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Intravenous lipid emulsion as an antidote in clinical toxicology: a systematic review

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Abstract. – OBJECTIVE: Intravenous lipid emulsions (ILE) were developed many decades ago to supply nutritional requirements to patients unable to obtain adequate enteral nutrition. The utility of ILE was extended to therapeutics, facilitating the delivery of drugs. More recently, the potential for ILE to act as an antidote for inversion of drug toxicity has been recognized. This review aims to summarize the literature on ILE therapy as an antidote. Suggested mechanisms of action, safety profile, and recommendations on the administration of ILE in cases of drug intoxication are highlighted.

MATERIALS AND METHODS: A complete literature survey was performed using the PubMed database search to collect available information regarding mechanisms of ILE action as an antidote, ILE administration for drug toxicity, and presentation of adverse events.

RESULTS: A total of 102 studies met the selection criteria for inclusion in the review. Mainly used for local anesthetics toxicity, ILE therapy has been expanded in clinical toxicology involving overdose treatment of drugs other than local anesthetics. Partitioning in a lipid phase of fat droplets is a mechanism named the lipid sink phenomenon that has primarily been described to explain this action of ILE and remains the most widely accepted. At the same time, recent research has also revealed several molecular mechanisms that may contribute to ILE efficacy.

CONCLUSIONS: ILE therapy comprises a recognized approach in clinical toxicology. Due to the lack of randomized clinical trials, recommendations on administration are based on animal studies and published cases. Thus, the constantly increased knowledge about ILE therapy supports the need for a detailed appraisal.

Key Words:
Lipid emulsion, Lipid therapy, Drug toxicity, Resuscitation.

Introduction

Intravenous lipid emulsions (ILE) were developed many decades ago as a source of essential fatty acids to supply nutritional requirements in case of not tolerated or insufficient enteral feeding. Primarily being a dense source of cellular energy, fats also affect many cellular functions such as the formation of cell membranes, involvement in signal cascades as second messengers, modulation of inflammation and platelet function, as well as cholesterol and endogenous steroids biosynthesis[1].

The utility of ILE was extended to therapeutics, facilitating the delivery of drugs that are poorly soluble in water and are not well absorbed from the gastrointestinal tract, and nutraceuticals, incorporating improved nutritional and physical properties due to modifications of new fatty acids[2,3].

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More recently, however, the potential for ILE to act as an antidote for drug toxicity, such as local anesthetics, has been recognized. This review aims to summarize the literature on the use of ILE as an antidote, as well as suggested mechanisms of action, safety profile, and recommendations on the administration of ILE in cases of drug intoxication.

Material and Methods

PubMed was searched from 1950 to December 2016 (MEDLINE search terms in "Appendix"). Two independent reviewers screened all potentially relevant titles and abstracts for eligibility. The selection was based on the criteria of suggestion of mechanisms of ILE action as an antidote, publication of cases of ILE administration for drug toxicity with a relatively clear outcome, defined as an immediate clinical improvement after ILE infusion, and presentation of adverse events assigned to ILE administration. Search results were limited to English-language publications, and further evaluation was performed by full-text. Finally, hand searching of the reference lists and using more targeted keywords (lipid emulsion AND atenolol) led to additional selections (Figure 1).

Physico-Chemical Characteristics of ILE

ILE is an oil-in-water emulsion. It consists of triglyceride-containing oils, a phospholipid emulsifier, and glycerine[4]. A pure soybean oil emulsion was the first commercially available and remains still the predominant fat source in parenteral nutrition[1,5]. Mixed lipid emulsions containing soybean oil, medium-chain triglycerides, olive oil, and fish oil, as well as pure fish oil emulsion, constitute newly developed fat emulsions available for parenteral use[1,5]. Egg yolk phospholipid is usually the emulsifying agent in a concentration of about 1%, while the emulsion comprises particles of a mean size less than 50 μm in diameter. The phospholipid emulsifier provides stability to the lipid compartment that is formed from these fat droplets by providing both a mechanical and an electrically charged barrier. The negative charged oil-water interface causes an electrostatic repulsive force between oil droplets that are dispersed in the internal phase of the emulsion and prevents coalescence and an increase in droplet size[2].

