Intravenous fat emulsions (IVFEs) were developed for use as a concentrated caloric source for patients who are unable to attain adequate nourishment via the gastrointestinal tract. Subsequently, IVFEs were found to be useful as a delivery vehicle for drugs that are poorly soluble in water. Although IVFEs are now used routinely in both of these clinical contexts, some concerns remain among clinicians regarding the safety of these preparations. Reported adverse events (AEs) associated with the use of IVFEs include hypertriglyceridemia, acute pancreatitis, cholestasis, and increased risk of infection.1-7 The risk of these AEs is particularly high in premature and small-for-gestational-age infants, in whom the use of IVFEs has resulted in death, with autopsy findings that include intravascular fat accumulation.8-9 The package insert for Intralipid (Baxter Healthcare Corp., Deerfield, IL), a widely used IVFE, also lists delayed AEs, including hepatomegaly, jaundice due to cholestasis, splenomegaly, throm-

OBJECTIVE: To review the current state of the science regarding intravenous fat emulsions (IVFEs), with an emphasis on their safety profile.

DATA SOURCES: Articles were identified via a search of the MEDLINE database, including publications from 1979 to December 2009, using a search string that included the terms parenteral nutrition, lipid emulsion, fat emulsion, IVFE, safety, adverse effect, neonate intralipid, and terms describing a range of specific adverse events (AEs) such as pancreatitis.

STUDY SELECTION AND DATA EXTRACTION: We selected articles that allowed us to compare the results of clinical trials involving delivery of medications via IVFEs with the historical use and effects of IVFEs in parenteral nutrition, with an emphasis on AEs. We focused on 2 drugs in current use that are administered intravenously in lipid emulsions: propofol and clevidipine.

DATA SYNTHESIS: Clearance of the fat particles in IVFEs is mediated by the enzyme lipoprotein lipase. AEs are more likely if the rate or duration of IVFE administration exceeds the enzyme’s clearance capacity. AEs are also more likely after administration of a 10% IVFE formulation than a 20% formulation, because the higher concentration of free phospholipid in the 10% formulation interferes with lipoprotein lipase activity. AEs can be reduced by administering IVFEs at a dosage ≤2.5 g/kg/day and at a rate ≤0.11 g/kg/h. The anesthetic agent propofol, which is formulated in a 10% IVFE, has been used clinically for 25 years. Typical AEs associated with propofol use include infection, high plasma triglyceride concentrations, and pancreatitis. Recent clinical trials involving clevidipine, which is formulated in a 20% IVFE, have demonstrated a low rate of lipid-related AEs.

CONCLUSIONS: The results of this review demonstrate that IVFEs are well tolerated when administered in accordance with guideline recommendations.

KEY WORDS: clevidipine, lipid emulsion, propofol, safety.


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bocytopenia, leukopenia, transient increases in the results of liver function tests, and the fat overload syndrome.\textsuperscript{10}

This article reviews the current science regarding IVFEs used in the US, with a focus on their safety profiles. Relevant literature for this review was obtained by conducting a search of the PubMed database from 1979 through December 2009, using the following search terms:

1. lipid emulsions OR fat emulsions OR propofol OR clevidipine AND safety OR adverse effects OR pancreatitis OR infection OR hypertriglyceridemia OR triglycerides OR liver OR cholestatic OR lipid metabolism OR lung OR pulmonary OR respiratory OR pharmacokinetics OR premature infants OR neonates OR anesthetic toxicity OR pharmacology OR pharmacokinetics;
2. parenteral nutrition AND guidelines OR metabolic effects OR lipid emulsions OR fat emulsions OR IVFE.

English-language articles identified by these searches were used to compare results from clinical trials of medications delivered via IVFEs (ie, medications formulated in lipid emulsions, where the lipid is used as a vehicle) with the historical use and effects of IVFEs used for parenteral nutrition (PN). The reference lists of these articles were also scanned for relevant articles and these, along with information from our personal libraries, were used to augment the search results. Review articles were not included unless suitable primary studies were unavailable. Unless otherwise stated, all data cited represent values for the mean ± SD.

Characteristics of IVFEs

IVFEs are complex pharmaceutical products, the clinical events and AEs of which are related to their composition (fat source, emulsifier), characteristics (oil-in-water emulsion), stability, and sterility.\textsuperscript{11-14} The unique characteristics of IVFEs must be considered when they are used for nutrition support or intravenous drug delivery. Full knowledge of these characteristics fosters appropriate and safe use of IVFEs for delivery of nutrition and lipophilic drugs that cannot be administered in aqueous vehicles.

IVFEs are oil-in-water emulsions consisting of 1 or more triglyceride-containing oils, a phospholipid emulsifier, and glycerin.\textsuperscript{15,16} Commercially available IVFEs in the US are made from soybean oil (Intralipid, Baxter Healthcare Corp., Deerfield, IL, or Liposyn III, Hospira, Inc., Lake Forest, IL) or combined safflower/soybean oil (Liposyn II, Hospira, Inc.). Phospholipid emulsifying agents such as egg phosphatidyl produce a barrier to prevent coalescence of oil droplets dispersed in the internal phase of the emulsion. The purpose of the emulsifying agent is to keep the mean particle size <0.50 µm, with a large diameter (>5 µm) tail of <0.05%, as proposed by the United States Pharmacopeia.\textsuperscript{17}

