil component can also occur.³⁸

Delayed or subacute reactions to ILE may also be seen, and are commonly referred to as 'fat overload syndrome' (FOS). These reactions usually are the result of the administration of excessive volumes or high administration rates overwhelming the endogenous lipid clearance mechanisms. Long-chain triglyceride emulsions administered at rates of administration above 0.11 g/kg/h can be associated with adverse effects.³⁷ Fat overload syndrome can also occur when ILE is administered to patients with decreased plasma clearance of lipids.^{35,37} In people, FOS can result in fat embolism, hyperlipidemia, hepatomegaly, icterus, splenomegaly, thrombocytopenia, increased clotting times and hemolysis.

Neurological complications associated with chronic administration of lipids have also been reported. Multifocal deficits and focal seizures have been observed in people with FOS. Histological evaluation of brain tissue have demonstrated perivascular edema and neutral lipid in the pericytes of many capillaries as well as intra-arteriolar and capillary neutral lipid emboli.³⁹

The use of ILE may have adverse alterations in pulmonary function, but the physiological effects appear to be variable. Administration of a 20% ILE in critically ill, septic patients, and in those suffering from acute respiratory distress syndrome (ARDS) resulted in an increase in the mean pulmonary artery pressure, increased venous admixture, decreased partial pressure of arterial oxygen (PaO₂) to fraction of inspired oxygen level (FIO₂), increased alveolar/arterial (A-a) partial pressure of oxygen gradient, and intrapulmonary shunting in patients.^{40,41} These changes resolved after discontinuation of ILE administration.⁴⁰ In another population of ARDS patients administered a 20% MCT/LCT emulsion (at 3.5 mg/kg/m for 1 h), changes

in bronchoalveolar fluid were seen, suggesting deterioration of the blood-gas barrier permeability, inflammation of lung tissue, and changes in alveolar surfactant characteristics.⁴² These changes were not observed in patients with normal lungs who were administered IFE at the same rate.⁴² The available data suggest that patients with ARDS may be at higher risk for developing temporary changes in pulmonary function and oxygenation parameters when administered ILE.³⁷ The changes in pulmonary function resulting from the infusion of ILE has been attributed to the products of lipid metabolism, decreased diffusion capacity due to lipid particle deposition in the reticulo-endothelial system, and decreased PaO₂ secondary to changes in pulmonary vascular tone. Changes in pulmonary vasculature tone are attributed to an increase in production of vasoactive prostaglandins. Few adverse effects were seen with ILE administration in patients with infectious pulmonary disease or chronic obstructive pulmonary disease.^{40,41} While this has not been evaluated in veterinary medicine, infusion of lipid has been used in rabbit models to induce acute lung injury. The rapid infusion of ILE in veterinary patients with potential underlying pulmonary disease must be carefully considered due to potential for species variation and response to ILE therapy.

Hypertriglyceridemia and lipemia are unavoidable consequences with the use of ILE. In people, hypertriglyceridemia is associated with an increased risk of cardiovascular disease and pancreatitis.⁴³ Historically, there have been concerns that dogs with severe hypertriglyceridemia are at increased risk for the development of pancreatitis and seizures, but a confirmed relationship between these disorders has not been proven.⁴⁴ Certainly, there is an increased incidence of pancreatitis in dogs with primary hyperlipidemias and many animals with pancreatitis have notable hyperlipemia, but a cause and effect relationship between transient hypertriglyceridemia and pancreatitis has not been demonstrated.⁴⁵

Finally, the specific formulation of the ILE itself may have varying physiologic effects or adverse events. Van de Velde *et al.*⁴⁶ compared the hemodynamic effects of 3 different ILE preparations in conscious, chronically instrumented dogs. Treatments consisted of Intralipid 20%,^a Medialipide 20%,^b or 20% omega-3 polyunsaturated fatty acids (PUFA) emulsion;^c all were administered at 7 mL/kg. Treatment with Intralipid^a alone led to a slight increase in heart rate (HR) and a transient decrease in arterial pH. Treatment with Medialipid 20%^b and the omega-3 PUFA^c emulsion resulted in a reduction in myocardial contractile performance. In cardiovascular compromised patients, the use of these latter 2 emulsions should be cautiously considered.