Once a fat emulsion is administered intravenously, an expanded intravascular lipid phase is formed. Partitioning of a lipophilic substance, such as local anesthetics, into this lipid phase leads to the reduction of its plasma concentration. The subsequent gradual difference in concentration of the lipophilic substance between target tissues and the aqueous plasma phase results in redistribution of the substance to the plasma and then to the lipid plasma phase[6]. The so-called "lipid sink" phenomenon constitutes the predominant mechanism that supports the use of ILE as an antidote for drug toxicity.

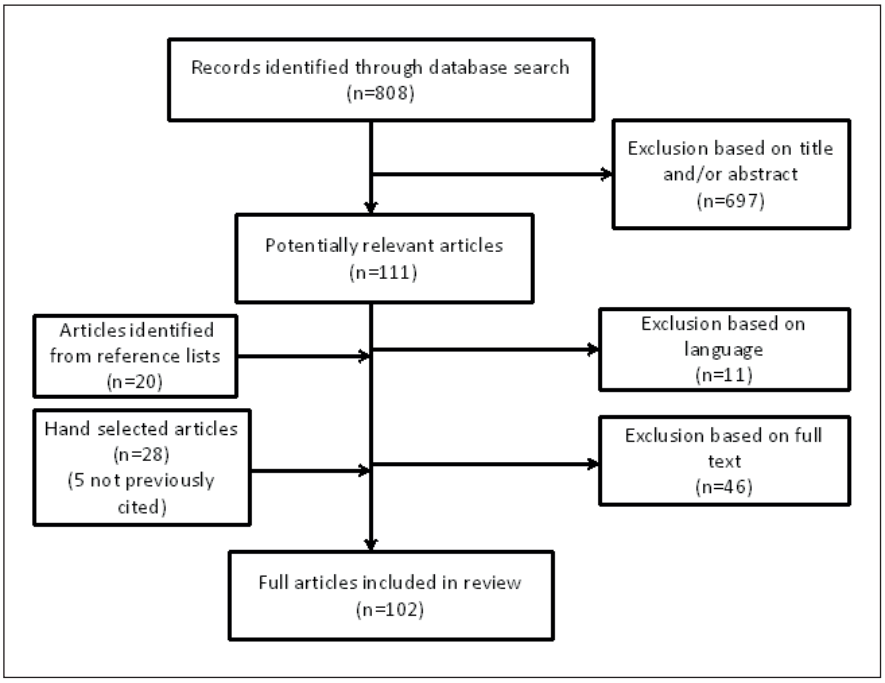

Figure 1. Flowchart of the study.

Local Anesthetics Toxicity

Local anesthetics (LAs) are medications that cause a reversible block of the transmission of a nerve impulse without any impact on the level of consciousness. Cocaine was the first successfully used LA agent in ophthalmic and dental procedures during the 19th century[7]. Synthesis of the amino ester procaine contributed to the elimination of several adverse effects of natural esters, such as euphoria and addiction. However, amino esters were gradually replaced by the newer amino amides that are less allergic and have an earlier onset of action[7]. Lignocaine is the most widely-used agent of this category, while articaine is considered to be the safest nowadays[8]. Despite these improvements in the chemical structure of LAs, systemic cardiovascular, and neurological adverse effects remain a significant complication.

The LAs are weak bases with poor water solubility. They consist of an aromatic ring, a connecting group (ester or amide for newer LAs), and an ionizable amino group. The unionized form is more lipid-soluble and facilitates the entrance of the LA molecule into neuronal cells via the lipid bilayer, while intracellular ionization enables the LA agent to bind to sodium channels and thus inactivate them reversibly. Binding also applies to the closed channels, which in this way remain inactivated and contribute to the interruption of nerve impulse propagation[9]. Other mechanisms of action of LAs that have been described are incorporation in the cell membrane, blocking of potassium channels, and anti-inflammatory effects mediated by G-protein coupled receptors[7,10].