IVFEs are designed to be similar to endogenous chylomicrons.\textsuperscript{18} They are cleared by the enzyme lipoprotein lipase, which hydrolyzes triglycerides, releasing free fatty acids, glycerin, and phospholipids (Figure 1). Three factors affect the plasma clearance of IVFEs: (1) phospholipid content (10% vs 20% IVFE), (2) particle size, and (3) infusion rate. The phospholipid content of the 10% and 20% formulations is the same; therefore, there is proportionally more free (not participating in emulsifying the oil) phospholipid available in the 10% formulation. Free phospholipids interfere with lipoprotein lipase activity (Figure 1), thereby decreasing IVFE clearance and increasing the potential for AEs. Clearance of 20% IVFE is faster than that of 10% IVFE due to its relatively lower concentration of free phospholipids and its larger particle size.\textsuperscript{19,20} The IVFE infusion rate is the third factor determining plasma clearance of IVFEs. Administration of an IVFE to adults at a rate >2.5 g lipid/kg/day may result in an excessive lipid load.\textsuperscript{21}

Once it is cleared from the plasma by various tissues, not all fat is oxidized. The fate of free fatty acids released from IVFE is dependent on its component oil. Soybean oil consists predominantly of long-chain triglycerides (LCTs).\textsuperscript{22} LCTs require a carnitine-dependent co-transport system in order to be taken up by mitochondria and subsequently oxidized.\textsuperscript{23} This process involves the conversion of the LCT into acyl coenzyme A (CoA), which is not sufficiently water soluble to pass into the 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, thereby completing its transport.

The phospholipid emulsifier provides stability to IVFEs by functioning as both a mechanical and electrical barrier. Phospholipid molecules have a polar (hydrophilic) and a nonpolar (lipophilic) end, and they orient themselves so as to create the oil-water interface. The polar ends toward the water exist in the neutral environment primarily in dissociated states, resulting in an anionic charge that creates a repulsive force, preventing the fat particles from coalescing.\textsuperscript{24} If these forces were not present, eventually the emulsion would fail (crack), the lipids would coalesce, and the IVFE, if administered, would produce fat emboli. Since the basis of the electrical barrier is the anionic charge, stability of the IVFE may be compromised by divalent cations (magnesium and calcium), trivalent cations (iron), or an acid pH (especially at pH <5).\textsuperscript{24-25} In most cases, even in the presence of these agents or conditions, complete destabilization of the emulsion takes time, the length depending on the concentration of the chemical and environmental conditions such as extreme temperatures.\textsuperscript{26} Over this time, the particle size of the emulsion may increase, which might result in excessive uptake by the reticuloen-
dothelial system (RES), causing a functional impairment in this system’s ability to clear bacteria.

**Uses of IVFEs**

**PARENTERAL NUTRITION**

IVFEs have been used for nutrition support for more than 50 years. PN formulations are calculated to meet the specific nutrient requirements of individual patients, with adequate energy supply and appropriate amounts of protein, carbohydrates, fat, fluid, electrolytes, vitamins, and trace elements. IVFEs have 3 primary uses in PN. First, they are an efficiently converted source of energy and help fulfill caloric requirements. For most adults, the caloric requirement ranges from 20 to 30 kcal/kg of body weight. Between 15% and 30% of nonprotein calories should be given as fat in a maximum dose of 2.5 g/kg/day. Second, IVFEs supply the essential fatty acids linoleic and alpha linolenic acids. To prevent essential fatty acid deficiency, 2–4% of the total caloric intake should be provided as linoleic acid and 0.25–0.5% as alpha linolenic acid. Third, IVFEs are 18 carbon fatty acids that contain multiple double bonds (polyunsaturated fatty acids) that serve as precursors to eicosanoids (via the arachidonic acid pathway). Eicosanoids contain 20 carbons and include prostaglandins, leukotrienes, thromboxanes, prostacyclins (thromboxane inhibitors), and lipoxins. These substances exert a variety of effects on platelet aggregation, neurotransmitter release, vascular function, immune response, and inflammatory activity.

**DRUG DELIVERY**

Much interest surrounds the use of lipid emulsions as drug delivery vehicles, due in part to the substantial proportion of new chemical entities that are poorly soluble in water and not well absorbed from the gastrointestinal tract. The use of lipid emulsions increases the bioavailability of such drugs after oral administration by keeping them in the dissolved state until absorbed. Lipid-based drug delivery systems also decrease the adsorption of lipophilic drugs onto plastic infusion sets, decrease the hydrolysis or oxidation of unstable drugs, and may reduce drug toxicity. Lipid emulsions concentrate in malignant ovarian tumor tissue and possibly leukemic cells, and thus may be used to target cytotoxic agents to malignant tissue. Drugs that use lipid emulsions as a vehicle include anesthetic agents and sedatives, analgesic and antiinflammatory agents, prostaglandins, and antihypertensives. There are 2 methods used in formulating drugs in lipid emulsions. The extemporaneous method involves salva-

**Figure 1.** Metabolism of parenteral lipid emulsions. Lipoprotein lipase (LPL) anchored to the endothelial cell layer of venous blood vessels hydrolyzes emulsion droplets into triglycerides (TG) and phospholipids (PL). TG remnants resulting from the peripheral hydrolysis of the emulsion droplets are further hydrolyzed by the liver at endothelial sites or within hepatocytes by the enzyme hepatic lipase (HL). TG released during peripheral hydrolysis acquire apolipoproteins (Apo) to form low-density lipoproteins (LDL; Apo B-100) and/or high-density lipoproteins (HDL; Apo E). LDL particles may be taken up by hepatocytes or macrophages (M), both of which express endocytic LDL receptors. PL released during peripheral hydrolysis can interact with HDL to acquire Apo E; this complex is subsequently converted to free-cholesterol–phospholipid complexes (FC) via interaction with endothelial cell membranes. PL-Apo E complexes can decrease the enzymatic activity of LPL (arrow X), potentially diminishing peripheral hydrolysis and thereby increasing TG concentrations and the number of emulsion droplets being shunted to the liver. FC complexes can inhibit the endocytic uptake of TG remnants by the liver (arrow X), again increasing TG concentrations.
tion of the drug and then admixture into a preformed, commercially available fat emulsion. In the US, the alkylphenol propofol and the dihydropyridine clevidipine are the only 2 drug formulations commercially available prepared by this method. Propofol, which is formulated in a 10% lipid emulsion, has been used since 1989 for anesthesia or sedation during procedures and surgery and since 1993 for sedation in mechanically ventilated patients. The more recently licensed calcium-channel blocker, clevidipine, is formulated in a 20% lipid emulsion that was approved in the US in 2008 for the reduction of blood pressure when oral therapy is not feasible or not desirable. The other method of preparation involves the addition of the drug to the oil phase prior to the homogenization process for the emulsion. Diazemuls (diazepam for injection) is an example of this type of formulation.

