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Role of Lipid Emulsions in Cholestasis Associated with Long-Term Parenteral Nutrition in Children

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ABSTRACT. *Background:* In children who depend on long-term parenteral nutrition (PN), liver disease is a major complication that may lead to end-stage liver failure requiring liver transplantation. *Methods:* This retrospective study investigated the influence of lipid emulsions on cholestasis onset in children receiving long-term total parenteral nutrition (TPN) with lipids. Ten children who presented with a total of 23 episodes of cholestasis, associated in 13 cases with thrombocytopenia, were studied. *Results:* Changes in the lipid delivery preceded these complications in more than half the cases. The temporary decrease in lipid administration led to normalization of bilirubin in 17 episodes. *Conclusions:* These data suggest that lipid supply is one of the risk factors for PN-associated cholestasis. The link between cholestasis and the reticuloendothelial system overload needs to be better understood. Prevention of cholestasis might include the decrease in the lipid load. When cholestasis occurs, lipid supply should be temporarily stopped, especially in the case of associated thrombocytopenia. (*Journal of Parenteral and Enteral Nutrition* **24**:345–350, 2000)

Parenteral nutrition (PN) is a standardized treatment in many instances of digestive dysfunction, such as short bowel syndrome or intractable diarrhea of infancy. Major advances in the area of PN over the last 20 years have led to the decrease in incidence of PN complications. However, one of the most threatening remains PN-associated liver disease and especially cholestasis, which can lead to cirrhosis and liver failure. Several risk factors for cholestasis have been identified in previous studies: some of them are direct consequences of the underlying digestive disease such as bacterial overgrowth, disruption of bile acid enterohepatic circulation, or absence of oral feeding to stimulate choleresis.[1–4] Risk factors directly related to the composition of the PN admixtures are less defined. The deleterious role of fat emulsions on biliary secretion has been suggested.[5,6] If hematologic disorders, such as fat overload with macrophage activation have been related to IV lipid emulsions,[7,8] no clear relationship has been demonstrated to date between these complications and PN-associated cholestasis. The present study attempted to establish such a relationship and reports the cases of 10 children receiving PN in whom cholestasis subsided in 17 episodes after suspension of lipid administration. Preventive measures and treatment are proposed.

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MATERIALS AND METHODS

Cholestasis episodes that occurred in 183 children receiving long-term PN included in a home PN program between 1989 and 1999 were analyzed retrospectively. Criteria for inclusion in the current study were a change in the mode or rate of lipid delivery before the cholestasis episode or suspension or reduction of lipid administration as the only change in nutrition and treatment at the time of the cholestasis onset. Criteria for exclusion were congenital liver disease, end stage-liver disease, high incidence of catheter infection, biliary lithiasis, documented or suspected viral infection or drug toxicity, documented or suspected sepsis and antibiotic treatment, intestinal surgery or obstruction during the month preceding each cholestasis episode. Sixteen children met the criteria for inclusion, but six were excluded because of frequent infections (6/6), surgical procedure (2/6) or end-stage liver disease (6/6) at the time of the cholestasis onset. Ten children, six boys and four girls, aged 6 months to 14 years at the time of cholestasis episodes were included in this retrospective study (Table I). One or several episodes of cholestasis per child occurred after 3 to 176 months of PN (Table I). All patients had depended on PN from birth. All had normal liver examination and blood tests at the time of beginning PN. Digestive diseases were short bowel syndrome (7 cases) and intractable diarrhea of infancy (3 cases). Cyclic PN was delivered over 12 to 16 hours nightly. The mean nonprotein-energy supply was 60 kcal/kg per day, range 30 to 120, (279 kJ/kg per day), with a 15% to 30% lipid-to-total nonprotein-energy ratio. The mean energy/nitrogen ratio was 200 kcal/g nitrogen (range, 110–350). Energy, nitrogen, and min-

