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Proceedings From FDA/A.S.P.E.N. Public Workshop: Clinical Trial Design for Intravenous Fat Emulsion Products, October 29, 2013

Daniel H. Teitelbaum, MD[1]; Peggi Guenter, PhD, RN[2]; Donna Griebel, MD[3]; Steven A. Abrams, MD[4]; Staffan Bark, MD, PhD[5]; Mary Baker, PharmD, MBA[6]; Karyn L. Berry, MD, MPH[3]; Bruce R. Bistrian, MD, PhD[7]; J. Thomas Brenna, PhD[8]; Denis Bonnot, MD[9]; Yvon A. Carpentier, MD[10]; Richard J. Deckelbaum, MD[11]; Mary Hise, PhD, RDN, CNSC[12]; Berthold Koletzko, MD, PhD[13]; Jay M. Mirtallo, MS, RPh, BCNSP, FASHP, FASPEN[14]; Andrew E. Mulberg, MD, FAAP, CPI[3]; Randall C. O'Reilly, PhD[15]; Jonathan Shaffer, MB[16]; Elke von Kleist, PhD[17]; Gary P. Zaloga, MD[12]; and Thomas R. Ziegler, MD[18]

Abstract

The development of intravenous fat emulsion (IVFE) is the culmination of physiological, biochemical, nutritional, and medical scientific advancements. IVFEs have the ability to deliver critical nutritional substrates to the patient. Recent literature purports that they may also play roles in modulation of immune functionality and pulmonary physiology, but data supporting these potential benefits are limited. While soybean-based IVFEs have comprised the dominant fat in U.S. markets, a number of other novel IVFEs may prove to optimize the care of children and adults in both hospitalized and home settings. The October 2013 U.S. Food and Drug Administration (FDA)/American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Public Workshop brought together scientists, researchers, and clinical experts to present updated clinical perspectives of IVFEs, including historical development, current state of usage throughout the world, and considerations for the regulatory approval of new IVFEs in the United States. (*JPEN J Parenter Enteral Nutr*. 2015;39:768-786)

Keywords

fatty acids; research and diseases; lipids; nutrition

Introduction

The purpose of this 1-day public workshop was to provide a forum to discuss the clinical development of intravenous fat emulsion (IVFE) products. This included the discussion of key issues in clinical trial design, including efficacy and safety outcome measures that would support the approval of these new IVFE products. This public workshop was the collaborative effort of A.S.P.E.N. and the FDA. Initial discussion at A.S.P.E.N. came from Dr Vince Vanek, the lead author of the IVFE novel nutrient position paper published in *Nutrition in Clinical Practice* and then from the A.S.P.E.N. Corporate Scientific Advisory Council chaired by Dr Daniel Teitelbaum. The goal was to bring regulatory bodies, clinicians, researchers, and industry together on behalf of our patients, with the ultimate goal of bringing new and safer IVFE products into the U.S. market. This proceedings paper is comprised of abbreviated abstracts from each speaker. The abstracts are vignettes of what was presented during the workshop. Neither the presentations nor the abstracts represent a consensus for future development of these IVFE products. The IVFE workshop laid the foundation for further discussions and actions regarding the development of IVFE products. Critical next steps for IVFE experts and stakeholders to consider include the identification of 1) evidence-based and clinically meaningful efficacy and safety endpoints for clinical trials and 2) populations to be studied. A full transcription of the public workshop can be accessed at http://www.regulations.gov/#!documentDetail;D=FDA-2013-N-0001-0088. To increase clarity, frequently used abbreviations can be found in Table 1. Please note: Some bibliography lists are numbered citations in the text, while others are further reading lists.

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Welcome

Donna Griebel

On behalf of FDA, I would like to welcome you all to today's meeting. I want to extend a very sincere thanks to A.S.P.E.N. for their critical role in bringing everybody together for this meeting and facilitating making this meeting happen. It wouldn't have happened without them so we are very, very grateful. I would also like to thank the members of the steering committee who helped develop the agenda for today's meeting

and worked together over the last few months with the members of the FDA to create today's agenda. The steering committee members included representatives from industry, from academia, professional societies, patients, and government (both FDA and NIH).

It's been many years since the first lipid emulsion products were approved, and we have limited availability in terms of range of lipid emulsion products on the market, as you all are aware. Over those decades, the concept and the framework for evidence-based medicine has evolved and is far removed today from where it was back in the days when the emulsion products were first approved. FDA is a public health organization and science-based, and we work within a framework of laws and regulations that tell us what we can and cannot do when we evaluate drugs for marketing applications. As we've looked at these new marketing applications in the context of today's scientific world, we must ask whether it's enough just to answer the question, "For this bag of product that will be infused into a patient, is it enough to say, well, it has calories and fatty acids in it?" Is that enough or is there more that we need to know to be responsible to our patients and to future caregivers? Are there additional questions that we need to answer? As science has evolved, so have the laws and regulations. There are over time newer methods available to the FDA to facilitate answering some of these questions in order to get products to the market expeditiously, and we can have some discussion of that as it comes up in today's meeting.

Overall, I would like to stress that today's meeting is intended to be a dialogue. It's not just a dialogue between the

From the [1]C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, Michigan; [2]American Society for Parenteral and Enteral Nutrition, Silver Spring, Maryland; [3]Division of Gastroenterology and Inborn Error Products, Office of Drug Evaluation III, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland; [4]Department of Pediatrics, Sections of Neonatology and USDA/ARS Children's Nutrition Research Center, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas; [5]Department of Surgery, Karolinska Institute, Stockholm, Sweden, and Department of Surgery, Visby Hospital, Visby, Sweden; [6]Hospira, Inc, Chicago, Illinois; [7]Harvard Medical School, Clinical Nutrition, Beth Israel Deaconess Medical Center, Boston, Massachusetts; [8]Division of Nutritional Sciences, Cornell University, Ithaca, New York; [9]Scientific Affairs, Business Unit, Parenteral Nutrition & Colloids, Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany; [10]Free University of Brussels (Université Libre de Bruxelles) and Lipid Nutrition Center, Brussels, Belgium; [11]Department of Pediatrics and Epidemiology, Institute of Human Nutrition, Columbia University Medical Center, New York, New York; [12]Baxter Healthcare, Deerfield, Illinois; [13]Dr von Hauner Children's Hospital, University of Munich Medical Centre, Germany; [14]The Ohio State University, College of Pharmacy, Ohio State University, Columbus, Ohio; [15]University of Colorado, Boulder, Colorado; [16]Intestinal Failure Unit, Salford Royal Hospital, University of Manchester, United Kingdom; [17]Hospital Care Division, B. Braun Melsungen AG, Melsungen, Germany; and [18]Division of Endocrinology, Metabolism and Lipids and Emory Center for Clinical and Molecular Nutrition, Emory University Hospital, Atlanta, Georgia.

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Corresponding Author:
Daniel H. Teitelbaum, MD, C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, MI, USA.
Email: dttlbm@med.umich.edu

Table 1. Frequently Used Abbreviations.

Abbreviation	Term
DHA	docosahexaenoic acid
DPA	docosapentaenoic acid
EFA	essential fatty acid
EFAD	essential fatty acid deficiency
EPA	eicosapentaenoic acid
ETA	eicosatetraenoic acid
FA	fatty acid
FFA	free fatty acid
FO	fish oil
GLA	γ-linolenic acid
HDL	high-density lipoproteins
IVFE	intravenous fat emulsion
LA	linoleic acid
LCT	long-chain triglyceride
LDL	low-density lipoproteins
MCT	medium-chain triglyceride
MUFA	mono-unsaturated fatty acid
OA	oleic acid
OO	olive oil
PFAT5	percentage of fat residing globules >5 μm
PN	parenteral nutrition
PUFA	polyunsaturated fatty acid
SO	soybean oil
TG	triglyceride
VLDL	very-low-density lipoproteins

FDA and you; it's a dialogue that we at the FDA want to hear amongst all of you, so there's going to be open microphones. We want to hear what the audience has to say, the questions, answers, and dialogue that happen between the moderators, speakers, and the members of the audience. For this reason, we strongly urge everybody to participate because what the FDA needs to hear is the discussion and its content.

I just want to reinforce that the patients are the chief stakeholders, and those patients include both adults and children. We hope that today's discussion will incorporate points that address the full population that benefit from these products.

Background/Overview

Utilization of IVFE Therapy in the United States

Peggi Guenter

This presentation is a brief history and overview of utilization of IVFE in context of PN use in the United States. All the way back to 1667, clinicians have been giving parenteral nutrition to patients through peripheral veins, and undoubtedly, there were some septic complications.[1] Not until clinicians were able to safely catheterize large vessels, were they able to give concentrated dextrose and protein, and that happened in the 1960s in the United States.[1] At that time, Drs Dudrick, Wilmore, Vars, and Rhoads reported on a neonate with intestinal atresia who was able to be fed intravenously with dextrose and protein hydrolysate for about 30 weeks, during which time she grew and developed normally.[2]

From the 1920s to the 1960s, multiple types of fat sources were used. There was one commercial product, Lipomul®, a cottonseed oil–based product that was withdrawn from the market due to a high incidence of adverse events. In the early 1960s, Swedish scientists developed successful fat preparation.[3] In the United States from the 1960s to the mid-1970s, PN was IV fat emulsion–free because there was no approved IVFE in this country until the mid-1970s.