Mechanisms of Action

The precise mechanism of action through which ILE increases the rate of recovery and augments conventional resuscitation efforts in various cases of lipophilic drug toxicosis is currently unknown. It is possible that the antidotal effects of ILE vary with the lipophilicity of the toxic agent or that >1 mechanism of action exists for a given toxicity. Current theories regarding ILE's mechanism of action are thought to relate to improved cardiac performance and a 'lipid sink' effect, which postulates that the toxic compound is sequestered into a lipid compartment within the blood stream.

Improved myocardial performance

The beneficial effects of ILE therapy may be linked to improvements in cardiac function through either the direct benefit of lipids on the myocardium or the reversal of cardiovascular dysfunction caused by the specific toxicant. Potential direct effects include the utilization of FFA as an energy source by the myocardium, an increase in intracellular calcium, α -adrenergic receptor mediated increased vasopressor effect, and the reduction of nitrous oxide and insulin-induced vasodilatation by ILE.

In theory, ILE can improve cardiac performance through provision of energy substrates to the myocytes in the form of FFA.^{10,13,36,47,48} In the resting myocardium, endogenous FFA are used as the preferred substrate for myocardial energy production. Research studies suggest that an increased availability of FFA can improve cardiac performance in the hypodynamic, postischemic myocardium.³⁷ The effects of increasing plasma triglyceride concentration in the stunned canine myocardium were investigated by Van de Velde *et al.*,⁴⁹ who reported an improvement in the functional recovery from myocardial ischemia when high doses of lipids were administered during the postischemic reperfusion phase.

After administration of ILE, the fate of the lipid component is thought to be similar to that of endogenous chylomicrons^{38,47,50,51}; these are cleared preferentially by striated muscle, followed by the viscera, myocardium, and subcutaneous tissues.⁴⁷ It is important to note that lipid particles in ILE do not contain cholesterol but are composed of phospholipid vesicles and triacylglycerol molecules.^{47,52} Administered lipids are first found in serum where they bind to apolipoproteins C and E,⁵² and are further broken down by lipoprotein lipase (LPL) to FFA and glycerol, which easily cross cell membranes. Once inside the cell, glycerol enters the glycolytic cycle and the FFA are transported into the mitochondria. The FFA binds to acetyl-coenzyme A (CoA), crosses the outer mitochondrial membrane and are then transported across the membrane by carnitine

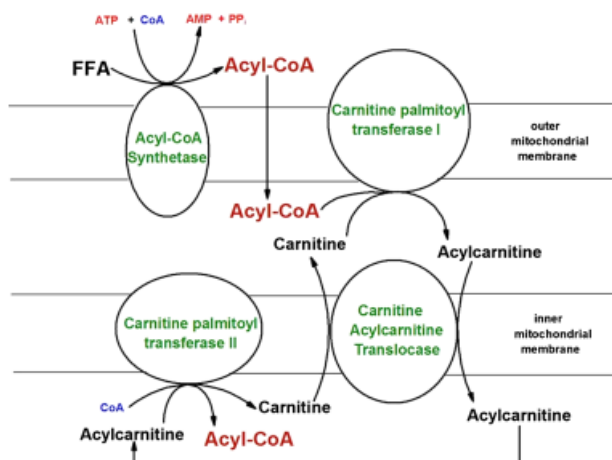


Figure 1: Once inside the cell, glycerol enters the glycolytic cycle and the FFA are transported into the mitochondria. The FFA binds to acetyl-coenzyme A (CoA), crosses the outer mitochondrial membrane and are then transported across the membrane by carnitine palmitoyl transferase I and across the inner mitochondrial membrane by carnitine acylcarnitine translocase. Once inside the mitochondria, the acyl-carnitine complex is unbound by carnitine palmitoyl transferase II to recreate the fatty acid–CoA complex.

palmitoyl transferase I and across the inner mitochondrial membrane by carnitine acylcarnitine translocase.³⁷ Once inside the mitochondria, the acyl-carnitine complex is unbound by carnitine palmitoyl transferase II to recreate the FA–CoA complex (Figure 1).

