CASE REPORT

Improvement of parenteral nutrition-associated cholestasis in an adult using fish oil-based parenteral nutrition

Lisa H Moyes,¹ Rizwana Hamid,² Juliet Clutton,¹ Karin A Oien,³
Ruth F McKee,¹ Ewan H Forrest⁴

¹University Department of Surgery, Glasgow Royal Infirmary, Glasgow, UK

²Department of Gastroenterology, Royal Alexandra Hospital, Glasgow, UK

³Department of Pathology, Glasgow Royal Infirmary, Glasgow, UK

⁴Department of Gastroenterology, Glasgow Royal Infirmary, Glasgow, UK

Correspondence to

Lisa H Moyes, University Department of Surgery, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK; lhmoyses@gmail.com

Received 11 October 2011
Accepted 14 January 2012

Abstract

Parenteral nutrition-associated cholestasis (PNAC) is a severe complication of parenteral nutrition. Standard feed preparations contain soybean and olive oil that are rich in ω -6 polyunsaturated fats, and which studies suggest can be hepatotoxic. Preparations containing fish oil, rich in ω -3 polyunsaturated fats, may be hepatoprotective and have been used in the critical care setting as immunotherapy. A case demonstrating dramatic improvement in liver function and overall clinical condition in an adult with PNAC and intestinal failure within 8 weeks of changing to a fish oil-based parenteral feed is reported. As far as is known, this is the first report of an adult patient whose parenteral nutrition-associated liver disease resolved after a parenteral nutrition lipid emulsion was changed to the fish oil-containing emulsion, SMOFlipid.

Background

Parenteral nutrition (PN) is a life-saving treatment for patients with intestinal failure. However, long-term PN may be associated with life-threatening complications. Hepatic complications (parenteral nutrition-associated liver disease (PNALD)) are seen in both adults and children receiving PN, although the patterns and incidence of liver disease differ between these patient groups. In adults receiving PN, abnormal liver function tests are common but the incidence of more advanced liver disease is relatively low, ranging from 7% to 14%.¹ The predominant histological finding in adults with PNALD is steatosis, although signs of intrahepatic cholestasis may develop later and may be persistent (parenteral nutrition-associated cholestasis (PNAC)). Unlike adults, PNAC rather

than steatosis is the commonest finding in neonates and infants. The main treatment of PNAC is to stop PN. Although this action can reverse the disease process, it is not always possible for patients who have a non-existent or non-functioning small bowel. As PNAC worsens, the patient may develop end-stage liver failure.

The aetiology of PNALD may be multifactorial. Recent evidence from animal models, and from case reports in neonates and infants, suggests that one major contributing factor predisposing these patients to PNALD may be the composition of the intravenous lipid emulsions. The lipid emulsions in widespread use are derived from soybean oils, which are rich in ω -6 fatty acids (ω 6FAs) and phytosterols that may contribute to liver injury.² Unlike soybean oil-based lipid emulsions, fish oil-based lipid emulsions contain high concentrations of ω -3 fatty acids (ω 3FAs) and evidence suggests that a fish oil-based emulsion has the potential to reverse PNAC in infants.^{3,4}

Here we present the first documented case report of an adult with intestinal failure and PNAC where treatment with a fish oil-containing emulsion was associated with a significant clinical and biochemical improvement in his PNAC. We believe our report sends an interesting and important message to all clinicians caring for those patients with nutritional problems and liver disease.

Case report

A 43-year-old man presented as an emergency with acute, severe abdominal pain. He had a significant history of vascular

Figure 1 Liver biopsy specimen. Severe acute cholestasis (bile stasis) in the parenchyma. Plugs of brown bile are seen both in hepatocytes, in their canaliculi which are dilated, and in macrophages.

disease, having had mesenteric and iliac artery stenting in the past. Laparotomy showed necrosis of the small bowel from the duodenojejunal flexure to the distal terminal ileum consistent with mesenteric infarction. A small-bowel resection was performed and he was left with a duodenostomy with most of his colon intact but not in continuity. He was discharged home from another hospital after 4 weeks with home PN, tolerating only small volumes of oral fluids. On discharge his weight was 56 kg and body mass index (BMI) 18.3. His PN regimen provided 11.55 g/day nitrogen, 800 kcal/day lipid and 800 kcal/day carbohydrate with appropriate electrolytes, vitamins (Cernevit, Baxter Healthcare, Newbury, UK) and trace elements (Decan, Baxter Healthcare UK). The lipid emulsion was ClinOleic 20% (Baxter Healthcare, UK), a mixture of refined olive oil (80%) and soybean oil (20%).