In early years, IVFE was used primarily to prevent essential fatty acid deficiency, and a typical dose for adults was 50 g of fat twice weekly and 0.5 g per kilogram per day for pediatrics. The trend in the 1980s to the 1990s was to use fat emulsion, often daily with administration of about 15%–30% of calories as fat.

In the United States, IVFE is used in a variety of ways. It is administered daily or 2–3 days weekly as a component of a total nutrient add mixture or infused separately from the base PN solution. IVFEs are also used intermittently as a source of essential fatty acids and not as an energy source in some individuals, including in patients with short bowel syndrome, as they are weaned from PN during intestinal rehabilitation and transition to oral diet, or in other types of patients transitioning to enteral nutrition. PN is given in many settings: home care, alternate care settings such as skilled nursing facilities and long-term acute care hospitals, and in acute care hospitals.

In terms of home care, in 1986 to the mid-1990s, there was the OASIS registry which was a combined Oley Foundation and A.S.P.E.N. project.[4] This registry of home PN patients, reported in 1986 and 1987, consisted of approximately 15,000–20,000 patients on home PN. We do not have any recent data nationwide but have started the A.S.P.E.N. Sustain™ registry and have data on 1200 patients in the last 2 years. The average IVFE dose for those patients is 67 g of fat per day for adults and about 10 g for pediatrics.

There are few historical data on the use of IVFE in acute care hospitals. One study reported in 1984 that there were 550,000 hospitalized patients receiving PN for an average of about 20 days.[5,6] The early 1980s was probably the height of PN utilization in the United States. After that, there was prospective payment and patients had shorter hospital stays with shifting certain diagnoses to use enteral instead of parenteral nutrition. Since then, there are more reliable data. Beginning in 1993, the Agency for Healthcare Research and Quality (AHRQ) has published data through the Healthcare Utilization Project (HCUP), which has the National Inpatient Survey data.[7] From this, PN utilization over time can be tracked. These data are pulled through ICD-9 procedure coding, and not per patient day or per patient, but by hospital stay or discharges. In 1993, there were 150,000 hospital stays where patients received

PN, and this number increased and at least doubled over time until 2010 when there were about 370,000 patients receiving PN per year.[7]

Interestingly enough, the latest HCUP data are from 2011, where there has been a decrease in PN usage, and our suspicion is that that's related to nutritional drug shortages. With so many products in the United States that are unavailable, providers are making hard decisions about how much PN they are prescribing. When you take this utilization data and normalize it per total discharges, you find that that trend is very similar, that there still is an increase, until the downturn in 2011. In looking at the 2011 statistics, in terms of patient characteristics, there are approximately 350,000 patients who receive PN, about one-third are under the age of 1 and about another third are over the age of 65 years. In terms of payer, Medicare is approximately a third, private insurance a third, and Medicaid approximately 25.0%, with the rest made up of uninsured or self-pay types of patients.[7] Since 1993, the use of PN and hence IV fat emulsion is on the rise with high use in both neonates and older adults. The use in alternate healthcare settings, such as long-term care and home care, is really unmeasured and difficult data to obtain. There is a need to look at these patterns and patient populations to help design clinical trials.

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Patient Perspective

Randall C. O'Reilly

To begin, I will share the story of my son, who was born with 20 cm of functional short bowel due to very long-segment Hirschsprung's disease. He has been on PN his entire life and developed PN-associated liver disease (PNALD) within his first months of life, experiencing total bilirubin levels as high as 20 mg/dL and level 4 cirrhosis. After 6 months we were able get him started on fish oil IVFE (Omegaven®) instead of soybean IVFE (IntraLipid®), and his condition improved dramatically. He is now 7 years old and thriving. At a more objective level, I will present data from a patient survey I conducted with 71 cases of soybean IVFE users and 28 fish oil IVFE users, showing that my son's experience is typical; there were over 50% of soybean IVFE patients who experienced PNALD, with a mean total bilirubin level of 9 mg/dL, and these symptoms were reversed in the 28 fish oil IVFE patients, who experienced 0% negative side effects, and had mean total bilirubin levels of 0.22 mg/dL. I would argue that from the patient perspective, we already have extremely compelling data now that merits approval of fish oil IVFE and other IVFEs that include something other than pure soybean oil. The survey respondents overwhelmingly selected "strongly agree" to the statement that the FDA should aggressively pursue approval of alternative IVFE formulations, and also responded with a mean "unsafe" opinion of the pure soy-oil based formulations that are currently available. IVFEs are, fundamentally, a food product providing essential nutrition; the only sense in which they are a drug is in the IV delivery, so the FDA's evaluation could be focused on ensuring proper emulsification and sterilization, while recognizing that people need to have options in what kind of nutrition works best for them. This could establish a lower standard of evidence required for approval: the standard of noninferiority, which given the extensive experience with alternative formulations in Europe, it would seem, could be made immediately, and would likely be greeted with considerable enthusiasm from the patient community. We are already heartened by the rapid approval of a new olive oil–soybean oil based IVFE (Clinolipid®) and are optimistic that this is a sign of further approvals to come in short order. Many impassioned patient comments from the survey are included, imploring the FDA to find a way forward toward approval of alternatives to soybean IVFE in one way or another. Finally, as a footnote, based on the presentations at this meeting, my son Max is now on 50% fish oil–based IVFE and 50% soy-based IVFE, at a total of 2 g/kg/d (instead of 1 g/kg/d of just fish oil–based), and in addition to the pure caloric benefits, his immune function seems stronger and his water transport (eg, dry skin) is markedly improved. This is one more data point in support of the notion that a more balanced approach to IVFE formulations may be best.

FDA Regulatory Framework

Karyn L. Berry

The Food and Drug Administration (FDA) is bound by various laws and regulations which provide the regulatory framework for its operations and decision making in approval of drugs. In 1938, the Federal Food, Drug and Cosmetic Act (FD&C Act) was passed by Congress. It required drug manufacturers to demonstrate that their products were safe.

In 1962, Congress amended the act (Kefauver-Harris Amendment) to require manufacturers to demonstrate "substantial evidence of effectiveness" of a drug prior to marketing

approval. This law specifies that this evidence must be derived from adequate and well-controlled clinical investigations. An adequate and well-controlled study is defined as a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. The study should be designed well enough so as to be able to distinguish the effect of a drug from other influences, such as spontaneous change, placebo effect, or biased observations.

Major elements of an adequate and well-controlled trial include 1) clear statement of objective, 2) valid comparison with a control to provide a quantitative assessment of drug effect, 3) method of selection of subjects provides an adequate assurance that they have the disease or condition being studied, 4) method of assigning subjects to treatment and control groups that minimizes bias, 5) adequate measures are taken to minimize bias on the part of subjects, observers, and analysts of the data, 6) well-defined and reliable outcome measures, and 7) analyses of the results that are adequate to assess the effects of the drug.

Endpoint assessment is a critical component of a well-conducted clinical. Clinical endpoints directly measure a therapeutic effect of a drug: an effect on how a patient feels (eg, symptom relief), functions (eg, improved mobility), or survives. A surrogate endpoint, on the other hand, predicts a clinical benefit. It does not directly describe how a patient feels, functions, or survives as a result of treatment. Drug approvals may be based on established surrogate endpoints, such as improvements in blood pressure.

The accelerated approval regulations, implemented in 1992, allow use of surrogate endpoints reasonably likely to predict clinical benefit for approval of drugs or biological products that are intended to treat serious or life-threatening diseases, and either that demonstrate an improvement over available therapy or provide therapy where none exists. The surrogate's likelihood of predicting clinical benefit may be based on epidemiologic, therapeutic, pathophysiologic, or other evidence. Such surrogates are less well established than surrogates that have been used to support regular approval, such as blood pressure. A drug is approved under the accelerated approval regulations on the condition that the manufacturer conducts clinical studies to verify and describe the actual clinical benefit.

Safety regulations apply to both before and after drug approval. Drug manufacturers are required to submit evidence of a drug's safety prior to approval. Safety surveillance continues after drug approval (postmarketing surveillance). The FDA Amendments Act (FDAAA) of 2007 includes provisions to address drug safety. A section of the Act authorizes the FDA to require postmarketing studies and clinical trials at the time of approval, or after approval, if the FDA becomes aware of new safety information (eg, data about a serious risk or an unexpected serious risk associated with use of the drug).

As the development of intravenous fat emulsions (IVFEs) in the United States moves forward, there are a number of challenges. IVFEs provide nutrition and calories, but recent literature has purported biochemical-based benefits, such as a decreased proinflammatory response, when the amount of ω-6 fatty acids in an IVFE is decreased and the amount of ω-3 fatty acids is increased. However, data supporting actual clinical benefits that are linked to these purported effects of newer IVFEs are limited. The goal of the workshop is to focus on the clinical development of IVFEs. This will include a discussion of 1) characteristics of clinical benefits related to IVFEs other than their being a source of calories/energy and 2) characteristics of adequate and well-controlled trials that would establish these additional clinical benefits.

