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Short Review Article **Subject:** Clinical Toxicology

The Role of Intravenous Lipid Emulsion in Clinical Toxicology: Review of the Current Literature

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Abbreviations

AAPCC; American Association of Poison Control Centers, ARDS; Acute respiratory distress syndrome, CCBs; Calcium channel blockers, CRRT; Continuous Renal Replacement Therapies, e.g.; for example, ILE; Intravenous lipid emulsion, LA; Local anesthetics, ml/kg; milligram per kilogram, RISK: Reperfusion Injury Salvage Kinase, ROS; Reactive oxygen species, ROSC; Return of spontaneous circulation, TCA; Tricyclic antidepressants, US; United States, USA; United States of America.

Introduction

Lipid emulsion or fat emulsion refers to an emulsion of lipid for human intravenous use. Emulsification is the process of breaking down the large fat globules into smaller globules and making them water soluble. Lipid emulsion is often referred to by the most common brand name of 'Intralipid'. It is an emulsion of 20% soy bean oil, 1.2% egg yolk phospholipids and 2.25% glycerin, and is available in 10%, 20% and 30% concentrations. [1]

The lipid emulsion provides a balanced lipid supply of essential fatty acids as linoleic acid (LA); an omega-6 fatty acid and the alpha-linolenic acid (α-ALA); an omega-3 fatty acid, and of other fats. It is used for intravenous nutrition and as a vehicle for delivery of some drugs (e.g. the anesthetic drugs propofol and etomidate). [2]

Intravenous lipid emulsion (ILE) is an established treatment for the local anesthetic-induced cardiovascular collapse. The theory underlying its use is that the lipid emulsion creates an expanded, intravascular lipid phase, that drives the offending drug from target tissues into the newly formed 'lipid sink'. Based on this hypothesis, lipid emulsion has been considered a candidate for the generic reversal of the toxicity caused by the overdose of any lipophilic drug. [3]

Lipid emulsions for intravenous administration became available in the United States in the 1970s to supply appropriate fat requirements to patients with intestinal failure. Its efficacy for treating non-local anesthetic overdoses across a wide spectrum of drugs like beta blockers, calcium channel blockers, pesticides, herbicides and several varieties of psychotropic agents are being studied. [4]

The ILE therapy is gaining acceptance in emergency rooms and other critical care settings as a possible treatment for lipophilic drug toxicity. While protocols exist for the administration of lipid emulsion in the setting of local anesthetics toxicity, no optimal regimen has been established for the use of ILE in the treatment of acute non-local anesthetic poisonings. More studies are conducted to shape the evolving recommendations for the lipid emulsion in the setting of non-local anesthetic drug overdose. [5]

Aim of the work

This work aimed at reviewing the studies that dealt with the administration of Overdose settings, in order to reach a conclusion of its potential use in Clinical Toxicology up to the current knowledge.

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Methods

A systematic review of the literature published since inception till October 2018 was done. Relevant articles were determined based on the key words 'ILE' and 'Clinical Toxicology'. Experimental studies on animals were included, as well as human studies and human case reports. Veterinary Toxicology and toxicity of animal drugs on animals were not included.

So, 112 studies were included from Pubmed, Cochrane database, Science Direct and the web of knowledge. Of these, 31 were on animals; 7 of them were excluded and 81 were in human; 58 met the pre-defined search criteria. Thus 82 studies were reviewed in this work.

Review of Literature

Intravenous lipid emulsion (ILE) is well-known for the treatment of the cardiotoxicity complicating the local anesthetics use. ILE is being introduced as a treatment option for other poisoning settings. However, the recommendations are not consistent. Different investigators reported different results of ILE use in poisoned patients. [6]

Stellpflug et al. (2010) reported a case of successful reversal of cardiac arrest after nebivolol ingestion in a multi-drug overdose patient. Nebivolol is a beta1-receptor blocker with 3-10 times more beta1 cardio-selectivity than metoprolol. [7]

Successful reversal of circulatory shock in a 52-year-old man intoxicated by glyphosate herbicide had made Han et al. (2010) to agree with the use of ILE together with the aggressive fluid and vasopressors support to treat glyphosate herbicide toxicity. [8]