Six months later he became jaundiced with cholestatic liver blood tests and his weight had fallen to 43 kg (BMI 14.5). Serological tests for viral hepatitis and autoimmune liver disease were negative. Endoscopic retrograde pancreaticocholangiography to rule out biliary obstruction was normal. As other potential causes of liver dysfunction were excluded, a liver biopsy was performed. The parenchyma showed severe acute cholestasis (bile stasis) (figure 1) and minimal steatosis without steatohepatitis. The portal tracts showed marked bile ductular proliferation and inflammation. Copper-associated protein was present in periportal hepatocytes, indicating chronic cholestasis. There was moderate portal fibrosis, again indicating chronic disease. These features were all entirely consistent with PNALD.

Despite a reduction in the lipid content of the PN and a trial of N-acetylcysteine supplementation there was no improvement in his liver function. He developed portal hypertension and bled from a gastric varix, requiring endoscopic haemostasis. It was felt

unwise to attempt to re-anastomose his blood because the remaining blood supply was through tenuous colaterals and could not be improved by angioplasty or stenting. He was referred for consideration of a small-bowel and liver transplant.

Treatment

Four months later, in light of his deteriorating liver function the feed was changed from 500 ml once weekly of ClinOleic 20% to SMOFlipid 20% (Fresenius Kabi Runcorn, UK), a mixture of soybean (30%), medium-chain triglycerides (30%), olive oil (25%) and fish oils (15%). At the same time he developed a stoma stenosis, which was revised allowing him to increase his oral fluids. Eight weeks later the patient returned to the clinic and was clinically less jaundiced with improvement in the liver function tests. There was a gradual normalisation of his serum bilirubin, transaminases and alkaline phosphatase levels (figure 2). His albumin rose from a nadir of 12 g/l to 37 g/l. A repeat upper gastrointestinal endoscopy showed resolution of the gastric varices. Over the course of his PN he had serial fibroscan assessments. These showed a progressive fall in liver stiffness after the introduction of SMOFlipid. Before changing to SMOFlipid the liver stiffness was 16.0 (IQR 3.1). Four months and 1 year after starting SMOFlipid the liver stiffness was 10.3 (IQR 2.6) and 8.8 (IQR 0.7), respectively.

Outcome and follow-up

After lengthy consideration, he underwent a multi-visceral transplant of stomach, liver, duodenum and pancreas in Cambridge. He was discharged 12 weeks postoperatively and, to date, shows no sign of transplant rejection. His nutrition is currently managed by naso-jejunal feeding with a current regimen of 1 litre of Nepro (Abbott Nutrition, Maidenhead, USA) and 2500 ml clear fluid a day.

He continues to receive regular input from general surgery, gastroenterology and hepatology services but remains well with occasional short-term admissions to assess renal function (latest urea: 7.3 mmol/l, creatinine: 126 μ mol/l) and nutritional status. His most recent BMI was recorded as 18.6, a significant improvement from a low of 14.9.

Discussion

PNALD, and specifically PNAC, is a recognised complication of PN. Studies report that 24–65% of patients receiving home PN develop biochemical cholestasis, with 10–30% of these developing end-stage liver disease within 2 years.¹

Aetiology of PNALD

Causative factors in PNALD may be patient or feed related. Patient factors include underlying primary diagnosis, medical comorbidities and drugs used to treat these diseases, the presence of sepsis, intestinal anatomy and continuity and the absence of enteral intake. PNALD has been shown to be related to small

Figure 2 Change in liver blood tests after introduction of SMOFlipid. AST, aspartate aminotransferase.

intestinal length in a number of studies,¹ and our patient had extensive resection of his small bowel. A recent study showed that cholestasis was less likely in patients with colon in continuity.¹ Our patient did not have this continuity, which may have been a contributing factor.