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Clinical Overview of IVFE

Currently Available IVFEs (U.S. and International)

Properties of the Fatty Acid Components of Intravenous Fat Emulsions

Richard J. Deckelbaum

The fatty acid components of lipid emulsion triglycerides have marked effects on their blood clearance, intracellular metabolism, and biological endpoints. While IV lipid emulsions are similar in size and structure to postprandial chylomicrons, in addition to triglyceride, emulsions contain excess phospholipids in the form of liposomes which affect their clearance from blood. Overall, blood clearance pathways of IV lipid emulsions are similar to chylomicrons. Emulsions are hydrolyzed in blood by lipoprotein lipase, followed by uptake of released fatty acids and remnant particles by liver and extrahepatic tissues. Different than chylomicrons, the most commonly used lipid emulsion worldwide, made from soy oil, is much richer in ω-6 linoleic acid (55% of total fatty acids by weight) and contains lower levels of other ω-6 and ω-3 unsaturated fatty acids compared with chylomicrons. Because of concerns related to "linoleic acid overload," new lipid emulsions containing different fatty acids have been introduced. About 3 decades ago, MCT-containing emulsions were introduced to replace ~50% of the soy oil in IV lipid emulsions. More recently, emulsions containing fish oils have been introduced, as well as emulsions containing olive oil.

Because of the higher solubility of MCT at the emulsion phospholipid water interface, MCT-containing emulsions are cleared much faster and efficiently in both in vitro systems as well as in vivo human studies. Fatty acids have marked effects on membrane structure and function, production and actions of cytokines and other immune factors, coagulation, vascular resistance, cell metabolism and signaling, as well as gene regulation. Thus, it important to understand the different biological effects of emulsion triglyceride fatty acids. Emulsions rich in ω-6 fatty acids generally enhance proinflammatory pathways, while those containing ω-3 fatty acids are anti-inflammatory. Importantly, the high linoleic acid content of soy oil emulsions may compete with ω-3 precursors to decrease production of the bioactive ω-3 fatty acids, EPA and DHA.

In addition to being anti-inflammatory, ω-3-rich triglyceride emulsions have different pathways of clearance from blood compared with ω-6 soy oil emulsions. While ω-6 emulsions utilize clearance pathways of lipoprotein lipase, the LDL receptor, and apolipoprotein E dependent pathways, ω-3 emulsion clearance is much less dependent on these pathways resulting in ω-3 emulsion clearance from blood by whole particle uptake into cells. EPA and DHA also generally increase expression of genes and proteins that enhance lipid metabolism, while they generally suppress proinflammatory genes and protein levels. With ω-3 fatty acids having important roles in cardiovascular outcomes (eg, decreasing arrhythmias), enhancing cognitive development and learning, improving visual development, controlling adverse immune inflammatory responses, reducing PN liver disease, and their "favorable" effects on gene expression, we predict that ω-3 fatty acids will have key roles in intravenous feeding.

It is expected that in the future, specific emulsions will be indicated for specific types of patients such as low-birth-weight infants and patients with inflammatory bowel disease, severe trauma, surgical responses, PN-related liver disease, and acute events such as stroke. Changing intravenous emulsion fatty acid compositions and mixing ratios might also allow specific emulsion targeting to specific tissues where they might have optimal effects for the different clinical challenges that will benefit from intravenous lipid emulsions.

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Indications for Different Populations in Different Clinical Settings

Yvon A. Carpentier

The first well-tolerated intravenous (IV) lipid preparation was made of soybean triglycerides (TG) emulsified with egg-yolk phospholipids. Its use started in Europe in the 1960s and allowed reduction of the high glucose load provided in the hypercaloric parenteral nutrition; this substantially lowered hyperalimentation-associated complications, namely in hypermetabolic patients. However, concerns were raised about the high ω-6 fatty acid (FA) content of soybean oil, particularly in intensive care unit (ICU) patients.

Second-generation lipid emulsions aim at reducing the ω-6 FA intake by substituting soybean with MCT and/or olive oil or by producing structured lipids (combining medium- and long-chain FA on the same glycerol molecule). These preparations help maintain a more balanced FA pattern in plasma and cell phospholipids, even over prolonged administration; in addition, they reduce the risk of peroxidative stress.

The concept of metabolic support (which focuses not only on calories and nitrogen, but on the pharmacological properties of some nutrients and other mediators) was developed in the 1990s and can be summarized as decrease quantity, increase quality. ω-3 FA can be considered as metabolic mediators; in addition, their concentration in cell membranes tends to decrease in many populations, since dietary intake of ω-3 FA is reduced while that of ω-6 FA has markedly increased.

Among the more recent emulsions, one is exclusively made of fish oil TG and has raised particular interest in infant and children PN. This is the focus of other presentations. Other preparations contain mixtures of fish oil, together with MCT, soybean oil, and also olive oil in one emulsion. Infusion of such preparations in people are associated with a rapid ω-3 FA incorporation in the membranes of important blood cells (WBC and platelets).

A number of studies are reported, which evaluate the effect of ω-3 FA enriched preparations, particularly in hypermetabolic (ICU and/or surgical) patients. In ICU patients, recent

meta-analyses consistently indicate a reduction of ICU and hospital stay in patients infused with ω-3 FA-containing preparations. Reductions of inflammatory responses, improvements in gas exchange (with decreased requirement for ventilation), and maintenance of liver function are also noted; still, if a trend toward reduced mortality is often reported, this does not yet reach statistical significance.

Surgical patients also appear to benefit from infusions of ω-3 FA enriched emulsions, with a decrease of ICU and hospital stay, reduced inflammatory reactions, preservation of immune response, and less infections and maintenance of endothelial and liver functions. Starting ω-3 delivery prior to the operation may prove beneficial. Recent research focuses on short-term infusions and administration of new preparations.

As a general rule, IV lipid emulsions should not be infused too rapidly. Rates in the range of 0.10–0.15 g of triglyceride per kilogram of body weight per hour (TG/kg bw·h) are generally appropriate. Special caution is required in subjects with high basal serum TG concentrations (>2–4 mmol/L or 170–350 mg/dL). TG levels should be monitored during (the first days of) infusions and infusion rate altered as needed, not to exceed values of 4–5 mmol/L (or 350–440 mg/dL).

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Clinical Issues With Dosing of Currently Available U.S. Therapy

Steven A. Abrams

Who receives IV lipids in the United States? 1) Very low birth weight (<1500 g) infants totaling about 55,000 each year in the United States (1.4% of births); 2) Infants with congenital bowel abnormalities or intestinal perforations; 3) Infants with infections/sepsis or necrotizing enterocolitis (NEC); 4) Infants with other major health issues, most notably congenital heart disease.

Generally, NICUs provide 3 g/kg/d of lipids as part of full PN. The most obvious reason for this is to maintain the percentage of calories from fat below 40%–50% to match breast milk ratios. Targeted triglyceride levels are variable and most NICUs accept <180–250 mg/dL although some target 150–180 mg/dL. Usually lipids are provided in the United States as 20% soybean IVFE. When an infant receives more than about 70 mL/kg/d of feeds, the percentage of calories from fat will exceed 50%. Generally we stop lipids at 80 mL/kg/d of feeds, with some exceptions in intestinal failure patients.

Lipid lowering in early cholestasis appears to benefit some infants. Clear data about this are lacking. Some do not respond, but how many "respond" depends on the definition of response and use of ω-3 fatty acid lipid emulsion at any given center. PN component shortages are a major struggle of long-term care at the present time for PN-dependent infants and may affect our perspective on lipid use and outcomes.

The current approach to management of intestinal failure in infants is to target growth as essential to a good outcome in this high-risk population. Thus, any nutritional approach must include a bioavailable source of intravenous fat. Limited enteral feeds do not meet this need in many infants. The population of

Table 2. Variables Studied for FDA Approval.

Safety	Intralipid® 10% or 20%	Efficacy	Intralipid® 10% or 20%
Parameter	Frequency	Parameter	Frequency
Triglycerides	Almost all studies	Albumin/total protein	Some studies
Liver[a]		Body weight	Pediatric studies
Vital signs	Many studies	Nitrogen balance	Some studies[b]
Hematology			
Coagulation			
Electrolytes			
Creatinine			
Urine analyses	Some studies		
Cholesterol			
Urea			
B-glucose			
Free fatty acids	A few studies		

[a]Liver, in the Safety column, includes total bilirubin, alkaline phosphatases, transaminases, and a few observations with bromsulphthalein test (BSP).
[b]Intralipid® 20%.

infants needing lipids is mixed and their nutritional needs are not the same, nor are there well-tested ideal products available in the United States to meet enteral or parenteral needs of this group.

Historical Overview of Endpoints Used for U.S. Approvals of Soy-Based IVFE Products

Intralipid® Approval in the United States

Staffan Bark

The first parenteral lipid emulsion used on the market in the United States was Lipomul® in 1956. It was based on cottonseed oil and consisted of mainly 45% linoleic acid, 30% oleic acid, and 20% palmitic acid with ω-6/ω-3 ratio of 54:1. Three European brands were also developed. The main problems with these emulsions were the severe side effects on the liver, and general intolerance made it impossible to use for more than short periods.