TABLE I
Description of the 23 cholestasis episodes (1 to 23) in 10 patients (a to j)

Patients and cholestasis episodes	Digestive disease	PN duration (months)	Lipids at the time of episode	Higher plasma bilirubin (μmol/L)	Lower platelet count (per mm^3) ± macrophage activation (MA)	Initial change in lipid delivery	Type of lipids if reintroduced
1 a	SBS	173	LCT	114	115,000	Stop	LCT
2 a		176	LCT	236	50,000	Stop	No lipids
3 b	SBS	57	MCT-LCT	173	200,000	Stop	MCT-LCT
4 b		73	MCT-LCT	172	160,000	Stop	MCT-LCT
5 b		90	MCT-LCT	330	100,000	Decrease	
6 b		137	MCT-LCT	78	210,000	Stop	MCT-LCT
7 c	SBS	30	LCT	50	120,000	Switch	
8 c		34	MCT-LCT	170	30,000	Stop	MCT-LCT
9 d	SBS	23	LCT	214	70,000	Stop	MCT-LCT
10 e	SBS	16	MCT-LCT	121	40,000 (MA)	Stop	MCT-LCT
11 e		45	MCT-LCT	82	180,000	Stop	MCT-LCT
12 f	SBS	4	LCT	195	190,000	Stop	No lipids
13 g	SBS	3	LCT	182	60,000	Stop	MCT-LCT
14 h	IDI	62	LCT	106	200,000	Stop	LCT
15 h		67	LCT	72	160,000	Stop	MCT-LCT
16 h		76	MCT-LCT	50	60,000	Stop	MCT-LCT
17 i	IDI	42	LCT	100	440,000	Stop	LCT
18 i		47	LCT	77	430,000	Stop	LCT
19 i		72	LCT	134	240,000	Switch	
20 i		105	LCT	229	75,000	Stop	LCT
21 i		117	LCT	289	75,000 (MA)	Stop	MCT-LCT
22 j	IDI	53	LCT	260	20,000	Stop	MCT-LCT
23 j		82	MCT-LCT	50	30,000 (MA)	Stop	MCT-LCT

SBS, short bowel syndrome; IDI, intractable diarrhea of infancy; LCT, long-chain triglycerides; MCT, medium-chain triglycerides; Decrease, decrease in lipid daily load (without stopping lipid delivery); Switch, from pure LCT lipid emulsion to mixed MCT)-LCT emulsion (without stopping lipid delivery); No lipids, definitive removal of lipid emulsions.

eral supplies were regularly adjusted to the age, weight, and height in order to fulfil the specific needs of normal growth.

Fat emulsions used were either Intralipid 20% (Pharmacia, Saint-Quentin en Yvelines, France), including 100% long-chain triglycerides (LCT), or Medialipid 20% (Braun Medical, Boulogne, France) including 50% LCT plus 50% medium-chain triglycerides (MCT). Vitamin E was systematically added to lipid emulsion (0.6 mg/g LCT).

Prevention of cholestasis was performed as usually recommended: maintenance of minimal oral feeding, nonabsorbable antibiotics in cases of proven bacterial overgrowth, cyclization of PN and, in some children, treatment with ursodeoxycholic acid.[9] Associated treatments varied with patients and time, including especially ranitidine, cholestyramine, racecadotil, antibiotics, and fungicidals.

Cholestasis

When cholestasis occurred (defined by an increase in plasma bilirubin over 30 μmol/L), biliary obstruction was ruled out by ultrasonography and viral infection by appropriate testing. When liver biopsies were performed, the specimens were routinely processed and stained with hematoxylin-eosin, Masson trichrome, and Perl's and Oil Red O. The following items were recorded: fibrosis, cholestasis, steatosis, presence of macrophages in portal spaces, and hemophagocytosis. Cholestasis, fibrosis, and steatosis were quantified, using a scale that is given in the Results section (Table II).

