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Reversal of Parenteral Nutrition–Associated Liver Disease in Two Infants With Short Bowel Syndrome Using Parenteral Fish Oil: Implications for Future Management

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ABSTRACT

Here we report the reversal of cholestasis in 2 infants with intestinal failure and parenteral nutrition–associated liver disease. Treatment involved the substitution of a conventional intravenous fat emulsion with one containing primarily omega-3 fatty acids. Biochemical tests of liver function improved significantly. One child was removed from the liver transplantation list because of improved hepatic function, and the second child had complete resolution of cholestasis while solely on parenteral nutrition. This suggests that fat emulsions made from fish oils may be an effective means of treating and preventing this often-fatal condition. A randomized, controlled trial is necessary to study the efficacy of this new approach to parenteral nutrition–associated liver disease.

PARENTERAL NUTRITION (PN) is a life-saving therapy for patients who are unable to absorb enteral nutrients secondary to insufficient intestinal length or function.[1] Before the development of PN, patients with insufficient gastrointestinal absorptive function commonly died of starvation and subsequent complications of malnutrition. Today, >30 000 US patients permanently depend on PN for survival.[2] Long-term use of PN, however, is associated with many complications including bloodstream infections, metabolic abnormalities, and others.[3] The most serious complication continues to be PN-associated liver disease (PNALD), the etiology of which is unclear. The most effective treatment for PNALD is increasing enteral energy intake while reducing PN, but this process can be challenging when intestinal function is poor.[4] In some cases of liver dysfunction in the setting of intestinal failure, liver/small intestine transplantation remains the only treatment option. Infants with PNALD have a mortality rate that approaches 100% within 1 year of diagnosis if they are unable to be weaned off PN or fail to receive a liver/small bowel transplant.[5] Recent evidence suggests that PNALD may be in part due to the soy oils in the fat emulsions, leading us to explore alternative products available elsewhere.[6,7]

CASE REPORTS

CASE 1. Patient 1 is a male born at 34 weeks' gestation (birth weight = 2.8 kg) who suffered an intrauterine midgut volvulus. He underwent an exploratory laparotomy at birth. The intestine, from the distal duodenum to the proximal descending colon, was lost from the volvulus, which left 22 cm of dilated duodenum and the distal colon. He underwent a serial transverse enteroplasty procedure, a recently described bowel-lengthening technique,[8] which lengthened the duodenum to ~51 cm. At 6 weeks of age, he underwent placement of a gastrostomy tube, multiple bowel anastomoses (7 total), and a sigmoid colostomy. The anastomoses were be-

Key Words: bilirubin, nutrition–infant, nutritional supplements, hepatic failure
Abbreviations: PN, parenteral nutrition; PNALD, parenteral nutrition–associated liver disease; PT, prothrombin time; CRP, C-reactive protein; AST, aspartate amino transferase; ALT, amino alanine transferase

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tween the duodenum and the colon and multiple sections of small intestine (1 cm each) that remained from the volvulus. At 3 months, bowel continuity was reestablished. He had intractable feeding difficulties and required PN since birth. At best, he has tolerated only 50% of his calories enterally, although he continued to receive 100% of his estimated energy requirements intravenously (355.64 J/kg per day [85 cal/kg per d]) because of minimal absorption. His PN regimen included parenteral lipid emulsions (Intralipid 20%; Baxter Healthcare/Fresenius Kabi, Clayton, NC), primarily composed of soybean oils (Table 1) at a dose of 3 g/kg per d (Fig 1A). At 6 weeks of age, liver biopsy showed cholestasis, steatosis, expansion of portal tracts with mild inflammation, bile duct proliferation, and mild fibrosis. A subsequent biopsy at 6 months showed progression of his liver disease to marked portal-portal bridging fibrosis. An abdominal ultrasound demonstrated hepatosplenomegaly without varices or ascites. Because of his intractable feeding difficulties and evidence of rapidly progressive PNALD, he was listed for a liver/small bowel transplant at 5 months of age.

