Parenteral Lipid Emulsions in Pediatric Nutrition: Evidence from Premature Piglet Model of PNALD

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Impact of Parenteral Nutrition Support in Premature Infants?

- In U.S., over 60,000 VLBW (<1,500 g) premature infants born per year.
- Total parenteral nutrition (TPN) due to feeding intolerance from GI immaturity

**Multi-center Network cohort all NICU admissions 4 years (N= 9547 infants)**

- 69% received PN in the first 14 days

*Christensen et al. J. Perinatology. 2007*
Direct bilirubin > 2 mg/dL
Increased serum bile acids and liver enzymes (GGT, ALT, ALP)
Histopathology: intracellular and intracanalicular cholestasis, steatosis, portal inflammation and periportal fibrosis.
Associated with chronic TPN (> 14 days) and incidence directly correlated to duration TPN.

- N = 1366 infants PN > 14 days
- 21% of all 9547 NICU infants

Christensen et al. J. Perinatology. 2007
Risk Factors and Pathobiology of PNALD

- Prematurity
- Lack of Enteral Nutrition
- Parenteral Nutrient Deficiency
- Sepsis/Inflammation
- Parenteral Toxicity
# New Generation Lipid Emulsions Are Emerging

<table>
<thead>
<tr>
<th><strong>Intralipid</strong></th>
<th><strong>SMOF</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Only FDA approved emulsion (~35 yr)</td>
<td>Soybean oil (30%)</td>
</tr>
<tr>
<td>• Soybean oil based</td>
<td>Medium chain TG (30%)</td>
</tr>
<tr>
<td>• (+) Phytosterols</td>
<td>Olive oil (25%)</td>
</tr>
<tr>
<td>• Enriched n-6 PUFA</td>
<td>Fish oil (15%)</td>
</tr>
<tr>
<td><strong>Omegaven</strong></td>
<td><strong>MCT</strong></td>
</tr>
<tr>
<td>• Limited FDA approval</td>
<td>• Not approved FDA</td>
</tr>
<tr>
<td>• Approved Europe</td>
<td>• Approved Pediatric Use (Europe)</td>
</tr>
<tr>
<td>• Fish oil based</td>
<td>• (+) Phytosterols</td>
</tr>
<tr>
<td>• No (-) Phytosterols</td>
<td>• “Balanced” fatty acid profile</td>
</tr>
<tr>
<td>• Enriched n-3 PUFA (DHA and EPA)</td>
<td></td>
</tr>
</tbody>
</table>

*All manufactured by Fresenius Kabi Inc.*
Why the Excitement About Lipid Emulsions?

- Approved compassionate use
- Orphan Drug Status (Feb 2008)
- 1 g/kg/d treatment PNALD

- Pediatric Trials w/ Omegaven registered (ClinicalTrials.gov)
  - Children's Hospital Boston
  - Baylor College of Medicine (TCH)
  - Univ. of Pennsylvania (CHOP)
  - Univ. of Cincinnati (CHMC)
  - Vanderbilt Univ.
  - Univ. Nebraska Med Ctr.
  - UCLA
  - Univ. British Columbia
  - North Shore Long Island JHS
Does Switch to Omegaven Cure PNALD Induced by Intralipid?


**TABLE 2. Baseline Characteristics of Patients in the Fish Oil and Soybean Oil Cohorts**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fish Oil (N = 42)</th>
<th>Soybean Oil (N = 49)</th>
<th>( P^† )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic and medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
<td>28 (67%)</td>
<td>31 (63%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Age (wk), median (IQR)</td>
<td>12 (8, 25)</td>
<td>7 (5, 12)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Birth weight (kg), mean ± SD</td>
<td>1.6 ± 0.86</td>
<td>1.8 ± 0.98</td>
<td>0.29</td>
</tr>
<tr>
<td>Gestational age (wk), mean ± SD</td>
<td>30 ± 5</td>
<td>32 ± 5</td>
<td>0.046</td>
</tr>
<tr>
<td>Duration of PN before enrollment (d), median (IQR)</td>
<td>63 (48, 118)</td>
<td>40 (21, 74)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

**A**

- **Intralipid** (1-4 g/kg/d)
- **Omegaven** (1 g/kg/d)
Question?

