Treatment of Parenteral Nutrition-Associated Liver Disease: The Role of Lipid Emulsions[1–3]

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ABSTRACT

Parenteral nutrition is a life-saving therapy for infants with intestinal failure. However, long-term parenteral nutrition carries the risk of progressive liver disease. Substantial data has implicated components of parenteral soybean oil in the pathogenesis of parenteral nutrition-associated liver disease (PNALD). Elevated serum concentrations of phytosterols, an abundance of omega-6 polyunsaturated fatty acids, and a relative paucity of α-tocopherol have been associated with the risk of cholestasis and hepatic injury observed in PNALD. Currently available treatment strategies include the reduction of the dose of administered parenteral soybean oil and/or the replacement of parenteral soybean oil with alternative parenteral lipid emulsions. The purpose of this review is to provide an overview of the pathogenetic mechanisms associated with the development of PNALD and the data evaluating currently available treatment strategies. *Adv. Nutr. 4: 711–717, 2013.*

Introduction

Parenteral nutrition has revolutionized the care of infants with intestinal failure by providing life-sustaining calories in the setting of inadequate absorption of enteral nutrients. However, long-term parenteral nutrition carries the risk of a progressive and potentially life-threatening liver disease (1). Parenteral nutrition-associated liver disease (PNALD) presents with jaundice and failure to thrive in children dependent on parenteral nutrition (2). PNALD is initially histologically characterized by intrahepatic cholestasis but can progress to fibrosis and cirrhosis with continued exposure to parenteral nutrition. Histologic evidence of cholestasis can be seen within 2 wk after starting parenteral nutrition. Varying degrees of fibrosis occur in the majority of children receiving parenteral nutrition for >6 wk (3). However, the diagnosis of PNALD is often made noninvasively by using biochemical markers. Commonly used criteria in children dependent on parenteral nutrition include 2 consecutive measurements of direct bilirubin >2 mg/dL without other causes of hepatic dysfunction (4,5).

PNALD occurs in 43–74% of infants with intestinal failure and can be fatal if treatment is delayed (5,6). Risk factors for the development of PNALD include preterm birth, low birth weight, macronutrient excess, trace element imbalances, frequent surgical procedures, lack of enteral feeding, prolonged use of parenteral nutrition, and recurrent sepsis from central venous catheter-associated infections (7). Over the last decade, the source of lipids has emerged as a major risk factor in the pathogenesis of PNALD, with substantial evidence indicating that harmful components of parenteral soybean oil contribute to the development of PNALD. Unfortunately, the only available FDA-approved parenteral lipid emulsion in the United States is composed of soybean oil (Intralipid, Fresenius Kabi).

Until recently, the primary treatment for children with PNALD was to stop parenteral nutrition and provide full nutrition enterally. However, tolerance of full enteral nutrition in children with intestinal failure may require prolonged intestinal rehabilitation over a period of years (8). Historically, infants unable to wean from parenteral nutrition and soybean oil to full enteral nutrition frequently developed end-stage liver disease and required liver and/or small bowel transplantation for survival (9). New insights into the pathogenesis of PNALD and the introduction of alternative lipid sources have allowed for the evolution of the management of

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PNALD. Progression of PNALD to end-stage liver disease is now rare and the need for liver transplantation has markedly decreased (10). The purpose of this review is to provide an overview of the pathogenetic mechanisms associated with the development of PNALD and currently available treatment strategies.

Parenteral Lipids in the Pathogenesis of PNALD

To prevent essential fatty acid deficiency and promote growth, patients dependent on parenteral nutrition also require parenteral lipids. However, the provision of lipids via the parenteral route causes metabolic disturbances that may predispose patients to hepatic dysfunction. Lipid metabolism in the liver depends on the route of administration. Lipids given enterally are absorbed by the enterocyte in the form of a micelle and packaged into chylomicrons for metabolism by the liver. Although the lipid particles in parenteral soybean oil emulsion mimic the size and structure of chylomicrons, they primarily contain omega-6 (n–6) PUFAs and TGs and are devoid of cholesterol or protein. With reduced cholesterol, lipolysis is limited and the liver is prone to the accumulation of lipid particles (11). Javid et al. (12) demonstrated this concept by inducing essential fatty acid deficiency in mice and subsequently providing lipids by either the enteral or parenteral route. Enteral lipid supplementation was protective against hepatic steatosis in a dose-dependent manner, whereas persistent and severe steatosis was observed with parenteral lipid administration.

