Intravenous Fat Emulsion: A Potential Novel Antidote

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ABSTRACT

Intravenous fat emulsions (IFE) are traditionally used as a component of parenteral nutrition therapy. Recently, IFE was used to resuscitate severe local anesthetic drug toxicity. This review focuses on the potential role of IFE in treatment of toxicity due to local anesthetics and other lipid-soluble drugs. The general properties of IFE, metabolic fate, and associated adverse events are described. Cases of local anesthetic toxicity treated with IFE are presented along with a discussion of the possible antidotal mechanisms. Initial investigations into the antidotal use of IFE for lipophilic central nervous and cardiovascular drug toxicity are also reviewed.

INTRODUCTION

The traditional use of intravenous fat emulsions (IFE) is to provide nutrition in the form of free fatty acids to patients who require parenteral nutrition. IFEs have recently been used in the setting of acute local anesthetic drug toxicity. This review focuses on the potential role of IFE in treatment of toxicity due to local anesthetics and other lipid-soluble drugs.

BACKGROUND

IFE as a component of parenteral nutrition therapy began in 1961, and its routine use continues today [1]. More recently, IFE has been used as a vehicle for delivery of highly lipid-soluble drugs such as propofol, paclitaxel, etomidate, and diazepam. IFE is generally composed of medium-chain triglycerides (MCT), long-chain triglycerides (LCT), or a combination of both. The most commonly used formulation consists of LCTs in concentrations ranging from 10–30% along with egg phospholipids and glycerol. The LCTs contain free fatty acids such as linoleate, oleate, palmitate, linolenate, and stearate. While IFE can be derived from a host of plant and marine sources, soybean oil is commonly used because it is a good source of the essential free fatty acids linolenate and linoleate [2]. The biological properties and metabolic fate of IFE are similar to those of endogenous chylomicrons [1]. Circulating

lipoprotein lipase hydrolyzes triglycerides, releasing the free fatty acids. The free fatty acids are then taken up by tissues and utilized as an energy substrate [1]. Once in the tissues, free fatty acids are transported into the mitochondria via carnitine translocase where they undergo primarily beta oxidation and, to a lesser extent, omega oxidation, ultimately producing stored energy as adenosine triphosphate.

SAFETY

A new antidote must have a low prevalence of adverse effects in order to be clinically useful. IFE has a very safe track record based on its frequent and longstanding use in parenteral nutrition therapy, including critically ill patients. The author's institution (a tertiary care, 900-bed teaching hospital) utilizes IFE in total parenteral nutrition preparations for approximately 60 patients each day. Adverse reactions are unusual and can be divided into two categories: those that are secondary to contamination of the intravenous solutions and direct reactions. Contamination of IFE solutions occurs during mixing of IFE into total parenteral nutrition preparations. Microbial and particulate contamination can result in infectious complications (sepsis) or venous irritation leading to thrombophlebitis [3]. Contamination risks are inherent to all hyperalimentation preparations due to required admixing, regardless of the component products. Infectious and

Keywords: Intravenous fat emulsion, cardiovascular drug toxicity, antidote

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irritant complications are unlikely to occur if IFE is administered alone.

Direct reactions to IFE are rare, but include pyrogenic reactions and fat overload. Immediate pyrogenic reactions can occur within the first 10–20 minutes of infusion. Symptoms associated with pyrogenic reactions include fever, chills, nausea, vomiting, headache, back pain, chest pain, dyspnea, and cyanosis. However, in clinical trials, pyrogenic reactions have been reported to occur in less than 1% of patients [4].

More delayed adverse reactions occur when fat emulsions are given in excessively high doses, leading to fat accumulation [5–8]. Manifestations of fat overload can include hyperlipidemia, hepatosplenomegaly, jaundice, seizures, hemolytic anemia, prolonged clotting time, thrombocytopenia, and fat embolism. These complications have been observed when IFE is administered at doses exceeding the capacity of fat metabolism or with impaired plasma clearance. The typical dose for adults is 2 g/kg/day (10 ml of 20% IFE/kg/day) infused over 3–6 hours [9,10]. The range of IFE dose in children is 0.4–4 g/kg (2.5–20 ml 20% IFE/kg) administered as a constant infusion over 24 hours [10]. There is no known maximum tolerated amount, but large volumes of IFE in parenteral nutrition are routinely and safely given. Total parenteral nutrition with 20% MCTs administered in a volume of 1000–3000 ml/day (200–600 ml MCT) is not associated with any adverse outcome [11]. The rate of administration may play a role in fat overload. Administration of isolated LCTs at rates exceeding 0.11 g (0.5 ml of 20% IFE)/kg/hour are associated with fat complications [12].

