



## Caso clínico

# An exclusively based parenteral fish-oil emulsion reverses cholestasis

Miryam Triana Junco<sup>1</sup>, Natalia García Vázquez<sup>2</sup>, Carlos Zozaya<sup>1</sup>, Marta Ybarra Zabala<sup>1</sup>, Steven Abrams<sup>3</sup>, Abelardo García de Lorenzo<sup>4</sup> and Miguel Sáenz de Pipaón Marcos<sup>1</sup>

<sup>1</sup>Neonatology Department, La Paz University Hospital, Madrid, España. <sup>2</sup>Pharmacy Department, La Paz University Hospital, Madrid, España. <sup>3</sup>Baylor College of Medicine, Houston, Texas. <sup>4</sup>Intensive Care Unit, La Paz University Hospital, Madrid, España.

### Abstract

Prolonged parenteral nutrition (PN) leads to liver damage. Recent interest has focused on the lipid component of PN. A lipid emulsion based on w-3 fatty acids decrease conjugated bilirubin. A mixed lipid emulsion derived from soybean, coconut, olive, and fish oils reverses jaundice.

Here we report the reversal of cholestasis and the improvement of enteral feeding tolerance in 1 infant with intestinal failure-associated liver disease. Treatment involved the substitution of a mixed lipid emulsion with one containing primarily omega-3 fatty acids during 37 days. Growth and biochemical tests of liver function improved significantly. This suggests that fat emulsions made from fish oils may be more effective means of treating this condition compared with an intravenous lipid emulsion containing soybean oil, medium -chain triglycerides, olive oil, and fish oil.

(*Nutr Hosp.* 2015;31:514-516)

DOI:10.3305/nh.2015.31.1.8284

Key words: *Cholestasis. Intravenous lipid emulsions. Infant.*

### Introduction

Parenteral nutrition (PN) is a life-saving nutritional support for premature and low-birth weight infants and other hospitalized infants. A challenge in the care of premature infants is to provide sufficient nutrition to meet their high metabolic needs for growth, but aggressive administration of PN increases the risk for

**Correspondence:** Miguel Sáenz-de-Pipaón Marcos.  
Hospital Universitario La Paz.  
Servicio de Neonatología.  
Pº de la Castellana 261. E-28046 Madrid, Spain.  
E-mail: msaenz.hulp@salud.madrid.org

Recibido: 24-X-2014.  
Aceptado: 25-XI-2014.

### UNA EMULSIÓN LIPÍDICA BASADA EXCLUSIVAMENTE EN ACEITE DE PESCADO REVIERTE LA COLESTASIS

#### Resumen

La nutrición parenteral prolongada produce daño hepático. Recientemente se ha comunicado el efecto de las emulsiones lipídicas intravenosas basadas exclusivamente en ácidos grasos omega-3 en la resolución de la colestasis. Lo mismo se ha observado con el uso de emulsiones lipídicas mixta derivadas del aceite de soja, coco, oliva y pescado.

Comunicamos la desaparición de colestasis y mejoría de la tolerancia enteral en un niño con enfermedad hepática asociada a nutrición parenteral. El tratamiento consistió en sustituir una emulsión lipídica mixta por otra que contenía de forma exclusiva aceite de pescado durante 37 días. El crecimiento y los datos bioquímicos de función hepática mejoraron de forma significativa. Este caso sugiere que emulsiones lipídicas intravenosas a partir de aceite de pescado pueden ser más eficaces para tratar la colestasis si se comparan con emulsiones mixtas.

(*Nutr Hosp.* 2015;31:514-516)

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Palabras clave: *Colestasis. Emulsiones lipídicas intravenosas. Lactante.*

metabolic liver disease. Intestinal failure-associated liver disease (IFALD), previously named PN-associated liver disease (PNALD), is one of the main complications of long-term PN.

Although reports of its incidence and severity vary, estimates suggest that approximately 10-30% of patients who receive PN will develop cholestasis and 40-60% of neonates with significant cholestasis who cannot tolerate enteral nutrition can eventually lead to end-stage liver disease and need for transplant<sup>1</sup>.

The etiology of IFALD is multifactorial; risk factors include prematurity, birth weight, sepsis, the initial illness and the absence of enterohepatic circulation. In the last years, there has been much interest in the role that the dose and composition of intravenous fat-

ty acid emulsions may play in the physiopathology of IFALD<sup>2</sup>.

Traditionally used soy based lipid emulsions (Intralipid®) are enriched with the fatty acids linoleic acid (n-6, 53%) and are also enriched with phytosterols, which are cholesterol-like molecules derived from soybeans. Several newer parenteral lipid emulsions have been developed in the past 10 to 15 years containing single source lipid or blends of lipids; these more recently developed lipid emulsions have been termed “new generation”. New generation parenteral lipid emulsions containing pure olive oil (Clinoleic®), pure fish oil (Omegaven®), or various blends of soy, olive, medium chain triglyceride, and fish oil (Lipofundin®, SMOFlipid®, Lipoplus®) have been approved in Europe.

Recent studies have demonstrated resolution of cholestasis in patients with IFALD using an intravenous lipid emulsion composed entirely of fish oil, commercially available as Omegaven® 10% (Fresenius Kabi, Hamburg, Germany)<sup>3</sup>. European studies have also demonstrated that mixed fatty acid emulsions, such as SMOF® (15% fish oil, 30% soybean oil) (Fresenius Kabi, Hamburg, Germany) resolve parenteral nutrition-associated jaundice<sup>4</sup>.

We present one of the first patients treated with Omegaven in Spain and the first one we know that reversed cholestasis with Omegaven® after being treated with SMOF®.