Several components specific to soybean oil have also been proposed to contribute to the development of PNALD. Notably, soybean oil is rich in phytosterols, which are plant-derived steroid compounds structurally similar to cholesterol (13). When plant products are consumed enterally, absorption of phytosterols is limited to 5–10% with limited excretion by conversion to bile acids (14–16). However, when plant products are given via the parenteral route, phytosterols are fully bioavailable with the same limitations in excretion, allowing the development of high, nonphysiologic, serum concentrations. Clayton et al. (17) demonstrated that for children with severe PNALD, plasma concentrations of phytosterols were as high as those in patients with hereditary phytosterolemia, reaching concentrations equal to or higher than in samples of 20% undiluted Intralipid. With a decrease in lipid intake, patients had lower plasma phytosterol concentrations and an associated improvement in liver function tests. Similarly, Ellegård et al. (18) demonstrated that patients with intestinal failure receiving parenteral nutrition had phytosterol concentrations over 5 times that of patients with intestinal failure that were not receiving parenteral nutrition and over 2 times that of healthy control patients. These studies and others show that high concentrations of serum phytosterols in parenteral nutrition-dependent children are correlated with PNALD and the severity of cholestasis (15,18,19). Prolonged use of parenteral soybean oil may lead to accumulation of phytosterol content in cell membranes and plasma lipoproteins and is associated with cholestasis in this population (17). Similarly, increased plasma phytosterol concentrations have been observed in infants receiving olive oil-based parenteral lipid emulsions (20).

The mechanisms by which phytosterols contribute to the development of PNALD remain under investigation. Administration of phytosterols in neonatal piglets increases serum bile acids and reduces bile acid-dependent bile flow, resulting in the development of cholestasis. Newborn piglets receiving phytosterol-free fish oil maintain normal bile flow and liver function tests (21,22). Furthermore, stimgasterol, the most abundant phytosterol in soybean oil, is an antagonist of the Farsenoid X Receptor (FXR) (23). Ligand-bound FXR normally suppresses 7-α-hydroxylase, the rate-limiting enzyme of bile acid synthesis (24,25). In murine models of cholestasis, mice receiving a synthetic FXR agonist, GW4064, had a significant improvement in hepatic transaminase concentrations. Marked decreases in alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, and a trend toward a decrease in bilirubin concentrations were noted in the mice that received the FXR agonist. Additionally, rats treated with GW4064 had less hepatocellular necrosis, inflammation, and bile duct proliferation on a liver biopsy than did rats treated with vehicle only (26). These studies suggest that an FXR agonist may be hepatoprotective and that phytosterols may contribute to the development of cholestasis by downregulating the suppression of bile acid synthesis.