**ANTIDOTE FOR LIPOPHILIC DRUG OVERDOSE**

Animal studies and case reports suggest that 20% IVFES aid resuscitation of hemodynamically compromised patients resulting from overdoses of lipophilic drugs including local anesthetics and verapamil. The emulsion may create a lipid plasma phase that extracts lipophilic drug molecules from the aqueous plasma phase, decreasing their distribution to tissue and also enhancing their redistribution back from the tissues. Animal model dosing has been 4–16 mL/kg. In humans a 100-mL bolus has been used; some also included 0.5–mL/kg/h infusions. Desired outcomes are return of spontaneous circulation or improved blood pressure. There are no standards for dosing, monitoring parameters, or desired outcomes. Further study is necessary before IVFES can be recommended for routine antidotal use.

**Adverse Events Associated with Use of IVFES**

The risk of AEs is affected by the rate of infusion, total daily dose, and duration of IVFE administration. It is also well recognized that some AEs associated with IVFE use occur as the result of administering the IVFE in excess of energy expenditure. The maximum elimination rate for IVFES is 3.8 g of fat/kg/24 hours (220–300 g of fat/day for 60- to 100-kg individuals, equivalent to 1–1.5 L of 20% IVFE). Beyond this rate, the clearing mechanism (lipoprotein lipase) for IVFES becomes saturated and the infused triglycerides accumulate in plasma. Some authors have attributed the AEs associated with IVFE infusion to increases in triglyceride concentrations. Others have pointed out differences in effect depending on whether the IVFE is composed of LCTs or medium-chain triglycerides (MCTs). LCTs are derived from soybean and safflower/soybean oil emulsions and have 16–18 carbon chain lengths, whereas MCTs are derived largely from palm kernel oil and have 8–10 carbon chain lengths. MCTs have the advantage of more rapid plasma clearance and tissue utilization, because their use is independent of carnitine cotransport into the mitochondria for further metabolism. Unfortunately, IVFES containing MCTs are not yet routinely used in the US.

**TOLERANCE RELATED TO INFUSION RATE**

Hansen et al. summarized tolerance to the soybean oil emulsion, Intralipid, from several controlled and uncontrolled studies and case reports from 63 centers (Table 1). The studies summarized in that report involved a variety of PN methods (Table 1). The AEs observed in adults were minimal. None of the adult patients received >2.5 g/kg/day of IVFE. Similarly, minimal AEs were reported for pediatric patients except when excessive daily doses were administered. This report was critical to facilitating the widespread use of IVFE in the US by demonstrating reasonable tolerance to its infusion when administered below the manufacturer’s recommended maximum infusion rate (Table 1). The poor tolerance to excessive rates of IVFE infusion in children was clearly demonstrated. This emphasizes the importance of maintaining the infusion rate of IVFE below the recommended maximum rate.

**IMMUNE SYSTEM EFFECTS AND RISK OF INFECTION**

The administration method of IVFE influences the immune system’s effects on the RES. The RES, which consists of phagocytic cells located in reticular connective tissue, mobilizes an immune system response to antigens. Functional status of RES cells in the liver, spleen, and bone marrow can be measured by technetium-99m sulfur colloid (TSC) clearance. Following intravenous administration, TSC is rapidly cleared by the RES from the blood, with a half-life of approximately 2.5 minutes. Uptake of the radioactive colloidal by organs of the RES is dependent upon both their relative blood flow rates and the functional capacity of the phagocytic cells. Usually, 80–90% of the injected TSC is phagocytized by the Kupffer cells of the liver, 5–10% by the spleen, and the balance by the bone marrow. Rimola and colleagues used the TSC clearance rate to estimate RES activity in 41 patients with cirrhosis. The group of patients with impaired RES phagocytic activity had significantly higher rates of bacterial infection and shorter short- and long-term survival than those whose TSC clearance rate was within the normal range (mean follow-up period, 28 ± 3 months). The effect on TSC clearance of infusing IVFE for 10 hours per day for 1 versus 3 days was studied in a prospective trial involving patients with various diagnoses (Tables 2 and 3). Although there was no statistically significant change in TSC clearance after a single 10-hour IVFE infusion (equivalent to a daily infusion of 0.13 g/kg/h), there was a significant decrease in
TSC clearance when the 10-hour infusion was repeated daily for 3 days. Thus, intermittent administration of IVFE appears to compromise in vitro assessments of RES function. In a subsequent prospective study, continuous infusion of IVFE for 3 days at a rate of 0.13 g/kg/h had no effect on TSC clearance (Table 3). This suggests that continuous infusion of IVFE is an acceptable alternative to intermittent, more rapid infusion. However, correlation of this in vitro test to clinical infections in patients receiving PN has not been demonstrated.

