The Art and Science of Infusion Nursing

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Review of Intravenous Lipid Emulsion Therapy

ABSTRACT

Intravenous fat emulsion (IVFE) is an important source of calories and essential fatty acids for patients receiving parenteral nutrition (PN). Administered as an individual infusion or combined with PN, the fats provided by IVFE are vital for cellular structural function and metabolism. The affinity of some medications to lipids has led to the use of IVFE as a treatment for any lipophilic drug overdose. This article will explain the available formulations of IVFE, administration, and maintenance issues, as well as the risks and benefits for various applications.

Key words: antidote, intravenous fat emulsion, IVFE, lipid, parenteral nutrition

Intravenous fat emulsion (IVFE) is a mixture of long-chain fatty acids originally formulated to provide essential fatty acids for patients on parenteral nutrition (PN) and a dense source of calories to help reduce the volume required for PN.[1,2] Before the development of IVFE, patients would develop essential fatty acid deficiencies. The deficiencies can present as cholestasis, steatosis, alopecia, dermatitis, and thrombocytopenia.[2] Patients' conditions could be complicated by excessive dextrose intake, which can cause hyperglycemia; increased carbon dioxide production; hepatic steatosis; and phagocyte destruction. Once the emulsion was developed, it was heralded as a breakthrough for patients who required long-term PN and who previously were limited to dextrose and amino acids for sources of their calories. The emulsion is a mixture of 3 fatty acids: omega-6, -3, and -9. In addition, alpha linolenic acid (ALA), which is used as a stabilizing agent for the emulsion, makes up a small percentage of the emulsion.[1] Vitamin E is also added to help reduce the oxidative stress of the emulsion components, as well as the oxidative stress on patients.[1-3]

POLYUNSATURATED FATTY ACIDS

Omega-3, omega-6, and omega-9 fatty acids make up the majority of the composition of the IVFEs available on the market. Omega-3 and omega-6 fatty acids are considered essential fatty acids.[1,2] Omega-6 fatty acids are metabolized to arachidonic acid, which leads to the production of proinflammatory mediators.[2,3] Omega-3 fatty acids are metabolized to eicosapentaenoic acid, which is metabolized to less proinflammatory metabolites.[1,2]

AVAILABLE FORMULATIONS

The first product available in the United States was released in 1961 and was made from safflower oil.[3] It consisted of 77% omega-6 fatty acids[2,3] but lacked ALA, which is an essential fatty acid.[4,5] So it provided some, but not all, of the essential fatty acids needed for patients dependent on PN to prevent fatty acid deficiency.

Since that time, additional products derived from soybean oil have come on the market. They include IVFE Intralipid (Baxter; Deerfield, IL), IVFE Liposyn III (Hospira; Lake Forest, IL), and IVFE Nutrilipid (B. Braun; Bethlehem, PA), which are currently available in the United States.[4,5] The soybean oil in these products provides a mixture of omega-6, omega-3, and

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The author has no conflicts of interest to disclose.

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DOI: 10.1097/NAN.0000000000000194

omega-9 fatty acids.[2,3] About 50% of the emulsion is made up of omega-6 fatty acids, as well as 25% omega-3 and 25% omega-9 fatty acids.[2] In 2013, the US Food and Drug Administration approved a new product, a mixture of soybean and olive oil called lipid injectable emulsion (Clinolipid; Baxter, Deerfield, IL).[6] The product would provide a more favorable lipid profile than those currently available on the market.[3] As of August 2015, however, this product had not yet become available on the market in the United States.

International Formulations

Formulations available internationally contain alternative sources of fatty acids, such as medium-chain triglyceride oils, and olive, fish, and soybean oils.[3] Products available outside the United States contain these oils in various ratios to provide a more balanced source of fatty acids with fewer proinflammatory effects.[3]

GUIDELINES FOR USE

IVFE is an essential component of PN to prevent essential fatty acid deficiency.[7] However, the proinflammatory nature and immunosuppressive effects of the formulations available in the United States limit the use of these agents as part of the initial PN prescription.[7] The American Society of Enteral and Parenteral Nutrition and Society of Critical Care Medicine suggest that IVFE be withheld for the first week of PN.[7]

