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Intravenous fat emulsion in clinical practice: nutrient and antidote

Intravenska emulzija masti u kliničkoj praksi: nutrijent i antidot

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Introduction

For more than 50 years intravenous fat emulsions (IVFEs), or intravenous lipid emulsions, have been used for nutritive support for patients who are unable to attain adequate nourishment *via* the gastrointestinal tract [1, 2]. This made IVFEs an important part of total parenteral nutrition regimens [3, 4]. Although used to meet the caloric requirements, their role is not only to provide fat as physiological nonprotein energy source, but also to prevent or correct essential fatty acids (FA_S) deficiency (linoleic acid and linolenic acid) [5]. These acids cannot be synthesized in the body, and they are important to maintain the normal composition of the structural body lipids, as well as in the synthesis of the various important metabolic mediators [6].

IVFEs advantages include limitation of likely side effects of infusing large amounts of glucose. Substituting some glucose calories with lipids reduces undesirable effects of high glucose such as hyperglycemia, excessive CO_2 production, and liver FA infiltration. Lipid emulsions provide different tissues with potentially liposoluble vitamins or therapeutic agents as IVFEs were found to be useful as a delivery vehicle for drugs that are poorly soluble in water. Some of these drugs include anesthetics, sedatives, cytotoxic drugs, analgesics, and anti-inflammatory agents. Those products are prepared by dissolving drugs in the vehicle, or by addition of the drug to oil phase prior to the homogenization process for the emulsion.

In recent animal studies and human case reports, IVFEs have been proven to be an effective antidote for treating useful toxicity effects from overdose of several lipid-soluble drugs including local anesthetics, calcium channel blockers, beta blockers, tricyclic antidepressants and other psychotropic agents [7].

Composition of IVFEs

IVFEs are complex pharmaceutical products consisting of one or more triglyceride-containing oils, a phospholipid emulsifier, glycerol and water for injection. The emulsifier produces a barrier to prevent coalescence of oil droplets dispensed in internal phase of emulsion and keeps the appropriate mean particle size. Their diameter generally ranges between 100 and 500 nm, with the mean value of 200−350 nm. Glycerol is used to isotonise and stabilize oil in the water emulsion.

The first well-tolerated emulsions were made of soybean or safflower oils or a mixture of both and they contained exceptionally long-chain triglycerides (LCTs). Today, a wide variety of lipid emulsions are available world-wide, differing in triglyceride and FA contents and in concentrations of certain components, such as phospholipid [8]. The differences in the proportion of phospholipid subcomponents can be found between the emulsifiers of different manufacturers, which may also influence the metabolism of lipid components. The most frequently used lipid emulsion contains LCTs, with FA chain lengths of 16 to 20 carbon atoms. For instance, one of the most commonly used commercial products (Intralipid® 20%) contains: purified soybean oil 200g/1,000 mL; purified egg phospholipids 1.2%; glycerol anhydrous. Water for injection and sodium hydroxide are added to adjust the pH so that the final product pH range is from 6 to 8.9, while simultaneously highly purified sodium oleate serves as coemulsifier. Organic phosphate presents approximately 15 mmol/1,000 mL. The product has an osmolality of approximately 350 mOsm/kg water. Energy content is 8.4 megajoules (2,000 kcal)/1,000 mL. The interior phase of this product includes purified soybean oil which predominantly includes LCT with a high amount (> 60%) of polyunsaturated FAs (PUFAs), which contain multiple double bonds.

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Soybean oil is a reliable source of essential FAs, in the form of linoleic acid (ώ -6 FA) and α-linolenic acid (ώ -3 FA) [9].