CASE 2. Patient 2 is a male born at 25 weeks' gestation (birth weight = 850 g) who developed an atrial perforation secondary to an umbilical venous catheter, requiring a pericardiocentesis. He also had severe hypotension, respiratory distress syndrome, and a patent ductus arteriosus that was treated with indomethacin and subsequently surgically ligated. At the same time, he underwent a laparotomy for repair of an isolated perforation of the terminal ileum. At 6 weeks of age, he was advanced to full feeds for ~1 week before developing feeding intolerance, abdominal tenderness with erythema, and bloody stools. He underwent a laparotomy, during which his abdomen was found to be encased in a hard dense mass of fibrous adhesion tissue with an intestinal perforation. This was treated with intraperitoneal drains. He was maintained exclusively on PN and Intralipid and developed worsening elevations in his hepatic enzymes, serum bilirubin, and prothrombin time (PT) and thrombocytopenia.

TABLE 1 **Comparison of Parenteral Fat Emulsions (10 g Fat/100 mL)**

Product	Intralipid (Baxter Healthcare/ Fresenius Kabi)	Liposyn II (Hospira)	Omegaven (Fresenius AG)
Oil source, g			
Soybean	10	5	0
Safflower	0	5	0
Fish	0	0	10
Fat composition, %			
Linoleic	50	65	0.1–0.7
α-Linolenic	9	4	<0.2
EPA	0	0	1.28–2.82
DHA	0	0	1.44–3.09
Oleic	26	17.7	0.6–1.3
Palmitic	10	8.8	0.25–1
Stearic	3.5	3.4	0.05–0.2

EPA indicates eicosapentaenoic acid; DHA: docosahexaenoic acid.

METHODS

In light of their worsening clinical conditions and on the basis of our recent laboratory findings suggesting that fat emulsions comprised of soybean oil (ie, Intralipid) may be contributing to their liver disease, an alternative intravenous fat emulsion was considered.[7] Each infant was given the omega-3–based emulsion Omegaven (Fresenius Kabi AG, Bad Homburg, Germany). Omegaven is not approved for use in the United States. Therefore, informed consent from the children's parents and emergency approval from our institutional review board and the Food and Drug Administration were obtained.

Patient 1 was started on Omegaven at a dose of 0.2 g/kg per d intravenously and advanced by 0.2 g/kg per d increments to a goal dose of 1 g/kg per d over a 14-day period. Patient 2 subsequently started at 0.5 g/kg per d for 2 days and advanced to 1 g/kg per d. Additional nonprotein calories were provided as carbohydrates. No other parenteral form of fat was administered. The same standards of care provided to all patients receiving PN solution were followed.[9]

Patient 1 received PN comprised of 15% dextrose and 2% amino acids (TrophAmine, B. Braun, Irvine, CA) infused over 11 hours daily. He received Omegaven at 1 g/kg per d infused over 11 hours, which provided 355.64 J/kg per day and 2.5 g/kg per d of protein. He also received breast milk at 15 mL/hour for 24 hours via nasoduodenal tube, which provided an additional 121.8 kJ/kg per d. When the goal Omegaven dose was reached, the total energy intake from breast milk, PN, and Omegaven was 478.8 kJ/kg per d and 2.9 g/kg per d of protein, with ~25% of his energy intake via the enteral route. Patient 2 was maintained solely on PN and Omegaven, receiving 441 kJ/kg per d, 3 g/kg per d of protein, 24.5 g/kg per d of carbohydrate, and 1 g/kg per d of fat.

Monitoring included the assessment at frequent intervals of serum electrolytes, complete blood counts, PT and partial thromboplastin time, serum triglycerides, lipid profiles, blood and urine glucose, renal function tests, C-reactive protein (CRP), and liver enzymes including aspartate amino transferase (AST) and amino alanine transferase (ALT).