Nutrient deficiencies, particularly vitamin E, zinc and essential amino acids, or toxicities of energy, carbohydrates and fat play an important role in the development of PNAC.⁵ Abnormal fat metabolism and the presence of intravenous phytosterols are thought to be important in the development of cholestasis. Excess phytosterols from parenteral feed accumulate in the liver and affect the function of hepatic transporters, reducing bile acid synthesis and flow, which precipitates the formation of biliary sludge and stones.² Phytosterols also affect neutrophil function, impairing phagocytosis and increasing the risk of sepsis. There is evidence that tumour necrosis factor α plays a role in the pathogenesis of cholestasis, possibly triggered by endotoxins.⁶

Management of PNAC

The management of PNAC remains problematic and suggested treatment includes stopping or limiting total parenteral nutrition with provision of oral nutritional support. Other factors influencing liver function should be treated, such as control of sepsis (eg, line infection), avoidance of exacerbating drugs, consideration of ischaemia and exclusion of choledocholithiasis. An accurate assessment of energy requirements and intake should be performed to avoid over feeding and the fat content of the feed should be reduced. PN solutions have high methionine:cysteine levels, which leads to oxidative stress and cholestasis. One report has

described an improvement in liver blood test abnormalities in three patients receiving N-acetylcysteine-supplemented PN associated with normalised red cell glutathione concentrations.⁷ However, our patient showed no improvement with N-acetylcysteine.

Rationale of fish oil-based lipid emulsions

Intravenous lipids are a useful critical component of PN solutions by providing essential fatty acids and energy-dense calories. However, fat emulsions have also been implicated as a significant cause of PNALD, and reducing lipid content has become standard practice in preventing PNALD, as mentioned above. In multivariate analysis, parenteral intake of a soybean-based lipid emulsion of >1 g/kg body weight a day has been shown to be associated with a relative risk (RR) of chronic cholestasis of 2.3 and a RR of advanced liver disease (fibrosis or cirrhosis on liver biopsy) of 5.5. Historically, intravenous lipid emulsions have comprised primarily soy-based emulsions, which contain significant quantities of phytosterols. This has led to the proposal that accumulation of phytosterols may play an important role in PNALD.² The soy-based lipid emulsions are also rich in $\omega 6$ FAs, with evidence emerging that these may have a major role in PNALD, and their effects may be reversed or ameliorated by substitution with olive oil-based or fish oil-based sources which are rich in $\omega 3$ FAs. The clinical experience with $\omega 3$ FAs in PNALD is limited but the effects have been dramatic in children with PNAC (see table 1).^{3 4 8–10}

Evidence from animal and clinical studies has shown that $\omega 3$ FAs may have two specific beneficial effects.¹⁰ First, they may prevent the development of hepatic injury by inhibition of de novo lipogenesis and stimulation of β -oxidation of fatty acids. This lowers levels of

Table 1 Summary of paediatric use of fish oil to reverse PN induced cholestasis

Reference	Study	Patients (n)	Pathology	Initial feed	New feed	Time to resolution of cholestasis	Outcome
³	Case report	2	Volvulus, perforation	Intralipid 20%; 3 g/kg/day	Omegaven; 1 g/kg/day	8.5 Weeks	Well; remain on PN
⁴	Cohort study	18 (fish oil); 21 (soybean)	NEC, gastroschisis, atresia, volvulus	Intralipid 20%; 1–4 g/kg/day	Omegaven; 1 g/kg/day	9.4 Weeks (fish) vs 44.1 weeks (soybean)	2 vs 7 deaths (fish/ soy); 0 vs 2 transplant
⁸	Case report	1	Volvulus	Lipofundin; 3 g/kg/day	Omegaven; 1.5 g/kg/day	8 Months	Well; remains on PN
⁹	Case report	4	NEC, atresia	Intralipid 20%; 3 g/kg/day	Omegaven; 1 g/kg/day	Three had complete resolution (7–16 weeks); one no resolution from ongoing sepsis	Three well; one death from end-stage liver failure
¹⁰	Retrospective cohort	12	NEC, volvulus, gastroschisis, wwatresia	Intralipid 20%; 2–3 g/kg/day	Omegaven; 1g/kg/day and Intralipid 1 g/kg/day	Nine had complete resolution in 24 weeks (7–27); three no resolution (ongoing sepsis)	Well; removed from transplant list