When a new product enters the market, efficacy and safety are always key concerns. Due to the problems with Lipomul®, Professor Arvid Wretlind and colleagues at Karolinska Institute, Stockholm, Sweden, started early to look for alternatives and conducted a long series of experiments in both animals and humans. They tested many different combinations of raw materials and emulsifiers. It was found that soybean oil emulsified by egg phospholipids (Intralipid®) was well tolerated compared with other emulsions. Intralipid® became available in Europe in 1962. Lipomul® was finally withdrawn from the U.S. market in 1965.

The U.S. Army (and Surgeon General) had for a long time looked for a safe lipid emulsion. Their research was behind the development of Lipomul®. They were immediately interested in the development of Intralipid® and a collaboration was established with Professor Wretlind. It took 13 years after European approval before Intralipid 10%® was approved by the FDA in 1975. Meanwhile, numerous single patient INDs were used to provide American patients with IV lipids when necessary. The first NDA (17-643 Intralipid 10%®) contains many reports from investigators. These reports were only observational, including only single or a few cases. They were all in adults and children under the age of 4 years. Adolescents were never studied. A survey of the parameters in the NDA reveals that they are exactly the same variables that we are following today, as summarized in Table 2.

NDA 18-449 for Intralipid 20%® was sent to the FDA in January 1980. However, the FDA requested to have data from the research by the U.S. Army done in the early 1960s with Intralipid® 20%. The U.S. Army also sponsored a study in Stockholm together with Arvid Wretlind, investigating biopsies from livers and spleens after infusions of Intralipid®. All these data were included in the Amended NDA in November 1980. During the period in between, the investigators of what can be called the pivotal studies continued to recruit patients to their studies. The largest study at the time ended up with 54 patients and compared safety of Intralipid 20%® vs Intralipid 10%®. The NDA for Intralipid 20%® also included many small studies without any clear statistical planning and mainly observational collection of laboratory data. Similar efficacy for both formulations of Intralipid® was demonstrated in many studies. The pediatric studies also showed efficacy by increased body weight, length, and head circumference, which all are standard parameters to follow in this patient group. The laboratory safety data were the

same as for Intralipid 10%®, and the table above applies also to the studies with Intralipid 20%®. However, additional observations of nitrogen balance were performed both in pediatric and adult patients.

Laboratory safety data were collected for both NDAs. Safety with respect to the impact on the liver was a main concern. Adults and the youngest children were studied. Efficacy was shown in some studies by registration of cumulative nitrogen balance and albumin/protein levels. Growth and body weight were registered in pediatric studies.

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Liposyn® Approval

Mary Baker

Liposyn® products were developed under Abbott Laboratories Hospital Products Division. Hospira spun off from Abbott Laboratories in May 2004. Products included Liposyn 10%® and 20%®, which were composed of 100% safflower oil, Liposyn II® 10% and 20% (50/50 soybean/safflower oil), and Liposyn III 10%, 20%, and 30% (100% soybean oil). The 30% Liposyn III is in a pharmacy bulk package for admixing.

The original Liposyn® formulation has a fatty acid composition of 77% linoleic and 0.1% linolenic. It was approved in May 1979 (10%) and October 1981 (20%). When Liposyn II® was approved in 1984, Liposyn® was discontinued and the NDA has been withdrawn. Clinical trials in Liposyn® were conducted in adult and pediatric patients. Triene/tetraene ratio was used to evaluate efficacy in phase II/III trials for Liposyn 10%®.

Liposyn II® was developed to increase the linolenic acid content. The fatty acid composition was 65.8% linoleic and 4.2% linolenic. Trials included a pediatric study comparing the original Liposyn® formulation with Liposyn II® and a comparative study of lipid clearance rate between Liposyn®, Liposyn II®, and Intralipid™®. Liposyn II® was approved in August 1984. A pediatric phase IV trial in neonates was completed in 1987.

Liposyn III® was approved in September 1984, based on literature. The composition is linoleic acid 54.5% and linolenic acid 8.3%. Liposyn III® 30% was studied in 20 adult postsurgical or medical patients. The dose was 1 g/kg/d over 10 hours given by direct infusion. Triglycerides, free fatty acids, and cholesterol were evaluated up to 24 hours after the start of the infusion. Liposyn III® 30% was approved in January 1998.

International Products: Description of Key Clinical Trials Submitted for Drug Approval in Other Countries

Lipoplus® Product Development (B. Braun)

Elke von Kleist

"First generation" lipid emulsions were developed to provide essential fatty acids (FA), namely ω-6 FA for parenteral nutrition (PN). Vegetable oils (eg, soybean oil), which are rich in these essential FAs, were chosen. In addition, the lipid emulsions also provided an alternative source of energy to reduce excessive glucose administration within a "total PN" regimen. Later, it was recognized that these lipid emulsions were associated with negative effects on the immune function, due to proinflammatory metabolites of the ω-6 FA. Thus, the development of lipid emulsions with a reduced amount of ω-6 FA was aimed at. In the "second generation" of lipid emulsions, soybean oil was partly replaced by immunologically neutral fat such as medium-chain triglycerides (MCTs) from coconut oil. MCTs are more easily hydrolyzed, the resulting medium-chain FAs are more readily oxidized than long-chain FAs, and the transport into the mitochondria is carnitine independent.

Lipoplus® belongs to the "third generation" lipid emulsion products. Based on the well-known use of the "second generation," a further reduction of ω-6 FA by ω-3 FA derived from fish oil was intended. The aim was to provide an alternative lipid emulsion for parenteral nutrition calorically equivalent to available lipid emulsions (first and second generation), but balancing essential FAs of both the ω-6 series and of the ω-3 series. The latter are provided as biologically active forms (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), recognizing scientific knowledge of the FA metabolism.

Three "key" clinical trials that were used for registration purposes are presented. Lipoplus® was used in abdominal surgery patients and in patients on mechanical ventilation, respectively, requiring total PN. Duration of treatment lasted from 1 day up to 13 days, mostly for 5 days. FA pattern, for example, incorporation of EPA and DHA into phospholipids, or the nonprotein respiratory quotient were used as primary efficacy endpoints. The incidence of adverse events was chosen for primary safety assessment. Explorative analyses were performed on the capacity to form leukotrienes from ω-3 FA incorporated into leukocyte membranes (efficacy) and on various clinical chemistry and hematology variables (safety).

Altogether, various phase II studies as well as two phase III studies were performed. Overall, 408 patients received this

third generation lipid emulsion consisting of soybean oil, MCTs, and ω-3 FA triglycerides derived from fish oil.

CLINOLEIC®/CLINOLIPID® Product Development

Mary Hise

CLINOLEIC® is a lipid emulsion for intravenous infusion indicated as a source of calories and essential fatty acids (EFA). In the United States, the product is called Clinolipid®, and the approved indication is for adults. It is not indicated for use in pediatric patients in the United States because there are insufficient data to demonstrate that Clinolipid® provides sufficient amounts of essential fatty acids in this population. In addition, the indication in the United States includes a "Limitation of Use" statement that states that the ω-3:ω-6 fatty acid ratio in Clinolipid® has not been shown to improve clinical outcomes compared with other intravenous lipid emulsions. CLINOLEIC® is comprised of a mixture of refined olive oil and refined soybean oil in an approximate ratio of 4:1 (olive:soy). The content of essential fatty acids (linoleic plus α-linolenic acid) in the finished product is 20% of the total fatty acids. CLINOLEIC® was first approved by the Mutual Recognition Procedure (MRP) with France as the Reference Member State in 1995 and has subsequently been approved in 51 countries (approved in 49 countries for pediatric patients) with approximately 55 million doses given.

CLINOLEIC® was developed to provide an intravenous lipid emulsion having a lower proportion of polyunsaturated fatty acids, while still providing an adequate amount of essential fatty acids to prevent and correct essential fatty acid deficiency in adult and pediatric patients requiring parenteral nutrition. CLINOLEIC® was formulated with a lower soybean oil content than currently marketed emulsions in order to reduce linoleic acid levels. However, CLINOLEIC® contains the same 5 major fatty acids, including the same EFA components (although different percentages of fatty acids) as the reference listed drug, INTRALIPID®. The original CLINOLEIC® dossier relied on Baxter's clinical and nonclinical data comparing CLINOLEIC® to INTRALIPID®, to support the safety and efficacy of the CLINOLEIC® product.

For the original MRP submission, the registration included a complete preclinical development section and 15 clinical studies in humans (n = 265 adults, n = 39 pediatric). Of these studies, 44 were pharmacological studies in healthy volunteers, 8 were safety and efficacy studies in adult patients, and 3 were safety and efficacy studies in pediatric patients. Primary and secondary endpoints for these trials were varied, including anthropometric measures and biomarkers of lipid and protein metabolism. Registrations in most other countries (ie, Australia, Latin America, and Asia) used the information from the European registration, with the most recent approval in Canada in 2010. For global expansion, an additional trial was completed in 200 patients. The primary endpoint for this noninferiority study was albumin. Prealbumin, lipid metabolites, and body weight were used as secondary end points.