Jovic-Stosic and his colleagues (2011) in Serbia, described a case of severe propranolol overdose, with atypical arrhythmia; wide complex tachycardia, which was successfully reversed to normal sinus rhythm with the lipid emulsion infusion. [9]

Livshits *et al*. (2011) in USA reported a case of improvement after severe bupropion toxicity, when ILE was used with the standard management to reverse ventricular tachycardia. However, the authors recommended more studies to further describe the role of ILE in such cases. [10]

French and colleagues (2011a) in USA reported a case of verapamil toxicity that showed a declining blood level of the drug and improvement of hypotension in the patient after receiving ILE together with the standard treatment of calcium channel blockers overdose. The authors concluded that intralipid may have helped in sequestering the fat-soluble drug 'verapamil' but the hemodynamic improvement is not solely related to the intralipid because calcium and hyperinsulinemia/euglycemia therapy were also given. [11]

Boegevig et al. (2011) in Denmark reported a case of successful reversal of acute life threatening QRS complex widening and prolonged QT interval following dosulepin overdose using intravenous lipid emulsion 20% in an unstable patient. [12]

Taftachi *et al*. (2012) in Iran, tried the infusion of 10 ml/kg of intralipid 10% to 15 non-local anesthetic poisoned patients, and stated that the ILE can improve GCS and decrease the blood glucose of the patients as compared to a matched control group who did not receive ILE. [13]

Geib *et al.* (2012) in USA did a multicenter retrospective study reviewing in-patients who received ILE for drug-induced cardiotoxicity between November 2007 and March 2009. They defined nine cases with drug-induced cardiovascular side effects, which were cardiac arrest or refractory shock. They found that ILE was associated with 55% survival but it did not improve the mean arterial blood pressure (MAP). So, the authors' recommendations were that ILE use should be restricted to individual cases after careful assessment, until further prospective studies can better evaluate the benefits and risks of ILE therapy. [14]

Amitriptyline is a lipophilic tricyclic antidepressant drug that causes cardio-toxicity in overdose. Perichon *et al*. (2013) in Australia found that giving ILE early after oral amitriptyline overdose in patients resulted in worse survival, no improvement in haemodynamics and higher blood amitriptyline concentrations in the ILE-treated patients than the patients given the standard treatment without ILE. The investigators suggested

that ILE either had facilitated drug absorption from the gastrointestinal-tract or had retarded drug redistribution after oral overdose. [15]

Meaney and colleagues (2013) reported a case of amlodipine overdose successfully treated with ILE without the use of hyperinsulinemic euglycemia which is a well-known treatment option in CCBs toxicity. [16]

Gil *et al*. (2013) in Korea reported that ILE had lowered the incidence of hypotension and arrhythmia in 22 patients with acute glyphosate intoxication. ILE administration seems to be an effective treatment modality in patients who ingested sufficient amount of glyphosate herbicide that is expected to bring about significant toxicity. [17]

Bartos and Knudsen (2013) from Sweden believed that ILE is capable of reversing the tachycardia of severe quetiapine toxicity. Quetiapine is an atypical antipsychotic, used for treatment of schizophrenia, bipolar mood disorder and major depressive disorder. It is also sometimes used as a sleep aid due to its sedating effect. [18]

Cave *et al*. (2013) in Australia found no difference between ILE and sodium bicarbonate in treatment of flecainide toxicity in a rabbit model. No increase was seen in the blood concentration of flecainide in the ILE group, suggesting no 'lipid sink' for flecainide in this model. Flecainide is a lipophilic anti-arrhythmic drug that blocks sodium and potassium channels causing arrhythmias and shock in severe toxicity. [19]

Harvey *et al*. (2014) stated that ILE enhanced the elimination of clomipramine; a TCA drug, in a rabbit model. [20]

Downes *et al.* (2014) tried ILE in treating sedatives overdose. They concluded that they did not find any clinically significant effect of intralipid in sedatives overdose. [21]

Cave and colleagues (2014) from Australia believed that more studies at different centers and different continents in the world are necessary to further elucidate the role of ILE in clinical toxicology. [22]

Lee *et al*. (2015) agree to be cautious in using ILE as a treatment option for poisoning and to be aware of its potential complications. [23]