IFE can disturb some diagnostic tests. Specifically, IFE interferes with spectrophotometric measurement of various forms of hemoglobin, causing falsely elevated methemoglobin concentrations. Therefore, methemoglobin testing is not reliable during IFE therapy [13,14].

The pulmonary physiological effects of IFE deserve detailed scrutiny because any toxicology use will likely occur in patients who are critically ill and receiving pulmonary support, including mechanical ventilation. Some authors suggest a deleterious pulmonary effect with IFE in critically ill patients, but the evidence is mixed. Initial case series showed that IFE resulted in lowered blood oxygen content, increased shunting, and pulmonary vasoconstriction when given to patients with respiratory failure and/or sepsis [15,16]. Subsequent clinical series identified patients with adult respiratory distress syndrome (ARDS) as having increased risk of pulmonary effects [17,18]. Patients with normal lung function or with pulmonary compromise but no ARDS did not demonstrate lowered oxygenation or pulmonary vascular changes [5,17]. In all 5 reports, the abnormal physiology was transient and returned to baseline after completion of IFE [15–18]. An investigation using an in-vivo rabbit model demonstrated that there must be pre-existing lung injury in order to induce lipid emulsion physiological changes [19]. More recently, two randomized clinical trials disputed earlier adverse pulmonary findings [20,21]. Both trials tested 2 lipid emulsions (LCT alone and combined LCT/MCT) versus saline in patients with ARDS. Neither lipid emulsion caused a

decrease in blood oxygen content or evidence of pulmonary vascular changes. In one study, combined LCT/MCT emulsion actually increased blood oxygen content [21]. Overall, the evidence is conflicting, but suggests that patients with ARDS may be at risk for some transient changes in oxygenation and pulmonary vascular tone during IFE administration.

The pulmonary changes have been attributed to enhanced inflammation, fat overload, and excessive rate of administration. There is consistent evidence that IFE, especially the LCT components, may augment inflammatory responses. For example: the essential fatty acid linoleate is a precursor to vasoactive prostaglandins [18]. In animal models, IFE induces pulmonary inflammation with altered oxygenation and vascular resistance that is blocked by indomethacin [19,22]. Bronchoalveolar lavage (BAL) from patients undergoing IFE therapy demonstrates evidence of inflammation as well [5]. The same study also suggests that fat emboli may contribute to altered physiology. Histological analysis of BAL material revealed an increase in fat-laden macrophages in the ARDS patients. Other authors associate adverse effects with infusion rates exceeding 0.11 g/kg/hour [12]. However, this argument is not supported by strong evidence, especially in regard to pulmonary effects. Three prospective clinical trials utilized IFE at or double this reported toxic threshold [5,20,21]. One trial noted transient pulmonary changes in ARDS patients only [5].

In summary, the adverse effect profile of IFE is limited. Even patients with ARDS, who may be at risk for complications, exhibit transient effects that do not necessitate cessation of IFE therapy. Thus, the adverse effect profile would not limit the expansion of use from nutritional support to adjuvant therapy for toxicology patients.

IFE AND LOCAL ANESTHETIC TOXICITY

Substantial animal research supports the use of IFE as an antidote for cardiovascular toxicity due to the anesthetic drug bupivacaine. In isolated perfused rat hearts, IFE treatment reversed bupivacaine-induced myocardial depression [23]. In isolated perfused guinea pig heart preparations, IFE reversed bupivacaine-induced QRS widening [24]. In intact rats, pretreatment with IFE increased the lethal dose of intravenous bupivacaine in a dose-dependent manner compared to control animal [25]. In a rescue arm of the same report, investigators found that 30% IFE increased the bupivacaine LD₅₀ by 50% compared to controls. Rescue effect with IFE therapy was also demonstrated in an intact canine model [26]. In the study, anesthetized dogs were overdosed with bupivacaine until they developed bradycardic arrest. Cardiac massage was instituted for 10 minutes after arrest and then animals received either 20% IFE or saline. IFE afforded 100% survival compared with 0% control animal survival. Additionally, cardiotoxic dogs treated with IFE had improved myocardial metabolic function as compared to control animals.