The action of LAs is not limited to the peripheral neural system. In case of sufficient concentration in other tissues, like the heart and central nervous system, cell membrane depolarization will also be affected. In this way, the systematic toxicity of LAs is explained. The central nervous system is considered more vulnerable to toxicity, while higher concentrations of LAs are usually required to cause adverse effects from the cardiovascular system. The central nervous system toxicity is presented as a biphasic process. An early excitatory phase includes lightheadedness, dizziness, headache, perioral paresthesia, visual disturbances, sedation, slurred speech, metallic taste, hypersalivation, muscle twitching, and tremors. Progression of toxicity may lead to tonic-clonic seizures. This may be followed by a depressive phase of coma and respiratory depression[11].

Cardiovascular signs are associated with more severe toxicity and are presented in three phases. Early signs consist of tachycardia and hypertension that are followed by a relatively rapid myocardial depression and hypotension. Standard resuscitation is usually unsuccessful, and a terminal phase of cardiogenic shock, peripheral vasodilation, and cardiovascular collapse is often inevitable[12]. On the contrary, evidence-based on animal research suggests that caution should be exercised in adding epinephrine to the treatment protocol of LA toxicity, as induced hyperlactatemia and acidosis may impair resuscitation[13].

Considering the lipophilic properties of LAs, ILE could be a potential antidote in the case of LA toxicity. Although evidence is relatively indirect, partitioning of lipophilic substances into the lipid plasma phase formed after ILE infusion is a widely accepted theory. Moreover, the direct effect of fatty acids on sodium channels has been described among ILE properties[14-17]. Thus, interference on sodium channels binding, the primary mechanism of LAs action, could also contribute to the role of ILE as a potential antidote. Although evidence of ILE benefit is limited, evidence from animal studies and case reports has led to the incorporation of ILE into the management of LA-induced toxicity in addition to standard life support[18] (Figure 2).

The Use of ILE as an Antidote in Humans

Reports of the use of ILE as an antidote in humans are relatively limited. Rosenblatt et al[19] reported the first successful use of intravenous lipids in a human case of bupivacaine systemic toxicity in 2006. Subsequently, hundreds of cases have been described, although about 45% of these were considered unsuccessful[20,21]. Of note, the existing reports do not concern LA toxicity only but include more drugs, such as cardiovascular drugs, antipsychotic agents, and herbicides. On the other hand, the lack of randomized clinical trials with sufficient power to detect meaningful differences is warranted in order to clarify the effectiveness of ILE rescue therapy[22].

Mechanisms of ILE Action as an Antidote

Lipid sink phenomenon

The lipid sink phenomenon is the mechanism that has primarily been described to explain the action of ILE and remains the most widely accepted. The formation of an expanded intravascular lipid sink leads to the reduction of the unbound concentration of a toxin in plasma and distribution from or-