Infusion of ILE increases the overall FFA pool and potentially overcomes the inhibition of mitochondrial FA metabolism induced by certain toxicants such as bupivacaine. Bupivacaine and other local anesthetics inhibit carnitine acylcarnitine translocase, thereby blocking FA transport into the mitochondria.^{36,37} Rapid administration of ILE, either by mass effect, competitive inhibition, or an unknown mechanism, may help to override this inhibition resulting in increased FFA utilization and energy production.^{36–38}

Myocardial performance may also be improved as a function of increased intracellular calcium concentration. Studies on isolated cardiac tissue have demonstrated that increased availability of FFA, particularly oleate, linolenate, palmitate, linoate, and stearate, stimulate the activation of voltage-gated calcium channels in the myocardium, increase cytosolic calcium concentrations, and increase cardiac function.³⁷ Typically, during acute myocardial ischemia, an increase in intracellular calcium concentrations can have detrimental effects; however, this increase may help improve cardiac function in cases of myocardial dysfunction secondary to calcium channel blocker toxicosis. Oxfenicine, a carnitine acyl transferase inhibitor, has been

Table 2: Pharmacologic drugs whose side effects may be potentially reversed by administration of intravenous lipid emulsion (ILE), with the Log *P* listed

Drug	Log <i>P</i> value
Amlodipine	1.90
Baclofen	1.30
Bupivacaine	3.64
Bupropion	3.47
Carbamazepine	2.30
Carprofen	4.13
Chlorpheniramine	3.17
Chlorpromazine	5.35
Clomipramine	3.30
Cyclosporine	3.00
Dexamethasone	1.83
Diazepam	2.82
Digoxin	1.26
Diltiazem	2.80
Indomethacin	4.27
Itraconazole	5.90
Ivermectin	3.50
Ketoprofen	3.12
Lidocaine	2.26
Loratadine	5.20
Metoprolol	1.88
Moxidectin	4.10
Naproxen	3.18
Nicotine	1.17
Nifedipine	3.22
Nifedipine	2.50
Promethazine	2.85
Trazodone	1.80
Verapamil	3.83
Vinblastine	3.69

used experimentally to block myocardial FFA oxidation.⁵³ Bania et al¹⁴ evaluated the effect of oxfenicine administration on ILE therapy for verapamil toxicosis in rats. This study demonstrated that administration of oxfenicine did not interfere with the beneficial effects of ILE, suggesting a reversal of the calcium channel blockade rather than myocardial utilization of the FFA as the mechanism of action.¹⁴

Drug sequestration or ‘lipid sink’ theory

The sequestration of lipophilic compounds into a newly created lipid compartment within the intravascular space can potentially explain the beneficial effects of ILE in cases of lipophilic drug toxicosis. This mechanism has become known as the lipid or pharmacological ‘sink’ and relies on the formation of a lipid compartment to which lipophilic drugs will be sequestered and remain.

The lipophilicity of a drug is somewhat related to its log *P* value (Table 2). The ‘*P*’ is a symbol representing the partition coefficient. Coefficients are a measure of

solubility of a compound between 2 solvents. Two solvents are chosen to determine the solubility of the compound; 1 hydrophilic (eg, water) and 1 lipophilic (usually octanol). By knowing if a drug is hydrophilic or lipophilic, one is able to determine where and to what extent a drug will distribute within the body. The partition coefficient is calculated from the following mathematical equation:

$$\log P_{\text{oct/wat}} = \log \left(\frac{[\text{solute}]_{\text{octanol}}}{[\text{solute}]_{\text{water}}^{\text{un-ionized}}} \right)$$

The higher the log *P* value the more lipophilic a drug or chemical becomes. The classical and most reliable method for determining log *P* is the 'shake-flask' method. In this process, a solute is dissolved first in each of the 2 solvents. The amount of distribution of the solute into the solvent is then determined by UV/VIS spectroscopy. High-performance liquid chromatography (HPLC) may also be used to determine the log *P* value of a substance. This method is much faster, but requires that the chemical structure be known.