Hematologic Disorders

Hematologic disorders were defined either as isolated thrombocytopenia (platelets < 150,000/mm^3) or as macrophage activation syndrome as previously described[8]: rapid onset of fever unresponsive to acetaminophen and antibiotics, hepatomegaly, splenomegaly, sometimes jaundice, and bleeding. Biologic patterns include thrombocytopenia, coagulation disorders, sometimes hyponatremia and hypertriglyceridemia. When bone marrow aspiration was performed, it was routinely stained, and in addition stained with May-Grunwald-Giemsa and Sudan Black, and thus examined for the presence of blue histiocytes and the presence of Sudan Black-positive fat vacuoles.

RESULTS

Liver Disease

The 10 patients experienced 23 episodes of cholestasis: plasma bilirubin above 30 μmol/L in all cases, range, 50 to 330 μmol/L (Table I). The delay between initiation of PN and a cholestasis episode was 5.7 ± 3.8 years. One child (child i) presented with five episodes and another (child b) with four episodes. A total of 9 liver biopsies were performed contemporary to cholestasis episodes in 7 of the 10 children (2 children underwent 2 biopsies). No biopsy was normal (Table II). All disclosed fibrosis of various degrees (no cirrhosis). Mild (5 cases) to severe (4 cases) cholestasis was present in all biopsies. Portal macrophages were found in 7 liver biopsies, while hemophagocytosis was found in only one biopsy.

TABLE II
Pathologic lesions observed in nine liver specimens, contemporary to cholestasis episodes (no. 5, 6, 7, 12, 13, 16, 21, 22, 23) in seven patients (b, c, f, g, h, i, j)

Patients and cholestasis episodes	Digestive disease	PN duration (months)	Higher plasma bilirubin (μmol/L)	Cholestasis (C0 to C4)	Fibrosis (F0 to F5)	Steatosis (S0 to S4)
5 b	SBS	113	330	C4	F2	S0
6 b		137	78	C1	F2	S1
7 c	SBS	30	50	C1	F3	S0
12 f	SBS	4	195	C3	F2	S2
13 g	SBS	3	182	C3	F2	S3
16 h	IDI	76	50	C1	F2	S1
21 i	IDI	117	289	C3	F1	S0
22 j	IDI	53	260	C2	F3	S0
23 j		82	50	C2	F4	S1

SBS, short bowel syndrome; IDI, intractable diarrhea of infancy.
Scale for grading cholestasis: C0, no cholestasis; C1, isolated bile-containing hepatocytes; C2, spreading bile-containing hepatocytes; C3, canalicular bile thrombi; C4, proliferation of bile ducts.
Scale for grading fibrosis: F0, no fibrosis; F1, portal fibrosis; F2, septal fibrosis involving <50% portal spaces; F3, septal fibrosis involving >50% portal spaces; F4, ring fibrosis; F5, cirrhosis.
Scale for grading steatosis: S0, no steatosis; S1, fat vacuoles found in <33% hepatocytes; S2, fat vacuoles found in <33% to 66% hepatocytes; S3, fat vacuoles found in >66% hepatocytes.

Changes in Lipid Supply Before the Onset of Cholestasis

At the time of onset of cholestasis, children received 24% ± 7% of their daily energy supply as fat; the frequency of delivery being 5.6 ± 1.2 days a week. The lipid infusion rate was 156 ± 48 mg/kg per hour. Lipids were 100% LCT in 14 episodes, and mixed MCT-LCT emulsions in the 9 others (Table I). Fifteen episodes of cholestasis occurred after changes in the mode of lipid administration, which in all cases was made in order to increase the energy supply because of slowing down of the weight gain. These changes included an increase in the number of lipid perfusions per week (with or without changing the total energy and lipid daily supply); an increase in the daily lipid load from 0.94 ± 0.89 g/kg per day to 2.2 ± 0.41 g/kg per day (with or without an increase in the weekly number of lipid infusions or increase in the rate of lipid delivery) in 11 episodes; a 10% to 25% increase in the total daily nonprotein energy supply, including an increase in the lipid supply and rate of delivery.