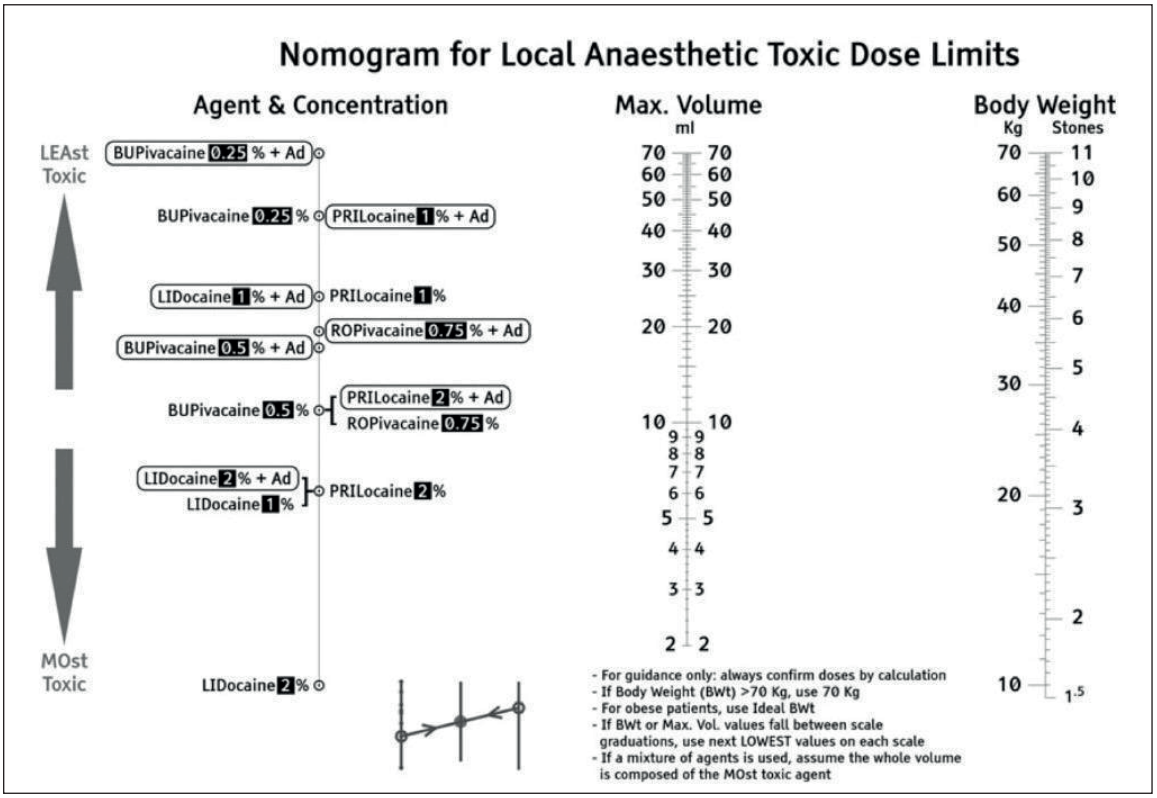

Figure 2. Nomogram for local anesthetic dose limits. (Figure is downloaded from Williams DJ, Walker JD. A nomogram for calculating the maximum dose of local anesthetic. Anesthesia 2014).

gan tissues to the bloodstream. Fat droplets form a lipid compartment, separated from aqueous plasma, into which lipophilic substances are partitioned[23]. Unfortunately, current evidence is scarce, and randomized controlled trials to investigate the mechanism of action are impossible to be performed.

Weinberg et al[24] firstly proposed that partitioning of bupivacaine into an expanded lipid phase, created after intravenous lipid infusion, was the predominant mechanism of inversion of bupivacaine toxicity in a rat model and suggested the potential for a novel treatment of LA cardiotoxicity. Subsequent reports of successful resuscitation with the use of ILE include mainly local anesthetics, calcium channel blockers (CCBs), beta-blockers, antidepressants, and antipsychotic agents, antihistamines and herbicides among others, referring to the treatment of toxicity of drugs that do not have a common mechanism and a site of action, chemical structure, and clinical effects[20]. Only high lipid solubility appears to be common among the drugs mentioned above. Indeed, the binding capacity of ILE is in close relation to the octanol/water distribution coefficient (log P) of a drug, a ratio which is usually used to measure the solubility of a chemical substance[25,26]. Mazoit et al[25] firstly evaluated the binding capacity of lipid emulsions for long-acting LAs of different solubility and found that LAs of high hydrophobicity, such as racemic bupivacaine and levobupivacaine, seem to be more rapidly cleared. Lipophilicity of LAs was also mentioned to affect ILE efficacy in an isolated rat heart model[27]. French et al[26] described the potential efficacy of ILE against toxicity of drugs other than local anesthetics. Lipid partition constant and volume of distribution of a drug were shown to predict the utility of ILE in reversing toxicity.