Recent case reports introduce the successful use of IFE in the resuscitation of 3 patients with local anesthetic toxicity, all

unresponsive to standard treatment. One patient developed seizures and cardiac arrest in temporal relationship to brachial plexus injection using a combination of bupivacaine and mepivacaine. After 20 minutes of unsuccessful resuscitation efforts with epinephrine, atropine, amiodarone, vasopressin, and defibrillation, a bolus of 100 ml of 20% IFE was given with immediate return of circulation. An infusion of 0.5 ml/kg/minute 20% IFE was subsequently started and continued for 2.5 hours [27]. In the second case, inadvertent overdose of ropivacaine during axillary nerve block resulted in a seizure, then bradycardic arrest. After 10 minutes of CPR and repeated doses of epinephrine, 20% IFE was administered using a 2 ml/kg bolus (100 ml) and 10 ml/minute constant infusion. After a total of 200 ml IFE (4 ml/kg), pulse and circulation returned [28]. In the third case, the patient developed seizures, hypotension, and widened QRS complexes after a lumbar plexus block with 1-bupivacaine. Metaraminol was given without change in ECG, heart rate, or blood pressure. Four minutes after cardiovascular collapse, 100 ml of 20% IFE was administered with immediate narrowing of the QRS complex and improvement in blood pressure [29]. All 3 patients recovered completely without neurological or other sequelae.

While the exact mechanism of IFE's antidotal action is not completely elucidated, there are at least 3 potential explanations. In the first mechanism, IFE creates a pharmacological sink for fat soluble drugs. In the blood, IFE exists as small fat droplets that provide a lipid compartment separate from the aqueous compartment into which lipophilic compounds may dissolve. For example, bupivacaine preferentially partitions into the lipid compartment by a 12:1 ratio [25]. By creating a serum lipid partition, the effective concentration of the lipophilic drug available to tissues is lessened. Support for the lipid sink mechanism comes from previously cited animal studies. In isolated heart preparations, IFE decreased overall bupivacaine tissue content by 70%. Coincident with the decline in tissue content, cardiodynamic outcomes returned to baseline faster than controls [30]. Lipid infusion with smaller droplet size than that of pharmaceutical fat emulsion demonstrated greater ability to sequester bupivacaine and more pronounced reversal of QRS prolongation [24]. Thus, the study showed a concentration response. The use of IFE may similarly decrease the effective concentration of other lipid soluble compounds for which enhanced elimination may be desirable but not amenable to standard extracorporeal techniques (i.e., hemodialysis).

The second potential mechanism involves augmenting cardiac energy supplies. Fatty acids are the primary substrate for myocardial ATP production in the nonstressed, resting heart. Although study results vary on the importance of fatty acid substrate during times of cardiac stress, some investigations indicate that augmented fatty acid supply improves cardiac performance in the ischemic, hypodynamic heart [31,32]. In addition to direct sodium ion channel antagonism, local anesthetic drugs may exert cardiotoxicity due to impaired energy substrate utilization. Local anesthetics, including bupivacaine, can impair fatty acid transport into cardiac mitochondria, ultimately depleting available

energy molecules. Specifically, they inhibit carnitine acylcarnitine translocase, an enzyme that facilitates the movement of fatty acids across the inner mitochondria membrane [33]. IFE may supply a sufficiently large amount of fatty acid substrate to overcome bupivacaine-induced fatty acid transport blockade. When critical energy substrates are restored, cardiac function is restored as well. Indirect support for this mechanism comes from an investigation in which IFE improved measures of contractility without significantly improving QRS prolongation [23]. There are no studies that specifically look at direct measures of cellular energy during drug toxicity and IFE therapy. However, one pilot study involving a rodent model of IFE therapy for verapamil, a calcium channel antagonist drug, argues against the fatty acid substrate mechanism [34]. In the study, rats were pretreated with an agent that blocks free fatty acid oxidation, then exposed to verapamil until toxic, and finally treated with IFE or control solutions. Fatty acid blockade did not diminish IFE hemodynamics or survival.

IFE may restore myocyte function by increasing intracellular calcium. In isolated cardiac tissue, free fatty acids directly activate the voltage-gated calcium channel similar to known calcium channel openers [35]. Calcium channel activation was demonstrated for unsaturated (linoleate, linolenate, and oleate) and saturated (palmitate and stearate) long-chain free fatty acids. These fatty acids are major constituents of IFE. In another isolated myocardial tissue model, oleate activated voltage-gated calcium channels with subsequent increased cytosolic calcium and associated increased performance [36]. While fatty acid-induced calcium accumulation is generally viewed as detrimental in ischemic tissue, additional cytosolic calcium may be beneficial in the case of nonischemic, drug-depressed myocardium. This may be especially important to calcium channel antagonist toxicity. Further studies are needed to fully elucidate the mechanism(s) of action of IFE. It is possible that all 3 potential mechanisms play a synergistic role in lipid therapy.