Hematologic Disorders

Hematologic disorders occurred in 9 of 10 patients, in conjunction with 13 episodes of cholestasis (Table I). In 6 episodes the platelet count had slowly decreased 7.5 ± 7.2 months before the onset of cholestasis. In the other 7, the decrease in platelet count was parallel to the increase in bilirubin level. Bone marrow aspiration was performed in 4 cases. Three disclosed an excess in blue histiocytes that were laden with Sudan Black-stained fat vacuoles, these findings being considered suggestive of lipid-induced toxicity.

Course of Plasma Bilirubin and Platelet Count After Stopping Lipid Administration

Changes in lipid delivery are summarized in Table I. Of 23 episodes of cholestasis in 10 children, lipid administration was stopped 20 times (1 to 4 times per child) over a period of 2 to 6 months; in 3 cases, no improvement of bilirubin concentration was observed, while in 17 cases, bilirubin plasma concentration decreased after stopping lipid administration, to below 30 μmol/L in 16 episodes (Fig. 1). In most cases plasma bilirubin decrease was rapid within the first month, reaching a normal concentration by 3.2 ± 2.0 months. In 3 cases, lipid delivery was not stopped; twice, pure LCT emulsion was switched to mixed LCT-MCT emulsion, leading to slow normalization of plasma bilirubin in 1 case while no improvement was observed in the other child who was already waiting for combined liver and small bowel transplantation. In the third case, lipid administration of mixed LCT-MCT emulsion was maintained to ensure a minimal lipid load and cholestasis slowly decreased.

Of 13 episodes including both cholestasis and thrombocytopenia, 12 led to interruption of lipid infusions. Normalization of the platelet count occurred in 11 cases within the first month after suspension of lipid infusion, while in one 14-year-old boy, platelet count remained below 120000/mm^3 several years after definitive removal of lipid infusions.

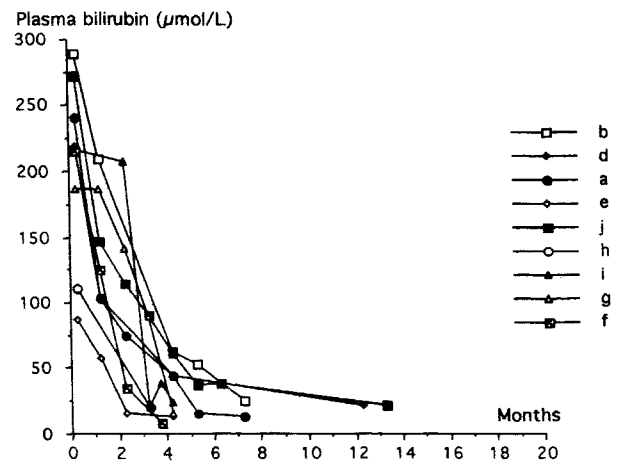

FIG. 1. Course of plasma bilirubin in the 9 children (all but child c) in whom cholestasis subseded after stopping lipid administration. One episode is represented for each child.

Deleterious Consequences of the Decrease in Lipid Supply

Essential fatty acid deficiency was documented in the three children in whom levels of eicosatrienoic and arachidonic acids (20:3 n-9 and 20:4 n-6) were measured after more than 3 months without lipids. The decrease in weight gain rate was constant in all children off lipids despite an increase in glucose supply.