Cardiac myocytes preferentially use fatty acids as the primary source of energy[28]. Thus, beneficial metabolic effects of lipid infusion could be a potential controversy for ILE mechanism of action. However, the efficacy of ILE against not only cardiac toxicity but also against central nervous system toxicity cannot be explained adequately by a metabolic hypothesis[6,29,30]. Neurons do not normally depend on lipids, and this fact is indirect evidence in support of "lipid sink" theory[14]. Nevertheless, symptoms of central nervous system toxicity

may be short-lived and self-limiting, and recovery may not be related to lipid treatment.

Alternative mechanisms of action

The metabolic effects of lipid infusion on cardiac contractility do not appear to be insignificant, as the partitioning of a drug into a lipid compartment could not explain the *in vivo* observed rapid onset of cardiac toxicity inversion. Long-chain fatty acids have been shown to increase intracellular calcium by directly activating I_{Ca}, possibly by acting at some lipid sites near the channels or on the channel protein itself[15]. An increase in voltage-dependent calcium currents in cardiac myocytes is associated with positive inotropic and chronotropic effects. Huang et al[15] described this action in 1992 in order to demonstrate that the accumulation of many fatty acids during myocardial ischemia enhances cytotoxic calcium overload and triggers calcium-dependent arrhythmogenic activity.

Mottram et al[16] demonstrated that fatty acids have a direct effect on the human cardiac sodium channel, modulating bupivacaine-induced tonic- and use-dependent sodium channel blockade. Xiao et al[17] had already supported the concept of competitive inhibition for closely approximated binding sites and the displacement of the offending drug in 2001. This may be one of the several mechanisms by which ILE manifests its beneficial effect in bupivacaine-induced cardiotoxicity and has also been confirmed from more recent studies[31,32]. Also, Sterh et al[33] suggested a significant direct positive inotropic effect of lipids in a rat model of l-bupivacaine toxicity. The use of isolated rat hearts exposed to lipid microemulsions was in order to avoid the additional effect of the lipid sink mechanism. Recently, Xanthos et al[34] demonstrated that ILE infusion could prevent hypotension in a swine model of amiodarone overdose. Similar findings had also been observed by Niiya et al[35] using a mixed lipid emulsion of olive and soybean oil. Attenuation of the hypotensive effects of amiodarone and increased cardiac output may confirm the mechanisms mentioned above of ILE impact on cardiac contractility.

Furthermore, inhibition of mitochondrial permeability transition pore opening has also been described as a potential mechanism of the successful rescue of bupivacaine-induced cardiotoxicity by ILE[36]. This action is mediated through fatty acid oxidation and has also been reported in a rat model of ILE cardioprotection against ischemia/reperfusion injury[37]. Nevertheless, the data assessing the relationship between improved mitochondrial function after ILE administration and the reverse of cardiotoxicity is controversial[38,39]. Finally, the involvement of opioid receptors and modulation of protein kinase B pathway have recently been described[40,41].

Although the molecular mechanisms of action of ILE may not be fully understood, existing data demonstrate a multifactorial effect. Emulsions used for parenteral nutrition are complexed mixtures of natural products, and this may explain the wide range of action. Further studies may enhance the comprehension of mechanisms of action of ILE and extend its use to more clinical cases of drug toxicity. Suggested mechanisms of ILE action are summarized in Table I.