Linoleic acid, an omega-6 fatty acid that yields prostaglandins and other inflammatory mediators via the arachidonic acid pathway, is believed to exacerbate the stress response and impair immune function. Due to the preponderance of linoleic acid in soybean oil emulsion, there is considerable interest in its effect on immune function and infections in critically ill patients. Effects of soybean oil emulsion on in vitro immune function tests, such as production of prostanoids and cytokines by T-cells, have been demonstrated, suggesting that its infusion has the potential

| Table 2. Clinical Studies of the IVFE Infusion Events Related to the Immune System |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Reference** | **Pts., N** | **Product** | **Oil** | **Dose** | **Dose per 24 h (g)** | **Infusion Rate (g/kg/h)** | **Infusion Duration (h)** | **Infusion Rate (g/h)** | **Plasma Triglycerides (mg/dL)** |
| Seidner & (1989) | 18 | Travamulsiona | Soybean | 20% | 68–100 | 0.13 | 10 | 6.8–10 |
| Jensen & (1990) | 8 | Travamulsion | Soybean | 20% | 68–100 | 0.13 | 12 | 5.7–8.3 | 62–374 |
| Battistella & (1997) | 57 | IVFE group = 30, no IVFE group = 27 | Intralipida 10% or 20% | Soybean | 25% of nonprotein calories (30 kcal/kg IBW per day) | NA | 0.05–0.075 | 10–12 | NA |
| Monson & (1986) | 23 | Intralipid 10% or 20% | 50% of calories (total calories calculated as 1.5 x E, kcal/daya) | NA | NA | NA | NA | NA |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen.

IBW = ideal body weight; IVFE = intravenous fat emulsion; NA = not available.

*aBaxter Healthcare Corp., Deerfield, IL.

bEstimated value of resting metabolic expenditure.

### Table 1. Clinical Experience with Intralipid 10%67

<table>
<thead>
<tr>
<th>Pts., N</th>
<th>Dose per 24 h</th>
<th>Infusion Infusion Period</th>
<th>Infusions, N</th>
<th>Adverse Events, N</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults, 133</td>
<td>20–60% of total calories</td>
<td>&lt;2.5 g/kg over 4 h</td>
<td>1–2 wk, except in 2 pts. (180 and 256 days)</td>
<td>2111</td>
<td>2</td>
</tr>
<tr>
<td>Pediatrics, 159</td>
<td>&lt;4 g/kg over 4 h</td>
<td>1–3 wk except 51 &gt;30 days and 5 &gt;100 days</td>
<td>3902</td>
<td>12</td>
<td>Minor local skin irritation, edema, or erythema (n = 4) transient increase in results of liver function test values (h = 3) fever and rash after 3rd of 30 infusions (n = 1)</td>
</tr>
</tbody>
</table>

Major tachycardia, tachypnea, hepatomegaly, elevation in ALT and AST, and thrombocytopenia after 2 inadvertent overdoses (n = 1) hepatosplenomegaly, leukopenia, thrombocytopenia resulting in discontinuation of therapy after 200 doses; dose was 6.7 g/kg/day during the last 57 days of therapy (n = 1) hepatosplenomegaly, hyperbilirubinemia after 16 infusions of 5.3 g/kg/day (n = 1) allergic reaction (wheezing, erythema, wheals, urticaria) after 11 days (n = 1)
to amplify inflammatory responses in stressed patients.\textsuperscript{32} To date, few data are available that associate these in vitro findings with clinical effects. In a prospective, randomized trial, Battistella and colleagues infused an IVFE according to the parameters shown in Table 2.\textsuperscript{41} The group that did not receive an IVFE during the first 10 days of PN spent significantly fewer days in the intensive care unit (ICU) and in the hospital and less time on mechanical ventilation. These patients also had less depressed T-cell function (ratio of median [upper and lower quartiles] lymphokine-activated killer cell activity) on day 5 compared with baseline (Table 3).\textsuperscript{61} The group receiving an IVFE had a nonsignificant increase in infections (2.4 vs 1.4 per patient). A concern regarding the methodology of this study is that the groups did not receive isocaloric PN and that the IVFE was infused over 10–12 hours. Thus, it is not known whether the observed effect was due to the soybean oil emulsion in the IVFE group or to a lack of calories. Other methodologic concerns with this study include the lack of blinding, the vagueness of some outcome parameters, the small number of patients, and the large standard deviations. The population included very sick trauma patients entered into the trial after 5 days of hospitalization, and the average number of days in the ICU was 24. Moreover, the question remains whether or not the clinical effect would be observed if a 20% emulsion, administered continuously over a 24-hour period, had been used. In contrast, the immunorestorative effect of IVFEs was reported by Monson and colleagues, who conducted a prospective crossover study in patients who were allocated to receive each of 2 equicaloric, equinitrogenous total PN (TPN) regimens (Tables 2 and 3).\textsuperscript{62} One formulation contained lipids (50% of caloric requirement), and the other was lipid-free. Both were administered for 7 days, with no washout period between regimens. These authors concluded that incorporation of a fat emulsion into a TPN regimen is immunostimulatory, with no evidence of immunosuppression. Even though the type of oil and formulation of IVFE have been shown to influence in vitro immunologic tests, the correlation of these findings with clinical outcomes and infections is minimal. The finding that the rate of infusion and whether the IVFE is administered continuously or intermittently influences in vitro testing of immunologic function leads one to question whether these effects are the result of the IVFE formulation or its administration method.