Follow-Up After Interruption of Parenteral Lipid Supply

Parenteral lipid supply was definitively stopped in 2 children who did not depend on TPN. In the other 18 cases, when lipid infusions were temporarily stopped, their reintroduction was attempted after normalization of plasma bilirubin and platelet count (Table I). The interruption of parenteral lipid supply lasted 3.6 ± 2.5 months. In 13 cases, the same lipid emulsion as before the cholestasis episode was reintroduced (pure LCT in 5 cases and mixed LCT-MCT in 8 cases). In 5 cases, a pure LCT emulsion was switched for a mixed LCT-MCT emulsion. In all cases, the lipid load was decreased at the time of lipid reintroduction, either by the decrease in the daily lipid supply and rate of delivery or by the decrease in the number of lipid infusions per week, usually one to two infusions per week at the beginning, then increasing without exceeding a 150 mg/kg per hour rate of delivery and four perfusions a week. However, 7 children experienced one or several relapses of cholestasis, with or without hematologic disorders, again leading to cessation of lipid infusions, with a mean interval of 17.9 ± 12.8 months between two consecutive episodes.

Situation at the Time of Study

One child has been weaned from PN after short bowel adaptation (child f). Four patients (children b, c, e, h) have been weaned from PN after a successful small bowel transplantation (combined with liver in 3 cases). Five children are still dependent on PN (children a, d, g, i, j). One does not need parenteral lipid supply and the other four tolerate a minimal parenteral lipid load, which prevents essential fatty acid deficiency but does not contribute to an optimal nonprotein energy supply. They are waiting for a combined small bowel and liver transplantation.

DISCUSSION

This report raises the hypothesis of the contribution of lipid emulsions to PN-associated cholestasis. According to our inclusion and exclusion criteria, 10 of the 183 children receiving long-term PN over the 10-year period studied presented with a lipid-associated cholestasis, which leads to an estimate of the prevalence of this complication of about 5%.

Liver disease is a major side effect of long-term PN. Fifteen years after the first reports[10,11] its pathogenesis is not completely understood. Disruption of bile acid enterohepatic circulation in case of ileal amputation, impairement in choleresis in the absence of oral feeding, bacterial overgrowth due to bowel obstruction, stasis, and lack of ileocaecal valvula are patient-dependent factors thought to contribute to PN-associated cholestasis.[1] One mechanism might be an increase in bile concentration of lithocholic acid.[12] Bacterial infections were also proposed as a cofactor in PN-related cholestasis because the sepsis-associated cholestasis has been well described in human and animal models.[13,14] Duration of PN is also a known risk factor.[3] All of the patients in the current study presented with several risk factors, although children who presented with an infection incidence higher than in our whole home PN pediatric population[15] were not considered as eligible for the study.

Qualitative aspects of PN are also a matter of debate. It was experimentally demonstrated that an excess in total energy delivered induces liver lesions, reversible when decreasing the energy supply.[16] The role of amino acids was suspected, either excess or lack of them,[17–20] and an excessive glucose supply might induce steatosis through the increase in *de novo* lipogenesis.[21]

Although lipids are necessary in patients receiving PN because of their high caloric value, low osmolarity and content in essential fatty acids, they are strongly suspected to be toxic in some cases. The metabolism of their oxidized fraction is relatively well known,[22] far less the destiny of the nonoxidized fraction, which is caught by the reticuloendothelial system in the liver[23] and also by the spleen, bone marrow, and lungs. Long-term administration of lipid emulsions might overload reticuloendothelial cells and induce their acute or chronic activation. It must be noted however that an excess of liver macrophages and portal infiltration with eosinophils has been previously described in PN-dependent patients but not attributed to lipid toxicity.[24] Accumulation of exogenous lipids in the liver Kupffer cells may also impair the clearance of endotoxins and increase their deleterious effect on the liver. Moreover, the peroxidation of exogenous lipids could produce toxic metabolites despite the simultaneous infusion of vitamin E.[25] Phytosterols contained in lipid emulsions may also have a deleterious effect on biliary secretion.[6]

In the current study, several arguments are in favor of the toxic role of parenteral lipids for the liver. First, it was observed that several episodes of cholestasis occurred after a recent change in the mode of lipid delivery. Second, hematologic disorders compatible with a macrophage fat overload occurred in 13 cases simultaneous with the onset of cholestasis and frequently improved together with cholestasis after suspension or decrease in lipid infusions.