US PHARMACOPEIAL CONVENTION STANDARDS

The US Pharmacopeial Convention has established standards to help ensure the uniform nature of all IVFE products available in the United States and to limit the probability of venous occlusion related to parenteral administration.[8] These include standards for the mean droplet diameter for lipid injectable emulsions: They must be less than 500 nm or one-half micron, irrespective of the concentration.[8] There are also standards for large globule content. These regulations stipulate that the volume-weighted, large-diameter fat globule limits of the dispersed phase for a given lipid injectable emulsion must not exceed 0.05%.[8] This is based on 0.05% as the maximum limit to prevent embolic events.[8]

STABILITY

The stability of IVFE is decreased when it is added to 3-in-1 PN mixtures—that is, mixtures containing the dextrose, amino acids, and fatty emulsion.[3,8] This can result in *cracking* of the emulsion, when the fat and the water phases of the emulsion separate. Omega-6 fatty acids are long-chain fatty acids, which offer greater emulsion stability.[3,8] Emulsions that contain medium-chain fatty acids offer less stability for the emulsion and are more likely to crack.[3,8]

USES

PN

IVFE can be used for several reasons, including the primary use in PN for adults, children, and neonates, as well as for treatment of local anesthetic toxicity and drug overdoses, in which it acts as an antidote.[3] For PN, it can be administered separately from the dextrose and amino acid solution (2 in 1). It also can be combined with the amino acids and dextrose in what is called *3-in-1*, or total nutrient admixture. Fat usually makes up about 20% to 30% of nonprotein calories with a maximum of 60% of total calories, or 2.5 g/kg/d.[6] To improve tolerability, doses usually are limited to 1 to 1.5 g/kg/d on day 1 of therapy for adult patients.[6] Additionally, the use of IVFE provides a dense calorie source to help decrease the volume of PN required.

Fat emulsion can also be used for pediatric and neonatal patients. The initial dose is usually 1 to 2 g/kg/d and is increased by one-half to 1 g/kg/d to a maximum of 3 g/kg/d.[4,5] Caution must be used when administering fat emulsion to neonates because of low rates of clearance and the potential for intravascular accumulation in lungs.[4,5]

Drug Toxicity, Lipid Rescue

IVFE can be used in the treatment of local anesthetic systemic toxicity (LAST).[9] This occurs when local anesthetic is introduced systemically instead of locally.[9] The increase in absorption can be the result of either accidental vascular administration or delayed tissue depot absorption.[9] Peripheral nerve blocks carry the highest risk, occurring in 0.075% to 0.1% of procedures.[9] Local absorption of the anesthetic can lead to arrhythmias, hypotension, and, ultimately, cardiovascular collapse and arrest.[9]

Lipid rescue is a proposed antidote for severe LAST.[9-11] Administration of intravenous (IV) lipid emulsion can aid in patient recovery in the event of cardiovascular collapse.[9-11] It is not completely understood how this helps reverse the systemic effects of the anesthetic.[10,11] The most widely accepted hypothesized mechanism of action is that fat emulsion creates a *lipid sink*.[10,11] The fat emulsion creates an expanded lipid phase, which draws the toxic drug from tissue into the lipid phase, where it is not available to exert its pharmacologic

action.[10,11] The other theory of why this is an effective treatment is that it counteracts local anesthetic inhibition of myocardial fatty acid oxidation.[10,11] Current recommendations for use of lipid rescue are derived from case reports and animal studies.[10,12] The optimal patient for the use of lipid rescue is still an area of debate. According to the American Society of Anesthesiologists (ASA), lipid rescue is not recommended at the first signs of LAST. However, ASA does note that, along with supportive care, lipid rescue can prevent progression in many cases.[13] Additionally, ASA notes that it is not recommended to wait until the patient has full cardiovascular collapse before initiating therapy.[9,13] The decision to initiate lipid rescue is based on the severity and progression of symptoms.[9,13]

There is also a role for the use of lipid rescue in nonanesthetic overdoses, such as with beta-blockers, calcium channel blockers, parasiticides, herbicides, and psychotropics.[12] The primary mechanism of action for these agents is the lipid sink, given the lipophilic nature of the agents involved in case reports.[12] To date, there are no consistent recommendations for the use of lipid rescue for overdoses, but it is a consideration to be made on a patient-specific basis.[12]