The immunologic effects of the soybean oil IVFE have caused concern for the use of propofol and clevidipine formulated in this IVFE. For comparison purposes, the dose rate of IVFE infusion for nutritional purposes is slightly higher than that experienced by a patient sedated with propofol at 50 µg/kg/min (0.72 g lipid/kg/24 h)\textsuperscript{40} or by a 75-kg patient who received clevidipine continuously at a rate of 5 mg/h (0.64 g lipid/kg/24 h).\textsuperscript{41}

**MICROBIAL GROWTH IN IVFEs**

In addition to affecting immune function, IVFEs, which do not contain preservatives, support the growth of gram-positive and gram-negative bacteria and fungi.\textsuperscript{43} Fungal strains grow more slowly, but still reach levels comparable to those of bacteria within 24 hours.\textsuperscript{43} Because the growth of the fungus *Malassezia furfur* is dependent on exogenous fatty acids, this organism grows readily in sebaceous glands and surrounding skin. Therefore, skin contamination of the intravenous catheter and perhaps the fat emul-

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**Table 3. Clinical Outcomes of In Vitro Studies on IVFE Infusion Events Related to the Immune System**

<table>
<thead>
<tr>
<th>Reference</th>
<th>In Vitro Studies</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TSC Clearance/min</td>
<td>T Cell Function</td>
</tr>
<tr>
<td>Seidne\textsuperscript{46} (1989)</td>
<td>↓ 0.46 ± 0.08 to 0.27 ± 0.03, p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Jensen\textsuperscript{11} (1990)</td>
<td>0.38 ± 0.09 to 0.41 ± 0.08, p = NS</td>
<td></td>
</tr>
<tr>
<td>Battistella\textsuperscript{61} (1997)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVFE group</td>
<td>0.65 (1.56–0.75)</td>
<td>0.95 (1.48–0.27)</td>
</tr>
<tr>
<td>non-IVFE group</td>
<td>1.2 (2.41–0.75)</td>
<td>1.4 (2.93–0.60)</td>
</tr>
<tr>
<td>p = 0.3</td>
<td>p = 0.02</td>
<td></td>
</tr>
<tr>
<td>Monson\textsuperscript{42} (1986)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-day crossover design with random assignment to equicaloric PN containing either IVFE or no IVFE</td>
<td>Augmented immunologic parameters including T-cell subsets, antibody-dependent cytotoxicity, basal and maximal interleukin-2 production in IVFE group</td>
<td>No difference</td>
</tr>
</tbody>
</table>

ICU = intensive care unit; IVFE = intravenous fat emulsion; LAK = lymphokine-activated killer cell activity; LOS = length of stay; NK = natural cell killer; PN = parenteral nutrition; TSC = technetium-99m sulfur colloid.
tion provides the necessary environment for sepsis associat-
ed with IVFEs in infants.84 Outbreaks of bacterial and fungal
infections in patients treated with propofol are related to ex-
cessively long hang time, poor aseptic technique, and con-
tamination of intravenous equipment.30,65,66 Propofol is now
formulated with disodium edetate or other preservatives that
retard the growth of microorganisms.67 The potential for in-
use contamination of IVFEs has led the Centers for Disease
Control and Prevention to limit the hang time for IVFEs to
12 hours when they are administered separately from PN,
with tubing changes every 24 hours.68 A propofol vial has a
hang time of 12 hours, and an opened syringe must be used
within 6 hours.40 Clevidipine, an intravenous antihypertensive
formulated as a 20% lipid emulsion without a preservative,
has a 4-hour hang time.41

**PULMONARY SYSTEM EFFECTS**

Administration of IVFEs may be associated with altered pul-
monary hemodynamics.31 It is argued that the effects of
IVFEs on pulmonary function are a consequence of hyper-
lipidemia.69 Triglyceride concentrations increase during a
single IVFE infusion, depending on the rate of infusion. For
example, in a prospective study involving 48 individuals
with various respiratory conditions (infections, chronic ob-
strictive pulmonary disease [COPD], acute respiratory dis-
tress syndrome [ARDS]), as well as those with normal lung
function, Hwang and colleagues found that infusion of 500
mL of a 10% fat emulsion over a 4-hour period (Table 4) in-
creased serum triglyceride concentration.70 When the same
infusion was administered to the subset of patients with
ARDS (n = 12) over an 8-hour period, triglyceride concen-
trations increased to a lesser extent. For both infusions, the
patients’ triglyceride concentrations returned to baseline val-
ues within 3–5 hours of discontinuation of the infusion.

The effects of IVFE infusion on *PaO$_2$* are better ex-
plained by ventilation/perfusion inequalities that result
from prostaglandins produced from LCT-containing
IVFEs.71-74 In a study cited above, the pulmonary effects of
rapid IVFE infusion were found to be insignificant for pa-
tients with infectious pulmonary conditions or COPD.70
However, patients with ARDS had significant decreases in
*PaO$_2$* during and up to 3 hours post a 4-hour infusion and
increased intrapulmonary shunting, suggesting ventilation-
perfusion inequalities (Table 4). These effects were re-
duced by slowing the rate of infusion from 4 hours to 8
hours. In another study of patients with ARDS, the effects
of administering IVFEs over 5 hours versus 10 hours were
compared (Table 4).75 The slow infusion resulted in a pul-
monary vasodilatory response and the fast infusion resulted
in vasoconstriction. No cause-effect relationship could be
demonstrated between measured concentrations of
prostaglandins and the observed pulmonary hemodynamic
response. Abbott and colleagues showed that continuous fat
infusion is also associated with greater oxidation of fat com-
pared with intermittent infusion.76 In a comparison of the ef-
effects of 12- and 24-hour infusions of a 10% lipid emulsion
(Table 4), these authors found that the respiratory quotient

<table>
<thead>
<tr>
<th><strong>Table 4. Clinical Studies of the IVFE Infusion Events Related to the Pulmonary System</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference</strong></td>
</tr>
<tr>
<td><strong>Clinical Effect</strong></td>
</tr>
<tr>
<td>Hwang$^{70}$ (1990); ARDS pts.</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Mathru$^{75}$ (1991); ARDS pts.</td>
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<tr>
<td></td>
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<tr>
<td>Abbott$^{76}$ (1984)</td>
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</table>

ARDS = acute respiratory distress syndrome; IVFE = intravenous fat emulsion.
(RQ) decreased during the 12-hour infusion (ie, there was increased lipoprotein oxidation during this period). However, 12 hours after the infusion had finished, the RQ had returned to baseline levels, indicating a gradual transition back to carbohydrate oxidation. In contrast, the RQ of patients who received the 24-hour infusion remained low throughout the treatment period. These findings suggest that continuous intravenous fat infusions are associated with increased lipoprotein oxidation, a factor that may decrease the risk of AEs.