Lou and colleagues (2014) from Canada, Switzerland and USA tried to explore the mechanism underlying ILE cardiac protection after ischemic heart injuries in Sprague-Dawley rats. They found that the fatty acids in the lipid emulsion had mediated the inhibition of the mitochondrial complex IV and activated RISK pathway which enhance post-ischemic recovery and it increases ROS production, which become removed by the ROS scavenger N-(2-mercaptopropionyl) glycine component of the intralipid solution. [24]

Kang *et al.* (2015) in Korea found that ILE treatment prolonged survival and improved the outcome in a rat model of CCB poisoning using diltiazem and nicardipine. [25]

Other investigators tried ILE in diphenhydramine toxicity in an animal model. Diphenhydramine is a moderately lipophilic antihistaminic. They found no difference in hypotension, QRS widening, or diphenhydramine levels between intravenous lipid emulsion group and the standard therapy group. [26]

Moshiri *et al.* (2016) in Iran stated that ILE can reverse the haloperidol-induced hypotension in rabbits. Haloperidol is a lipophilic butyrophenone antipsychotic drug. [27]

A larger multi-national collaborative work group provided evidence-based recommendations for the use of ILE in poisoning. They said that ILE is useful in reversing cardiac arrest complicating local anesthetics especially bupivacaine toxicity, and that they are neutral regarding ILE use for all other toxins. [28]

Thus, up to the current knowledge, ILE can reverse the cardiovascular or neurological features in cases of local anesthesia toxicity, and there are reports of ILE benefits in other cases of poisoning, but there is currently no consensus of its role in order to indicate it as a treatment or an antidote option in other kinds of toxicity. [29]

Reported side effects of ILE is increasing blood lipid content that interferes with interpretation of glucose, magnesium and common laboratory analytes [30] and cause obstruction of circuits and failure of renal replacement therapy [31], in addition to

pancreatitis, ARDS [32] and severe triglyceridaemia. [33]

Also, Murphy and colleagues (2016) in USA investigated the value of ILE therapy for dihydropyridines-induced shock in swine. They found that lipid treatment did not improve the nifedipine vasodilatory hypotension or restore the circulation in any animal. Thus, they concluded the non-promising results of the ILE in calcium-channel blockers toxicity in this animal model. [34]

Hayes and lipid Emulsion Workgroup from USA and Canada in 2016, reviewed 114 full-text articles that described the use of ILE as an antidote in poisoning settings, 27 were animal studies, and 87 were human studies. The adverse effects associated with acute ILE administration included acute kidney injury, cardiac arrest, ventilation perfusion mismatch, acute lung injury, venous thromboembolism, hypersensitivity, fat embolism, fat overload syndrome, pancreatitis, extracorporeal circulation machine circuit obstruction, allergic reaction, and increased susceptibility to infection. The authors recommended further safety studies to be conducted and the dose and indication of the ILE to be adjusted with every individual case of intoxication. [35]

Wu and Juurlink (2017) in Canada described selected cases of loperamide toxicity in which ILE was beneficial. Loperamide is a non-prescription opioid that is widely used in the treatment of diarrhea. It is safe for a great degree but its toxicity results in adverse cardiovascular and central nervous effects. [36]

Corwin et al. (2017) described a unique neurologic and metabolic toxicity when ILE was given in a high total dose as an antidote for mepivacaine toxicity in an 11-years-old girl. Notable adverse effects of ILE in the case were tachypnea, and tachycardia, hypersomnolence, apparent metabolic acidosis, blood was grossly lipemic and a non-contrast brain magnetic resonance imaging showing high signal in the dural veins. The lipemia cleared over three days and the patient recovered uneventfully. However, the authors highly recommend cautious antidotal application of lipid emulsion infusions. [37]

In relation to its potential benefits in cases of drugs of abuse, Ghadiri et al. (2017) tried ILE in methamphetamine-intoxicated rats, and found that it reduced the mortality in rats, stereotyped behavior, hyperthermia and pulmonary complications. The investigators concluded that ILE may have the same beneficial effects in patients with acute methamphetamine intoxication and may save the life of patients with acute methamphetamine intoxication who do not respond to the standard initial therapy. [38]

