A systematic review on intravenous lipid emulsion.

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Abstract

Intravenous lipid emulsion (ILE) therapy is an emerging, but unproven therapy for refractory cardiotoxicity due to lipid-soluble drugs. Its promise was first recognized in a rat model of bupivacaine toxicity. and has gained visibility in the clinical arena after reports of its use for bupivacaine and other drug toxicities. Evidence for ILE in the management of drug-related cardiotoxicity is limited at this time to animal studies and human case reports. Animal models have demonstrated improved survival from drug-induced cardiotoxicity from bupivacaine, clomipramine, propranolol, atenolol, and verapamil when ILE is administered during resuscitative efforts. Human case reports in the literature document recovery from cardiovascular collapse due to poisoning from bupivacaine, ropivacaine, bupropion/lamotrigine, mepivicaine/bupivacaine, and levobupivacaine.

Keywords: Intravenous lipid emulsion, Lipid-soluble drugs, Cardiotoxicity, Ropivacaine.

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Introduction

Intravenous lipid emulsions (ILE) have been used for decades as parenteral nutrition with Food and Drug Administration (FDA) indications for caloric supplementation and essential fatty acid deficiency. Lipid emulsion is also used as a carrier for lipid-soluble medications, most notably propofol. The benefits of lipid emulsion for bupivacaine poisoning were first suggested in a rat model by Weinberg et al 1998. The subsequent study in dogs by Dr. Weinberg and the first report of use in humans by Rosenblatt et al. In 2006 have brought about a paradigm shift in the management of acute local anesthetic toxicity toward utilization of ILE. The lipid emulsion workgroup was established as a collaborative effort among the American Academy of Clinical Toxicology, the European Association of Poison Centres and Clinical Toxicologists, the American College of Medical Toxicology, the Asia Pacific Association of Medical Toxicology, the American Association of Poison Control Centers, and the Canadian. Association of Poison Control Centers.8This article presents the workgroup's recommendations regarding the use of intravenous lipid emulsion therapy in poisoning for a preselected set of toxins. These recommendations are based on the results of four systematic reviews derived from a comprehensive analysis of the published evidence and further followed by an expert consensus. Intravenous lipid emulsion (ILE) has recently received much attention in the treatment of acute local anaesthetic toxicity and a variety of other non-local anaesthetic poisonings.

Indications

- ILE is used for the toxicity caused because of intentional or unintentional administration of lipophilic agent.
- It is used in emergency rooms and critical care units as a potential rescue therapy for acute toxicities and poisonings.
- Drug class including tricyclic antidepressants, calcium channel blockers, beta-blockers, antipsychotics, insecticides, and organophosphate poisoning.

Literature Review

Dosage and administration

Adult: the infusion rate can be increased to 1 ml/minute. Not more than 500 ml of intralipid® 20% (20% i.v. Fat emulsion) should be infused into adults on the first day of therapy. The dose can be increased on the following day. The daily dosage should not exceed 2.5 g of fat/kg of body weight. Intralipid® 20% (a 20% IV fat emulsion) should make up no more than 60% of the total caloric input to the patient. Paediatric: the dosage for premature infants starts at 0.5 g fat/kg body weight/24 hours (2.5 ml intralipid® 20% (20% i.v. Fat emulsion) and may be increased in relation to the infant's ability to eliminate fat [1]. The maximum dosage recommended by the american academy of pediatric is 3 g fat/kg/24 hours the initial rate of infusion in older pediatric patients should be no more than 0.05 ml/minute for the first 10 to 15 minutes. If no untoward reactions occur, the rate can be changed to permit infusion of 0.5 ml of intralipid® 20% (20% i.v. Fat emulsion) /kg/hour. The daily dosage should not exceed 3 g of fat/kg of body weight3 intralipid® 20% (20% i.v. Fat emulsion) should make up no more than 60% of the total caloric input to the patient.

Mixing guidelines and limitations

Investigations have been conducted which demonstrate the compatibility of intralipid® 20% (a 20% i.v. Fat emulsion) when properly mixed with either novamine® or 8.5% travasol® or 10% travasol® amino acid injections without electrolytes for use in tpn therapy. The following proper mixing sequence must be followed to minimize ph related problems by ensuring that typically acidic dextrose injections are not mixed

with lipid emulsions alone: 1. Transfer dextrose injection to the tpn admixture container 2. Transfer amino acid injection 3. Transfer intralipid® 20% (a 20% intravenous fat emulsion) note: amino acid injection, dextrose injection and intralipid® 20% may be simultaneously transferred to the admixture container. Admixing should be accompanied by gentle agitation to avoid localized concentration effects. These admixtures should be used promptly with storage under refrigeration (2-8°c) not to exceed 24 hours and must be completely used within 24 hours after removal from refrigeration. It is essential that the admixture be prepared using strict aseptic techniques as this nutrient mixture is a good growth medium for microorganisms [2].