**LIVER FUNCTION EFFECTS**

Three types of hepatobiliary disorders are associated with PN therapy: steatosis, cholestasis, and gallbladder sludge/stones. Reported prevalence rates of PN-associated liver disease (PNALD) vary greatly.

Steatosis occurs more often in adults, usually presenting within 2 weeks of the initiation of PN as mild elevations of liver enzyme and bilirubin levels. It is usually benign and may resolve even while PN continues. Steatosis appears to be related to overfeeding and is less common now since fewer calories are administered to patients today.

Excessive dosage of IVFEs is implicated in the development of cholestatic jaundice in patients receiving long-term PN. In a small, prospective, randomized study designed to compare the effects of 2 different amino acid solutions and of low- (1500 mL once a week) and high- (3 g/kg/day for a mean duration of 45 days) dose 10% Intralipid in adults receiving PN, Salvian and Allday found that daily administration (high dose) was associated with significant increases in alkaline phosphatase, bilirubin, and cholesterol levels. These data suggested cholestatic changes. Liver biopsies of the high-fat group showed well-preserved hepatocytes with no evidence of necrosis or fatty infiltration. However, there were periportal, mixed inflammatory infiltrates along with bile duct proliferation in the portal triads associated with canaliculal bile plugs. In comparison, the low-fat group had only moderate fatty infiltration of the hepatocytes. Subsequently, this group found progressive cholestatic jaundice in 10 of 18 adult patients who received 3 g/kg/day of IVFE for at least 20 days. Initial changes included an increase in serum alkaline phosphatase concentration (>/=400 IU), followed at first by a gradual, then by a more rapid, increase in bilirubin concentration. Liver function returned to normal and cholestatic jaundice improved when the dose of IVFE was lowered or PN was discontinued. These data were instrumental in establishing the maximum daily dose of IVFE at 2.5 g/kg/day.

Gallbladder sludge may result from gallbladder stasis during PN therapy, probably because the lack of oral intake reduces cholecystokinins release, which decreases bile flow and gallbladder contractility. A prospective study involving 23 adults with severe gastrointestinal disease who were assigned to PN found gallbladder sludge in 6% of patients during the first 3 weeks of therapy, 50% during the fourth to sixth weeks, and 100% after 6 weeks. Nearly half of the patients who developed sludge also developed gallstones. However, in this study, both the overall caloric dose (59 nonprotein kcal/kg per day) and the rate of lipid administration (53% of nonprotein calories) equal to a dose in the range of 2.8–3.1 g/kg/day were substantially higher than that recommended by current guidelines. These doses are approximately twice (total calories) and 3 times (total lipids) the currently accepted maximums. Moreover, in approximately half of the patients, the IVFE infusion, admixed in the PN, was administered intermittently over 12 hours. In the other patients, the fat emulsion was administered separately from PN over a 3- to 6-hour period. Both 10% and 20% Intralipid preparations were used. The differences in methodology between this 26-year-old study and current practice suggest that the clinical findings are unlikely to be relevant today.

**HYPERTRIGLYCERIDEMIA AND PANCREATITIS**

Reported rates of hypertriglyceridemia in patients receiving PN range from 6% to 38% and depend upon the patient population studied and the doses used. Hypertriglyceridemia may occur as a result of IVFE administration if the rate of infusion exceeds the capacity of lipoprotein lipase to clear triglycerides or if the patient has risk factors for the development of hypertriglyceridemia. In a prospective, observational study of adult patients receiving PN, hypertriglyceridemia (serum triglyceride concentration >265 mg/dL) developed in 62 of 249 (24.9%) patients who received <1.5 g/kg/day of lipids and 6 of 11 (54.5%) of those who received >1.5 g/kg/day. The risk of hypertriglyceridemia was significantly increased by the presence of renal failure (OR 10.56; 95% CI 3.35 to 33.28), serum glucose >180 mg/dL (OR 2.63; 95% CI 1.19 to 5.81), prednisone doses >0.5 mg/kg/day (OR 7.98; 95% CI 3.13 to 20.29), pancreatitis (OR 4.38; 95% CI 1.66 to 11.53), or sepsis (OR 4.48; 95% CI 2.04 to 9.83). Moreover, hypertriglyceridemia occurred in 62 of 215 (28.8%) patients with one or more risk factors, but in only 6 of 45 (13.3%) patients without risk factors. Thus, triglyceride concentrations should be monitored frequently, at baseline and weekly thereafter, in patients on PN with known risk factors.

In a retrospective study involving 159 patients admitted to an ICU who received propofol in a 10% IVFE for 242 hours, hypertriglyceridemia (serum triglyceride concentrations >/=400 mg/dL) developed in 18%. Compared with patients without hypertriglyceridemia, those with hypertriglyceridemia were older (53 ± 15.6 vs 41 ± 13.2 years, p = 0.04), were less likely to be on a surgical than a medical unit (10% vs 71%, p = 0.002), remained longer in the ICU (median 8.6 [range 2–53] vs 4.1 [1–26] days, p = 0.01), and received propofol for a longer period (median 3.7
[range 1–16] vs 2.1 [1–12] days, \( p = 0.04 \)). Because these patients received 10% IVFE, it is possible that the high phospholipid concentration, combined with the prolonged duration of the infusion, exceeded the capacity of lipoprotein lipase to clear triglycerides and contributed to the occurrence of AEs.