In addition, the lipid content of soybean oil is primarily composed of ω-6 PUFAs. Both ω-6 PUFAs and ω-3 (n–3) PUFAs serve as precursors of proinflammatory and antiinflammatory eicosanoids and prostaglandins (27). Increased or excess intake of ω-6 PUFAs, especially linoleic acid, results in higher amounts of proinflammatory mediators (e.g., nuclear factor-κB, IL-6, tumor necrosis factor-α) (28,29). Arachidonic acid, one the major downstream metabolites of linoleic acid (ω-6 PUFA), is the key substrate for the synthesis of 2-series prostaglandins and thromboxanes via the cyclooxygenase pathway and the 4-series leukotrienes via the lipoxgenase pathway (27). The products of those pathways promote inflammation by secreting IL-6, which is involved in leukocyte chemotaxis and vasodilation. More importantly, the most potent of these downstream products, prostaglandin E2 and leukotriene B4, have been shown to play active roles in chronic inflammatory diseases such as asthma, rheumatoid arthritis, and ulcerative colitis (30). It should be noted, however, that arachidonic acid is also a precursor for epoxyeicosatrienoic acids via the cytochrome 450 pathway, known to reduce inflammation by decreasing leukocyte adhesion and downregulating nuclear factor-κB (31,32). However, ω-6 PUFAs predominantly give rise to proinflammatory mediators, whereas ω-3 PUFA-derived mediators are largely antiinflammatory (27). EPA, which is derived from α-linolenic acid (an ω-3 PUFA), acts as a competing substrate for the cyclooxygenase and lipoxygenase pathways as previously described, producing 3-series prostaglandins and thromboxanes and 5-series leukotrienes, respectively (33). These mediators tend to be more antiinflammatory, thereby countering the ω-6 PUFA products in the inflammatory cascade. EPA and its

downstream product, DHA, bind to PPARα/γ and G-protein coupled receptors GPR-120 and GPR-40, resulting in a downregulation of nuclear factor-κB and inhibition of inflammatory pathways (34,35).

The source of parenteral lipids administered appears to influence the inflammatory milieu in animal models of PNALD. Yeh et al. (36) compared serum inflammatory markers in rats receiving either parenteral safflower oil (plant based) or fish oil, showing higher concentrations of thromboxane A2, a potent proinflammatory agent, in rats receiving parenteral safflower oil. Lee et al. (37) examined mice consuming an enteral diet of either menhaden oil (ω-3 PUFAs) or soybean oil (ω-6 PUFAs) after bile duct ligation. At 4 and 8 d, the mice fed the soybean oil had more histologic evidence of inflammation, apoptosis, and necrosis compared with mice fed mehaden oil. Liver function tests were similar between the groups. Similarly, Chen et al. (38) studied the extent of hepatic injury after bile duct ligation in rats fed standard chow and given i.p. injections of either DHA or saline. The rats in the DHA group had downregulation of nuclear factor-κB expression, reduced leukocyte accumulation, and decreased fibrogenesis. Therefore, induction of a proinflammatory milieu by parenteral soybean oil administration may contribute to the hepatic inflammation associated with PNALD.

Parenteral soybean oil is also relatively deplete in α-tocopherol, a potent antioxidant (39). Oxidative stress occurs when cellular by-products of reactive oxygen species and hydrogen peroxide are not utilized or neutralized within the cell (40). In conjunction with antioxidant enzymes (e.g., superoxide dismutase, catalase, and glutathione peroxidase), antioxidants (e.g., glutathione, tocopherol, and ascorbic acid) scavenge for these prooxidant species and neutralize them into stable products (41). Oxidative stress has been proposed as the "second hit" in hepatosteatosis, leading to cellular injury and hepatic apoptosis secondary to abnormal fat accumulation (42). In the study by Kalish et al. (43), a metabolomic analysis of mice receiving oral parenteral nutrition and either parenteral soybean oil or fish oil, lower concentrations of α-tocopherol and higher concentrations of lipid peroxidation products were found in the soybean oil group. Similarly, Hong et al. (44) reported that rabbits receiving parenteral soybean oil had decreased superoxide dismutase activity (an antioxidant enzyme), increased lipid peroxidation, and increased apoptosis compared with rabbits receiving parenteral saline.

Current Strategies for the Treatment of PNALD

Growing evidence implicating parenteral soybean oil in the pathogenesis of PNALD has contributed to the evolution of management strategies for children with PNALD. Two approaches have been proposed for the treatment of PNALD: lipid restriction and lipid modification. Lipid restriction reduces the extent of exposure to parenteral soybean oil and may attenuate the deleterious effects described above. Lipid modification replaces parenteral soybean oil with parenteral fish oil.

