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Intravenous Lipid Emulsion: The Solution for Many Toxic Confusions?

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Author Details
*Dr Soorya Suresh**
Department of Emergency Medicine, AIIMS, India

*Corresponding author
Dr Soorya Suresh, Department of Emergency Medicine, AIIMS, India

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Abstract

From its initial use in total parenteral nutrition, Intravenous Lipid Emulsion (ILE) has now evolved as an antidotal agent in many drug overdoses. Following its introduction in the field of toxicology for the management of Local Anesthetic Systemic Toxicity (LAST), especially bupivacaine, it has now been studied in various other drug overdoses associated with pesticides, insecticides, antiarrhythmics, etc. Researchers have postulated multiple mechanisms of action attributing its role in managing a wide range of lipophilic cardiotoxic agents. However, owing to the limited availability of good quality evidence, its utility in toxicities other than those associated with local anesthetic agents has not yet been highly recommended. Further large-scale studies in this regard are hence the need of the hour to make the best use of these agents.

Abbreviations: ILE: Intravenous Lipid Emulsion; LAST: Local Anesthetic Systemic Toxicity; TPN: Total Parenteral Nutrition; LA: Local Anesthetic; TCA: Tri Cyclic Antidepressants; AHA: American Heart Association; SSRI: Selective Serotonin Reuptake Inhibitors; ECMO: Extra Corporeal Membrane Oxygenation

Introduction

Intravenous lipid emulsions are sterile nanometer-sized droplets of triglyceride oil in water stabilized by phospholipid surfactant. The initial use of Intravenous Lipid Emulsion (ILE) dates back to the 1960s when it was initially used for Total Parenteral Nutrition (TPN). Subsequently, the use of intravenous lipid emulsion for Local Anesthetic Systemic Toxicity (LAST) was studied during the late 1990s when it was found that carnitine deficiency was associated with increased susceptibility to Local Anesthetic (LA) toxicity. This paid way to animal studies to explore the utility of ILE in cases of LAST. The earlier studies in this regard showed that animal models treated with ILE required doses higher than regular doses of LA to induce cardiac arrest and similarly cardiac arrest secondary to local anesthetic toxicity was successfully treated with ILE [1]. With these data in the background, the earlier usage of ILE in humans for LAST started in the early 2000s. From resuscitating LAST to various other toxicologic agents, ILE has now become a popular agent in emergency departments and critical care settings [1,2]. After almost 25 years in the field of toxicology for various indications, let's now discuss in this narrative review the evidence and practical considerations regarding the use of ILE in various toxicologic cases.

Mechanism of Action

Various mechanisms, both pharmacokinetic and pharmacodynamic based have been postulated to explain the antidote-based action of ILE, however, the exact mechanism or contribution of each mechanism remains unknown [1].

a. **Lipid sink theory:** One of the most popular theories, it states that triglycerides in ILE act as lipid sink in blood drawing lipophilic drugs away from tissues and blood, thereby making them non-available to target organs. Contrary to a static lipid sink theory, researchers now propose a lipid shuttle theory where it is postulated that ILE acts as a scavenger of lipophilic drugs from blood and organs with high blood flow and then helps in redistributing them to other organs like muscles for storage and liver for detoxification.

b. **Metabolic theory:** Increases mitochondrial fatty acid utilization and thereby enhances cell energy production.

c. **Membrane and inotropic theory:** By limiting toxic agents' interference with Na+ channels and promoting intracellular calcium entry by voltage dependent calcium channels.

d. **Cytoprotection theory:** by the activation of Protein kinase B.

e. **Nitric oxide theory:** Inhibits endothelial nitric oxide synthase and thereby decreases nitric oxide-induced vasodilation.

f. **Pharmacokinetic theory:** by acceleration of liver shutting.