ILE for the Toxicity of Other Drugs

Calcium channel blockers

Calcium channel blockers are commonly prescribed in a variety of cardiovascular diseases. However, their widespread use coincides with an increased incidence of unintentional and deliberate poisonings. In the 31st Annual Report of the American Association of Poison Control Centers, cardiovascular drugs were mentioned as the seventh most frequent substance category involved in human exposures[42]. They have also been characterized as the category with the fourth-fastest rate of increase in exposures with more severe outcomes[42]. Miscellaneous cardiovascular drugs are the second most frequent generic category associated with exposure-related fatalities, while CCBs are considered responsible for at least 11730 pharmaceutical exposures and 73 deaths in 2013 in the United States[42].

Despite those mentioned above, the treatment of CCB intoxication is supported by low-quality evidence[18]. Management is typically supportive due to the shortage of available antidote. Alternative approaches have led to animal studies for the investigation of lipid emulsion efficacy in CCB poisoning[43,44]. Tebbutt et al[43] reported in 2006 that ILE treatment prolongs survival and doubles

Table I. Suggested mechanisms of ILE action.

Lipid sink phenomenon
Direct activating to calcium channels
Displacement of the offending drug of sodium channels
Inhibition of mitochondrial permeability transition pore opening
Involvement of opioid receptors
Modulation of protein kinase B pathway

median lethal dose in a rat model of verapamil toxicity, while a less marked decrease in heart rate was mentioned. Subsequently, Bania et al[44] demonstrated that ILE treatment had more positive hemodynamic effects in comparison with the standard resuscitation strategy. These animal studies were followed by case reports of successful administration of ILE to patients with CCB intoxication. The first human case was published by Young et al[45] in 2009. Despite the high number of reports, however, ILE is not still proposed by the current guidelines for the treatment of CCB poisoning. Interestingly, a recent consensus document suggests ILE as rescue treatment for the therapy of patients in refractory shock or peri-arrest period despite increasing doses of inotropes and vasopressors[46].

Beta-blockers

Animal studies in rodents with propranolol toxicity have demonstrated reduced QRS prolongation, amelioration of bradycardia and hypotension, and prolonged survival after ILE administration[47-49]. However, lipid infusion failed to improve hemodynamic instability in a similar study of atenolol toxicity in a rabbit model[50]. These controversial findings placed doubt on the efficacy of ILE against beta-blocker intoxication. Nevertheless, atenolol is a beta-blocker more hydrophilic than propranolol, and thus, pharmacokinetics may have contributed to the results of the studies mentioned above. Although case reports in humans did not pertain to beta-blockers of high hydrophilicity, ILE has been incorporated into current guidelines as a treatment adjunct for beta-blocker toxicity[18]. Some reports include the moderately lipophilic metoprolol, co-administration of hyperinsulinemia/euglycemia therapy might be crucial yet[51,52]. Further study appears to be necessary for elucidating the effect of ILE on beta-blocker toxicity.

Other drugs

A significant number of reports describe the use of ILE in human cases of toxicity of drugs other than local anesthetics. The first report was published by Sirianni et al[53] in 2008 and described a deliberate poisoning of bupropion and lamotrigine that led to seizure activity and cardiovascular collapse. Standard efforts of cardiopulmonary resuscitation were unsuccessful, while sustained circulation was restored rapidly after the administration of ILE. Serum bupropion levels before and after lipid infusion affect triglyceride levels, a finding that is consistent with the lipid sink phenomenon as the predominant mechanism of toxicity reversion. However, the authors did not observe a similar fluctuation for lamotrigine, a drug of low lipophilicity that is rarely reported for severe cardiotoxicity, at any rate.

Cases of ILE efficacy as an antidote for poisoning from psychotropic drugs have also been described, with amitriptyline, citalopram, and quetiapine being the most commonly reported[19]. Previous animal studies have demonstrated the beneficial effect of ILE compared to normal saline and sodium bicarbonate in clomipramine intoxication even though it might not be attributed through sequestration to circulating lipid droplets[54-57]. In contrast, the hemodynamic effects of ILE in a rat model of amitriptyline toxicity were not significant[58].