Suspension of lipid emulsions in PN-dependent children is not free of risk. As expected, prolonged lipid removal induced growth retardation and essential fatty acid deficiency.[26] The increase in daily glucose supply is not a satisfactory prevention of failure to thrive because of the induced insulin resistance[27] and the risk of subsequent liver steatosis. We were unable to document any hypothetic protective effect of mixed 50% MCT-50% LCT emulsions.

It has to be emphasized that combined liver and small bowel transplantation has been performed in 3 of our 10 patients and that 3 others are also waiting for a combined transplantation. At the time of decision for transplantation, all presented with a severe liver dis-

ease: advanced septal fibrosis (involving > 50% of portal spaces) or ring fibrosis. The contribution of lipid toxicity and repeated cholestasis episodes to liver impairment may be hypothesized because cholestasis is a well-known risk factor for development of liver fibrosis. On the other hand, one could suggest that liver lipid intolerance occurs in case of preexisting PN-associated liver disease.

Lipid-induced complications have to be taken into account in the decision for small bowel transplantation (SBT) in children with irreversible digestive disease.[28] Failure to thrive secondary to repeated or prolonged lipid suspension might be an indication for isolated SBT, before the development of severe liver disease. The liver status should be checked regularly by plasma liver tests and liver biopsies in children on waiting list for isolated SBT, especially in case of mild liver fibrosis at the time of decision for isolated SBT. We have recently showed that in a group of children on total PN severe liver fibrosis may appear over the first 4 years of life and then rapidly progress from septal fibrosis to cirrhosis.[29] Children who are sensitive to lipid toxicity might be at risk for rapid course of liver fibrosis. Taking into account the waiting period for transplantation, planning to combine transplantation in children presenting with lipid intolerance and severe liver fibrosis could be suggested.

Rules of lipid administration in PN-dependent children may be proposed as follows: Maximal daily amount of 2 to 2.5 g/kg per day, with a maximal infusion rate of 150 mg/kg per hour, no more than 5 lipid infusions weekly, and maximal lipid-to-energy ratio of 25%. In children receiving lipid emulsions, liver tests and platelet count should be monitored regularly. When cholestasis occurs, biliary obstruction, infection, or drug toxicity should be ruled out by appropriate investigations. Decrease in platelet count below 150,000/mm^3 associated with an increase in plasma transaminases, *a fortiori* an increase in plasma bilirubin, should lead to strong suspicion of lipid toxicity when all other explainations are ruled out. Bone marrow aspiration, liver biopsy, and temporary suspension or decrease in lipid infusion should be discussed. Lipid infusion should be stopped until normalization of bilirubin level and platelet count. Essential fatty acid deficiency has to be carefully checked. In cases of persistent cholestasis after a 2-month suspension of lipid infusion, an irreversible course of the liver disease could occur. Reintroduction of lipid emulsions should be attempted under strict supervision, below the previous dosage, beginning with one or two perfusions a week. Medium-chain based emulsions (50% MCT) might help to minimize the LCT load and theoretically their hepatic deposition[30] and long-term toxicity but neither the current study nor other clinical data have demonstrated any effects of MCT-based emulsions to prevent or to reverse long-term PN-associated cholestasis or hematologic complications. Emulsions based on olive oil might also reduce the risk of lipid toxicity due to peroxydation by decreasing the amount of linoleic acid.[31]

To conclude, this study suggests a relationship between lipid emulsions, macrophage activation syndrome, thrombocytopenia, and cholestasis in a pediatric population homogeneous for liver disease risk factors. Because lipids are indispensable in PN-dependent children, we recommend prevention through limitation of lipid supply and infusion rhythm to the patient's theoretical oxidizing capacity.[22] The preventive role of long-term use of emulsions containing low proportion of polyunsaturated fatty acids needs to be explored in further studies.

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