## Case report

Patient is a male born at 31+2 weeks' gestation, who suffered gastroschisis. He was admitted in our hospital at 9 days of life after intestinal resection. The intestine, from 15 cm distal to pylorus to the distal descending colon was lost, which left 15 cm of small intestine 7 cm of sigmoid colon. He received total PN since birth. At admission, we started trophic feedings that had to be stopped at 16 days of life because of nosocomial sepsis by *Klebsiella oxytoca*. At the same time, he presented a progressive increase of bilirubin, up to 15,7mg/dl direct bilirubin (21,4mg/dl total bilirubin). They gradually lower, but after sepsis resolution, still persisted hyperbilirubinaemia and intractable feeding difficulties. At best, he tolerated only administration 10 cc/kg/day. His PN regimen included parenteral lipid emulsions (SMOF® 20%; Fresenius Kabi, Hamburg, Germany) at a dose of 2.8 g/kg per d. In light of the laboratory findings, total bilirubin of 5.2mg/dl and direct bilirubin of 4.1mg/dl, an alternative intravenous fat emulsion was considered. The infant was given the omega-3 based emulsion Omegaven® (Fresenius Kabi, Hamburg, Germany) at a dose of 1g/kg/day. Informed consent from the infant's parents was obtained. Monitoring included the assessment at frequent intervals of serum electrolytes, complete blood counts, serum triglycerides, blood glucose and liver enzymes including

aspartate amino transferase (AST) and amino alanine transferase (ALT).

The AST and ALT concentrations normalized. Cholestasis, defined as a direct bilirubin concentration > 2mg/dL, resolved within 24 days despite the continuing PN requirement. After initiation of therapy with Omegaven®, our patient presents an improvement in enteral tolerance, up to 85cc/kg/day 35 days after initiation of Omegaven®. Therapy with Omegaven® is stopped after 37 days, with transaminases and bilirubin in normal values. The patient did not suffer any complication related to Omegaven® administration, the levels of triglycerides remain in the normal limits (99 mg/dl) and he showed gain in weight, length and head circumference.

## Discussion

The etiology of IFALD, one of the main complications of long-term PN, remains unclear. A number of causes of IFALD have been proposed. Recent studies have implicated the use of soy based lipid emulsions in the etiology of IFALD. Phytosterols are found in soybean oil. Phytosterols are known to impair bile flow and enhance steatosis contributing to hepatic injury<sup>2</sup>. Soybean oil is composed mainly of omega-6 fatty acids, which produce a cascade of pro-inflammatory compounds<sup>2</sup>.

Different studies have demonstrated that when 1g/kg/day of exclusive fish oil is used benefits cholestasis resolutions and reestablishment of enteral nutrition. Fish-oil contains mainly anti-inflammatory omega-3 fatty acids and has higher level of alpha tochoferol. High omega-6:omega-3 fatty acids ratios also affect lipid metabolism by regulating fat storage. As fat accumulates in hepatic cells results in hepatic injury.

SMOF®, being a mixed emulsion (30% soybean, 30% MCT, 25% olive oil, 15% fish oil), would have intermediate results between Omegaven® e Intralipid®, as it has been shown in animal models<sup>5</sup>. Different authors have compared SMOF® with Intralipid®, proving that SMOF® reduces total and conjugated bilirubin levels. That suggests that a reduction in the proportion of soy-based lipids could reduce bilirubin. There are any human studies that compare SMOF® and Omegaven® but the animal models suggest that even small amounts of soy plant based lipid emulsions could contribute to hepatic injury. That is why, in certain cases, such as our patient, the administration of a 100% fish oil emulsion could be beneficial

Omegaven® is administrated at a dose of 1g/kg/day. Some authors associated its benefit to the reduction of lipid provision<sup>6</sup>. However, Nehra et al<sup>7</sup> have recently shown that neonates receiving soybean oil-based lipid emulsion at 1g/kg/d and those receiving the lipid emulsion at 2-3g/kg/d did not differ in cholestasis grade.

Although the reduction in lipid provision (1g/kg/d) and the increase in the amount of carbohydrates to provide adequate calories, would suppose an increment in lipogenesis and a theoretical essential fatty acid deficit, that has not been described; there has not been found either a growth delay in patients treated with Omegaven<sup>®</sup>. On the other side, reduction of soy based lipid emulsions to 1g/k/d could lead to a essential fatty acid deficit<sup>9</sup>. There are no data about the effect of lipid reduction on neurologic development.

Sepsis was a confounding factor in our patient, as with its resolution bilirubin level was reduced; however, with Omegaven<sup>®</sup> administration, not only bilirubin was reduced but also made possible enteral feeding tolerance, up to 100cc/kg./d, with normal growth. Reestablishment of enteral feeding has been already described by other authors<sup>10</sup> and could be due to the anti-inflammatory properties of omega-3 fatty acids and alpha tocopherol.

Although the improvement and even resolution of cholestasis with Omegaven<sup>®</sup> has been reported in many publications, that may not reflect a similar histologic regression, as has been already pointed out<sup>11</sup>. In addition, all the studies are directed to the treatment of an advanced grade of hepatic damage and is still unknown if Omegaven<sup>®</sup> could be also useful in the prevention of IFALD.

We conclude that this brief report describes that administration of exclusively fish oil-based emulsions resolved cholestasis. This therapy may offer a potential solution when mixed emulsions do not revert cholestasis. More studies are needed to know the exact mechanism by which omega-3 fatty acids help to reestablish enteral feeding. A randomized, controlled trial is necessary to determine the efficacy of an exclusively fish oil-based emulsion compared with a mixed lipid emulsion in the treatment of IFALD.

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