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Short Report

Fish oil-based emulsion for the treatment of parenteral nutrition associated liver disease in an adult patient

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SUMMARY

Background & aims: Reversal of parenteral nutrition associated liver disease with fish oil emulsion (FO) has been reported in infants. We report a similar case in an adult patient.
Methods: A 58 year-old female on home parenteral nutrition for a short bowel syndrome due to Crohn's disease, showed a progressive worsening of liver steatosis, and a persistent increase of the plasma liver function tests (LFTs). LFTs, serum alpha-tochopherol, red blood cell membrane fatty acids and liver histology were evaluated before and after an 8 month treatment with FO.
Results: The patient's LFT's improved. There was an increase of the n-3 and a decrease of the n-6 series of fatty acids in erythrocyte membrane. There was an approximate 30% increase in vitamin E status. Before FO, liver histology showed a non-alcoholic steatohepatitis with grade 2 steatosis and inflammation and stage 3 fibrosis. After the treatment, steatosis and inflammation were grade 1, whereas fibrosis remained at stage 3.
Conclusions: Infusion of FO was associated with consistent changes of cell membrane fatty acid structure and with mild improvement of vitamin E status. A potential role of FO in decreasing liver steatosis and inflammation with no change of liver fibrosis might be suggested.

1. Introduction

Hepatic dysfunction has been described in 15–85% of patients on home parenteral nutrition (HPN) for intestinal failure.[1] Chronic cholestasis with associated inflammation and more rapid progression to fibrosis, portal hypertension and end-stage liver disease are the predominant feature in neonates and children, whereas steatosis and steatohepatitis with a slower evolution are the principal lesions in adults.[2] The pathogenesis is mutifactorial, including parenteral nutrition, intestinal failure and systemic related factors. Thus, both the definitions of parenteral nutrition associated liver disease (PNALD) and of intestinal failure associated liver disease (IFALD) are used. HPN hyperalimentation, excess or deficiency of some nutrients, frequent surgical procedures, lack of enteral intake, presence of a short bowel, small bowel bacterial overgrowth, sepsis related to central venous catheters (CVC) or to the underlying diseases, and immaturity of the liver in children, have all been reported to play a role in pathophysiology of liver disease.[1,2] PNALD is a major cause of HPN-failure, which is an indication for a life-saving combined liver-intestinal transplantation.[3]

In the recent years it has been reported the reversal of severe cholestasis in infants when a fish oil-based intravenous lipid emulsion (FO) (Omegaven®, Fresenius Kabi), rich in n-3 polyunsaturated fatty acids (PUFA), was used instead of, or in addition to, a soybean-based lipid emulsion (SO), rich in n-6 PUFA.[4–6] No data has yet been published in adults.

We report the case of an adult patient on HPN for short bowel syndrome (SBS) who developed a PNALD, treated with FO.

2. Case report

A 59 year-old female (height 153 cm, body weight 38–45 Kg) was on HPN since 1990 because of an SBS due to intestinal resections for the treatment of Crohn's disease (residual bowel: jejunum 60 cm and

Abbreviations: HPN, Home parenteral nutrition; PNALD, Parenteral nutrition associated liver disease; IFALD, Intestinal failure associated liver disease; CVC, Central venous catheters; FO, Fish oil-based lipid emulsion; SO, Soybean-based lipid emulsion; OO, Olive oil-based lipid emulsion; PUFA, Polyunsaturated fatty acids; EPA, Eicosapentaenoic acid; DHA, Docosahexaenoic acid; NASH, Non-alcoholic steatohepatitis; LFTs, Liver function tests; SBS, Short bowel syndrome.

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Table 1
Characteristic of the home parenteral nutrition program and outcome of body weight, liver function tests and vitamin E nutritional status during treatment with Omegaven®, in a patient with parenteral nutrition associated liver disease.