Pharmacokinetics of poisons after administration of lipid emulsion

After the ingestion of poison in the body by the administration, inhalation or by any other method they get into the body. Infusion of lipid emulsion, make them to distribute to the body. Decreases the elimination half-life and movement of poison from 1 compartment to other compartment decreased. The content of drugs in the brain, myocardium, lung, kidney, spleen, and muscle was reduced as the intravenous lipid emulsion interrupt in the distribution of poisonous substances. However, the lipophilic poison content increases in the liver was increased at a consecutive interval of time which help in the fast metabolism of the drug in the liver. The clearance rate of poisonous substance increased and also the half-life of the lipophilic poisons was prolonged. Looking all these factors above the concentration of toxins in the plasma get decreased. The lipid compartment in the body creates a transport effect by removing the lipophilic drugs from the organs. In this way, organs with high blood flow get detoxified.

Composition

Typically, dietary fats are emulsified by bile salts in the intestinal lumen and hydrolyzed by pancreatic lipases for take-up by intestinal enterocytes. The freed long-chain FAs are bundled into chylomicrons for passage into lymphatic channels and, eventually, into the venous framework. Short-and medium-chain FAs might be retained from enterocytes straightforwardly into the flow as free FAs bound to egg whites. These cycles have managed to guarantee that FAs can be moved in the circulatory system in a steady structure for energy needs.

Fatty acids

The functionality of the Triacylglycerol (TAG) molecules is determined by the type of FA esterified to the glycerol backbone and the stereospecificity of the linkage. The saturated FAs (SFAs) belonging to medium-chain triglycerides (MCTs) feature in some LE formulations. Longer carbon chains with the 22-carbon docosahexaenoic acid (DHA) and the 20-carbon eicosapentaenoic acid (EPA) are also known in LE formulations.

Phospholipid emulsifiers

Emulsions are frameworks that comprise of 2 immiscible fluid stages, 1 of which is scattered all through the other fine beads. Lipid emulsions for intravenous use comprise of oil suspended in a fluid scattering. The scattering comprises of phospholipid that is normally as lecithin from egg yolks, glycerol, and water. Oil is acquainted with the scattering under ceaseless blending conditions, and globules are framed comprising of TGs the oil encompassed by a phospholipid monolayer. More modest globule sizes give ideal strength in the blood. Two globule size determinations that the United States Pharmacopeia requires of intravenous lipid emulsions are a mean globule size of <500 nm and a level of fat globules >5 mm of<0.05%. Globule size can be made more modest by expanding the phospholipid proportion. This has been affirmed in investigations of industrially accessible lipid emulsions exhibiting that those containing higher rates of oil in a given measure phospholipid emulsifier have a higher level of fat globules of >5 mm esteems and mean globule sizes than emulsions with lower oil fixation [3].

Oil sources for parenteral lipid emulsions

There are a few oils utilized in the creation of lipid emulsions for intravenous organization. Each varies as for FA content, EFAD potential, and phytosterol and a-tocopherol content.

Soybean oil: Soybean oil was the TG wellspring of the primary lipid emulsion produced and effectively managed for intravenous use in PN.18Soybean oil has a high phytosterol concentration, with ;300 mg phytosterol/100 g oil6.4-7.5 mg/100 g oil. There are higher amounts of other tocopherols (i.e., g-tocopherol), but they do not have the same antioxidant potential of a-tocopherol.

Safflower oil: Safflower oil is another plant-based oil that is rich in n-6 PUFAs and contains phytosterols. Its FA composition consists of 77% n-6 LA ;15% n-9 oleic acid, and virtually non-3 PUFAs. Safflower oil, like soybean oil, is high in phytosterols containing;450 mg/100 g oil. However, unlike soybean oil, safflower oil has greater antioxidant potential with substantially more a-tocopherol, at;34 mg/100 g oil.

Olive oil: Olive oil is a third plant-based oil utilized in intravenous lipid emulsions; nonetheless, in contrast to soybean and safflower oils, the FA structure of olive oil is;85% of insignificant oleic corrosive, just;4% of fundamental n-6 FA LA, and is essentially devoid of PUFA. The phytosterol concentration of olive oil is lower than soybean and safflower oils.