Continuation of the trials on animals, Londoño and colleagues (2017) tried single pass dialysis of 5% lipid solution for ivermectin-intoxicated dogs and found that it helped clearance of the toxin and full recovery of the animals. Thus, they suggested that use of lipid solutions may be an adjunctive detoxification strategy for highly lipophilic herbicides such as ivermectin. [39]

Chhabria et al. (2018) tried infusion of 100 ml of 20% intravenous lipid emulsion for 40 organophosphorus poisoning-diagnosed patients, together with the standards of care of such cases, and found reduced durations of mechanical ventilation, decreased length of hospital stays, and earlier resolution of hypernatremia, however, no significant differences in mortality rates or haemodynamics between those patients and the control patients who received the classic treatment protocol of organophosphorus poisoning without any ILE therapy. [40]

Smolinske et al. (2018) reported 459 of the fatal poisoning cases in the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) in which ILE was administered. They found that 50% of the included cases involved either a calcium channel blocker or beta-adrenergic blockers, and less than 25% of the cases had involved a substance for which the Lipid Emulsion Working Group found evidence to support its use. The authors reported no response in 45% of cases, unknown response in 38%, transient/minimal response in 7%, ROSC (7%), and immediate worsening in 3%. Possible adverse reactions included: ARDS in 39 patients, lipemia causing a delay in laboratory evaluation in three cases, lipemia causing failure of a CRRT filter in two cases, worsening or new onset seizure in two cases, asystole immediately after administration in two cases, and fat embolism in one case. [41]

The authors concluded that the cases of failure of ILE outnumber the cases of success of this therapy, and that it is mostly used after cardiac arrest induced by local anesthetic drugs, and its use for other drugs poisoning and overdoses is uncertain and needs evaluation by robust controlled clinical trials. [41]

Chhabra et al. (2018) searched 1274 cases of suspected bupropion ingestion from a single poison center during the period from 1 January 2009 through 31 December 2015. They identified nine cases who received ILE therapy. Of these, four patients died and five survived. One of the survivors had neurologic sequelae necessitating placement in a long-term care facility. The authors stated that patients' complications after ILE administration were common and included continued hypotension in 7 patients, recurrent seizures in 3 patients, ARDS in two patients, and renal failure in one patient. Hence, the authors' concluded that ILE administration does not show the magnificent benefits given in some publications and that there should be more robust studies for this option of treatment in intoxicated patients. [42]

So, clinicians are advised to be careful when considering ILE as a treatment in poisoning cases, and should be very cautious if a dose in excess of 12.5 mL/kg/day will be administered, the maximum daily dosage recommended by the U.S. Food and Drug Administration for nutritional supplementation. Careful monitoring of total doses administered across institutions and hospital wards is essential to avoid the harmful effects of antidotes misuse. [37]

Summary and Conclusion

ILE is used to reverse the LA-induced cardiotoxicity. It is suggested as a treatment option for other kinds of toxicity. However, there is not yet an established evidence for its benefit in drugs/chemicals toxicity other than the LAs toxicity. Furthermore, there are reports about many side effects arising from the use of ILE in clinical toxicology practice. Amongst these side effects are the increasing lipaemia, interference with the interpretation of common laboratory analytes, obstruction of circuits and failure of renal replacement therapy, in addition to pancreatitis, ARDS and severe triglyceridaemia.

The high mortality and complications after the use of ILE in some studies warrants a solid characterization of ILE indications and regimens with individualized case assessment and follow up.

There is a need for more robust studies to allow for the production of useful practice guidelines for this therapy.

Until more data is available, clinicians are advised to take great care if considering a dose in excess of 12.5 mL/kg/day, the maximum daily dosage recommended by the U.S. Food and Drug Administration for nutritional supplementation. Careful monitoring of the total doses administered is important to avoid the harmful effects of antidotes misuse.

List of Abbreviations

AAPCC; American Association of Poison Control Centers, ARDS; Acute respiratory distress syndrome, CCBs; Calcium channel blockers, CRRT; Continuous Renal Replacement Therapies, e.g.; for example, ILE; Intravenous lipid emulsion, LA; Local anesthetics, ml/kg; milligram per kilogram, RISK: Reperfusion Injury Salvage Kinase, ROS; Reactive oxygen species, ROSC; Return of spontaneous circulation, TCA; Tricyclic antidepressants, US; United States, USA; United States of America.

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Author Contributions

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