Lipid restriction. Traditionally, parenteral soybean oil has been administered at a dose of 2–3 g/(kg · d) (45). However, in recent years, some institutions have utilized reduced lipid dosing in an effort to decrease the incidence of PNALD (46–48). Studies have shown a decrease in the incidence of PNALD when lipid dose is decreased to $\leq$1 g/(kg · d) (5,49). However, the developmental consequences of the restriction of essential fatty acids on a growing neonate are unclear. In 2012, Cober et al. (49) examined serum bilirubin concentrations, growth, and essential fatty acid deficiency in infants receiving parenteral nutrition with parenteral lipids at 3 g/(kg · d) compared with those receiving parenteral nutrition with parenteral lipids at 1 g/(kg · d) twice weekly. Infants in the lipid restriction group were found to have a significant reduction in total bilirubin concentrations during the 8 wk of treatment [change in slope of -0.73 mg/(dL · wk) vs. 0.29 mg/(dL · wk), respectively, $n = 31$/group; $P = 0.0017$]. Weight and head circumference age-adjusted Z-scores were found to be the same between groups. However, 8 of 13 patients had an increased triene: tetraene ratio (>0.05 but <0.2), suggesting a trend toward essential fatty acid deficiency. Considering the importance of lipids in early brain development, even mild essential fatty acid deficiency may have long-term deleterious consequences for the growing infant (50,51).

Sanchez et al. (5) reported outcomes in patients who received a decrease in parenteral lipid dosing from 2–3 g/(kg · d) to 1 g/(kg · d). Infants treated with the reduced lipid dose were found to have a significantly lower incidence of PNALD compared with infants treated with the higher lipid dose (22% vs. 43%, $n = 132$ and 82 respectively; $P = 0.003$). Weight gain and weight-for-age at discharge were found to be the same between groups. Although no patient was found to develop clinical signs of essential fatty acid deficiency, screening for biochemical essential fatty acid deficiency was not performed in this study.

In a prospective, randomized controlled trial, Rollins et al. (52) randomly assigned infants >26 wk gestation who received at least 50% of calories from parenteral nutrition to standard [3 g/(kg · d)] or reduced [1 g/(kg · d)] lipid dosing. Outcome measures of the study included biomarkers of liver function, growth, and serum fatty acid concentrations. Infants in the reduced lipid dose group were found to have a lower rate of increase in conjugated bilirubin from baseline (0 vs. 1.3 mg/dL; $P = 0.04$) compared with the standard dosing group. The weight-for-age Z-score was found to increase at a higher rate in the standard dosing group (0 vs. -0.06; $P = 0.02$) compared with the reduced group. However, the enrollees in this study were not dependent on parenteral nutrition for total caloric intake. Furthermore, the percent of calories from enteral sources was variable, with study participants receiving breast milk, formula, or both, making these results of uncertain significance with regard to the population of infants dependent on PN for all of their caloric needs.

However, a study by Nehra et al. (53) demonstrated no difference in the incidence of cholestasis in surgical neonates treated with i.v. lipids at 1 g/(kg · d) vs. 2–3 g/(kg · d)

(51.7% vs. 43.8%, n = 29 and 32, respectively; P = 0.61). There was also no difference between groups in the time to onset of cholestasis, with patients developing cholestasis in 32.6 ± 24.1 d in the lipid reduction group and 27.7 ± 10.6 d, in the standard lipid dosing group (P = 0.48).