Log *P* is a ratio of unionized solute concentrations dissolved in 2 solutions. It does not accurately determine the lipophilicity of ionized compounds. Because most drugs are ionizable by adjusting pH, log *P* values may not accurately predict a compound's behavior in drug overdoses resulting in an acidemia or if pH is altered through alkalization therapy.⁵⁴

Drugs are determined to be lipophilic if their log *P* > 1.0. Based on the log *P* and therefore, lipophilicity of the drug, compartmentalization of the drug occurs into this temporary lipid phase storage depot. In theory, this results in a higher concentration of drug or toxicant in the plasma with less free drug available to the tissues, therefore decreasing its toxic effects.^{2,27,29,36,37,47,48} The 'lipid sink' theory has also been supported with toxicoses involving chlorpromazine,²⁷ bupropion,¹⁷ mepivacaine,⁵⁵ and bupivacaine.¹

In a study by Mazoit *et al.*,³¹ the *in vitro* binding ability of multiple local anesthetics (eg, bupivacaine, levobupivacaine, and ropivacaine) to 2 different types of commercially available ILE were evaluated. Specifically, a 20% LCT soybean-based ILE was compared with a 20% ILE containing a 50% mixture of both LCT and MCT. This study demonstrated that the maximum binding capacity was dependent on the emulsion and the dissociation constant specific to the LA. Both ILE solutions showed capability of binding all 3 LA, but the affinity of this LA to ILE was up to 3 times higher for the 20% LCT solution. This study provides strong supportive evidence regarding the affinity of LA drugs to ILE, potentially explaining their efficacy. The ability for LA to bind appears to be negatively affected by acid-

ification of the solution but positively altered by an increase in temperature.³¹ This factor may need to be taken on consideration when administering ILE to critically ill animals with severe acid-base disturbances or temperature abnormalities.

Current Published Human Research Information and Data

The descriptions of ILE use in human medicine are predominantly found in case reports. Initial case reports were related to the use of ILE as a treatment in cases of LA-related CPA that was unresponsive to cardiopulmonary cerebral resuscitation (CPCR). In 2006, the first case study was published involving a patient who developed seizures and cardiac arrest shortly after receiving a nerve block with a mixture of bupivacaine and mepivacaine.⁵⁶ After 20 minutes of unsuccessful CPCR, 100 mL of a 20% ILE was administered (1.2 mL/kg, IV bolus), followed by an additional constant rate infusion (CRI) (0.5 mL/kg/min, IV, over 2 h). Sinus rhythm and return of spontaneous circulation occurred shortly after administration of the ILE bolus. No long-term neurologic complications occurred, and the patient recovered uneventfully. Similar reports have since been published demonstrating an amelioration or reversal of the adverse effects of bupivacaine,^{3,5,57} mepivacaine,¹⁸ and ropivacaine¹⁹ with ILE. Recently, Marwick *et al.*⁵⁷ reported the recurrence of cardiotoxicity in a patient treated previously with ILE for bupivacaine-related cardiac arrest, emphasizing the importance of prolonged monitoring and the potential necessity of repeat ILE treatment with LA toxicosis.

Additional examples of toxicoses successfully treated with ILE have been published since the initial reports of ILE use in LA toxicological studies. One such study reported the co-ingestion of a lethal dose of bupropion, a unicyclic aminoketone antidepressant, and lamotrigine, a phenyltirazine derivative, used in the treatment of seizures and bipolar disorders. This patient was treated with 100 mL (1.8 mL/kg, IV bolus) of a 20% ILE after 52 minutes of unsuccessful life support. Almost immediately after ILE administration, palpable pulses were detected with progressive improvements in the QRS complexes and cardiovascular parameters. The patient was eventually discharged from the ICU with mild neurological dysfunction. Bupropion plasma concentrations performed during this episode revealed a peak plasma concentration after ILE administration, supporting the 'lipid sink' hypothesis, where bupropion was potentially shifted into the plasma compartment, allowing it to be cleared later from the body. A similar increase in plasma concentration of lamotrigine, a less lipophilic drug, did not occur.¹⁷ In another

recent case report, ILE successfully reversed pulseless ventricular arrhythmias secondary to haloperidol, an antipsychotic drug.²⁰ Since then, multiple case reports of ILE in the successful management of intentional verapamil,¹⁵ quetiapine,^{21,58} and sertraline²¹ overdose have also been reported.