Published reports of ILE therapy are constantly extending and have already included cases of several lipophilic drugs, such as antiarrhythmic agents[59-63], the first-generation antihistamine diphenhydramine[64], anti-malarial medications chloroquine and hydroxychloroquine[65,66] and a recent case of caffeine intoxication[67].

Interestingly, some reports are describing an improvement after water-soluble drug intoxication. These reports should be evaluated thoughtfully, as polysubstance intentional ingestion is usual, especially in cases of psychotropic drug poisoning[42]. Of note, drugs of unknown solubility are also included in the reported cases, such as the herbicides aconite and glyphosate-surfactant, while animal studies on amphiphilic cocaine revealed controversial results[68-71].

Safety of ILE Administration

Severe pulmonary adverse events have been reported after the use of ILE for parenteral nutrition, especially in newborns, with the coalescence of oil droplets, leading to the increase of their size, and subsequent fat embolization appearing to be the main causal factor[72]. Exposure to divalent and trivalent cations or an acid pH are considered potential factors of emulsion instability, while exposure to a high temperature does not seem so crucial[2,73]. Nevertheless, complete degradation requires prolonged exposure to these extreme conditions. Headaches, jaundice, hepatosplenomegaly, and spontaneous hemorrhage may also be presented, in addition to respiratory distress, constituting the so-called fat overload syndrome, a well-known complication of ILE administration in parenteral nutrition[5].

In contrast, the administration of ILE for inversion of drug toxicity has not been associated with such complications[74]. Also, in an extraordinary case of amlodipine poisoning, cardiopulmonary implications were not presented despite the fallacious apprehension of therapeutical protocol that resulted in an excessive administration of 2 liters of ILE[75]. On the other hand, two cases of immediate asystole following ILE infusion have been reported[76]. Despite the temporal association, a clear causative explanation was not defined yet.

ILE-related adverse events have been evaluated in recent studies in order to define the maximum safe dose. In a rodent study, Hiller et al[77] used the "Dixon-up-down" method and determined the median lethal dose (LD_{50}) of ILE 20% at 67 ± 11 ml/kg. Although LD_{50} is not the final parameter for the evaluation of drug safety, in this study, it was significantly larger than the dose that is usually administered. In the same study, histological analysis of major organs tissue did not reveal any pathological findings at myocardium, central nervous system, pancreas, and kidneys. Although the transient effects of ILE were revealed at pulmonary and liver tissues, these findings were observed only after large doses of ILE (> 60 ml/kg). On the contrary, ASRA recommends ILE at a dose of 10-12 ml/kg in 30 minutes[78].

Hyperlipidemia in the form of hypertriglyceridemia or chylomicronemia is one of the well-accepted underlying causes of acute pancreatitis. Chylomicrons are triglyceride-rich lipoprotein particles that are present in the circulation when triglycerides are above the level of 900 mg/dl and are large enough to occlude the pancreatic capillaries, resulting in inflammation. The release of pancreatic lipase and enhanced lipolysis mediates inflammation, edema, and necrosis[79]. Despite the fact that lipid emulsions are designed to be similar to endogenous chylomicrons, there is only one case of acute pancreatitis that is associated with ILE administration, while reports of chemical hyperamylasemia without symptoms are more frequent[74,80,81]. Furthermore, lipemia interferes with blood samples analysis, especially when spectrophotometric techniques are performed for laboratory examination.

As a consequence, hematology and biochemistry values are commonly affected after lipid infusion, even at not extremely high triglyceride levels. Hemoglobin and platelet levels may be elevated, while liver and coagulation tests may be affected[74,82]. Blood collection prior to ILE administration and brief high-speed centrifugation of serum can be used in order to decrease the possible influence of ILE on treatment decisions and patient care[13,83].

Hypersensitivity and allergic adverse effects are also potential complications of ILE administration, although only one case of bronchospasm has been reported among patients that received ILE for drug intoxication[84].

