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Impact of intravenous lipid emulsions on liver function tests: Contribution of parenteral fish oil

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ABSTRACT

Objective: Lipids in parenteral nutrition (PN) have been linked to liver damage. The aim of this study is to 1) determine whether the incidence of alterations in liver function tests (LFTs) changes over time among hospitalized adult patients receiving PN; 2) evaluate whether the alteration in LFTs varies with the pattern of lipid administration; and 3) study the relationship between LFT alterations and fish oil (FO) emulsions.

Methods: Patients treated with PN over 4 y were included. Demographic, clinical, nutritional, and analytical variables were collected. LFTs (γ-glutamyl transferase [GGT], alkaline phosphatase [AP], alanine aminotransferase [ALT], and total bilirubin [BIL]) were collected during PN treatment. Differences in LFTs were studied with *t* tests for paired samples. To match the type of lipid with each of the LFTs studied, four multivariate statistical models were performed. Significance was reported with the 95% confidence interval (CI) at $p < 0.05$ (two-tailed).

Results: We studied 1555 patients. LFT alterations at baseline were high and increased during PN treatment except ALT. GGT and AP showed significant increases from baseline values. In the multivariate study, daily dose of FO ($g \cdot kg^{-1} \cdot d^{-1}$) was associated with a significant decrease in GGT (B = −11.189; 95% CI, −19.799 to −2.578) and in AP (B = −5.250; 95% CI, −10.263 to −0.237). Daily dose of vegetal oil (g/kg) had a tendency for a significant increase in GGT (B = 0.441; 95% CI, −0.107 to 1.039) and AP (B = 0.312; 95% CI, −0.023 to 0.648).

Conclusions: GGT and AP increased throughout the clinical course of PN administration. These alterations had a multifactorial component. The administration of FO was associated with a significant decrease in the levels of GGT and AP.

Introduction

In patients on parenteral nutrition (PN), alteration of liver function tests (LFTs) and subsequent liver complications are frequent and have a multifactorial component. After some days of PN therapy, LFTs begin to rise and liver complications occur in a variable percentage of patients, ranging from 30% to 100% [1–3].

One of the most important risk factors described is the amount and type of lipids administered [4,5]. Thus, hepatic steatosis may occur with high amounts of intravenous lipid emulsions (ILE) [6–8]. The source of ILE may increase the risk for developing abnormal liver function [6–10] and, in recent years, the role of parenteral phytosterols in the onset of liver disorders has been shown, mainly in the pediatric population and in patients on long-term PN [8,11]. Therefore, ILE should be used with caution in patients who are septic [8,12,13] and those with conditions that impair hepatic clearance of fatty acids [8,13].

The use of fish oil (FO) ILEs and their influence on liver disorders has become an important area of study in pediatric patients [14]. Studies in hospitalized adult patients that show improved LFTs with FO administration are scarce [15]. Table 1 summarizes studies about lipid emulsions and liver function. In 2003, in a randomized trial, we studied the use of olive oil (OO) emulsions alone or with FO in a group of high-risk surgical patients undergoing elective, major abdominal surgery

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Table 1
Summary of data on lipid emulsions and liver function