		Baseline Jul 2008	Aug 2008	Sept 2008	Oct 2008	Nov 2008	Dec 2008	Jan 2009	Feb 2009
HPN program									
Infusions/week (No. of days)		6	7	7	6	6	6	5	5
Amino acids/infusion (g)		40	40	40	50	50	50	50	50
Glucose/infusion (g)		160	160	160	180	180	180	180	180
Lipids/infusion (g, type)		40, olive	40, olive	40, olive	60, olive	60, olive	60, olive	60, olive	60, olive
Omegaven/infusion (g)		7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Total energy/BEE (weekly)		1.03	1.20	1.20	1.29	1.29	1.29	1.07	1.07
Oral diet (Kcal/day)		1350				1600		1850	1600
Nutritional status									
Body weight (Kg)		40.0	40.0	38.9	40.0	41.9	42	43.7	43.8
Body Mass Index (Kg/m2)		17.1	17.1	17.0	17.1	17.9	18.0	18.7	18.7
Biochemistry	N.V.								
Total bilirubin (mg/dL)	0.20–1.10	0.69	0.40	0.32	0.6	0.58	0.6	0.51	0.44
Coniugated bilirubin (mg/dL)	<0.30	0.25	0.16	0.15	0.25	0.24	0.23	0.21	0.16
AST (U/L)	<32	41	33	43	44	28	32	29	24
ALT (U/L)	<31	25	22	38	33	21	20	22	13
γ-GT (U/L)	<36	129	89	105	100	81	63	65	38
Prothrombin time (%)	>70	77	80	86	81	85	88	87	90
Platelets (×103/mL)	150–400	118	125	108	102	94	90	95	144
C-Reactive Protein (mg/dL)	<0.8	0.10	0.04	0.17	0.16	0.24	0.18	0.18	0.97
Albumin (g/L)	>35	37	42	43	40	38	36	41	39
α-tocopherol (mmol/L)	11.6–46.4	20.2–21.5		29.1	25.5	20.7	32.9		34.7
α-toc/(Col + Trigl) (mmol/mmol)	>4	3.6–4.4		5.7	4.6	3.7	5.8		5.5

Baseline, July 2008: data at starting Omegaven infusion; α-tocopherol represent the range observed during the previous 3 years. Oral diet: no alcohol consumption. HPN, home parenteral nutrition, BEE, basal energy expenditure calculated according to Harris-Benedict formula, AST, aspartate aminotransaminase; ALT alanine aminotransaminase; γ-GT, gamma-glutamyl transpeptidase.

left colon). Since 2004, a mild Crohn's disease activity in the residual colon was treated with 2 mg/Kg/body weight of azathioprine.

In 1998, liver ultrasonography showed for the first time a mild diffuse steatosis. Liver function tests (LFTs: total and direct bilirubin; aspartate aminotransferase, AST; alanine aminotransferase, ALT; γ-glutamyl transpeptidase, γ-GT; alkaline phosphatase, AP) were normal until 2003. In 2003, after a gastrointestinal surgical procedure (strictureplasty and cholecystectomy) complicated in the post-operative period by a CVC-related sepsis, the plasma concentrations of AST and γ-GT increased above the upper limits of the normal range. AP increased too, but it was considered related to the cholecystectomy. Liver ultrasonography showed a steatosis of moderate degree in 2004 and of severe degree in 2005. The common causes of liver disease were excluded, such as alcohol consumption, viral hepatitis and drug toxicity. The frequency of the administration of the SO (Intralipid® 20%, Fresenius Kabi, 50 g per infusion) in the PN formulation was decreased from 6 to 3 per week. Then, it was replaced with an olive oil-based lipid emulsion (OO) (Clinoleic® 20%, Baxter SpA, 50 g per infusion), with a lower content of n-6 PUFAs. No improvement of liver steatosis and of LFTs occurred. Platelet count which ranged from 160–215.000/mL before 2004, decreased to 115–130.000/mL. In June 2008, a liver biopsy was performed, and in July 2008, the infusion of an FO (Omegaven® 10%) in addition to the PN formulation containing OO, was started at the dosage of 75 ml (7.5 g of lipids)/day of infusion. The all-in-one parenteral bags were integrated with vitamins (Cernevit®, Baxter) 1 vial for 4–5 days/week and trace elements (Decaven®, Baxter) 1 vial for 2 days/week. FO was given for 8 consecutive months.