RESULTS

Both patients tolerated the infusion of Omegaven without incident. Direct bilirubin levels at the initiation of therapy with Omegaven are shown in Figs 1 A and B. Cholestasis, defined as a direct bilirubin level >2 mg/dL, resolved in both infants within 60 days despite their continuing PN requirement. In both cases, the AST and ALT values also normalized. Weekly CRP levels were

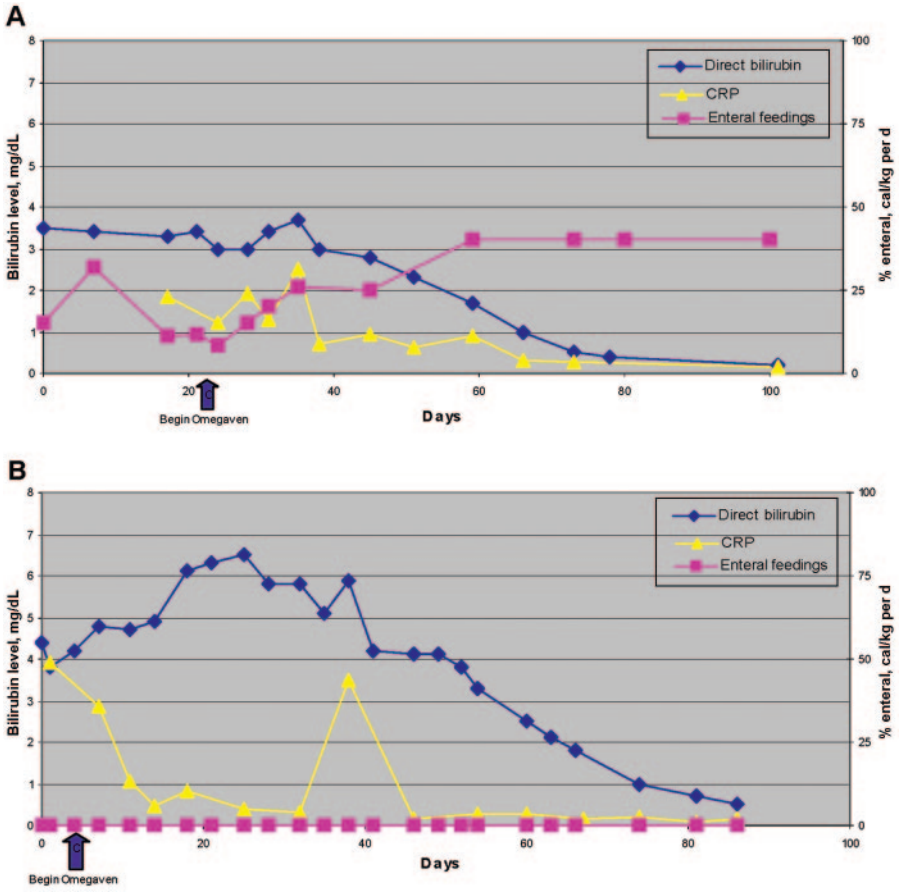

FIGURE 1
Baseline and follow-up values for direct bilirubin and CRP versus enteral intake (1 cal = 4.184 J) from the start of parenteral fish oil therapy. A, patient 1; B, patient 2.

obtained to monitor systemic inflammation. When the Omegaven was started, the CRP levels for both infants were elevated but decreased immediately before normalization of their hepatic enzymes (Fig 1).

After initiation of therapy with Omegaven, patient 1 continued to have intractable feeding difficulty with a high gastrostomy and stool output. He tolerated <50% of his total calories enterally and continued to receive almost 100% of his estimated energy needs intravenously. Despite this, his laboratory studies normalized, and he was removed from the liver/small bowel transplantation list. He is now 15 months old and remains on PN and Omegaven. He has had no evidence of bleeding or essential fatty acid deficiency. His direct bilirubin level remains within the reference range. He has continued to grow and achieve his developmental milestones appropriately.

Patient 2 is now 4 months old and has continued to be exclusively parenterally fed. His ALT, AST, PT, and platelet counts have normalized, and his cholestasis has resolved.