The most recent approval occurred in the United States on October 3, 2013 (CLINOLEIC® name changed to CLINOLIPID®). The New Drug Application (NDA) included clinical studies enrolling a total of 386 adult and 198 pediatric patients treated with CLINOLEIC® or CLINOLEIC® containing multichamber products. The NDA submission contained the following:

- 23 Baxter-sponsored efficacy and safety studies:
  - 14 studies in adult patients (n = 261 CLINOLEIC®, n = 179 INTRALIPID®, n = 69 other lipid)
  - 1 study in elderly patients (n = 10 CLINOLEIC®, n = 9 treated with enteral feeding)
  - 3 studies in pediatric patients (n = 39 CLINOLEIC®, n = 39 INTRALIPID®)
  - 5 uncontrolled studies:
    - 4 studies in adult patients (n = 115 CLINOLEIC®)
    - 1 study in pediatric patients (n = 159 CLINOLEIC®)
- Review of published literature: (evaluation of safety, efficacy, and exposure):
  - 18 adult studies (n = 3539 CLINOLEIC®, n = 357 soybean oil–based lipid emulsion)
  - 14 pediatric studies (n = 298 CLINOLEIC®, n = 206 soybean oil–based lipid emulsion)

As part of this approval, postmarketing commitments included a phytosterol analysis program, a human factor study, and additional clinical trials with CLINOLIPID®.

SMOF Product Development in Adults: A 28-Day Study

Jonathan Shaffer

A randomized double-blind prospective study was performed in 11 centers in 7 different countries (Poland, Denmark, France, Netherlands, Israel, Australia, and the United Kingdom). It compared 28 days of either soybean based (Intralipid®) or soybean, MCT, olive oil, fish oil based (SMOF®) lipid as a part of a regime of parenteral nutrition given to stable patients already on parenteral nutrition because of intestinal failure. Institutional review board approval was achieved in each center. Seventy-five patients were randomized and 2 patients received no study medication, giving an intention to treat a population of 73 (34 in the SMOF® group and 39 in the Intralipid® group).

The 2 groups were demographically similar except that the SMOF® group were older (53.2 vs 45.2 years, $P = .02$). More than 50% of all patients had a diagnosis of short bowel syndrome. There were no differences in the exposure to study medication or duration of study days. Both groups had comparable daily doses in intravenous lipid [1.3 (±0.3) in the SMOF® group and 1.3 (±0.2) g/kg/d in the patients randomized to

Intralipid®]. There was no difference in biochemical values between the 2 groups at the start of the study. While no values varied outside the laboratory reference range, the ALT, AST, and total bilirubin mean values went up in the Intralipid® group and down in the SMOF® group. There were no significant changes in the markers of inflammation (CRP, IL6, and sTNF-RII). The SMOF® group did demonstrate significant increases in serum α-tocopherol, eicosapentaenoic acid, and docosahexaenoic acid and a decrease in the ω-6/ω-3 fatty acid ratios, while there were no changes in the Intralipid® group.

Author's experience: I helped set up our adult Home Parenteral Nutrition (HPN) program in 1980. The vast majority of patients had short bowel syndrome and <5% have had a cancer diagnosis. In 1996, I was able to have our hospital recognized as having 1 of 2 national intestinal failure units in England. By 2013, we have treated >580 patients, with 20 patients on the program for >20 years. In a recent review, we have had 160 deaths, 134 from the underlying or other diseases and 26 related to HPN complications. For the last 5 years our catheter infection rate has been 0.25/1000 catheter days. Our patients on average require 5 nights of intravenous feed of amino acids, glucose, minerals, and vitamins and the majority have 1–2 nights of lipid per week. Only a tiny minority are nil by mouth; the vast majority eat, if only for psychological reasons.

At the start of our program, the only lipid option was Intralipid®. By the 1990s, with the advent of the newer emulsions, we were able to use these new preparations, initially for Intralipid® intolerance, but gradually in the majority of new home patients. The advent of SMOF® in 2005 gave us an extra option. We have found that in 3 of our patients with raised bilirubin levels, where we suspected the lipid may have been responsible, changing the patient to SMOF® from Intralipid® resulted in an improvement in their blood parameters. We are now using SMOF® in nearly all our new HPN patients.

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Omegaven and SMOFlipid Product Development

Denis Bonnot

From the wide use of Intralipid® and other 100% soybean oil–based fat emulsions, there has been the emergence of cholestasis associated with prolonged administration. Also raised have been concerns with the high content of ω-6 fatty acid (FA) linoleic acid in soybean oil and the resultant high ω-6/ω-3 ratio.

Omegaven®. To widen the array of FAs supplied in fat emulsions, Fresenius Kabi first developed a fish oil–based fat emulsion, with the ω-3 FAs, EPA, and DHA representing approximately 50% of the FAs.

Replacing 10%–20% of the standard fat emulsion with Omegaven® results in a more balanced FA supply, with the amount of linoleic acid decreasing and the ω-3 FAs increasing with a resulting decrease of the ω-6/ω-3 ratio. The supply of the essential FAs linoleic acid (ω-6) and alpha-linolenic acid (ω-3) remains within the recommended range.

Clinical development included four phase I trials assessing tolerance and pharmacokinetics. Five phase II trials were performed in patients with doses ranging from 10% to 20% of 1–2 g/kg/d of the fat emulsion, given over 1–2 weeks.

In the soybean oil + Omegaven® group, efficacy assessment showed a significant increase of EPA and DHA in blood phospholipids and a marked increase of ω-3 series-derived eicosanoids versus the soybean oil only group. No safety concerns were revealed.[1,2]

Omegaven® was first registered in 1998 and is currently marketed in 39 countries in Europe, Asia, and Latin America, with an estimated 870,000 patients having received Omegaven®.

SMOFlipid®. Fresenius Kabi later developed a more balanced fat emulsion, SMOFlipid®. Mixing different sources of fatty acids (soybean oil 30%, medium-chain triglycerides 30%, olive oil 25%, and fish oil 15%) provides a wide array of FAs from saturated to polyunsaturated. The supply of essential FAs remained within recommendations. Compared with Intralipid®, there is a lower amount of linoleic acid and a higher amount of ω-3, thereby decreasing the ω-6/ω-3 ratio.

Clinical development included two phase I trials assessing pharmacokinetics. Two phase IIb-III short-term trials in premature infants, one 4-week phase III study in infants aged 1 month to 11 years, two 5-day trials, and one 4-week trial in adults were performed comparing SMOFlipid® to soybean oil fat emulsions. Treatment dose ranged from 1 to 2 g/kg/d in adults and from 0.5 to 2 g/kg/d in infants, up to 3.5 g/kg/d in premature infants. Duration of the studies ranged from 5 to 7 days in hospitalized patients up to 4 weeks in patients requiring home PN.

Safety was confirmed as determined on clinical and laboratory parameters, which did not reveal differences between the groups. Efficacy assessment showed a significant increase in EPA and DHA content in blood phospholipids and changes in synthetized eicosanoids resulting from the decreased ω-6/ω-3 ratio. Changes in laboratory nutritional parameters and body weight in pediatrics were similar between the study groups, as all fatty acids have an equivalent caloric value.[3-5] SMOFlipid was first registered in 2004 and is currently marketed in 62 countries in Europe, Asia, Australia, Latin America, and Canada, with an estimated 700,000 patients having received SMOFlipid®.

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Knowledge Gaps in the Investigation and Use of New Parenteral Lipid Emulsions

Bruce R. Bistrian

The identification of knowledge gaps in the investigation and subsequent use for new parenteral lipid emulsions in the United States is to a large degree speculative and subject to the bias of the proposer. With that caveat, 3 of the areas of considerable uncertainty in my estimation are as follows:

1. The impact of different lipids and mixtures on the systemic inflammatory response and its implication(s) for clinical outcome
2. The effects of baseline nutritional status and criticality of illness on response(s) to parenteral lipids
3. The possible revision of maximal infusion rates and doses related to novel properties of new lipid emulsions