Liver histology on liver samples taken by transparietal biopsy, were performed before and at the end of the treatment period and was assessed according to Brunt classification for non-alcoholic steatohepatitis (NASH).[7] Red blood cell membrane fatty acids were assessed one week, 1 and 2 months after starting FO. Clinical outcome and biochemistry were assessed monthly.

Body mass index (BMI) was calculated with Quetelet's formula [wt (kg)/ht^2 (m)] and basal energy expenditure with the Harris–Benedict formula.[8] The total energy supplied by the HPN infusion was estimated weekly as a percentage of the basal energy expenditure (BEE):(total Kcal provided by HPN × the number of infusions/wk)/(BEE × 7). Plasma α-tocopherol was analysed by reversed-phase HPLC and erythrocyte membrane fatty acid analysis was performed by gas chromatography, as previously described.[8] Vitamin E nutritional status was evaluated by the plasma ratio α-tochopherol/(cholesterol + triglycerides).

Data on the patient's outcome are reported in Table 1. No HPN-related complication, no clinical flare up of the underlying disease and no adverse event related to Omegaven® occurred. HPN infusions were 6–7 per week for the first 6 months, then 5 per week for the last two months. The total energy given by HPN per

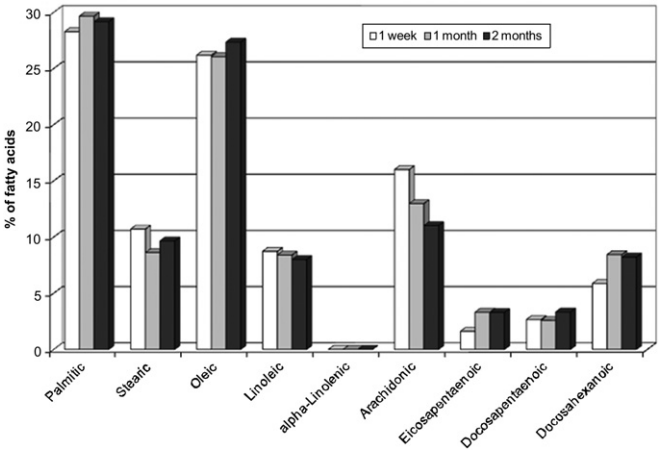

Fig. 1. Erythrocyte membrane fatty acids after 1 week, 1 month and 2 months of treatment with parenteral fish oil emulsion.