DISCUSSION

PNALD is typically seen with prolonged PN use and is characterized by elevations of serum aminotransferases, bilirubin, and alkaline phosphatase. Histologic alterations include steatosis, steatohepatitis, and cholestasis and, in some cases, progresses to fibrosis and cirrhosis.[10,11] Risk factors for PNALD include young age, premature birth, low birth weight, long-term use of PN, absence of enteral nutrition, prolonged diverting enterostomies, gastrointestinal mucosal disease, bacterial sepsis, and multiple operative procedures.[12] A number of causes of PNALD have been proposed, including nutrient deficiencies (taurine, choline, vitamin E, zinc, and essential fatty acids) and excesses (energy, carbohydrates, amino acids, and fats).[13,14] Treatment options are limited[15]; it is a condition associated with relatively high mortality. Teitlebaum et al[16] noted in their case series of infants with short bowel syndrome that there was a 78% associated risk of death in those infants whose direct bilirubin level remained ≥3 mg/dL for >3 months. Intravenous fat emulsions have been implicated in predisposing patients to PNALD because of their phytosterol content.[6] Phytosterols, such as those contained in soybean oils, are thought to have a deleterious effect on biliary secretion. Accumulation of lipids in the hepatic Kupffer cells and hepatocytes may further impair liver function. Animal studies have shown that intravenous fat emulsions, such as those prepared from fish oil that are high in eicosapentaenoic and docosahexaenoic acids, do not impair bile flow and may actually diminish fat

accumulation in comparison to conventional fat emulsions.[7] In fact, some practitioners advocate the practice of discontinuing lipid infusion totally when patients develop signs of PNALD, a practice that could be detrimental in infants who are already at risk of developing essential fatty acid deficiency because of their limited fat stores.[14] In addition, compensation for the loss of parenteral fat calories with a higher carbohydrate intake may increase the risk of steatosis. Soybean-based lipid emulsions are comprised mainly of omega-6 fatty acids that are relatively proinflammatory. They also contain phytosterols that have been suggested to contribute to liver injury. Other sources of intravenous fat emulsions, such as olive and safflower oil, are not available commercially unless in combination with soybean oils. Fish oil–based emulsions are available in Europe but are only used as a supplement with conventional lipids. These emulsions are not used as monotherapy because of the concern for developing essential fatty acid deficiency, which may explain why PNALD has not been eliminated in those countries in which such products are available. When provided alone, fish oil lipid emulsions provide sufficient arachidonic acid to prevent essential fatty acid deficiency.[17] They also contain eicosapentaenoic acid which has the greatest effect of any fatty acid to reduce triglyceride production in the liver. Taken together, we hypothesized that the administration of fat emulsion rich in fish oils (ie, Omegaven) in place of Intralipid would improve PN cholestasis in infants with short bowel syndrome and PNALD and that there would be sufficient arachidonic acid in fish oil to prevent clinical essential fatty acid deficiency.

Enteral nutrition, when tolerated, helps to protect against development of PNALD.[18,19] Furthermore, once PN-induced cholestasis is established, it is commonly believed that reversal may only occur once the patient is receiving all or a majority of energy intake enterally. Javid et al[20] reported that hyperbilirubinemia associated with PNALD permanently normalized after the start of full enteral nutrition and discontinuation of PN. In their case series, normalization of bilirubin occurred in 11 patients within 4 months of PN withdrawal and the institution of full enteral nutrition. Only 1 patient improved, over a 6-month period, while continuing to receive PN as enteral calories were advanced. In our experience, patient 1's serum bilirubin normalized in 7 weeks while he continued to receive minimal calories enterally (Fig 1A). Similarly, patient 2's biochemical indices normalized in 8 weeks without any enteral feeds (Fig 1B).