The systemic inflammatory response, particularly as it relates to the pathogenesis and treatment of sepsis and septic shock, has been recently reviewed[1] and in its most simplified form is a combination of numerous proinflammatory and anti-inflammatory components with the former producing potential damage to host tissue by collateral injury during its battle with pathogens and with the counterinflammatory response causing immunosuppression while attempting to contain injury and induce repair.[1] Therapeutic attempts to influence this process by anticytokine therapy and activated protein C have not been successful, and immune stimulatory therapies have not been tested.[1] Different lipids have been extensively shown to influence the systemic inflammatory response but in a more modest manner than anticytokine therapy, and they act particularly through down-regulation of proinflammatory cytokine response and the production of less proinflammatory and procoagulant eicosanoids as well as more active healing and repair through other lipid mediators.[2] Thus, it is difficult to predict but unlikely that in a heterogeneous population of critically ill, changes in lipid type would affect mortality rates, which has been the principal endpoint used to date in the experimental therapies of sepsis and septic shock. Early evidence using fish oil as the candidate lipid, which has the greatest impact so far on the systemic inflammatory response, has not shown benefit for mortality or morbidity[3] supporting this contention. However, that does not mean there was a less critically ill population to be used, such as following major thoraco-abdominal surgery, that improvements in morbidity such as infection rates and length of stay might be favorably improved. Such patients are common, have high rates of immunosuppression and postoperative infection and high risk for prolonged stays, and often require parenteral nutrition. Preliminary evidence for efficacy using these endpoints has been confirmed in a meta-analysis of the use of fish oil emulsions.[4] This comparison of the effects of anticytokine therapy and nutritional lipid administration based on the degree of systemic inflammatory response might be considered analogous to the lack of effect of anticytokine therapy on mortality in severe systemic inflammation as seen in sepsis and septic shock but with substantial improvement in morbidity when such therapy is applied chronically in diseases like rheumatoid arthritis, psoriasis, and inflammatory bowel disease, which have a more modest systemic inflammatory response occurring on a chronic basis. Another potential avenue of investigation would be to define a more homogeneous group of the critically ill such as those with ARDS where the impact of the lipid on eicosanoid production might be particularly effective to improve morbidity. There is substantial preliminary evidence for the beneficial impact of a full enteral formula containing a novel mixed lipid in this setting.[5] Perhaps a study of parenteral feeding with novel lipids would be worthwhile in ARDS, but it would be important to study the lipid as a component of a complete nutritional formula, because it has been shown that the individual components without full feeding are not effective in ARDS[6] as might have been anticipated.[7] A final consideration is the degree of immunosuppression and/or immunomodulation to be anticipated with several candidate lipids. The most proinflammatory are those containing the ω-6 fatty acid, linoleic acid as the principal component, with medium-chain triglycerides being essentially neutral, high oleic acid–containing lipids having a modest benefit for immune modulation with lipids with a high content of the ω-3 fatty acids, eicosapentaenoic, and docosahexaenoic acid, having the most profound immunomodulatory effect.[2] Perhaps disease states should be categorized as to whether their adverse impacts are due to excessive proinflammation or excessive immunosuppression before deciding which lipids to study and whether the control arm should be an equal amount of lipid that has the contrary effect in order to maximize the difference rather than the use of a no lipid control.

For critically ill patients in intensive care units, there has been recently demonstrated a clear effect of baseline nutritional status as reflected in the BMI on clinical outcome.[8]

Those with a BMI <18.5 kg/m^2 have a dramatically increased mortality rate with a paradox in the obese in that the optimal BMI for survival is 42.6 kg/m^2.[8] While it is easy to understand why the malnourished with poor energy reserves do not fare well, particularly given the inadequate feeding characteristic in the critically ill, it is likely that the improved survival of the morbidly obese also relates to their energy stores, making them able to compensate to a greater degree for inadequate intakes. However, this situation may impact feeding regimens as well. Obviously in the malnourished at least, energy requirements should be provided, and given the adverse impact of excessive parenteral glucose in the critically ill,[9] parenteral lipids should be a component of such feeding. Whether novel lipids provided to meet full or nearly full energy requirements have clinical benefits for this group should be studied separately from the obese, where hypocaloric feeding might be appropriate as an alternate feeding strategy. Moreover, the obese and the morbidly obese are now a quite sizable group. At least one-third of Americans are obese, and recent data show a much greater increase for the morbidly obese, approaching 6% of the population. What should be the role for new parenteral lipids in such patients? Preliminary evidence suggests benefits for hypocaloric feeding over full feeding to meet energy requirements.[10] In such a situation, the patient fed a lipid-free regimen remains on a mixed-fuel system with the fat burned coming from endogenous stores. A number of questions arise. Should added lipid to such regimens be hypocaloric in amount? Should there be controls of no added lipid along with conventional soybean oil? Shouldn't baseline nutritional status be a determinant for study entry?

A final brief issue entails the limits on dosing of new parenteral lipids for study. Because it had been shown that rapid infusion rates could on the one hand block reticuloendothelial system function and thereby lead to infection, and on the other foster excessive production of eicosanoids that reversed hypoxic vasoconstriction or increased pulmonary artery pressures, a dose of .11 g/kg/h was identified from these studies that did not have these effects.[11] Since some of these proposed lipids have improved clearance rates[12,13] and very different effects on eicosanoid production,[2] should studies be performed to identify these characteristics, even though in clinical study rates of infusion might be limited to those that have been established as safe for the control infusion, soybean oil?

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Clinical Outcome Measures Based on Clinical Benefits Other Than Nutrition/ Calories

Thomas R. Ziegler

IVFEs provide critical energy sources and essential fatty acids, both of which are important for cell and organ function, immunity, wound healing, and convalescence. The charge of this lecture was to discuss the data to support specific endpoints as a clinically meaningful outcome measure or as a surrogate in clinical design of trials to test the safety and efficacy of IVFE products. However, earlier clinical trial data on classic clinical outcome measures due to different IVFEs (eg, mortality, infection, length of stay [LOS]) in nutrition support research have often not incorporated rigorous study designs. There remain major areas of uncertainty in most areas of nutrition support in the intensive care unit setting, the hospital ward setting, and in patients requiring home PN. PN with IVFE (in a total nutrient admixture or given separately) has become routine, despite lack of rigorous comparative effectiveness trials of the various modalities. Guidance to date has been based largely on expert opinion and on data from observational and small clinical trials, while limited information on alternative substrates from proper randomized controlled trials (RCTs) is available.

Soybean oil–based IVFEs have been available (and used routinely in the United States) for over several decades. Alternative IVFEs (soybean oil, fish oil, olive oil, structured lipids, combinations [SMOF]) have been used worldwide (except in the United States) for many years. No significant adverse effects have been reported to date with regard to these alternative IVFEs. Soybean oil–based IVFEs are associated with cholestasis in infant short bowel syndrome, leading to use of lipid restriction and alternative IVFE strategies (eg, IV fish oil). In adults, previous concerns of proinflammatory/pro-oxidative stress effects of soy-based IVFEs may have been overstated given existing data.

Data to support specific endpoints as a clinically meaningful outcome measure or as a surrogate are lacking, and the surrogate biomarkers in IVFE research have not been linked to clinical outcomes. With regard to mortality as an endpoint in IVFE nutrition research, advantages are that this endpoint is easy to measure and is a gold-standard outcome; disadvantages are that patient mortality is a nonspecific for IVFE (or PN) intervention because many factors influence it (underlying diseases, age, adequacy of medical/surgical care, etc). Infectious complications would be an adequate outcome variable for a specific IVFE product, but disadvantages include nonspecificity (as in mortality). In addition, infections need to be validated with an infectious disease specialist as they are difficult to accurately diagnose in many cases (eg, ventilator-associated pneumonia). Time on mechanical ventilation is easy to measure and could be a good outcome variable if true for a specific product, but disadvantages are that this endpoint is nonspecific for intervention, as many factors influence it (underlying diseases, age, adequacy of medical/surgical care, etc).

Nutritional support or specific nutrient interventions are essential when malnutrition or depletion of a specific nutrient is the primary (or a major) contributor to mortality and morbidity. The uncertainty arises around what is a meaningful endpoint when the nutritional treatment is an ancillary, albeit an important, intervention (eg, impact of IVFE to support cells, organs, wounds, and overall metabolism with substrate, energy, and essential fatty acids). The group discussed whether we may be setting the bar too high in IVFE research. One significant area of uncertainty is the problem that nutritional assessment is currently imprecise, and new methods (eg, metabolomics) hold promise to further define biomarkers for assessment of individualized nutritional status and response to nutritional therapy.

Further discussion of the group centered on what could be optimal clinical endpoints (assuming rigorous clinical research design features) in future research on IVFEs: 1) Should mortality, LOS, infections, and time on ventilator be primary or secondary endpoint, versus being used primarily as safety endpoints? 2) Should normalization of low blood levels of a nutrient, or stability of a nutrient or metabolic pathway (eg, evidenced by stable or improved blood essential fatty acids, free fatty acids, triglycerides), be adequate endpoints? 3) Are novel study designs needed (eg, single-arm studies with historical controls)? 4) Should composite clinical outcome endpoints be used? 5) Should noninferiority studies be the goal for outcome studies of essential nutrients?

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Intravenous Fat Emulsion Safety

Jay M. Mirtallo

Fat emulsions are complex pharmaceutical formulations whose infusion affects many different biological processes and organ systems. As a formulation, these effects are the result of the oil, as well as other components of the preparation. Fat emulsions are oil-in-water emulsions using an egg yolk phosphatide as an emulsifier. The preparation also contains glycerol for tonicity, which allows safe infusion into the vein. Adverse effects are

not only the result of the fat (inflammatory effect, predisposition to lipid peroxidases during storage and use, and phytosterol content) used for the emulsion but also the emulsifier (clearance of infused fat, allergy, and particle size or stability). Soybean oil emulsions have a wide variety of adverse effects reported in the literature affecting immune function and coagulation and resulting in hepatobiliary disease, pulmonary compromise, and fat overload syndrome. Most of these effects could be related to exceeding the manufacturer's recommended dose or administering the emulsion at rates in excess of the body's clearance rate.

A few of the adverse event reports correlated these findings with hypertriglyceridemia. This led to recommendations to withhold, discontinue, or decrease the dose of fat emulsions when triglyceride levels were >400 mg/dL for adults and >200 mg/dL for neonates. This recommendation assumed the elevated triglycerides were the result of infused rather than endogenously produced triglycerides. The caution for hypertriglyceridemia was for the potential to induce pancreatitis in adults and hyperlipidemia and fat overload in neonates.