Coconut oil: Coconut oil is principally composed of TGs containing six- to twelve-carbon medium-chain FAs [medium-chain TGs (MCTs)]. Lauric acid (dodecanoic acid; 12:0) comprises;50% of its FAs, and the other MCTs, Caprylic acid (octanoic acid; 8:0) and capric acid (decanoic acid; 10:0), comprise ;8% each. Other FAs in coconut oil include stearic acid (octadecanoic acid; 18:0) (2%), OA (6%), and LA (2%). Coconut oil has a low phytosterol concentration at ;70 mg/100 g oil. b-Sitosterol comprises ;70% of the coconut oil

phytosterols, and stigmasterol and campesterol comprise the remainder. The a-tocopherol concentration of coconut oil is very low, at ;0.2–2 mg/100 g oil.

a-Tocopherol: The main form of vitamin E used in LEs is tocopherol occurring as a, b, g-, or ơ-isoforms. Addition of a-tocopherol into LEs is to prevent peroxidation in susceptible PUFA-rich lipids because of the unsaturated double bond.

Vitamin K: Phylloquinone or vitamin K1 is important for normal blood clotting, and a deficiency would prolong the clotting time.

Mechanism of action

The exact mechanisms of action of lipid emulsion infusion to treat toxic poisoning is not known of the major component for the binding property of the emulsion among its component like 20% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, water and sodium hydroxide is an unknown factor. The mechanism which is responsible for the action of lipid emulsion is “lipid sink theory” which states the mechanism responsible for lipid emulsion-mediated resuscitation in cases of systemic toxicity induced by lipophilic drugs and non-lipophilic drugs.This theory states that highly lipid-soluble drugs like local anaesthetics and non-local anaesthetic drugs, are immersed into the lipid emulsion of the plasma and removed from the tissues affected by toxicity. After toxins are ingested in the body "lipid sink" is established and a concentration gradient develops between tissue and blood, which cause local anaesthetics and toxic substance to move away from the heart or brain (areas of high concentrations) to the "lipid sink". The emulsified portion of intravenous lipid emulsion therapy forms the fat droplets in the body form a lipid compartment in the body, in which lipophilic substances are theoretically partitioned when infused into the blood which forms the aqueous part.

Some of the theories mentioned that the mechanism of action of intravenous lipid emulsion therapy is cardio tonic and post conditioning effects from lipid infusion which will improve the cardiac output and preload through volume expansion. And thus the established that overall lipid emulsion therapy will play a very important role in the improvement in cardiac function and improvement in BP. Intralipid improves the contractility in stimulating myocardial contraction animal study by a reduction in the myocardial toxic substance content. Lipid emulsion therapy surges the intracellular fatty acid content in the body which overcome the decreases the ATP production in cardiomyocyte. This occurs under normal aerobic conditions as fatty acids are the preferred substrate for oxidative phosphorylation. In this process about 80-90% of cardiac adenosine triphosphate are generated. But under any circumstances if fatty acid transport is intermittent, ATP production will decrease which have a negative impact on myocyte survival which potentially leading to cardiac toxicity. Intravenous lipid emulsion therapy opens the calcium (Ca) channels, long-chain fatty acids activated the voltage-gated Ca channels in isolated cardiomyocytes.

ADRs of ILE: One hundred fourteen articles were analysed for their report of acute adverse events that followed the therapeutic use of ILE for TPN or for the treatment of poisoning.32 The articles were divided into human (87 articles) and animal (27 articles) studies.33 We assigned each publication to an adverse event category to facilitate analysis. The final level of evidence was reported as per the GRADE system.

Cardiovascular effects: Fatal cardiac arrest and death were reported in neonates receiving Intralipid at 0.08-0.15 g/kg/h (0.4-0.75 ml/kg/h for ILE 20%) as part of TPN therapy. Compared with saline, ILE plus heparin increased blood pressure, heart rate, QTc dispersion, and plasma concentrations of epinephrine and free fatty acids [4].

Haematological effects: The emergence of disseminated intravascular coagulation (DIC), which had a fatal outcome.

Acute kidney injury: AKI occurred in three of nine patients receiving various doses of 20% Intralipid for overdose of various cardiotoxic medications, though AKI was not defined and no laboratory markers were reported. AKI developed in an 47-year-old female after Intralipid administration in the setting of diltiazem poisoning.