Interaction of ILE with other drugs is not well demystified. No adverse events were observed in the case of co-administration with atropine, bicarbonate, or calcium[44,54]. On the contrary, results from a rat model of bupivacaine overdose suggest that caution should be exercised in adding epinephrine to a lipid emulsion treatment protocol, as induced hyperlactatemia and acidosis was the suggested mechanism that epinephrine over a threshold dose impaired lipid resuscitation[85]. Based on these findings, ASRA emphasized that the pharmacological treatment of local anesthetic systemic toxicity is different from other cardiac arrest scenarios and recommended to avoid doses of epinephrine above 1 mcg/kg[78]. Of note, a recent experimental study suggests that co-administration of levosimendan may be beneficial[86]. The adverse effects of ILE administration reported in human cases of clinical toxicology are summarized in Table II[84].

Table II. Adverse effects of ILE administration reported in human cases of clinical toxicology.

Cardiovascular effects
Brady/asystolic arrest
Hematologic effects
DIC
Renal failure
Metabolic acidosis
Pulmonary adverse effects
Acute lung injury
ARDS
VQ mismatch
Hypersensitivity and allergic adverse effects
Bronchospasm
Vascular occlusion and line complications
DVT
Superficial thrombosis
Phlebitis
CVVHF circuit clot
ECMO line interference
Immune modulation
Sepsis
Lipemia, hypertriglyceridemia related
Hyperamylasemia
Pancreatitis
Laboratory interference

Administration of ILE According to Current Guidelines

The 2015 European Resuscitation Council (ERC) Guidelines on Resuscitation recommend an initial bolus of 1.5 ml/kg intravenously over 1 minute, followed by a continuous infusion of 15 ml/kg/h. In case of persistent cardiovascular collapse, bolus should be repeated two more times at 5-min intervals. The infusion should be continued, at least since hemodynamic recovery has been obtained or until the maximal dose of 12 ml/kg. Standard resuscitation should be performed according to ALS guidelines[18]. These guidelines include the particular circumstance of cardiovascular collapse and cardiac arrest attributable to LAs toxicity, while ILE is also mentioned in beta-blocker intoxication[18]. The American Heart Association extends the recommendation to neurotoxicity of LAs and suggests that it may be reasonable to administer ILE to patients with other forms of drug toxicity who are failing standard resuscitative measures. Despite the weak and conflicting evidence, the prognosis of patients who are failing standard resuscitative measures is poor, and empiric administration of ILE in this situation may be sensible[87].

The optimal ILE dose is not well determined, and it is relatively empiric; it comprises a general statement based on recommendations for the toxicity of local anesthetics. ASRA has published a more detailed practice advisory on LAs toxicity in 2010, in which the need for decreasing the epinephrine dose to less than 1 mcg/kg is highlighted[78] (Table III). Regarding the intraosseous administration of ILE, the only available data are derived from animal experiments[88].

Table III. Lipid emulsion 20% therapy for local anesthetic toxicity according to ASRA (values in parenthesis are for 70 kg patient).

Bolus 1.5 ml/kg (lean body mass) intravenously over 1 minute (~100 ml)
Continuous infusion 0.25 ml/kg/min (~18 ml/min; adjust by roller clamp)
Repeat bolus once or twice for persistent cardiovascular collapse
Double the infusion rate to 0.5 ml/kg/min if blood pressure remains low
Continue infusion for at least 10 minutes after attaining circulatory stability
Recommended upper limit: approximately 10 ml/kg lipid emulsion over the first 30 minutes

Conclusions

ILE therapy comprises a recognized approach in clinical toxicology. Lack of randomized clinical trials appears to be inevitable, and recommendations on ILE administration is mainly based on animal studies and case reports. Nevertheless, ILE therapy has been expanded in the intoxication of drugs other than local anesthetics. Not only the lipid sink phenomenon but also molecular mechanisms have been suggested in order to explain this wide range of ILE efficacy. Having a favorable safety profile, ILE empiric administration in situations of failed standard resuscitation may be sensible.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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