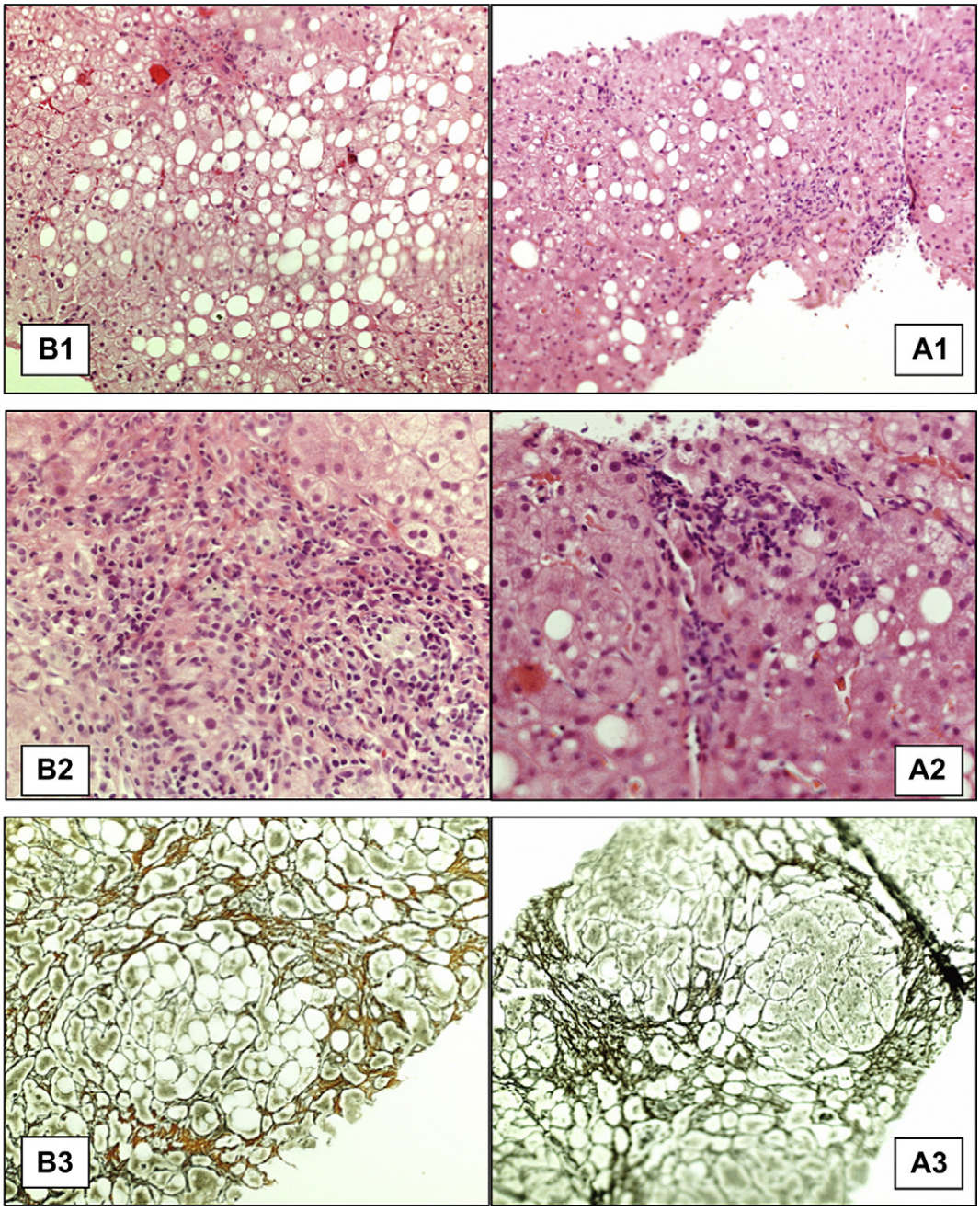

Fig. 2. Liver biopsy histology, before (B) and after (A) 8 month of treatment with parenteral fish oil emulsion. B1) Diffuse steatosis, predominantly macrovesicular in 40% of hepatocytes in this field (Hemotoxylin and eosin, ×100). B2) Moderate mixed inflammation, made of lymphocytes and neutrophils located in the lobule. In the upper right corner the hepatocytes are enlarged, with clear cytoplasm and ballooning (Hemotoxylin and eosin, ×200). B3) Perisinusoidal fibrosis, which is the characteristic fibrosis in steatohepatitis, appears golden brown in reticulin stain (×100). A1) Diffuse steatosis, predominantly macrovesicular in 15% of hepatocytes in this field (Hemotoxylin and eosin, ×100). A2) Mild mixed inflammation, made of lymphocytes, plasmacells and neutrophils together with few ballooned hepatocytes (Hemotoxylin and eosin, ×200). A3) The mild nodularity is due to fibrosis with septa in reticulin stain (×100).

week was about 1–1.3 times the BEE for 6 out of the 8 months. The amount of OO per day of infusion was about 1 g/Kg body weight for the first 3 months, then it was increased to about 1.5 g/Kg. Glucose was infused at a rate of about 5 mg/Kg/min (160 g/infusion during the first 3 months, then 180 g/infusion). A mild spontaneous increase of oral intake was observed. Body weight was stable during the first 3 months, then a 10% increase was observed. The HPN infusion was reduced to 5 days/week during the last 2 months. LFTs progressively improved. Platelet count did not change. The indices of Vitamin E nutritional status showed an approximate 30% increase with respect to 3 years before the FO supplementation.