Stability and pharmacokinetics of IVFEs

The emulsifying agent is phospholipid from fractionated egg lecithin. Phospholipid emulsifiers are important in the development and function of cell membranes as they provide stability to IVFEs by functioning as not only a mechanical but also as an electrical barrier. Phospholipid molecules have a polar (hydrophilic) and a nonpolar (lipophilic) end, and they orient themselves in order to create the oil-water interface. The polar ends toward water exist in the neutral environment mostly in the dissociated states. This results in an anionic charge that creates a repulsive force, thus preventing fat particles from coalescing. This role is very important because if it were not for these forces, the emulsion would crack, lipids would coalesce, and IVFEs, if administered, would produce fat emboli. Since the basis of the electrical barrier is the anionic charge, IVFE stability might be compromised by divalent cations (magnesium and calcium), trivalent cations (iron), or an acid pH (especially at pH < 5). In most cases, even in the presence of these agents or conditions, complete destabilization of the emulsion takes time, depending on the concentration of chemical and environmental conditions such as extreme temperatures. During this period, the particle size of emulsion may increase, and this might result in excessive uptake by the reticuloendothelial system, causing a functional impairment in this system's ability to clear bacteria [10].

The structure of all IVFEs is similar to endogenous chylomicrons (a core composed of triglycerides surrounded by a layer of phospholipids). But, there are no cholesteryl ester molecules in the core of emulsion particles and there are only small amounts of free cholesterol and no apoproteins on their surface.

They are cleared by enzyme lipoprotein lipase, which hydrolyzes triglycerides, releasing free FAs, glycerin, and phospholipids. The dosage, phospholipid content, particle size, and infusion rate all have an impact on the plasma clearance. The rate of free FAs released from IVFE depends on its component oil. Soybean oil consists mainly of LCTs which require a carnitine-dependent cotransport system in order to be taken up by mitochondria and subsequently oxidized [11]. This process involves converting the LCTs into acyl coenzyme A (CoA), which is not sufficiently water soluble to pass into mitochondria. Carnitine picks up the acyl component of acyl CoA (acylcarnitine) and transports it across the mitochondria matrix where the acylcarnitine equilibrates with CoA to form acyl CoA within the mitochondria, completing its transport in this way. Once cleared from the plasma by various tissues, not all fat is oxidized.

The IVFEs clearance is decreased when free phospholipids interfere with lipoprotein lipase activity. Due to IVFEs lower concentration of free phospholipids and its larger particle size its clearance is 20%, which is relatively fast. The third factor determining plasma clearance of IVFEs is the infusion rate. A recommended maximum dosage of IVFEs for adults, as a nutrient, is 3.0 g triglycerides/kg of body weight/day.

Metabolic effects of IVFEs

The FA composition influences the metabolic effects of IVFEs administration. The intravascular metabolism of emulsion particles includes various processes. FAs in LCTs are the main component of cell membranes, and responsible for membrane structural integrity. Not only do they influence the biophysical and biochemical properties of membranes, but also serve as precursors of potent, short-lived oxylipids that modulate signal transduction between the cell membrane and the nucleus [12]. Long chain PUFAs metabolites serve as precursors of eicosanoids, which are of great physiological importance [13]. Eicosanoids contain 20 C and include prostaglandins, leukotrienes, thromboxanes, prostacyclins and lipoxins. These substances have an impact on a variety of processes like platelet aggregation, neurotransmitter release, and vascular function. Such properties can have an influence on many other biochemical and physiologic functions related to inflammatory, immune, and protective reactions. This means that PUFAs reduce the levels of total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.

Essential FA deficiency may result in clinical sequelae including disturbances in cardiopulmonary function, infection, bleeding, dermatitis, hepatic dysfunction [12].

Fatty changes in the liver are linked to a reduction in albumin synthesis and mRNA downregulation of antioxidant enzymes which may cause the production of reactive oxygen species, the promotion of oxidative stress in the hepatocyte membrane, functional damage to the liver and consequently growth delay and death.

Antidote use of IVFEs

Over the last few years many experimental and anecdotal evidence showed that IVFEs can reverse some hemodynamic, electrocardiographic and neurological parameters and potentially decrease morbidity and mortality in poisoned patients. Recently, IVFEs in the form of Intralipid® 20% have been used in clinical practice for reducing the bioavailability and toxicity of lipophilic poisonous agents in circulation. It has been suggested that several mechanisms could explain why IVFEs might work as antidote to an overdose of cardiotoxic drugs, including calcium channel blockers, beta blockers, digoxin, local anesthetics, tricyclic antidepressants, antipsychotics, atypical antidepressants, and mood stabilizers[14-16].