More studies are needed to determine whether lipid restriction is efficacious for the prevention of PNALD. In addition, careful attention should be paid to neurological and behavioral outcomes in children receiving long-term PN with respect to lipid dose. The importance of ω-3 PUFAs in brain development is highlighted in the lipid composition of the brain, which is 50% DHA by neuronal membrane weight (51). Term infants benefit from the transfer of large amounts of DHA late in the third trimester (54). However, preterm infants are relatively deplete in these important fatty acids and especially at risk of fatty acid deficiencies with intestinal failure. Supplementation of long-chain PUFAs does not significantly improve intelligence or visual development in preterm infants receiving full enteral nutrition (55). However, the consequences of under-provision of fatty acids in infants receiving full parenteral nutrition on neurological outcomes is unknown. Published recommendations for enteral DHA and arachidonic acid dietary content are 0.2% of total fatty acids for term infants and 0.35% for preterm infants (56). Parenteral soybean oil provides DHA and arachidonic acid as 0.2% of total fatty acids (Intralipid, Fresenius Kabi). Although this is sufficient for term infants, preterm infants receiving parenteral nutrition at the standard dose of lipids [2–3 g/(kg · d)] may not be receiving sufficient PUFAs compared with enterally fed preterm infants. Lipid restriction in preterm infants for the prevention of PNALD may further reduce the amount of DHA and arachidonic acid provided. Additional studies are required to ensure that the lipid reduction is safe and sufficient for brain development and growth in preterm infants dependent on parenteral nutrition.

Lipid modification: fish oil monotherapy. Parenteral fish oil (Omegaven, Fresenius Kabi) was introduced to the United States in 2004 for compassionate use in treating preexisting PNALD. The first use of parenteral fish oil therapy for PNALD was reported by Gura et al. (57), where 2 infants experienced resolution of cholestasis and improvement in liver function after replacement of parenteral soybean oil with fish oil. One of the 2 patients was removed from the waiting list for liver transplantation due to the observed clinical improvement. Subsequently, Gura et al. (4) reported outcomes in 18 infants treated with fish oil that were compared with a historical cohort of 21 infants treated with soybean oil. The fish oil group had 2 deaths and no transplants, whereas the soybean oil group had 7 deaths and 2 liver transplants. Puder et al. (58) subsequently reported outcomes in contemporary cohorts, where 42 children were treated with fish oil and 49 children were treated with soybean oil. Children receiving parenteral fish oil exhibited resolution of cholestasis 8.6 times faster than children receiving soybean oil. A significant decrease in mortality and/or transplantation was observed in the fish oil group compared with the soybean oil group (9.5% vs. 34.7%, respectively; P = 0.005). Increased survival was noted in the fish oil group despite the fact that children within the fish oil group were more premature in birth, had longer exposure to parenteral nutrition, and had a higher mean direct bilirubin at initiation of fish oil than children in the soybean oil group. Liver transplantation was performed in 6 infants in the soybean oil group, whereas none were required in the fish oil group. Small case reports of infants with intestinal failure and PNALD from other institutions have also demonstrated resolution of cholestasis and survival after replacement of parenteral soybean oil with fish oil (59–61).

Premkumar et al. (62) reported outcomes in 57 infants treated for PNALD with parenteral fish oil between 2007 and 2011. All infants were under the age of 6 mo at initiation of fish oil and most were born preterm (median gestational age of 28 wk). Cholestasis resolved with fish oil therapy in 82.5% of infants. Ten infants died during the study period, though none of the deaths were due to complications of fish oil therapy or liver failure. Nine of the 10 infants who died did not demonstrate resolution of cholestasis: 3 had end-stage liver disease prior to treatment with fish oil and 4 died after redirection of care due to poor prognosis from multiple comorbidities.