IFE AND OTHER TOXINS

Most recently, IFE was used in the resuscitation of a patient after overdose with bupropion and lamotrigine. This is the first clinical use of IFE for nonanesthetic drug toxicity. In this case, suicidal bupropion ingestion resulted in coma, wide QRS tachycardia, seizure, and cardiac arrest. Following 50 minutes of standard resuscitation with sodium bicarbonate, epinephrine, transcutaneous pacing, norepinephrine, magnesium, and calcium, a 100-mL bolus of 20% IFE was given with return of spontaneous circulation 1 minute later. The patient's hospital course was prolonged, but the patient recovered with mild tremor, mild memory deficits, and fine motor incoordination. Serial bupropion levels correlated with serum triglyceride levels, suggesting a lipid sink effect of IFE therapy [37].

As demonstrated in the case report, lipid emulsion may be useful to treat severe central nervous system or cardiac toxicity due to other highly lipophilic drugs. Investigations have

Summary of Intravenous Fat Emulsion Treatment

Author	Year	Model	Toxin	IFE protocol	Primary Outcome and Results
Weinberg, et al.	1998	rat	bupivacaine	Pretreatment: 15 mL/kg of 10%, 20% or 30%	Increased mean lethal dose
Weinberg, et al.	2003	dog	bupivacaine	Rescue: 4 mL/kg bolus of 20% followed by 0.5 mL/kg over 10 mins	Increased survival time; improved hemodynamics, PO ₂ and pH
Cave, et al.	2006	rat	propranolol	Pretreatment: 16 mL/kg of 20%	Trend toward improved survival time; improved HR; decreased QRS prolongation
Cave, et al.	2005	rat	thiopental	Rescue: 8 mL/kg of 20%	Trend toward decreased respiratory depression
Bania, et al.	2007	dog	verapamil	Rescue: 7 mL/kg of 20%	Improved MAP; increased survival
Tebbutt, et al.	2006	rat	verapamil	Rescue: 12.4 mL/kg of 20%	Increased survival time and LD ₅₀ ; slower development of bradycardia
Yoav, et al.	2002	rat	clomipramine	Simultaneous: 2.5 mL of 10%	Improved survival time
Harvey, et al.	2007	rabbit	clomipramine	Rescue: 12 and 8 mL/kg of 20%	Improved MAP and survival time
Bania, et al.	2005	mouse	organo phosphate	Pretreatment: 15 mL/kg of 20%	No change in the LD ₅₀

evaluated IFE as a potential antidote for selected antipsychotics, barbiturates, cyclic antidepressants, organophosphates, and anti-hypertensive drugs.

Fat emulsion decreased free drug and increased survival in a toxic rabbit model of chlorpromazine, a phenothiazine antipsychotic agent [38]. Investigators found that lipid emulsion lowered the concentration of free chlorpromazine in the blood from 2% to 1% in vitro. In the second part of the study, pretreatment with IFE resulted in 100% survival at 2 doses (25 mg/kg and 30 mg/kg) of chlorpromazine, while the control animals only survived the lower dose. Thiopental, an ultra-short-acting barbiturate commonly used to induce general anesthesia, produced less respiratory depression when treated with 8 ml/kg bolus IFE [39]. Although no absolute differences were seen in the respiratory rate between control and experimental animals, respiratory rates appeared to recover faster in the IFE group. The use of lipid emulsion reduced mortality following exposure to clomipramine, a tricyclic antidepressant. Rats given a mixture of intravenous clomipramine formulated in fat emulsion had 80% survival versus zero survival when clomipramine was dissolved in saline [40]. In studies done in a rabbit model of intravenous clomipramine overdose, IFE outperformed sodium bicarbonate with regard to reversal of hypotension and rate of normalization of QRS duration [41]. In a more toxic arm of the study, clomipramine was infused until animals were near cardiovascular collapse. Animals then received either 20% IFE or 8.4% sodium bicarbonate. Only animals treated with IFE survived to the end of the experiment (albeit only a 10-minute rescue protocol). Human experience evaluating fat emulsion therapy and tricyclic antidepressants is limited to healthy volunteers taking therapeutic amitriptyline

(75 mg each night). Following 10 days of drug therapy, volunteers received either 500 ml 20% IFE or sham saline infusion, then serial plasma drug levels were measured. Investigators found no statistically significant difference in amitriptyline levels between groups and concluded that there was no role for a lipid emulsion in tricyclic antidepressant intoxication [42]. This study is limited by the fact that the drug was in steady state and at therapeutic plasma concentration, whereas in acute overdose, much larger amounts of drug are ingested and initial plasma concentrations are higher, especially during the distribution phase. Perhaps IFE is more effective when there is a greater mass of drug present in the vascular compartment to sequester.