The "lipid sink" phenomenon is the most widely accepted mechanism of action for IVFEs. When infused into an aqueous medium such as blood, emulsified fat droplets form a lipid compartment into which lipophilic substances are theoretically partitioned. They are drawn into the "lipid sink" and a concentration gradient develops between tissue and blood. It causes poisonous agent to move away from tissue receptors in the heart or the brain (areas of high concentrations) to the "lipid sink" [17, 18]. This mechanism suggests that one of the important

parameters in the design of antidotal emulsion may be the partition coefficient of the agent in the emulsion. After trapping the poison, the emulsion will be metabolized slowly, allowing the patient's liver to chemically detoxify and excrete the toxin released from emulsion droplets.

This theory complies with animal studies on lipid rescue. They show greater efficacy, improving survival time and increasing median lethal dose with the use of IVFEs, after experimental overdoses of many lipid soluble drugs including the most liposoluble beta blockers (propranolol) [19], calcium channel blockers (verapamil) [20, 21], antidepressants (clomipramine) [22, 23] and local anesthetic [17, 24–27]. In an experimental rat model, Weinberg et al. [17] demonstrated that radiolabeled l-bupivacaine when added *in vitro* to lipid-treated rat plasma preferentially moves to the lipid phase. In further experiments on an isolated heart model, Weinberg et al. [24] showed that infusion of lipid emulsion produces faster removal of radiolabeled bupivacaine from myocardial tissue compared with controls. The follow-up experiments examined the efficacy IVFEs in anesthetized dogs after intravenous overdose of bupivacaine. All dogs receiving lipid infusion recovered normal blood pressure and ECG traces after 10 min of lipid therapy, while all control animals died [25].

It was observed that IVFEs act faster *in vivo* settings than it was anticipated based on a simple lipid sink mechanism. Stehr et al. [26] demonstrated that lipid emulsion reverses bupivacaine-induced contractile depression at concentrations that are too low to provide a significant "lipid sink" phenomenon, suggesting a metabolic explanation for the positive effect. According to the bioenergetics theory, a large bolus of FAs provides energy substrate for a failing myocardium. Theoretically, lipid emulsion could result in the increase of intracellular FA content. FAs are the main substrates for energy generation in cardiomyocyte and represent the source of more than 80% of cardiac adenosine triphosphate (ATP) under normal conditions. Eledjam et al.[27] demonstrated that pretreatment of isolated myocardial strips with ATP prevents depression of contractility caused by toxic agents. It is possible that massive lipid infusion may result in increased intracellular FA content which may contribute to the enhancement of ATP synthesis in the cardiomyocyte. Van de Velde et al. [28] suggested such mechanism by demonstrating that infusion of 20% lipid emulsion improves cardiac contractility in a dog model. Huang et al. [29] demonstrated that FAs activate calcium channels in ventricular myocytes, so except for increasing intracellular FA content and improving ATP synthesis, positive inotropic effect of lipid emulsion may be the result of calcium influx. Blood pressure elevation due to central sympathetic activation may contribute to beneficial hemodynamic effects of lipid emulsion [30]. It is possible that lipid rescue resuscitation is a combination of all of these mechanisms [18].

Although the exact mechanisms of action of lipid emulsion infusion in treating poisoning are still not clear enough, it can be supposed that the key components are the binding property of the emulsion, characteristics of a toxic agent (liposolubility and mechanism of action).

Multiple animal models were used to compare recovery after local anesthetics and other liposoluble drugs overdose treated with IVFEs *vs* standard resuscitation protocols [31, 32]. They suggest that lipid infusions are more effective than placebo or standard antidotal therapies. They show no interaction with drugs used in standard treatment of poisoning. These studies have led to numerous human case reports which demonstrated beneficial effects of lipid emulsion in treatment of lipophilic drugs overdose. However, as randomized controlled clinical trials are not possible in this field, the evidence in humans has to be limited to case reports and small case series.