Evidence and Recommendations on the Use of ILE

Various animal as well as human studies exist on the utility of ILE in various toxicological cases like local anesthetics, and other lipophilic agents like Tri Cyclic Antidepressants (TCA), calcium channel blockers, beta-blockers, organophosphates, cocaine etc [1-3]. Numerous studies on animal models have shown the beneficial effects of ILE in a wide range of lipophilic drugs and this encouraged the use of ILE for resuscitating drug overdoses and toxicologic cases in humans [2,4]. Even though case reports and a few RCTs have been published in this regard, we still lack well-designed large RCTs and high-quality evidence. Multiple case reports have shown clinical benefits and

successful resuscitation using ILE, heterogeneity in presentation, nonadherent to standard protocol in the administration of ILE, lack of large-scale RCTs, publication bias, and underreporting of unsuccessful cases are the key limitations of the available resources and evidence [5]. The most commonly used dose of ILE was 20% formulation with an initial IV bolus of 1.5ml/kg followed by an infusion at 15ml/kg/hr for 30 minutes and an additional bolus of 1.5ml/kg in case of persistent hemodynamic instability. Further researches on a large scale would be warranted to explore the role of ILE in non local anesthetic drug toxicity, the optimal dose of ILE to be administered, the maximum duration of infusion, role of continuous infusion vs intermittent boluses.

Local Anaesthetic Systemic Toxicity (LAST)

Published data on ILE has shown a beneficial role in the reversal of cardiovascular and neurological features in some cases of local anesthetic toxicity [6-8]. The Lipid Emulsion Workgroup experts strongly recommend the use of ILE along with standard ACLS in bupivacaine-induced cardiac arrest [1]. Even though the evidence is limited regarding other local anesthetic agents, they recommend the use of ILE when other standard treatment fails. A recent 2023 American Heart Association (AHA) update on the management of cardiac arrest due to toxicological causes is in agreement with the Lipid Emulsion Workgroup experts as AHA mentions ILE as a Class I recommendation in the resuscitation of life-threatening local anesthetic toxicity, especially from bupivacaine [9].

Non-local Anesthetic Drug Overdose

The role of ILE in other lipophilic agents like Class I antiarrhythmic, TCAs, Selective Serotonin Reuptake Inhibitors (SSRI), organophosphates, beta-blockers, calcium channel blockers, etc have been reported in the literature as case reports, case series, and small RCTs [10-13]. However, because of the lack of good quality evidence, the Lipid Emulsion Workgroup experts remain neutral concerning the use of ILE in toxicological causes other than LAST [1]. Similarly, 2023 AHA updates gave a Class III recommendation on the use of ILE in toxicological causes like β blockers and calcium channel blockers [9]. At the same time given the limited evidence available so far ILE may be considered as a last resort in these cases when other standard resuscitation measures fail. When access to other beneficial therapies like extracorporeal removal techniques or Extra Corporeal Membrane Oxygenation (ECMO) exists, they should be preferred over ILE in the context of a lack of high-quality evidence favoring ILE.

Adverse Effects

Adverse effects associated with lipid emulsions are widely reported from patients receiving long-term administration, especially TPN. Data on adverse effects in rescue therapy as in toxicology cases in limited. Adverse effects reported with ILE are directly proportional to the duration of therapy [1,14] (Table 1).

Table 1: Adverse effects associated with ILE.

1.	Hypertriglyceridemia
2.	Pancreatitis
3.	Acute kidney injury
4.	Acute respiratory distress syndrome
5.	Hypercoagulable state
6.	Anaphylaxis
7.	Thrombophlebitis
8.	Fat embolism
9.	Interference with laboratory analysis
10.	Increased susceptibility to infections

Effect of ILE on Extracorporeal Removal Techniques and ECMO

ILE and extracorporeal removal techniques or ECMO have been used simultaneously or in succession in the management of drug toxicity. Various adverse events associated with ILE have been reported in such cases which range from fat emulsion agglutination, clogging, and malfunction of the membrane oxygenator, to increased clot formation in the circuits. Physicians managing such cases should be aware of these potential complications and should weigh the benefit of ILE over these adverse effects [15].

Conclusion

Available evidence and guidelines support the use of ILE as a first-line agent in cases of LAST. There is a lack of high-quality evidence on the use of ILE for various other toxicologic cases. When access to other beneficial therapies like extracorporeal removal techniques or extracorporeal membrane oxygenation exits, they should be preferred over ILE in the context of a lack of high-quality evidence favoring ILE. Further studies on a large scale would be beneficial in expanding the clinical indications of ILE.

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