Several biochemical mechanisms have been proposed to explain the beneficial potential of parenteral fish oil in the management of PNALD. Fish oil supplementation decreases hepatosteatosis by inducing signaling pathways that inhibit de novo lipogenesis and stimulate the β-oxidation of fatty acids (63). Therefore, parenteral fish oil may be less likely to accumulate in the liver than parenteral soybean oil. In addition, unlike soybean oil, parenteral fish oil contains no phytosterols and may not trigger the cholestasis associated with high concentrations of serum phytosterols. Fish oil is also rich in ω-3 PUFAs and tocopherols, which may result in less inflammation and oxidative stress. Chen et al. (38) reported reduced hepatic inflammation, ductal proliferation, and fibrosis in rats fed a diet rich in DHA compared with standard rodent chow after common bile duct ligation. Decreased lipid peroxidation and elevated antioxidant enzymes were also noted in the DHA-rich diet group. Other animal models of PNALD have demonstrated similar decreases in inflammation, oxidative stress, and cholestasis with oral and/or parenteral fish oil administration (36,43,44). Furthermore, downstream metabolites of ω-3 PUFAs, called resolvins, protectins, and maresins, have been identified as active mediators of the resolution of inflammation (64). González-Périz et al. (65) reported that administration of resolvin E1 to mice that are genetically predisposed to fatty liver resulted in decreased hepatosteatosis and hepatic inflammation. These mechanisms in concert may explain the benefits of parenteral fish oil in the treatment of PNALD, though the absence of parenteral soybean oil may be the dominant benefit.

Lipid modification: mixed lipid emulsions. The utility of newly developed mixed lipid emulsions in the treatment of

PNALD is also under investigation, though results have not been as dramatic as those seen with fish oil monotherapy. SMOFlipid (Fresenius Kabi) is a mixed lipid emulsion containing 30% soybean oil, 30% medium-chain TGs, 25% olive oil, and 15% fish oil. Muhammed et al. (66) evaluated the use of SMOFlipid in the treatment of PNALD, defined as a persistently elevated bilirubin of 4.1 mg/dL. Outcomes were compared in 8 children with PNALD treated with the mixed lipid emulsion (SMOFlipid) and 9 children who received parenteral soybean oil only in the 3-y period prior to the availability of SMOFlipid. After 6 mo of therapy, there was no significant difference in median bilirubin between the 2 groups, with a median bilirubin of 1.1 mg/dL (range 0.35–12.5 mg/dL) in the SMOFlipid group and 10.8 mg/dL (range 0.6–15.7 mg/dL) in the Intralipid group. ($P = 0.058$). However, there was a difference in Δ median bilirubin, with a decrease of 5.8 mg/dL in the SMOFlipid group and an increase of 4.6 mg/dL in the Intralipid group.

The use of Clinoleic (Baxter), composed of 80% olive oil and 20% soybean oil, in combination with parenteral fish oil (Omegaven) has also been studied for the treatment of PNALD. Angsten et al. (67) compared morbidity and mortality in 20 infants treated with a 1:1 ratio of Clinoleic and Omegaven with a historical cohort of 18 infants treated with Intralipid only. They observed a decreased mortality from liver failure in the mixed lipid group (10%) compared with the parenteral soybean oil group (33%). Cholestasis resolved in all surviving patients in the mixed lipid group but in only 2 surviving patients in the soybean oil group. Liver transplantation was not required for any children in either treatment group. These studies suggest that mixed lipid emulsions may provide some benefit to children with PNALD, though none have compared outcomes with fish oil monotherapy.

In conclusion, long-term parenteral nutrition is a lifesaving therapy for children with intestinal failure but carries the risk of life-threatening liver disease. Although the pathogenesis of PNALD is multifactorial, the increased phytosterols, proinflammatory ω-6 PUFAs, and oxidative stress associated with parenteral soybean oil may all contribute to this disease. Current strategies for the treatment of PNALD include reduction in the dose of administered parenteral soybean oil and/or replacement of soybean oil with alternative lipid emulsions. Results have been mixed for lipid restriction strategies, though some institutions utilize lower doses of soybean oil due to the potential benefits. Fish oil monotherapy is an effective and safe treatment for PNALD, with multiple studies demonstrating its use associated with resolution of cholestasis and reduction in mortality and morbidity. The use of mixed lipid emulsions for the treatment of PNALD is under investigation. Available studies suggest that mixed lipid emulsions are associated with less cholestasis and mortality than parenteral soybean oil therapy. However, the efficacy of mixed lipid emulsions and fish oil monotherapy has not been directly compared. Furthermore, studies with long-term follow-up and a focus on children with advanced PNALD and cirrhosis are lacking and needed.

Acknowledgments

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