The first successful clinical application of IVFEs (Intralipid® 20%), was noted in 2006. Rosenblatt at al. [33] used it to resuscitate a patient in prolonged bupivacaine−related cardiac arrest. After more than 20 min of asystole and no response to advanced cardiac life support the use of lipid emulsion reversed systemic toxicity, including seizures, electrocardiogram abnormalities, and cardiac arrest without neurological sequelae. A few months later, Litz et al. [34] reported on the rescue of a patient in asystolic cardiac arrest secondary to the accidental overdose of ropivacaine. After 10 min of unsuccessful cardiopulmonary resuscitation, they administered a bolus of 100 mL of 20% lipid emulsion followed by continuous infusion of 10 mL *per* min. After the total IVFE dose of 200 mL, spontaneous electrical activity continued and cardiac output was restored. The first successful use of lipid emulsion as an antidote for non-local anesthetic drugs was in a 17-year-old girl who had developed seizures and cardiovascular collapse after massive ingestion of bupropion and lamotrigine. The patient had cardiac arrest with ventricular fibrillation and pulseless electrical activity. After 70 min of unsuccessful standard cardiopulmonary resuscitation, a 100 mL intravenous bolus of 20% lipid emulsion was administered, as the last attempt to restore hemodynamic stability. Normal vital signs were restored within one min of IVFEs administration [35]. IVFEs have been used to reverse coma caused by sertraline and quetiapine overdose [36]. Young et al. [37] published the first human case of verapamil toxicity of a patient who was in shock that was refractory to standard resuscitation therapy, but was resolved with administration of IVFE 20% within 5 min. Several reports on successful treatment of beta blockers toxicity have been published in recent years [38–43].

Soon after the case report by Rosenblat et al. [33] was published, Weinberg [7] established a Web site www.lipidrescue.org as a widely informational resource about local anesthetic and toxicity from other drug classes. Based on this experience Weinberg [7] has recommended a dose regimen for clinical use. A bolus of Intralipid® 20% 1.5 mL/kg over a min was recommended with subsequent 0.25 mL/kg min. A bolus can be repeated every 3 or 4 min up to the dose of 3 mL/kg total dose until circulation is restored. Infusion should be continued until hemodynamic stability is achieved and the rate increased to 0.5 mL/kg/min if blood pressure drops. The total maximum dose is 8−10 mL/kg. This is the current protocol recommended by the Association of Anesthetists of Great Britain and Ireland [44], the American Society of Critical Care Anesthesiologists, the American Society of Anesthesiologists Committee on Critical Care Medicine, and the Resuscitation Council of the UK. In 2010 the

American Society of Regional Anesthesia published a practice advisory on local anesthetic toxicity, stressed the lipid's role in local anesthetic systemic toxicity [45]. The guidelines included the use of intravenous lipid emulsion as an adjunct to airway management and good cardiopulmonary resuscitation, stating: "... lipid emulsion therapy can be instrumental in facilitating resuscitation, most probably by acting as a lipid sink that draws down the content of lipid-soluble local anesthetics from within cardiac tissue, thereby improving cardiac conduction, contractility, and coronary perfusion".

Adverse events associated with the use of IVFE

The clinical events and adverse effects of IFVEs are related to their composition, characteristics, stability and sterility.

It is contraindicated in patients with severe hyperlipemia, liver insufficiency, hemophagocytic syndrome, hypersensitivity to egg-, soy- and peanut protein (risk of cross-allergy reactions) or to any of the active substances or excipients.