Reference	Study
Home parenteral nutrition: Children	
Gura et al. (Pediatrics 2006)[16]	Case series of two patients. Discontinuation of SO and initiation of FO 0.2 $g \cdot kg^{-1} \cdot d^{-1}$ advanced by 0.2 $g \cdot kg^{-1} \cdot d^{-1}$ to a goal of 1 $g \cdot kg^{-1} \cdot d^{-1}$. Biochemical markers of liver disease improved. Patient 1: removed from liver transplant list. Patient 2: complete resolution of PNALD while on PN.
Gura KM et al. (Pediatrics 2008)[17]	In an open-labeled prospective study with historical cohort. Discontinuation of SO and initiation of FO at 0.5 $g \cdot kg^{-1} \cdot d^{-1}$ advanced to a goal of 1 $g \cdot kg^{-1} \cdot d^{-1}$ over 12 h vs SO 1–4 $g \cdot kg^{-1} \cdot d^{-1}$ over 24 h. Reversal of PNALD of 9.4 wk in the FO group vs. 44 wk in the control group ($P = 0.002$).
Puder M et al. (Ann Surg 2009)[18]	Open-labeled prospective study with historical cohort. Discontinuation of SO and initiation of FO at 0.5 $g \cdot kg^{-1} \cdot d^{-1}$ advanced to a goal of 1 $g \cdot kg^{-1} \cdot d^{-1}$ over 12 h vs SO 1–4 $g \cdot kg^{-1} \cdot d^{-1}$ over 24 h. Three deaths and one liver transplant reported in the FO group compared with 12 deaths and six liver transplants in the control group.
Diamond IR et al. (J Pediatr Gastroenterol Nutr 2009)[19]	Retrospective cohort study. Combination of SO and FO with goal ω-6: ω-3 of 1:1-1:2. PNALD reverses in nine of 12 infants treated with a combination of a SO and FO (four patients had complete reversal of PNALD while receiving a combinations of SO and FO; five patients did not have reversal of disease until after SO discontinued).
Goulet O et al. (JPEN 2010)[20]	Prospective, randomized, double-blind study. SMOF vs. SO in patients receiving PN. Biochemical markers of liver disease lower in SMOF group compared with SO group.
Soden JS et al. (J Pediatr 2010)[21]	Case series of two infants with intestinal failure. Hepatic fibrosis persisted after FO treatment, despite improvements of cholestasis.
Angsten G et al. (JPEN 2012)[22]	Case series of 20 neonates with short bowel disease. Treated with FO in combinations with SO/OO. Direct bilirubin normalized in all 14 survivors, with median time for reversal of cholestasis of 2.9 mo. AST, ALT, and GGT were slightly elevated 3 mo after initiating treatment but were all later normalized in the survivors.
Skouroliakou M et al. (Nutr Clin Pract 2012)[23]	Prospective, observational study, two groups of preterm neonates. SMOF vs SO. Duration of parenteral fat administration rather than the type of lipid was independently associated with the presence of cholestasis.
Muhammed R et al. (J Pediatr Gastroenterol Nutr 2012)[24]	Retrospective cohort study. SMOF vs SO. PNALD resolved in five of eight patients in the SMOF group and two of nine patients in the SO.
Seida JC et al. (JPEN 2013)[25]	Revision of ω-3 FA emulsions used in children with intestinal failure and other conditions, concluded that the best available evidence at present only supports the use of ω-3 FA supplementation to improve biochemical outcomes of intestinal failure-associated liver disease in young children dependent on PN.
Home parenteral nutrition: Adults	
Jurewitsch B et al. (JPEN 2011)[26]	One patient. Changed from SO to blend of FO 0.25 $g \cdot kg^{-1} \cdot d^{-1}$ with SO 0.25 $g \cdot kg^{-1} \cdot d^{-1}$. Over subsequent 4 wk, the mixed-lipid regimen curtailed the increase in liver enzymes but did not reduce BIL levels. It was subsequently decided to discontinue SO therapy and to give only FO at 0.25 $g \cdot kg^{-1} \cdot d^{-1}$. As a result, total BIL levels rapidly fell.
Xu Z et al. (Clin Nutr 2012)[27]	Open-labeled study in 15 adult patients with short bowel syndrome who developed cholestasis while receiving SO. SO partially replaced by FO $\leq$ 10 g/d ($\sim$0.15–0.2 $g \cdot kg^{-1} \cdot d^{-1}$). BIL normalized after 4 wk of treatment. Differences in ALT values statistically significant. Nevertheless, even when GGT values also decreased, statistically significant differences were not found.
Venecourt-Jackson E et al. (Nutrition 2013)[28]	One patient. Change from SO to a total FO. BIL decreased over ensuing 8 wk, with normalization of transaminases by 10 wk.
Burns DL et al. (JPEN 2013)[29]	One patient. 5 wk of FO (45 g/d 5 d/wk). BIL decreased from 12.4 to 4.2 mg/dL. AP initially increased but subsequently declined to a stable pretreatment value and transaminases slightly decreased initially and then remained stable.
Short-term parenteral nutrition	
Piper SN et al. (Eur J Anaesthesiol 2009)[30]	Prospective, randomized, double-blinded trial, 44 postoperative patients. SMOF vs. SO/OO Significantly lower ALT values were observed at day 2 and day 5 in the SMOFlipid group.
Zhu X et al. (JPEN 2013)[31]	Prospective, randomized 98 adults undergoing liver transplantation. FO vs. LCT:MCT. Total daily lipid intake was 1 g/kg. ALT improved significantly after 9 d of FO supplementation (0.2 $g \cdot kg^{-1} \cdot d^{-1}$) compared with LCT:MCT.
Pawlik D eta al. (JPEN 2013)[32]	Randomized a group of low-weight new-born infants. Intravenous SO/OO plus FO or SO/OO alone. After 22 d, 3 infants in FO group developed cholestasis compared with 20 infants in standard group.

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate transaminase; BIL, total bilirubin; FO, fish oil; GGT, γ-glutamyl transferase; LCT, light-chain triglycerides; MCT, medium-chain triglycerides; OO, olive oil; PN, parenteral nutrition; PNALD, parenteral nutrition associated liver disease; SO, soy oil