Soybean oil emulsions have immune system effects. The effect on the reticuloendothelial system is related to duration and infusion rate where effects are minimized by continuous infusion (rather than intermittent infusion). The effects on immune mediators have been assessed with variable results and inconsistent correlation with infectious complications. The direct effect of intravenous fat emulsions on infections is due to the in-use contamination of the product by *Malassezia furfur*. Immune effects of one study associated with decrease in LOS in the ICU and hospital are responsible for the guideline recommendation to withhold fat emulsions for the first 7 days of parenteral nutrition therapy in critically ill patients.

The pulmonary effects of soybean oil emulsions are dependent on the rate of infusion and disease condition. Hyperlipidemia is associated with alveolar diffusion difficulties. Short-term (4 hours) fat infusions increase triglyceride levels in patients with pulmonary disease. There is no significant effect of hypertriglyceridemia on those with pneumonia or COPD. But a significant decrease in Pao_2 as well as increased intrapulmonary shunting was found in ARDS patients, effects of which were reduced by slowing the infusion rate. Infusion rate of fat emulsions influences pulmonary vasculature with fast infusions, causing vasoconstriction and slow infusions resulting in vasodilatation.

Parenteral nutrition–associated liver disease is a serious complication of parenteral nutrition in children and adults receiving long-term PN. Prevalence of PNALD in adults increases with duration of PN: 55% at 2 years, 64% at 4 years, and 72% at 6 years. The role of fat emulsions in the development of PNALD could be related to the fat source, phytosterol content, and the dose. Phytosterols are inefficiently metabolized to bile acids by the liver and may impair bile flow. Phytosterol levels are increased in short bowel patients receiving soybean oil emulsions. The dose of fat emulsion >1 g/kg/d in patients receiving long-term PN is associated with chronic cholestasis and severe PNALD. Cholestatic jaundice in long-term adult PN patients resulting from high doses of fat emulsions was instrumental in defining the maximum daily dose at 2.5 g/kg/d.

New fat emulsions may improve the safety of fat emulsion use in PN in a variety of ways. For soy-allergic patients it could provide a source of essential fatty acids. With improved stability, the fat particle size could be maintained over longer periods under various conditions of storage and transportation. Formulations with monounsaturated fat and/or including antioxidants that counteract lipid peroxidases reduce this potential. New fat formulations may also test the limits of dose, rate of infusion, and duration of safe therapy that now exist for soybean fat emulsion.

A final consideration in safety is the system by which it is delivered to the patient. Medication errors occur with fat infusions separately infused from PN, usually at the administration node. The cause is related to misinterpretation of the order or improper programming of the infusion pump. The lack of a standard method of ordering fat emulsions is a continual problem in clinical practice.

Complications of intravenous fat emulsions are often related to the dose, infusion rate, and particle size of the emulsion, the incidence and consequences of which may be minimized by following recommended dosing guidelines. PNALD is a serious disorder that may warrant cautious use of soybean oil fat emulsion in long-term PN patients. Elevated triglyceride levels are a frequent reason to decrease or discontinue fat emulsion therapy. New fat emulsions have the potential to resolve some of the safety issues of soybean emulsions.

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Strengths and Limitations of Biochemical Markers and Diagnosis of Essential Fatty Acid Deficiency

J. Thomas Brenna

Dietary essential fatty acids (EFAs) are required nutrients because they cannot be biosynthesized de novo from general carbon sources such as acetate by humans. The 2 families of EFAs are defined by their biochemical structures and are known as ω-6 and ω-3. The principle dietary parent fatty acids were studied starting in the 1950s[1] and established that ω-6 linoleic acid (LA, 18:2ω-6) prevented the major clinical symptom of EFA deficiency (EFAD), scaly skin, and attendant polydipsia due to the compromised water barrier.[2,3] Later work clearly established that the ω-3 alpha-linolenic acid (ALA, 18:3ω-3) is the analogous ω-3 parent fatty acid. Detailed biochemical studies showed that both LA and ALA are precursors for the long-chain polyunsaturated fatty acids (PUFAs), ω-6 arachidonic acid (AA or ARA, 20:4ω-6), and ω-3 eicosapentaenoic acid (EPA, 20:5ω-3), and ω-3 docosahexaenoic acid (DHA, 22:6ω-3), which are further converted to eicosanoids and docosanoids and also are required for structural integrity of the brain, retina, and neural tissue. Accordingly, LA and ALA are metabolically essential primarily as precursors for long-chain PUFAs rather than for functions specific to LA and ALA themselves. Importantly, AA, EPA, and DHA are all available from dietary animal foods, specifically meats and seafood, whereas, with rare exceptions, vegetable sources contain only LA and ALA.

The main biochemical marker for EFAD is Mead acid, an ω-9 fatty acid that is structurally the most similar PUFA that can be synthesized de novo from acetate or metabolism of oleic acid. Mead acid (20:3ω-9) is nontoxic, and its normally low level in plasma phospholipids rises significantly when PUFAs are not available to replace AA. The triene/tetraene ratio developed in the 1960s for ω-6 deficiency is measured in plasma phospholipids as the ratio of Mead acid to ARA; a value of [20:3ω-9]/[20:4ω-6] >0.4 indicates EFAD. Fat-free IV infusions of the 1975s caused a rapid increase of this parameter, especially for continuous infusion.[4] Importantly, Mead acid is synthesized specifically in response to low LA.[5] Neither the growth rate of young animals nor Mead acid rise is a good marker for ω-3 deficiency. A rise in ω-6 docosapentaenoic acid (DPA, 22:5ω-6), the ω-6 structural analog of ω-3 DHA, is a more reliable marker for excess ω-6 LA and deficient ω-3,[6] although there are no norms for this parameter and measurements have not been standardized to diagnosis. Accordingly, no good short-term markers are currently available for low ω-3 levels.

The systematic responses of plasma phospholipids to dietary fat and, by implication, IV fat were worked out with animals in the 1960s with continuing work through the present decade, clarifying various details. LA and ALA are PUFA/EFA components of conventional injectable emulsions; thus, details of their conversion to active long-chain PUFAs are of most importance. In general, and somewhat surprisingly, low total PUFA, <2% of total fatty acids, combined with a balance of LA and ALA militate to provide maximal synthesis of long-chain PUFAs.[7] Apart from this, inclusion of preformed EPA and DHA would obviate concerns about adequate ω-3 synthesis. Current evidence strongly suggests that infants consuming preformed DHA have more rapid brain and visual development than those who rely on LA and ALA for all long-chain PUFAs.[8]

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Impact of Emulsion Components and Populations on Endpoints Selected

Berthold Koletzko

What we basically want from parenteral nutrition (PN) is a safe supply of energy and nutrients. In pediatrics, you can measure that by normal growth and normal development. We can also measure that by metabolic and endocrine response using blood lipids, lipoproteins, fatty acids, markers of oxidation, antioxidant status, phytosterols, glucose, insulin, and other markers. As we break down various types of lipids, we know that the

structure will change the energy supply. While medium-chain triglycerides (MCTs) have about 16% less chemical energy than long-chain lipids (LCTs), this is relatively a small difference. Importantly, we know that MCTs are very rapidly transported into mitochondria and rapidly oxidized, far more rapidly than LCTs. If you provide lipid emulsions with MCT/LCT and compare them with soybean emulsion, the MCT/LCT lipids lead to higher oxygen consumption in the immediate period after infusion. In other words, a higher thermogenic effect is found with MCTs. In addition, energy extraction does not only depend on chain length, but varies with different types of fatty acids that exchange oxidation. For example, alpha-linolenic acid is oxidized to CO_2 to a far greater extent than linolenic acid in humans, and this may affect body composition.

All commercially available lipid emulsions provide enough essential fatty acids to effectively prevent linolenic deficiency. The only caveat is the 100% marine oil lipid emulsion, and I don't think we have the data to conclude these would be safe in providing adequate essential fatty acids if given as a sole source of lipids over a prolonged period of time. MCT is the preferred substrate for oxidation, leading to better incorporation of ω-3 and ω-6 fatty acids into plasma lipids. From a pediatric point of view, the perinatal period is one of rapid brain growth and development. The brain incorporates a considerable amount of DHA as well as arachidonic acid from 25 weeks gestation onward to term births and on to about 2 years of age.

As one looks at the composition of soybean oil IVFE (SOFE), while they provide a lot of essential fatty acids, they are very different from what we eat and from what is in human breast milk. We are concerned about this provision of high PUFA amounts with SOFE because this high level of PUFA, largely above metabolic needs, is suppressing conversion to LCTs, which are relevant from a biological effect. SOFE does not provide any appreciable amounts of long-chain ω-3 fatty acids, and thus there is high risk of toxic peroxidation actions. As well, provision of SOFE leads to markedly high levels of linolenic acid that you would not see in a fetus or a preterm infant who receives human milk. If we provide, instead, an olive oil/soy combination, there is still an increase of linolenic acid but far less than in the SOFE group. So with the olive oil/soy combination we have a pattern that was much more similar to human milk–fed infants, and we do not see any signs of EFAD.