Recent evidence has demonstrated that lipids are targeted differently depending on their route of administration.[21] Enteral lipids are absorbed by the enterocyte in the form of a micelle and packaged into chylomicrons for ultimate disposal in the liver. These particles rapidly acquire apolipoproteins from circulating high-density lipoproteins and can subsequently be metabolized by the liver.[22] The emulsified particles of Intralipid mimic the size and structure of chylomicrons but differ in their content.[23] The mechanism of omega-3 fatty acid clearance is unknown but seems to be largely independent of the pathways identified above. Omega-3 fatty acid emulsions have been shown to decrease de novo lipogenesis, prevent or attenuate PN-induced hepatosteatosis in mice, rats, and piglets, and ameliorate the severity of high-fat diet-induced hepatosteatosis in rats.[24,25] Omega-3 fatty acids can interfere with the arachidonic acid pathway of inflammation. They can displace arachidonic acid from tissue fatty acid pools, thereby reducing the substrate for eicosanoid-synthesizing enzymes and subsequent inflammation.[26]

On the basis of experience in animal models, it seems that omega-6 fatty acid emulsions such as Intralipid are not cleared and targeted similarly to enteral chylomicrons.[27] Therefore, these fatty acids accumulate in the liver and thus contribute to a steatotic liver despite the prevention of fatty acid deficiency. Additional fat accumulation results because they may not be as effective in limiting de novo lipogenesis. This steatosis, according to the "2-hit" theory of liver injury, would make the liver susceptible to oxidative injury.[28] On the basis of animal models, we propose that omega-3 fatty acid emulsions derived from fish oil may prevent the development of hepatic injury through inhibition of de novo lipogenesis, the reduction of arachidonic acid–derived inflammatory mediators, prevention of essential fatty acid deficiency through the presence of small amounts of arachidonic acid and ample amounts of eicosapentaenoic acid, and improved clearance of lipids from the serum.

CONCLUSIONS

This brief report describes a new use of a fat emulsion consisting solely of fish oils to reverse severe PN cholestasis in 2 infants, one receiving >50% and a second receiving 100% of his energy intake parenterally. From historical data, neither patient would be expected to improve but instead would develop progressive liver disease. Both infants' cholestasis resolved within 8 weeks. This new therapy may offer a potential solution in the treatment or prevention of hepatotoxicity in PN-dependent patients and may provide an alternative therapy to avoid the morbidity, mortality, and the need for liver/small bowel transplantation in children and adults who are dependent on PN and provide the time necessary for bowel adaptation. A randomized, controlled trial is necessary to determine the efficacy of this new treatment.

REFERENCES

1. Wilmore DW, Dudrick SJ. Growth and development of an infant receiving all nutrients exclusively by vein. *JAMA.* 1968; 203:860–864