ADMINISTRATION

Nutrition

IV lipid emulsions are limited in their hang time because of the risk of infection.[14] Lipid emulsions are associated with contamination with *Malassezia furfur*.[15,16] *M furfur* and other fungal infections are associated with contaminated lipid emulsion.[15,16] *Candida* species bloodstream infections are also associated with PNs, but this may be a factor of the immunosuppressive effects of the agent.[3,7] PN prepared with all 3 macronutrients in 1 bag is only stable for 20 hours once mixed.[3] Delivery of PN via 2-in-1 bags containing dextrose and amino acids, and hanging the lipid emulsion separately, has the advantage of prolonged stability, but the lipid emulsion is only stable to be hung for 12 hours.[3]

IV administration set changes are also required on a regular basis to reduce the risk of infection.[14] The tubing used to administer fat emulsions—those combined with amino acids and glucose in a 3-in-1 admixture or infused separately—must be replaced within 24 hours of initiating the infusion.[14] The tubing used for separate lipid infusions also must be changed every 24 hours.[14] In addition, if the lipid is being administered by means of a separate infusion, it must be hung higher than other infusions because of low specific gravity.[14]

Filtering is required of some IV lipid products available on the market in the United States. For lipid injectable emulsion (Clinolipid; Baxter, Deerfield, IL) and IVFE Intralipid, a 1.2 micron or larger filter is required.[4,5] IVFE Nutrilipid also requires a 1.2 micron filter, and it is recommended that administration in di(2-ethylhexyl) phthalate-containing IV sets be avoided.[4,5] IVFE Liposyn III does not require a filter for administration.[4,5] Care also must be taken when using 3-in-1 solutions because they can obscure signs of precipitation. Pharmacists and other individuals compounding these products must take care to ensure that calcium and phosphorous concentrations are within acceptable ranges, using standard precipitation curves dependent on the amino acid product used.

Lipid Rescue

In instances of lipid rescue, the emulsion is given as a bolus dose of 1.5 mL/kg over 1 minute followed by continuous infusion.[13] The bolus dose may be repeated every 5 minutes up to 3 mL/kg total dose. A maximum of 2 repeat doses is permitted until adequate circulation is restored.[12,13] The bolus dose is followed by a continuous infusion of 0.25 mL/kg/min for 30 to 60 minutes.[12,13] This rate may be increased to 0.5 mL/kg/min if blood pressure decreases or the clinical situation begins to worsen.[12,13] A total recommended dose of 10 mL/kg is recommended.[12,13]

MONITORING

As with any medication, there is the potential for an allergic or adverse reaction associated with administration.[4,5] During the initial infusion, patients should be monitored closely for allergic reactions such as dyspnea, cyanosis, or fever.[4,5] The products currently on the market in the United States have an emulsion derived from egg phospholipids, so they are contraindicated in patients with egg allergy.[4,5] Patients also must be assessed for longer-term adverse reactions that may develop, such as elevated triglycerides.[4,5] High doses are associated with elevated triglycerides, possibly due to saturation of the elimination mechanism.[4,5] Along with elevated triglyceride levels, patients should be assessed for signs and symptoms of pancreatitis. Patients should be assessed for elevated triglycerides daily on initiation and adjustment of lipid emulsion dose for 2 days, and weekly thereafter. Patients also will need to be assessed for hepatic tolerability of the fat emulsion by assessing liver function tests and bilirubin.[4,5] Some hepatobiliary disorders associated with PN therapy include steatosis, cholestasis, and gallbladder sludge or stones.[4,5]

CONCLUSION

IV lipid emulsion offers many patients life-sustaining therapy. As new products come onto the market, it is hoped patients will be able to benefit more from this

therapy and suffer fewer adverse events. The use of agents that are less proinflammatory and potentially anti-inflammatory could improve patient outcomes, both acutely and for long-term nutrition management. In addition, given the nature of the product being dispensed, care must be taken on administration to ensure that patients receive the therapy without complications. Advances in research have provided information on nonnutritional uses for lipid emulsion, such as with drug toxicity and aiding in the implantation of embryos during artificial insemination. The use of lipid emulsion as a rescue agent for intentional and unintentional overdoses and administrations provides a new treatment modality for an agent that has been on the market for many years. The use of the agent in this manner is pioneering a new mechanism of action for the treatment of overdoses for lipophilic pharmaceutical agents. Knowledge of this agent and its properties continues to expand, and future advances in preparations and uses will continue.

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