DHA provision to preterms has been highly spoken of in recent years. Perhaps the most impressive set of data come from a randomized trial in a small number of preterm infants from Australia who were randomized to standard DHA dose versus high DHA dose. At 18 months, there is a benefit on development in girls but not boys. However, more importantly, the rate of severe mental retardation is reduced to one-half with the higher amount of DHA. So there is a trend in neonatology to provide more DHA, which is easy to achieve enterally but difficult to achieve parenterally. Studies that provide marine oil lipid emulsions in infants have led to increased eicosapentaenoic acid, but little or modest effects on DHA. Meta-analysis of lipid emulsions with marine oils did not show changes in mortality in surgical adult patients. However, this meta-analysis showed a near 50% reduction in rate only of infections and a significant reduction of length of stay. All of this would translate into huge economic savings. When looking at the very low birth weight population, a meta-analysis comparing new versus old IVFE showed a significant effect: a 25% lower sepsis rate with new emulsions. This 25% lower sepsis rate makes it very difficult for us now to use a soybean oil emulsion in very low birth rate infants.

With regard to parenteral nutrition–associated cholestasis (PNAC), we feel strongly that if you prevent catheter infection, you can prevent most of these cases. The exciting data from Boston show that with the use of 100% marine oil at a low dose, there was resolution of PNAC in almost half of the patients. Interestingly, very similar results were reported previously from the group in Paris without marine lipids, but with a temporary cessation of SOFE. So, it is important to ask, is it really the marine oil that does the trick, or what is the precise mechanism leading to PNAC resolution? Potentially, this could be due to the antioxidant protection through ω-3 fatty acid. We feel this needs to be evaluated further.

In terms of what populations should be studied, clearly surgical patients are a prime candidate. In infants and children, we are particularly interested in the preterms and the critically ill ICU patients, and that would include surgical infants. An additional group would be children on long-term home PN. Another question is of ethnic and genetic subgroups. To my knowledge, this has not been very much considered so far. This is a question that is particularly relevant for the United States, because we know that African Americans differ in their genotype for fatty acid metabolism. They have predominantly a genotype of the fatty acid that desaturates with fast PUFA conversion. Such variation has been hypothesized as one of the reasons why there is such a difference in cardiovascular disease risk between Caucasians and African Americans. In terms of outcome measures, development of weight is a good measure, as are body composition, energy intake, and expenditure. Additional clinical endpoints include length of ICU stay, infections, respiratory function, ventilation days, and mortality.

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Clinical Issues in Designing a Trial of IV Lipids With Currently Available Products in the United States

Steven A. Abrams

Challenges and opportunities exist for conducting clinical research in infants and children related to novel intravenous fatty emulsions (IVFEs). It is important to identify these pediatric-specific issues to enhance the development and investigation of new products for use in the United States.

A key issue is to determine what population group will be the subjects of any investigations. It is likely that the majority of infants receiving IVFEs are very low birth weight (VLBW) infants. Many current feeding protocols for healthy VBLW infants, such as the "Guidelines for Acute Care of the Neonate"[1] from Baylor College of Medicine, recommend stopping IVFE by about 1 week of life in otherwise healthy VLBW infants. Thus, research in this group would generally be short term and might not fully reflect either safety or efficacy of the products being tested.

Another group that might be studied are infants at risk for needing long-term intravenous nutrition. This group consists of infants with congenital bowel wall defects such as gastroschisis and omphalocele, infants with intestinal atresia or abnormalities such as Hirschsprung's disease, and infants born with a normal intestine but who suffered an injury to it such as a perforation or necrotizing enterocolitis.

Current neonatal intensive care (NICU) practice includes limitation in the length of time that arterial and central venous access lines are maintained. Furthermore, phlebotomy is limited in this group. Usually, a maximum of 2–3 mL/kg/d of blood can be withdrawn for research purposes at one time and 6–8 mL/kg/d over longer periods of time. In infants who are <1.0 kg, this is a very tight limitation and may restrict research-related testing.[2] Families will not consent to research that requires multiple blood draws without a clear benefit to their infant. Most laboratory tests performed for research need to be those that are required for routine medical care, such as serum triglycerides and glucose.

Families, physicians, and institutional review boards are generally supportive of nutrition research in the NICU setting. They understand that virtually all products used in high-risk infants were at one time evaluated in clinical research protocols. There are a number of large centers that care for a considerable number of such high-risk infants on a daily basis and are experienced in conducting such research.

IVFEs are often started in high-risk infants within hours of birth. Therefore, recruitment and consent must be done before birth or very soon after delivery if randomization is to be done before receiving any IVFE. Infants transferred from community hospitals to large children's hospitals often have had IVFE already started.

The ability of parents to provide meaningful research consent around the time of birth of a sick or small infant is uncertain. Full disclosure of possible risks of involvement in research is needed. Medical care teams available outside of weekday work hours may not be able to do this well. Trainees may not be fully aware of the risk-benefit ratio of the research study and may not be ideal for obtaining consent at off hours.

However, many high-risk mothers are admitted >24 hours before delivery. Antepartum or prenatal visits are often ideal times to approach families and discuss research protocols. The primary research team can do consenting then. Most lipid emulsions to be tested have extensive history of research and clinical use outside of the United States, providing a basis for discussions and consideration of the risk-benefit of participation in the research. One possibility to improve subject recruitment is to allow up to 24 hours of "standard lipid" prior to intervention in a protocol.

Neonatologists are interested in the safety of providing a full dose of IVFE to their patients (usually 3 g/kg/d) and the effects of any novel product on liver function tests, serum triglyceride levels, and growth. Thus, the primary research outcomes from studying a new product are therefore likely to be growth and measures of tolerance in small infants. Secondary outcomes might assess additional biochemical findings as is feasible. Long-standing unresolved shortages of PN and lipid components may be problematic in terms of study design and implementation.

In summary, there is a critical need for research into new lipid emulsions in the United States. However, study design issues are complex and need prereview at multiple levels. It is feasible in a multicenter study to compare current IVFEs with novel interventions/products and the primary research group would be infants at risk for needing long-term PN. How to deal with recruitment, phlebotomy, the development of complications, such as cholestasis, and the use of multicenter consistent nutrition protocols are resolvable barriers to implementation of these research protocols.

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Intravenous Fat Emulsions—Other Aspects of Clinical Trial Design

Gary P. Zaloga

Intravenous lipid emulsions are complex suspensions of triglycerides that contain many different fatty acids with different biological actions. The primary goals of administering lipid emulsions are the provision of nutrition (ie, energy and essential fatty acids) and/or treatment of a disease process (ie, therapeutic goal). It is the desired product "claim" or "indication" that determines the study design. The study may evaluate a nutritional or therapeutic claim and may seek superiority or noninferiority of the claim versus a standard treatment. In addition to establishing efficacy of the lipid in supporting the claim, clinical studies should also establish safety.

The primary study endpoint should be an outcome variable that is directly related to the study product, clinically relevant, and easily measurable in a clinical trial. Endpoints are usually a biomarker or a patient-specific structural or functional endpoint. Biomarker endpoints must be validated for disease development, severity, or progression (including nutritional status). In general, there is a lack of validated biomarker endpoints for lipid emulsions. Patient specific endpoints include signs and symptoms, patient functions (ie, mobility), adverse events, and tissue damage. The most common nutritional endpoints for lipids are the supply of energy (assessed by body weight, lean body mass, growth, muscle function) and essential fatty acids (assessed by fatty acid profiles and the triene-tetraene ratio). However, there are numerous confounding factors that affect these endpoints that include the catabolic response to illness or injury, exercise, disuse atrophy (such as bed rest), levels of anabolic hormones, comorbid conditions, and genetic susceptibility. There are numerous possible physiologic or disease therapeutic endpoints that include treatment of cholestasis, postoperative infections, hyperglycemia, inflammatory bowel disease activity, and oxygenation in patients with pulmonary injuries. In general, therapeutic endpoints should be disease specific and may be studied independently of the use of parenteral nutrition. Therapeutic effects of lipids may be very difficult to demonstrate due to numerous confounding factors.

Most nutritional studies should be randomized, controlled (preferably double-blinded) comparative studies. Due to ethical concerns regarding limiting of nutrition to patients unable to consume nutrients enterally, most nutritional studies of intravenous lipids compare a new lipid emulsion to a standard lipid emulsion. The duration of a study is primarily determined by the efficacy and safety endpoints. There must be time to demonstrate efficacy via the chosen endpoints. The average time for use of parenteral nutrition in hospitalized patients is 7–10 days, and many patients also receive enteral nutrition during this time period. The short time for treatment and lack of validated short-term endpoints complicate study of lipid emulsions in these patients. One should choose a study population that is relevant to use of the lipids as a nutritional agent or therapy. The study populations should be chosen and matched so as to eliminate as many confounding variables as possible and should require the treatment for a duration that is long enough to evaluate the study endpoints. The dose of lipid should be consistent with the desired effect as a nutritional or therapeutic agent and must be demonstrated to be safe. Thus, most doses of a nutritional lipid will be administered at 20%–40% of energy requirements while therapeutic effects may require dose-response studies to determine the optimal and safe dose.

Conclusions

Daniel H. Teitelbaum

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Donna Griebel

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