Do New Generation Lipid Emulsions Prevent PNALD When Given at High Lipid Loads?
Premature, Cesarean-Derived Piglet Model

- Delivery at 105 d gestation (~90% term-115 d)
- Nutritional support via TPN or enteral formula
- Sufficient respiratory function
- Immature intestinal function (NEC sensitive)
- Immature liver function?
Impact of Parenteral Lipid Composition on PNALD
(Study Design)

- Premature, cesarean-derived, piglets (108 d gestation = 7-day preterm)
- Dietary Treatment Groups (Birth to 14 days age)
  - Enteral Fed: Cows-milk formula (6 feeds/day- 240 ml/kg)
  - TPN + **Intralipid**: Dextrose, amino acids, vitamins, minerals (Intralipid)
  - TPN + **Omegaven**: Dextrose, amino acids, vitamins, minerals (Omegaven)
  - TPN + **SMOF**: Dextrose, amino acids, vitamins, minerals (SMOF-lipid)
    - (Equal fluid, protein, energy intake; lipid intake = 5 g·kg⁻¹·d⁻¹)
- Endpoint measurements:
  - Serum and tissue markers of liver function and metabolism
  - mRNA expression bile acid target genes
<table>
<thead>
<tr>
<th></th>
<th>Intralipid (n=12)</th>
<th>Omegaven (n=13)</th>
<th>SMOF (n=7)</th>
<th>Enteral (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth wt., kg</td>
<td>1257</td>
<td>1280</td>
<td>1289</td>
<td>1224</td>
</tr>
<tr>
<td>Weight gain, g·kg⁻¹·d⁻¹</td>
<td>45.80</td>
<td>53.25</td>
<td>54.34</td>
<td>58.74</td>
</tr>
<tr>
<td>Liver wt., g/kg</td>
<td>47.8</td>
<td>47.6</td>
<td>41.6</td>
<td><strong>32.4ᵃ</strong></td>
</tr>
<tr>
<td>Spleen, g/kg</td>
<td>4.90</td>
<td>4.36</td>
<td>5.73</td>
<td><strong>2.00ᵃ</strong></td>
</tr>
<tr>
<td>Sm. Int wt. g/kg</td>
<td>19.7</td>
<td>19.6</td>
<td>20.2</td>
<td><strong>52.5ᵃ</strong></td>
</tr>
<tr>
<td>Heart, g/kg</td>
<td>7.52</td>
<td>8.36</td>
<td>9.11</td>
<td>6.51</td>
</tr>
<tr>
<td>Cerebrum, g/kg</td>
<td>11.78</td>
<td>10.58</td>
<td>11.79</td>
<td>10.22</td>
</tr>
<tr>
<td>Kidney, g/kg</td>
<td>10.7</td>
<td>10.1</td>
<td>7.8</td>
<td>9.2</td>
</tr>
</tbody>
</table>

ᵃ Different from ALL TPN groups (P<0.05)
Serum Markers of Cholestasis and Biliary Injury

**Total Bilirubin**

- ENT (n=7)
- Intralipid (n=12)
- Omegaven (n=13)
- SMOF (n=7)

* P<0.05 vs ENT
† P<0.05 vs IL

**GGT**

Day 0 vs Day 14

**Serum Bile Acid (Day 14)**

Day 0 vs Day 14

**Liver Bile Acid (Day 14)**

Day 0 vs Day 14
Histopathological Evidence of Liver Injury

- Pericholangitis
- Acute cholangitis-Ballonning
- Portal PMN
- Normal
Homologous Structure of Cholesterol, Bile Acids and Plant Phytosterols
<table>
<thead>
<tr>
<th>Phytosterol</th>
<th>Intralipid</th>
<th>SMOF</th>
<th>Omegaven</th>
<th>Enteral</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Sitosterol</td>
<td>580</td>
<td>258</td>
<td>&lt;1</td>
<td>15</td>
</tr>
<tr>
<td>Campesterol</td>
<td>151</td>
<td>50</td>
<td>&lt;1</td>
<td>8</td>
</tr>
<tr>
<td>Stigmasterol</td>
<td>135</td>
<td>50</td>
<td>14</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Total phytosterols</td>
<td>866</td>
<td>358</td>
<td>14</td>
<td>23</td>
</tr>
</tbody>
</table>
### Plasma Phytosterol Concentrations