Work with IFE as an antidote to antihypertensive drug toxicity has recently been published. Intravenous lipid emulsion ameliorated toxicity from verapamil, a phenylalkylamine calcium channel antagonist agent [43]. Rats were infused with verapamil at a toxic rate, followed by treatment with either saline or 12.4 ml/kg of 20% IFE. The lipid infusion doubled survival time and the verapamil LD₅₀. A recent canine model of verapamil toxicity tested the addition of IFE to traditional resuscitation [44]. Animals received atropine and calcium followed by 7 ml/kg 20% IFE or saline rescue. Dogs that received IFE maintained hemodynamics despite continued verapamil infusion, while those of control animals progressively declined. Most important, IFE conferred increased survival at 2 hours versus controls (100% vs. 14%). Similarly, a small pilot study using propranolol, an antihypertensive agent with both β -adrenergic receptor and sodium channel blocking properties, showed promising effects with IFE [45]. In rats, pretreatment with 16 ml/kg IFE prevented QRS prolongation seen in control animals. Investigators also reported a

trend towards increased survival and attenuation of propranolol-induced bradycardia. The study was limited by a small number of subjects. Further study is warranted for propranolol.

Although most studies have demonstrated benefit, not all IFE studies show positive effect. Lipid emulsion pretreatment did not alter the LD₅₀ in a murine model of organophosphate toxicity using paraoxon [46].

SUMMARY

Intravenous fat emulsion has promise as an antidote for highly lipophilic drugs that can cause rapid cardiovascular or central nervous system collapse. Evidence from animal investigations supports this concept, as does the initial clinical experience with the treatment of local anesthetic drug toxicity. The overall safety profile of infused lipid is promising. Additionally, IFE is practical to stock as an antidote from a pharmacy standpoint. It is inexpensive (hospital cost = \$9.00/500 ml), does not require special storage, and has a 2-year shelf life. Thus, IFE is attractive to stock in an emergency department for the uncommon case of drug-induced cardiovascular collapse. If not utilized, IFE can easily be cycled into parenteral nutrition stock towards the end of its 2-year shelf life, thereby eliminating any waste. However, there are several questions that need to be addressed prior to widely adapting IFE to resuscitation of drug-induced cardiovascular collapse.

First, the mechanism by which IFE confers benefit needs better delineation. If IFE acts as a preferential lipid sink as most studies suggest, it may prove valuable in sequestering highly lipid soluble compounds other than local anesthetics from target tissues. On the other hand, if the purported action is due to enhancing fatty acids as cellular energy substrates, it may not be beneficial for drug-induced shock, in which the myocardial preference for energy substrates is carbohydrates, not free fatty acids [47,48]. The only study that addresses IFE mechanism refutes the latter [44]. Second, safety in the setting of acute drug toxicity is not defined. Large doses were well tolerated in three cases of local anesthetic toxicity [27–29]. Will the same safety profile hold true when large doses may be needed over a longer period of time to treat other cardiovascular toxins? Drugs such as cyclic antidepressants, calcium channel antagonists, and β -adrenergic blockers have more prolonged duration of action and elimination compared to local anesthetics, and will likely require larger total doses of IFE. Animal models also suggest that large doses of IFE will be required to treat cyclic antidepressant or antihypertensive drug overdose. In these studies, doses of IFE ranged from 8 to 16 ml/kg 20% IFE [43–45]. The clinical trials of IFE in critically ill patients suggests that large doses can be given safely over several hours [5,20,21]. However, experimental models looking at cyclics and cardiovascular agents did not address adverse effects, especially at large doses. Could IFE inadvertently enhance some organ toxicity? IFE is used as a vehicle to deliver fat soluble drugs such as propofol. It is possible that drug sequestered by IFE from one tissue compartment may then be preferentially delivered to another compartment. For example, could IFE increase

drug penetration into the central nervous system with a resultant increased neurotoxicity, despite alleviating direct cardiac toxicity? The improved survival in the experimental models serves as indirect evidence that this concern may be moot, but no study directly assesses preferential organ toxicity [40,41,43,44].

The research endeavors and preliminary clinical experience with IFE treatment of local anesthetic toxicity yields the promise of a readily available, cheap, and safe adjuvant therapy for other lipophilic drugs with serious central nervous system or cardiovascular toxicity. The opportunity is ripe for additional laboratory and clinical research.

The authors have no potential financial conflicts of interest to report.

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