In 2 separate publications, hypotension and cardiovascular collapse induced by β -adrenergic receptor blockers (eg, propranolol and carvedilol) were successfully treated with ILE.^{7,23} IV lipid emulsion has also been successfully used to resolve severe neurological dysfunction and hypotension resulting from an overdose of doxepin, a norepinephrine and serotonin reuptake inhibitor.²²

The use of ILE has not been shown to be effective in all cases of lipophilic drug toxicosis. This is supported by a retrospective, multicenter case review of patients who were treated with ILE for drug-induced cardiotoxicity. The drugs involved include verapamil in 3 patients, amlodipine in 2 patients and tricyclic antidepressants (TCA) in 3 patients. Co-ingestion of drugs was present in some patients. In this small case review, a total of 7 cases received ILE, but only 4 responded and survived; that said, no adverse reactions were reported with the ILE therapy.³⁰

Recently, the use of ILE therapy has been recommended by the Washington State Poison Center as treatment for human patients intoxicated with lipophilic drugs. They reported clinical improvement after ILE administration in patients suffering from bupivacaine, bupropion, carbamazepine (anticonvulsant), hydrochloroquine (antimalarial), and flecainide (class Ic antiarrhythmic) toxicosis.⁶ Although 1 patient with flecainide toxicosis eventually died, the symptoms (including seizures and hypotension) resolved with ILE administration.

Human reports of iatrogenic overdoses with ILE have been documented in by West²⁴ and Bora.⁵⁹ West et al²⁴ reported a case of a 71-year-old woman undergoing treatment of amlodipine toxicosis; ILE was administered due to progressive deterioration of clinical signs. An initial bolus of 20% ILE (1.5 mL/kg, IV) was administered followed by a CRI (0.25 mL/kg/min, IV) of ILE. The ILE was accidentally continued for 4.5 hours, with a total administered volume of 3,265 mL. Severe hyperlipidemia, described as a 'creamy tomato soup,' interfered with hematologic and serologic evaluation. The patient temporarily improved on second day of hospitalization, but ultimately died. The precise cause of death was not described. In the second case (unrelated to a drug toxicosis), a 6-day-old premature infant received a dose of 66.6 mL/kg instead of 7.5 mL/kg of a 20% ILE (IV over 1 h).⁵⁹ Carnitine, which is involved in the transport of long-chain FAs across the

mitochondrial membrane for energy production, was supplemented in the form of levocarnitine (60 mg, IV) in an attempt to improve lipid metabolism after this ILE overdose. The carnitine was given 10 hours after ILE administration. This infant survived with no reported complications. In human medicine, neonates and infants have decreased carnitine biosynthetic capacity and are at risk of developing carnitine deficiency, particularly when receiving PN.⁶⁰

Current Published Veterinary Information

In contrast to the available human data, most of the animal publications are in the form of experimental studies. One of the first investigations with ILE was performed in 1974, and evaluated a rabbit model of chlorpromazine toxicosis both in vivo and in vitro.²⁷ In the in vivo arm of the study, chlorpromazine (30 mg/kg, IV) resulted in the death of all control animals, but in none of the animals in the ILE pretreated group. An in vitro portion of this study also evaluated the addition of ILE to rabbit blood, and found that it significantly decreased the fraction of free chlorpromazine available. A similar study evaluated the effect of co-administration of a 20% ILE on the pharmacokinetics of cyclosporine in rabbits and found that the concurrent administration of ILE decreased the total body clearance and volume of distribution of cyclosporine.²⁸

A number of subsequent studies evaluating the use of ILE in LA toxicoses have been published in the past decade. In 1998, Weinberg et al¹ evaluated the effects of pretreatment with ILE in a rodent model of bupivacaine-induced asystole. In the ILE-treated group, the LD₅₀ of bupivacaine increased by 48%.¹ Several years later, Weinberg et al² evaluated the effect of saline fluid administration versus ILE in the treatment of bupivacaine-induced cardiotoxicity in 12 dogs. In this study, bupivacaine was administered at 10 mg/kg, an established toxic dose that causes circulatory collapse in dogs. Once patients succumbed to CPA, CPR with internal cardiac massage was instituted for 10 minutes. The animals then received similar volumes of either saline fluid administration or a 20% ILE (4 mL/kg, IV, over 2 min, followed by 0.5 mL/kg/min, IV, over 10 min). Strikingly, all animals in the saline control group failed to achieve cardiovascular improvement and died, while all of the ILE-treated patients survived, achieving near baseline blood pressure (BP) and HR 30 minutes after ILE administration. Another study by Weinberg et al⁶¹ evaluated the effects of ILE after induction of asystole with bupivacaine in the isolated rat heart. They found a faster ROSC followed by a return of cardiac function and a more rapid loss of bupivacaine from heart tissue in the ILE group.⁶¹