<table>
<thead>
<tr>
<th></th>
<th>Intralipid (n=8)</th>
<th>SMOF (n=7)</th>
<th>Omegaven (n=9)</th>
<th>Enteral (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-Sitosterol</strong></td>
<td>51.1 ± 4.4&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>17.6 ± 2.0&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>&lt;1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.7 ± 1.8</td>
</tr>
<tr>
<td><strong>Campesterol</strong></td>
<td>10.7 ± 3.2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.6 ± 0.9&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>0.7 ± 0.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8.2 ± 1.7</td>
</tr>
<tr>
<td><strong>Stigmasterol</strong></td>
<td>3.2 ± 1.4</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>2.0 ± 1.3</td>
</tr>
<tr>
<td><strong>Total phytosterols</strong></td>
<td>65 ± 7.2&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>20.7 ± 2.3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.7 ± 0.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16.9 ± 2.6</td>
</tr>
</tbody>
</table>

** mean ± SEM, µmol/L from day 14

<sup>a</sup> Different from Enteral group (P<0.05).

<sup>b</sup> Different from SMOF group (P<0.05).

<sup>c</sup> Different from Omegaven group (P<0.05).
Phytosterol Concentrations

* P<0.05 vs. ENT
† P<0.05 vs. IL
$ P<0.05 vs. OV
TPN Suppressed FXR-Bile Acid Synthesis Target Genes

FXR mRNA

SHP mRNA

CYP7A1 mRNA

* P < 0.05 vs ENT
† P < 0.05 vs IL

FXR-Mediated Bile Acid Homeostasis
TPN-induced Suppression of FXR Target Genes

**FXR mRNA**
- ENT: 600, IL: 400, OV: 200, SL: 0 (with * indicating significance)

**BSEP mRNA**
- ENT: 800, IL: 600, OV: 400, SL: 200 (with * indicating significance)

**NTCP mRNA**
- ENT: 125, IL: 100, OV: 75, SL: 50 (with * indicating significance)

**OSTα mRNA**
- ENT: 125, IL: 100, OV: 75, SL: 50 (with * indicating significance)

**Diagram**:
- **FXR** regulates **BSEP**
- **CYP7A1** and **Bile Synthesis**
- **OSTα** and **NTCP** involved in bile acid transport

**Legend**:
- Blood
- Hepatocyte
- Bile

**FXR-Mediated Bile Acid Homeostasis**
New Generation Emulsions Prevent TPN-induced Steatosis

Liver Triglycerides

* P<0.05 vs ENT  † P<0.05 vs TPN
Summary Points

- In TPN-fed piglets, soy-based lipid emulsions induce metabolic dysfunction
  - hepatic steatosis and cholestasis
  - Increased bile acid pool size and phytosterolemia
  - Inflammation and peripheral insulin resistance
- In TPN fed piglets, new generation lipid emulsions
  - supported normal weight gain and energy expenditure vs. enteral formula.
  - Prevented/reduced hepatic cholestasis and steatosis
  - Reduced phytosterolemia and bile acid pool size
  - Suppressed hepatic inflammatory response
Clinical and Scientific Relevance

- Soy-based lipid emulsions are not optimal for hepatic metabolic function in some TPN-fed infants, especially when given for extended periods.
- New generation lipid emulsions (Omegaven & SMOF) appear effective in prevention of liver disease even at high lipid loads equal to Intralipid.
- Lipid emulsion associated liver disease may be dose-dependently related to phytosteroolemia.
- Cellular and molecular mechanisms that explain beneficial effects of new lipid emulsions are not all explained by phytosteroolemia.
- Phytosterols antagonize bile acid-induced FXR gene expression.
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Milton Finegold

Erasmus Medical Center
Hester Vlaardingerbroek

University of Amsterdam
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