The manufacturers recommend laboratory studies for all lipid emulsions. These include complete blood count, serum electrolytes, blood glucose, serum proteins, parameters for liver function, serum and urinary osmolality and monitoring of triglyceride levels on daily basis. This is the major preventive measure in avoiding overfeeding and liver injury. Serum triglyceride levels can rise rapidly if the capacity to clear them is compromised as is the case in genetically caused impaired metabolism. As a consequence, overdosage and fat overload syndrome might occur. Patients with impaired lipid metabolism and liver function, uncompensated diabetes mellitus, pancreatitis, hypothyroidism and sepsis require monitoring of the serum triglyceride concentration.

It is also important to stress that lipemia can interfere with some laboratory analysis. This is why the producers recommend analysis after 5−6 h without the use of lipids.

Undesirable effects connected with IVFEs administration include a slight rise in body temperature, chills, lack of appetite and nausea/vomiting (with less than 1% incidence), the feeling of warmth or blueness, head and bones ache, and in very rarely – priapism. Other adverse effects are extremely rare, less than one *per* one million infusions. If the symptoms of overdose occur, they are usually reversible if infusion is discontinued. However, an excessive amount of FAs, particularly linoleic acid, may alter the structure and the function of the cellular membrane and increase oxidative stress. A high content of FAs and their limited content of α-tocopherol, in long-term use of soybean oil–based emulsions may reduce α-tocopherol in plasma lipoproteins and deplete antioxidant defenses [46]. The risk of lipid peroxidation may be increased. This is particularly worrying in situations when patients are often exposed to oxidative stress under intensive care conditions.

Although LCT-based lipid emulsions have been shown to be safe and clinically well−tolerated, several studies showed that they might interfere negatively with the immune system. Since 1970s studies on the effects of FAs on the inflammatory response and the immune system have indicated a potential role of lipids in modulating inflammatory and immunological functions. An increased ratio of ώ-3 to ώ-6 FAs intake inhibits the metabolism of arachidonic acid and results in decreased production of proinflammatory cytokines such as interleukin (IL) 6, IL-8, tumor necrosis factor-α, and other inflammatory mediators such as platelet activating factor and adhesion molecules [47]. A high concentration of unmetabolised FAs increases the production of immunosuppressive (E2 series) prostaglandins. Pulmonary dysfunction may result from the release of vasoactive amines produced of excessive prostaglandin E_2 levels. Moreover, a large amount of the infused LCTs is not readily oxidized, due to the relative deficiency of carnitine or inhibition of the carnitine acyltransferase system for translocating LCTs across the inner mitochondrial membrane in critically ill patients [48]. On the other hand, other studies did not confirm the negative effects of LCT-based lipid emulsions on the immunological response or even showed beneficial effects. A meta-analysis by Wirtitsch et al. [49] has not revealed any effects of the lipid regimen on the evolution of the immunological status or mortality in humans.

Future research

In many animal and human studies the efficacy and safety of IFVEs 20% as a calorie source have been demonstrated. The results obtained experimentally and clinically in the past years demonstrated the safety and efficacy of Intralipid® 20% for use in total parenteral nutrition.

Animal studies and additional human reviews in further research on efficacy and safety of IFVEs 20% as an antidote, will shed more light on lipid therapy according to the best rate and total dose of infusion that follows bolus dosing; efficacy when used in conjunction with other resuscitative measures and assessment; the risk of recurrence of toxicity once the lipid infusion is stopped; dosing parameters of lipid administration adjustment for different patient population especially hepatic and renal-impaired. They will also show whether the other available lipid emulsions have the same effects as rapid infusion of Intralipid® 20%. Until that evidence is obtained, lipid emulsion is recommended in the resuscitation of local anesthetic and highly lipophilic medication toxicity refractory to conventional models of resuscitation with significant hemodynamic, neurological or cardiovascular symptoms [50-52].

Conclusion

Beside the fact that intravenous fat emulsions have been used for decades for nutritional support, intravenous fat emulsions also can reverse some hemodynamic, electrocardiographic and neurological parameters and potentially decrease morbidity in poisoned patients. Although it is not yet considered a generic first-line treatment in cases of unknown drug overdoses, the use of intravenous fat emulsions should be strongly considered, particularly in failed resuscitations.

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