2. Howard L, Ament M, Fleming CR, Shike M, Steiger E. Current use and clinical outcome of home parenteral and enteral nutrition therapies in the United States. *Gastroenterology.* 1995; 109:355–365
3. Buchman AL. Complications of long-term home total parenteral nutrition: their identification, prevention and treatment. *Dig Dis Sci.* 2001;46:1–18
4. Teitelbaum DH, Tracy T. Parenteral nutrition-associated cholestasis. *Semin Pediatr Surg.* 2001;10:72–80
5. Wales PW, de Silva N, Kim JH, Lecce L, Sandhu A, Moore AM. Neonatal short bowel syndrome: a cohort study. *J Pediatr Surg.* 2005;40:755–762
6. Clayton PF, Whitfield P, Iyer K. The role of phytosterols in the pathogenesis of liver complications of pediatric parenteral nutrition. *Nutrition.* 1998;14:158–164
7. Alwayn IP, Gura K, Nose V, et al. Omega-3 fatty acid supplementation prevents hepatic steatosis in a murine model of nonalcoholic fatty liver disease. *Pediatr Res.* 2005;57:445–452
8. Kim HB, Lee PW, Garza J, Duggan C, Fauza D, Jaksic T. Serial transverse enteroplasty for short bowel syndrome: a case report. *J Pediatr Surg.* 2003;38:881–885
9. Collier SB, Richardson DS, Gura KM, Duggan C. Parenteral nutrition. In: Hendricks KM, Duggan C, Walker WA, eds. *Manual of Pediatric Nutrition*. 3rd ed. Hamilton, ON, Canada: BC Decker; 2000:242–287
10. Freund HR. Abnormalities of liver function and hepatic damage associated with total parenteral nutrition. *Nutrition.* 1991; 7:1–5; discussion 5–6
11. Mullick FG, Moran CA, Ishak KG. Total parenteral nutrition: a histopathologic analysis of the liver changes in 20 children. *Mod Pathol.* 1994;7:190–194
12. Beath SV, Davies P, Papadopoulou A, et al. Parenteral nutrition-related cholestasis in postsurgical neonates: multivariate analysis of risk factors. *J Pediatr Surg.* 1996;31:604–606
13. Moss RL, Haynes AL, Pastuszyn A, Glew RH. Methionine infusion reproduces liver injury of parenteral nutrition cholestasis. *Pediatr Res.* 1999;45:664–668
14. Colomb V, Jobert-Giraud A, Lacaille F, Goulet O, Fournet JC, Ricour C. Role of lipid emulsions in cholestasis associated with long-term parenteral nutrition in children. *JPEN J Parenter Enteral Nutr.* 2000;24:345–350
15. Teitelbaum DH, Tracy TF, Aouthmany MM, et al. Use of cholecystokinin-octapeptide for the prevention of parenteral nutrition-associated cholestasis. *Pediatrics.* 2005;115:1332–1340
16. Teitelbaum D, Drongowski R, Spivak D. Rapid development of hyperbilirubinemia in infants with the short bowel syndrome as a correlate to mortality: possible indication for early small bowel transplantation. *Transplant Proc.* 1996;28:2699–2700
17. Gura KM, Parsons SK, Bechard LJ, et al. Use of a fish oil-based lipid emulsion to treat essential fatty acid deficiency in a soy allergic patient receiving parenteral nutrition. *Clin Nutr.* 2005; 24:839–847
18. Zamir O, Nussbaum MS, Bhadra S, Subbiah MT, Rafferty JF, Fischer JE. Effect of enteral feeding on hepatic steatosis induced by total parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 1994;18:20–25
19. Meehan JJ, Georgeson KE. Prevention of liver failure in parenteral nutrition-dependent children with short bowel syndrome. *J Pediatr Surg.* 1997;32:473–475
20. Javid PJ, Collier S, Richardson, D, et al. The role of enteral nutrition in the reversal of parenteral nutrition-associated liver dysfunction in infants. *J Pediatr Surg.* 2005;40:1015–1018
21. Javid P, Greene AK, Garza J, et al. The route of lipid administration affects parenteral nutrition-induced hepatic steatosis in a mouse model. *J Pediatr Surg.* 2005;40:1446–1453
22. Hall RI, Grant JP, Ross LH, Coleman RA, Bozovic MG, Quarfordt SH. Pathogenesis of hepatic steatosis in the parenterally fed rat. *J Clin Invest.* 1984;74:1658–1668
23. Ferezou J, Bach AC. Structure and metabolic fate of triacylglycerol- and phospholipid-rich particles of commercial parenteral fat emulsions. *Nutrition.* 1999;15:44–50
24. Araya J, Rodrigo R, Videla LA, et al. Increase in long-chain polyunsaturated fatty acid n-6/n-3 ratio in relation to hepatic steatosis in non-alcoholic fatty liver disease patients. *Clin Sci (Lond).* 2004;106:635–643
25. Van Aerde JE, Duerksen DR, Gramlich L, et al. Intravenous fish oil emulsion attenuates total parenteral nutrition-induced cholestasis in newborn piglets. *Pediatr Res.* 1999;45:202–208
26. Bellenger J, Bellenger S, Clement L, et al. A new hypotensive polyunsaturated fatty acid dietary combination regulates oleic acid accumulation by suppression of stearoyl CoA desaturase 1 gene expression in the SHR model of genetic hypertension. *FASEB J.* 2004;18:773–775
27. Zaman N, Tam YK, Jewell LD, Coutts RT. Effects of intravenous lipid as a source of energy in parenteral nutrition associated hepatic dysfunction and lidocaine elimination: a study using isolated rat liver perfusion. *Biopharm Drug Dispos.* 1997;18: 803–819
28. Day CP, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology.* 1998;114:842–845

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