Omegaven: pure fish oil preparation.

NEC, necrotising enterocolitis; PN, parenteral nutrition.

substrates for triacylglycerol synthesis, thereby reversing hepatic steatosis. Second, they are immunomodulatory as they are precursors for less inflammatory eicosanoids than those derived from arachidonic acid, a ω 6FA. In addition, ω -3 fatty acids may reduce tumour necrosis factor α production.⁶

Conclusion

Our patient is, to our knowledge, the first adult patient to show resolution of PNALD after his PN lipid emulsion was changed to SMOFlipid, containing fish oil. It would appear the improvement in liver function was related to the feed but, clearly, further studies are needed to fully understand and evaluate the efficacy of this treatment. However, in the absence of alternative treatments, changing to fish oil containing PN may be beneficial.

Learning points/take home messages

- Liver disease in patients with PN is often multifactorial.
- Causative patient-related factors may be the underlying primary diagnosis, associated comorbidity, drugs used to manage the condition, the presence of sepsis and intestinal anatomy and continuity.
- PN composition can lead to liver disease, often owing to excess phytosterols.
- Fish oil containing PN may be an alternative to reducing or stopping total parenteral nutrition in PNAC, which is especially important for patients in whom oral nutritional supplementation is not an option.
- The place of fish oil-containing lipids in patients without established liver disease is not yet clear.

Patient consent Obtained.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

References

1. Lloyd DA, Zabron AA, Gabe SM. Chronic biochemical cholestasis in patients receiving home parenteral nutrition: prevalence and predisposing factors. *Aliment Pharmacol Ther* 2008;**27**:552–60.
2. Llop JM, Virgili N, Moreno-Villares JM, *et al*. Phytosterolemia in parenteral nutrition patients: implications for liver disease development. *Nutrition* 2008;**24**:1145–52.
3. Gura KM, Duggan CP, Collier SB, *et al*. Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. *Pediatrics* 2006;**118**:e197–201.
4. Gura KM, Lee S, Valim C, *et al*. Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. *Pediatrics* 2008;**121**:e678–86.
5. Nightingale JM. Hepatobiliary, renal and bone complications of intestinal failure. *Best Pract Res Clin Gastroenterol* 2003;**17**:907–29.
6. Forrest EH, Oien KA, Dickson S, *et al*. Improvement in cholestasis associated with total parenteral nutrition after treatment with an antibody against tumour necrosis factor alpha. *Liver* 2002;**22**:317–20.
7. Mager DR, Marcon M, Wales P, *et al*. Use of N-acetyl cysteine for the treatment of parenteral nutrition-induced liver disease in children receiving home parenteral nutrition. *J Pediatr Gastroenterol Nutr* 2008;**46**:220–3.
8. Ekema G, Falchetti D, Boroni G, *et al*. Reversal of severe parenteral nutrition-associated liver disease in an infant with short bowel syndrome using parenteral fish oil (Omega-3 fatty acids). *J Pediatr Surg* 2008;**43**:1191–5.
9. Cheung HM, Lam HS, Tam YH, *et al*. Rescue treatment of infants with intestinal failure and parenteral nutrition-associated cholestasis (PNAC) using a parenteral fish-oil-based lipid. *Clin Nutr* 2009;**28**:209–12.
10. Diamond IR, Pencharz PB, Wales PW. Omega-3 lipids for intestinal failure associated liver disease. *Semin Pediatr Surg* 2009;**18**:239–45.