In an isolated rat heart study, Zausig *et al*⁶² evaluated the effects of ILE on bupivacaine, ropivacaine, and mepivacaine induced cardiac arrest. Bupivacaine was the most potent and most lipophilic agent tested, with mepivacaine being the least. They found that ILE failed to decrease recovery times as defined by time to first signs of cardiac activity; however, a significant improvement in recovery time to sinus rhythm, HR, and rate perfusion pressure (RPP, which is based on systolic BP \times HR) was observed in the bupivacaine-treated hearts but not in the ropivacaine or mepivacaine groups. This study supports the theory of drug sequestration after administration of ILE in cases of lipophilic drug-induced cardiotoxicity and that this effect appears to be dependent on the lipophilicity of the drug.

Two separate rodent studies further compared saline, epinephrine and ILE in the treatment of bupivacaine-related cardiac toxicosis.^{63,64} Rodents treated with ILE showed a statistical improvement in RPP compared with the other groups. The ILE group also had a higher arterial pH, arterial oxygen tension, and central venous oxygen saturation. In contrast, the saline and epinephrine groups had a higher incidence of ventricular arrhythmias, hyperlactatemia, hypoxia, and acidosis.⁶³ Hiller *et al*⁶⁴ compared the effect of increasing doses of epinephrine with ILE therapy in a rodent model of bupivacaine toxicosis. In this study, all the animals in the ILE-treated group achieved ROSC with slower but more sustained recovery. This study suggested a potential benefit of administration of low-dose epinephrine (1–2.5 μ g/kg) concurrently with ILE in LA-related cardiotoxicity. Similar to the previous report, pulmonary edema and hyperlactatemia were also noticed in the high-dose epinephrine groups.

Recently, DiGrigorio *et al*⁶⁵ evaluated the effects of vasopressin alone (VASO) or in combination with epinephrine (VASO+EPI) as compared with ILE in the treatment of bupivacaine-induced asystole in rats. The RPP and tissue perfusion parameters were better in the ILE-treated rats as compared with the other 2 groups (VASO versus VASO+EPI), but there was no difference in systolic BP between groups. Wet to dry lung ratios were higher in the animals treated with VASO alone or in combination with EPI. The authors concluded that vasopressin administration in the scenario of LA-cardiac toxicosis could be associated with a negative outcome.⁶⁵

Other studies have found mixed results when evaluating the use of ILE with vasopressors in models of cardiac failure. Hicks⁸ and Mayr,⁶⁴ evaluated ILE administration after the administration of epinephrine and vasopressin in a swine model of bupivacaine-induced CPA. Hicks *et al*⁸ found no beneficial effects of administration of ILE. Potential explanations proposed

by the authors include the following: the dose of epinephrine and vasopressin administered before ILE was too high (resulting in adverse effects) or that the model used and the type of CPR applied may have also influenced the outcome. For example, pigs appear to be more susceptible to LA toxicity as compared with dogs. Mayr *et al*⁶⁴ conducted a nonblinded swine study comparing ILE with a combination of epinephrine and vasopressin. To stimulate seizure activity, mechanical ventilation was temporarily suspended in both groups after LA administration; this was designed to mimic the effect of apnea and hypoxia. Within 60 seconds after CPA, CPR was initiated; however, ROSC was not achieved in any of the ILE-treated individuals, but all of the subjects in the vasopressor group survived. It has since been demonstrated in pigs that hypoxia lowers the threshold of bupivacaine-related seizures and cardiovascular side effects.⁶⁷ Furthermore, a study using a rabbit model evaluated the effects of ILE administration in the treatment of hypoxia-related CPA and found no improvement with the ILE-treated animals.⁶⁸ These studies underline the importance of basic life support optimizing oxygenation, ventilation and coronary perfusion, and suggest that careful consideration of the potential benefits and risks of ILE therapy be weighed appropriately. In cases of severe hypoxemia, with non-lipophilic drug toxicosis, or with unknown toxicants, ILE may not be beneficial.^{66,68} The consideration of whether or not ACLS drugs are affected by ILE also needs to be considered, but has not been investigated to the authors' knowledge.