Metabolic acidosis: Metabolic acidosis in one of nine patients being treated with ILE in response to drug-induced cardiotoxicity. The clinical course of a preterm infant who received an overdose of Intralipid 20% (24 g/kg or 250 ml) over 60 min. The child had laboratory values of a pH of 7.25, a PCO2 of 35mm Hg, and a PaO2 64 of mm Hg, which improved with administration of sodium bicarbonate, 2 mEq/kg. The patient’s oxygen saturation was 92%, with evidence of ARDS. It is unclear how, or if, ILE administration and the metabolic acidosis were related.40

Pulmonary adverse effects: A premature infant who received an unintentional overdose of almost 30 ml/kg of 20% Intralipid VR over 1.75 h and then became dusky and hypoxia. Echocardiography demonstrated pulmonary hypertension. The effect was transient and self-resolute, so TPN with ILE was eventually resumed.41 Several articles specifically addressed V/Q mismatch as a complication of ILE. The earliest one describes eight preterm infants who died after administration of Intralipid VR.

Hypersensitivity and allergic adverse effects: Reaction severity includes diffuse pruritus45; diffuse urticaria and dyspnea46; urticaria rash; skin blistering; and diffuse erythema, shortness of breath, and tachypnea with subsequent development of ARDS and eath. In most cases, the reactions resolved when ILE was stopped and without treatment with antihistamines and/or glucocorticoid therapy. One report indicated hypersensitivity to ILE containing LCT in three cancer patients. Re-exposure to LCT and exposure to marginally different formulations of MCT solutions without soybean lecithin were well tolerated. One out of 48 patients receiving ILE rescue was reported to have bronchospasm after administration.

Vascular occlusion: Development of priapism in two patients after infusion of 500 mL of IntralipidVR 20% or LiposynTM (a safflower oil emulsion) during long-term TPN therapy. Priapism in a 70-year-old man who received 1500 ml of IntralipidVR 20% daily following emergency surgery.

Deep vein thrombosis/phlebitis: DVT in 3 of 9 patients who received ILE for poisoning. Two of them received a bolus with a subsequent infusion, and one patient received three boluses. The total doses of ILE were not reported.

Infection susceptibility and inflammation adverse effects: A patient 500 mL of an ILE 10% for 2 days (total dose, 1 L) for nutritional support following ingestion of a corrosive agent, which caused an esophageal injury. He experienced an acute catatonia, mutism episode associated with ecchymosis. Severe thrombocytopenia (platelet count of 11,000 cells/lL) and leukopenia (1500/cells/lL) were reported. All symptoms and types of cytopenia resolved within 24 h after discontinuation of the ILE infusion. Found decreased monocyte function (chemotaxis) following administration of Intralipid. Fat overload syndrome, hypertriglyceridemia, lipemia, hyperamylasaemia, pancreatitis, cholestasis Fat overload syndrome, hypertriglyceridemia, lipemia, hyperamylasaemia, pancreatitis, and cholestasis are among the most commonly reported adverse effects associated with ILE rescue.

Discussion

Contraindication

The contraindicated patients with Intravenous lipid therapy are pathologic hyperlipemia, lipoid nephrosis or acute pancreatitis severe egg allergy.

Complication

While administration of intravenous lipid emulsions several complications were observed. These complications occur when the lipid emulsion is given as an antidote or nutritional therapy. It can be divided into two complications immediate and delayed complications. Immediate complications include pyrogenic reactions and fat overload. Delayed complications are seen with higher doses of lipid infusion.

Monitoring

During Intravenous initial infusion, patients should be monitored for allergic reaction such as dyspnea, fever, cyanosis. The product of an emulsion derived from egg phospholipids so patients were contraindicated with egg allergy. Due to higher dose patients may also develop long term adverse reactions such as increased level of triglycerides, due to saturation of the elimination mechanism. On initiation, patients should be monitored for elevated triglycerides daily, after 2 days and thereafter lipid emulsion dose should be adjusted. By assessing liver function tests and bilirubin hepatic tolerability of the fat emulsion should be assessed. Some hepatobiliary disorders associated with PN therapy include steatosis, cholestasis, and gallbladder sludge or stones [5].

The future perspects

Intravenous lipid emulsion therapy is one of the important methods in future by clinical experience. While practising the treatment will improve and impede the patient survival. One important advance in achieving this goal will be the implementation of a global registry to allow collation and analysis of a comprehensive database of lipid resuscitation cases. In future we can improve patient safety and save lives.

Conclusion

Since its initial proposal for bupivacaine toxicity, ILE therapy has become recognized as the standard treatment for LAST and is recommended for local anaesthetic mediated cardiac arrest. Furthermore, ILE therapy has been used for experimental rescue treatment of other lipophilic drug overdoses, toxicities, and toxin antidotes, though with variable success.

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