Erythrocyte membrane fatty acid pattern showed an increase of the n-3 PUFA, n-3 eicosapentaenoic acid (EPA, from 1.6% to 3.3%) and the n-3 docosahexaenoic acid (DHA, from 5.8% to 8.4%), and a decrease of the n-6 arachidonic acid (from 16.0% to 12.9%), between day 7 and day 30 after starting Omegaven®. No further changes were observed at day 60. (Fig. 1)

Before starting FO, liver histology showed a NASH with grade 2 steatosis and inflammation and stage 3 fibrosis. After 8 months of treatment, the degree of steatosis and inflammation decreased to grade 1, whereas fibrosis remained at stage 3. (Fig. 2)

3. Discussion

Data from this case report add information to those from previously published studies on the use of Omegaven® in children with PN-associated cholestasis, by reporting the variation of the cell membrane fatty acid pattern and of the vitamin E nutritional status and describing the liver histology after a long term infusion of Omegaven® in an adult patient with PNALD without cholestasis.

According to the Omegaven® composition, as reported by the manufacturer,[4] giving 7.5 g/day of Omegaven® we administered 0.97–2.1 g of EPA and 1.05–2.32 g of DHA for each day of infusion. This dosage, given for 6–7 day/week, was associated with an increase of the n-3 PUFA and a decrease of n-6 PUFA in the fatty acid pattern of the erythrocyte membrane, which was stable after 30 days of administration.

During the period of treatment the indices of vitamin E nutritional status showed an approximate 30% increase in comparison to the previous period. This could have been due both to the vitamin E content of Omegaven® and to the increased frequency of infusion of lipid emulsion during the study period. Omegaven® contains 200 mg/L of α-tocopherol. This means that receiving 75 ml of Omegaven®, our patient was supplemented with 15 IU of α-tocopherol for each infusion day. We cannot say if this supplementation played some role in the observed decrease of steatohepatitis. Recently it has been demonstrated that oral supplementation of α-tocopherol, 800 IU daily, is effective in improving steatosis and lobular inflammation, but not fibrosis, in adults with NASH.[9]

Our patient had a NASH of severe degree, which followed the systemic inflammatory reaction associated with an abdominal surgical procedure complicated by a CVC-related sepsis in the post-operative period. This event could have been the secondary hit which triggered the evolution of the pre-existent steatosis for which the first hit could have been a long term HPN with a nutritional formula containing more than 1 g/Kg/day of SO (1.20 g/Kg), rich in n-6 PUFA and phytosterols.[1,2,10] The decrease of the administration of SO from 6 to 3 times a week, its replacement with an OO, with a lower content of n-6 PUFA and phytosterols than SO,[11] were not followed by improvement of LFTs and liver ultrasonography features. The decision to perform a liver biopsy was taken because of the presence of severe liver steatosis associated with a ratio of AST to ALT grater than one and a decease of platelet count, which could suggest the presence of liver fibrosis.[3,12]

After the FO infusion period there was a remarkable improvement of steatosis and steatohepatitis grading but not of liver fibrosis staging, which remained stable. Improvement in steatosis and inflammation occurred notwithstanding the treatment with FO was associated with an increase in energy load by HPN, namely total LE by OO, and with an increase in patient body weight. This finding would suggest a potential role of FO in decreasing liver steatosis and inflammation in adult patients with PNALD, and supports the need for studies aimed at proving it. The lack of improvement of fibrosis is consistent with a recent report in 2 infants on parenteral nutrition for intestinal failure who developed liver cholestasis and who were treated for 9–11 months with Omegaven®.[6] Liver histology showed a reduction of inflammation and cholestasis, whereas portal fibrosis remained unchanged or increased. The last observation was considered in agreement with studies in cell culture models and in animals on parenteral nutrition, which would suggests that n-3 PUFA may accelerate fibrogenesis.[6]

In conclusion, this case report on an adult patient with PNALD, characterised by a NASH of moderate-severe degree, indicates that FO at a dosage of about 0.2 g/Kg/day per 5–7 days/week, may have been associated with an increase of n-3 PUFA and a decrease of n-6 PUFA in cell membranes, with a mild improvement of the vitamin E nutritional status and with a decrease of liver steatosis and inflammation without change of fibrosis. Further research into the efficacy and safety of FO for the treatment of PNALD in adult patients is required.

Statement of authorship

All the authors have substantially contributed to the study and have approved the conceptions and drafting of the manuscript.

Conflict of interest

None.

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