In the past decade, there have been a number of experiments evaluating the use of ILE therapy in nonlocal anesthetic lipophilic drug toxicoses. Lipid therapy proved to be superior to saline and sodium bicarbonate in the treatment of clomipramine-induced hypotension in the rabbit model.¹⁰ Similar results have since been reported evaluating thiopentone-induced respiratory depression,⁶⁹ verapamil cardiotoxicity in rats,¹⁶ and propranolol-induced hypotension in rabbits.²⁵

Bania *et al*⁴⁷ evaluated the effects of ILE in a canine model of verapamil toxicity resuscitated with atropine, calcium and saline. After induction of the cardiotoxic effects of verapamil, subjects received atropine (0.04 mg/kg), calcium chloride (15 mg/kg), and 0.9% saline bolus (20 mL/kg, 15 min). The animals were randomized to receive a 7 mL/kg over 30 minutes of a 20% IFE or a similar volume of 0.9% saline solution. No animals in the ILE group died. Six out of 7 animals in the saline-treated group did not survive. The IFE group showed better MAP, base excess and a higher maximal ventricular pressure compared with controls.

In a study by Perez *et al*,¹³ investigators determined the optimal dose of ILE in a rodent model of verapamil

toxicosis. In this study, a bolus dose of 18.6 mL/kg of ILE conferred the greatest benefit to survival. They also reported that a bolus dose of 24.8 mL/kg showed better improvement in mean arterial blood pressure (MAP), base excess, and HR compared with controls, but had no added benefit in survival. In this unique study, the lipid emulsion was administered at a rate of 2.48 mL/min.

The first clinical case report of the use of ILE in veterinary medicine was described by Crandell et al,²⁶ where the use of 20% ILE was used to treat a 16-week-old female Jack Russell Terrier with moxidectin toxicosis. In this case, 2 mL/kg (IV, bolus) was administered, followed by 4 mL/kg/h (0.07 mL/kg/min, IV) for 4 hours. This was initiated 10 hours after the toxic exposure, and repeated approximately 25 hours after exposure (0.5 mL/kg, IV, over 30 min). Since then, individual case reports have been anecdotally reported, but have not been published to date of this review. Toxicology advisors from an animal poison control^d have also had anecdotal success based on recommendations, treatment, and case management with ILE.

Recommendations

Initial human dosing guidelines for ILE administration stem from 2 main sources: a publication entitled *Guidelines for the Management Of Severe Local Anesthetic toxicity*⁷⁰ by the Association of Anesthetists of Great Britain and Ireland (AAGBI) and by publications authored by Dr. Guy Weinberg, who created a website where the use of ILE is well described.³⁴ Following the publication of these guidelines, there was an increase in both the availability and willingness to utilize ILE in human hospitals, particularly in areas where LA drugs were administered.⁷⁰ These dosing recommendations were based on experimental animal studies and human case reports. Currently in veterinary medicine, there is no established recommended dose for ILE administration in the treatment of LA or other lipophilic drug toxicosis. Dosing of ILE in veterinary medicine is extrapolated from human data and the use of ILE is considered extra label.

When administering ILE, one can consider the recommended dose and rate of ILE administration for nutritional therapy. In human medicine, the general recommended dose for ILE in people ranges from 0.4–4 g/kg/d in children to 2 g/kg/d in adults.^{33,37} If using a 20% ILE, this last dose is represents a volume of 10 mL/kg/d. This is similar to what is recommended in veterinary medicine, although this rate has and can be exceeded for veterinary PN requirements.^e

The current human guidelines for the use of ILE in the treatment of LA toxicosis recommend that infusion

with ILE should only be attempted when standard resuscitation protocols have failed to establish adequate ROSC and that CPR should continue during ILE administration. Dosage recommendations of a 20% ILE are: 1.5 mL/kg (IV, bolus over 1 min), followed by a CRI of 0.25 mL/kg/min (IV, for 30–60 min). The bolus dose can be repeated twice in 5-minute intervals if CPA persists. If progressive hypotension is noticed, the CRI rate of administration can then be further increased to 0.5 mL/kg/min (IV).⁷¹ A total limit of 8 mL/kg/d has been suggested.³⁴