Acute pancreatitis is reported infrequently following propofol administration.\(^5\) For example, in a prospective trial of 40 children undergoing short-term administration of propofol, elevated triglyceride levels were found in 10% and elevated pancreatic enzyme levels in 5%, although no child had symptoms of pancreatitis.\(^7\) Similarly, in the previously mentioned study of 159 patients receiving propofol, 3 (10%) of the 29 patients with hypertriglyceridemia developed pancreatitis (amylase concentration \( \geq 125 \) IU/L, lipase concentration \( \geq 60 \) IU/L, abdominal computed tomography scan or clinical examination findings consistent with pancreatitis). The overall incidence of pancreatitis in this study was thus 1.9% (3 of 159 patients).\(^8\)

Clevidipine is formulated in a 20% IVFE; thus, it would be expected that the risk for hypertriglyceridemia would be lower than that for agents formulated in a 10% IVFE. In clinical trials, most patients receiving clevidipine were treated with doses of 16 mg/h or less, which, for a 70-kg individual, is a fat dosage of 0.09 g/kg/h, 18% lower than the recommended maximum of 0.11 g/kg/h. To reduce the risk of hypertriglyceridemia, no more than 1000 mL is recommended per 24-hour period.\(^4\) In a prospective, open-label, single-group study, 131 patients who presented with acute severe hypertension received clevidipine intravenously for at least 18 hours (as specified in the protocol).\(^8\) Among the 126 patients included in the safety analysis, the median total volume of clevidipine infused was 336.3 mL, the median infusion duration was 20.66 hours, and the median maximum 24-hour lipid dose was 0.74 g/kg/day (range 0.0–4.3 g/kg/day).\(^8\) Decreases in triglyceride concentration from baseline to 6 hours post-infusion were observed in 47.4% of patients, increases in 47.4%, and no change in 5.2%.\(^8\) The median triglyceride concentration did not change significantly from baseline to 6 hours post-infusion, and there was no correlation between change in triglyceride concentration and total lipid load.\(^8\) The recommended maximum lipid dose of 2.5 g/kg/day was exceeded in 11 (8.7%) patients; however, even in these patients, there was no correlation between change in triglyceride concentration and lipid load.\(^8\) No AEs attributable to hyperlipidemia, such as pancreatitis or pulmonary compromise, were observed. In another prospective, randomized, open-label trial in which clevidipine was used for median durations of up to 7 hours in 752 cardiac surgery patients, there were no reports of elevated triglyceride concentrations, nor were lipid-related AEs noted in comparison with active comparators.\(^8\)

Premature Infants and Small-for-Gestational-Age Neonates

IVFEs are an integral part of the PN regimen in neonates.\(^9\) Prolonged use of PN in neonates can lead to PNALD, manifested by elevated direct bilirubin concentrations, in some cases progressing to hepatic failure. Deaths in preterm infants following infusion of IVFEs have also been reported, although they are now uncommon.\(^9\) These AEs are due to the low concentrations of lipoprotein lipase found in premature infants and small-for-gestational-age neonates, which cause those receiving IVFEs to have lower clearance of IVFEs and increased free fatty acid plasma concentrations.\(^9\) Based on tolerance tests, mature infants are able to clear the infused lipid more rapidly than are less-mature infants. Regardless of gestational age, the neonate whose size is appropriate for gestational age can clear the emulsion more rapidly than one who is small for gestational age.\(^9\) Infants should receive 20% rather than 10% lipid emulsion to improve clearance of triglycerides and cholesterol. Serum triglyceride concentrations should be maintained at <150 mg/dL to 200 mg/dL in neonates.\(^9\)

Christensen and colleagues, in a historic cohort analysis of 1366 neonates receiving PN for at least 14 days, investigated the factors predictive of PNALD.\(^6\) Neonates receiving PN for 14–28 days (n = 894) had a 14% incidence of PNALD; those receiving PN for 29–56 days (n = 382) had a 43% incidence; those receiving PN for 57–100 days (n = 94) had a 72% incidence; and those receiving PN for >100 days (n = 14) had an 86% incidence. Groups of patients identifiable on the first day of life as having the highest risk of developing PNALD were those with a birth weight <500 g (OR 30.7; 95% CI 9.5 to 109.2) or 500–749 g (OR 13.1; 95% CI 4.9 to 83.9), gastroschisis (OR 20.3; 95% CI 4.9 to 83.9), and jejunal atresia (OR 24.0; 95% CI 9.0 to 64.1).

Patients Receiving Vitamin K Antagonist Therapy

Administration of IVFEs has been reported to cause a decrease in prothrombin time in a patient taking warfarin.\(^8\) Switching from warfarin to heparin restored the target level of anticoagulation, and changing to a lipid-free PN formulation allowed warfarin to be resumed. An in vitro study found that the addition of Intralipid in therapeutic concentrations to blood from patients receiving warfarin resulted in statistically significant but clinically unimportant decreases in prothrombin time (mean \( \pm \) SEM change in prothrombin time, 50 \( \mu \)g/mL fat emulsion, \(-0.29 \pm 0.07\) seconds; 100 \( \mu \)g/mL fat emulsion, \(-0.23 \pm 0.06\) seconds; 200 \( \mu \)g/mL fat emulsion, \(-0.29 \pm 0.05\) seconds; \( p < 0.05 \) for all).\(^9\) The vitamin K (phylloquinone) content of IVFE products is related to the vegetable oil used in its preparation and its concentration. The concentration averages 13.2–30.8 \( \mu \)g/dL for the 10% emulsion and 27–68 \( \mu \)g/dL for the 20% emulsion.\(^9\)
Fat Overload Syndrome

The fat overload syndrome results from the excess accumulation of serum lipids, the acute onset of which is characterized by fever, jaundice, irritability, spontaneous hemorrhage, and hyperlipidemia. Other findings include lethargy, tachycardia, tachypnea, headache, nausea, vomiting, abdominal pain, hepatosplenomegaly, and cough with occasional hemothysis. Most reports described children (maximum recommended dose of 3 g/kg/day) aged 10 months to 9 years and the syndrome was associated with large daily doses of 3.3–5.4 g/kg/day over long periods of time (28–114 days). This disorder exemplifies the extreme effects of IVFES when administered beyond recommended daily doses and infusion rates.

Summary

IVFESs have been used in clinical practice for over 50 years, first in PN and later for drug delivery, with an acceptable AE and safety profile. Known AEs associated with IVFE use include interference with the immune system, pulmonary function, and hepatic function, and elevation of triglyceride concentrations. These events, which are primarily associated with long-term administration of IVFE, can be minimized by infusing the IVFE continuously rather than intermittently over shorter, more frequent periods and not exceeding a dose of 2.5 g/kg/day or an infusion rate of 0.11 g/kg/h. Use of a 20%, rather than a 10%, IVFE further reduces the risk of hypertriglyceridemia. Lipid concentrations should be closely monitored in patients receiving IVFESs who are at high risk for hypertriglyceridemia. By taking these precautions, clinicians can substantially reduce the risk of AEs in patients receiving IVFESs.

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Los artículos se identificaron a través de la Selección de artículos que nos permitieran comparar La eliminación de las partículas grasas presentes en las EGIV 699

Emulsiones Grasas Intravenosas: Aplicaciones Actuales, Perfil de Seguridad e Implicaciones Clínicas

JM Mirtallo, JF Dasta, KC Kleinschmidt, y J Varon


EXTRACTO

OBJETIVO: Revisar el conocimiento científico actual sobre las emulsiones grasas intravenosas (EGIV) con especial énfasis en su perfil de seguridad.


SELECCIÓN DE FUENTES DE INFORMACIÓN Y MÉTODO DE EXTRACCIÓN DE INFORMACIÓN: Seleccionamos artículos que nos permitieran comparar los resultados de ensayos clínicos sobre la administración de medicación EGIV con referencia al uso histórico y efectos de las EGIV en la nutrición parenteral, con especial énfasis en los EA. Particularmente, nos centramos en dos fármacos de uso actual que se administran por vía intravenosa en forma de emulsiones lipídicas: propofol y clevidapina.

SÍNTESIS: La eliminación de las partículas grasas presentes en las EGIV está mediada por la enzima lipasa lipoproteica. La probabilidad de EA es mayor si el ritmo o la duración de la administración de EGIV superan la capacidad de eliminación de la enzima. La probabilidad de EA también es mayor tras la administración de una formulación EGIV al 10% que una formulación al 20%, debido a que la mayor concentración de fosfolípidos libres en la formulación al 10% interfiere con la actividad de la lipasa lipoproteica. Los EA pueden reducirse mediante la aplicación de las EGIV a una dosis ≤2.5 g/kg/día, y un ritmo ≤0.11 g/kg/hora. El agente anestésico propofol, con una formulación de EGIV al 10%, se ha utilizado en la práctica clínica durante 25 años. Los EA típicos incluyen infección, altas concentraciones de triglicéridos en...
plasma, y pancreatitis. Los ensayos clínicos recientes sobre clevidapina, con una formulación de EGIV al 20%, han demostrado una tasa baja de EA relacionados con los lípidos.

CONCLUSIONES: Los resultados de esta revisión demuestran que las EGIV son bien toleradas cuando se administran de acuerdo con las recomendaciones de administración.

Traducido por Enrique Muñoz Soler

Les Emulsions Lipidiques Intraveineuses: les Applications Actuelles, le Profil de Tolérance et les Implications Cliniques
JM Mirtallo, JP Dasta, KC Kleinschmidt, et J Varon

RÉSUMÉ
OBJECTIF: analyser l'état actuel de la science concernant les émulsions lipidiques intraveineuses (IVFE) en mettant l'accent sur leurs profils de tolérance.

REVUE DE LITTÉRATURE: De 1979 à décembre 2009, une recherche MEDLINE a identifié des articles à l'aide des termes: nutrition parentérale, émulsion lipidique, émulsions grasses, IVFE, tolérance, effets secondaires, intralipides chez le nouveau-né. En outre, des termes décrivant une variété d'effets secondaires spécifiques des pancréatites ont également été identifiés.


RÉSUMÉ: La clairance des particules grasses dans les IVFE a pour origine l’enzyme lipoprotéine lipase. Les effets secondaires sont plus probables si le taux ou la durée de l’administration excède la capacité de clairance de l’enzyme. Les effets secondaires sont également plus probables après une administration d’IVFE d’un dosage de 10% qu’avec un dosage de 20%. En effet, la plus forte concentration en phospholipides libres dans le dosage 10% interfère avec l’activité de la lipoprotéine lipase. Les effets secondaires peuvent être réduits par l’administration des IVFE à un dosage inférieur ou égal à 2,5 g/Kg/jour et un taux inférieur ou égal à 0,11 g/kg/heure. Le propofol, agent anesthésique qui est présent dans une émulsion lipidique d’IVFE de 10%, est utilisé cliniquement depuis 25 ans. Les effets secondaires typiques incluent des infections, des concentrations plasmatiques en triglycérides élevées et des pancréatites. Des essais cliniques récents incluant la clevidipine, médicamente présent dans une émulsion d‘IVFE de 20%, ont mis en évidence un faible taux d’effets secondaires liés aux lipides.

CONCLUSIONS: Les résultats de cette analyse mettent en évidence que les IVFE sont bien tolérées lorsqu'elles sont administrées selon les directives recommandées.

Traduit par Thierry Youmbi