Based on the available information, the authors suggest administration of a bolus in the range between 1.5 and 4 mL/kg (0.3–0.8 g/kg, IV, over 1 min), followed by a CRI of 0.25 mL/kg/min (0.05 g/kg/min, IV, over 30–60 min) as a generally conservative protocol in dogs. In animals that are nonresponsive after this traditional dosing protocol, additional individual bolus aliquots can be administered slowly at up to 7 mL/kg (1.4 g/kg, IV). The authors have recommended intermittent bolusing at 1.5 mL/kg every 4–6 hours for the initial 24 hours with anecdotal success. In addition, in light of the fact that ILE can be administered to meet 100% of resting energy requirements of dogs and cats, it is likely safe to assume that follow-up CRI doses of 0.05 mL/kg/h can be continued until clinical signs improve (not to exceed 24 h). That said, there have been no safety studies evaluating the use of ILE in the clinically poisoned veterinary patient, and careful monitoring and risk assessment is important.

If an effective therapy or antidote is already well established in the field of veterinary toxicology, the continued use of traditional therapy is recommended (eg, pyrethrin toxicosis in cats) over ILE due to the unknown effects of ILE administration in the face of other drug therapy (eg, antidote administration). If, however, the patient has undergone cardiovascular collapse secondary to LA toxicosis or any other lipophilic drug, or demonstrates significant clinical signs of toxicosis (eg, baclofen, ivermectin, moxidectin), the use of ILE should be strongly considered. However, it is important that tissue perfusion and oxygenation be maximized before administration of ILE. Administration of ILE increases FFA concentration, which may have negative inotropic effects and may induce cardiac arrhythmias in the hypoxic myocardium.^{36,66,68} Appropriate medical management, adequate volume resuscitation and oxygenation are imperative in the treatment of the critically ill patient with a lipophilic compound intoxication prior to any consideration of the use of ILE.

Finally, the use of heparin, which elicits significant effects in lipid metabolism, has been clinically used to prevent secondary complications from ILE administration. While heparin can potentially minimize hyperlipidemia (and secondary risks associated with FOS)

seen with ILE administration, its routine use with ILE therapy is not currently recommended. As heparin causes the release of LPL and hepatic lipase from the endothelium, it can potentially act as the rate-limiting step in the metabolism of triglycerides.⁴³ Nasstrom *et al*⁷² reported the effects of continuous heparin administration on LPL, and found that the LPL released as a result of heparin administration has a short half-life and storage depletion occurs soon after administration. If heparin administration is considered with ILE therapy, it should be ideally used as a CRI in order to have continued effects on LPL concentrations, and in those patients that are at high risk for FOS or secondary effects from severe hyperlipidemia. The use of heparin should be carefully considered with concurrent ILE therapy, as administration of heparin may potentially reduce the lipid compartment in the blood and therefore the beneficial properties of ILE when used for the treatment of a lipid soluble toxin. Until further studies evaluate the underlying mechanisms of action of how ILE therapy works and is influenced by LPL, the judicious use of heparin should be reserved for those patients likely to develop FOS or at high risk for developing complications from ILE.

The administration of ILE for the treatment of LA or other lipophilic drug toxicity in veterinary medicine is still in its infancy and its potential is currently unknown. The judicious use of this new 'antidote' should be considered based on the lipophilic nature of the drug. The higher the affinity of a drug for lipids, the more suitable it is to be reversed by administration of ILE. Table 2 is a list of therapeutics whose side effects can be potentially reversed by administration of lipids, including drugs such as ivermectin⁷³ and baclofen.

As Picard *et al*⁷⁰ stated: 'Treatment with ILE has not been and probably never will be proven to be unquestionably superior to 'orthodox' treatment for local anesthetic intoxication in humans but the experiments on animals and case reports are increasingly suggestive. 'Standard resuscitation protocols should be exhausted before considering this therapy and the potential side effects should be strongly evaluated before administration of ILE as a potential antidote in cases of lipophilic drug toxicosis. Further research in both the veterinary and human field needs to be performed to determine a truly effective and concurrently safe dose of ILE therapy.

Footnotes

- ^a Intralipid 20%, Baxter Healthcare, Deerfield, IL.
- ^b Medialipide[®] 20%, Vidal, Boulogne, France.
- ^c 20% omega-3 PUFA emulsion: experimental formulation.
- ^d Pet Poison Helpline, Minneapolis, MN.
- ^e Remillard R, DVM, MS, DACVN, personal communication.

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