Intravenous Lipid Emulsions and IFALD: Different Products and Different Approaches

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Disclosures

– Member, Pharmaceutical Advisory Board/consultant
  • B. Braun       Pfizer

– Member, Scientific Advisory Board/consultant
  • Fresenius Kabi  Baxter       Otsuka

– Research Support
  • Fresenius Kabi  Northsea Therapeutics

– Royalties
  • UpToDate       Omegaven

– Consultant
  • Wolters Kluwer

– Special government employee
  • FDA  Pharmacy Compounding Advisory Committee
Learning Objectives

Upon completion of this session, the learner will be able to:

1. Review the development of intravenous lipid emulsions
2. Describe why intravenous lipid emulsions were originally thought not to contribute to the etiology of IFALD
3. Discuss how to apply the currently available ILE in clinical practice

I will be discussing off label use of approved products.
Intravenous Lipid Emulsions

Functions

• Source of essential fatty acids
• Alternative to carbohydrates as a source of non-protein calories
Relationship to ILE and IFALD
Why wasn’t it considered sooner?
Dudrick Method of PN Provision

- ILE free
- Relied on high carbohydrate intake
- To prevent EFA deficiency
  - Blood transfusions
  - Topical oils

Patients developed liver disease!
European Method of PN Provision

• Intralipid (pure soybean oil) approved in Europe in 1962
• Used egg yolk phospholipid emulsifiers
• Allowed for lower carbohydrate intake

Liver disease still occurred!
Clinical Conundrum
Liver Disease Occurs with or without ILE!

QED:
Everyone knows it’s not the lipids
What’s Common to ALL ILE Products

- 1.2% egg yolk phospholipids
- 2.25%-2.5% glycerin
- Sodium hydroxide
- Sterile water for injection
What’s Different Among ILEs

- Alpha tocopherol content
- Inflammatory characteristics due to oil source
- Phytosterol content

Typically not included on the product label!
21st Century
Soybean Oil Lipids Implicated in Liver Disease

• Colomb, et al.
  – “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.” (JPEN Nov-Dec 2000;24(6):345-50)

• Javid et al.
  – “The route of lipid administration affects parenteral nutrition-induced hepatic steatosis in a mouse model. Mice administered ILE through the enteral route protected against PN-associated hepatic injury in comparison to IV ILE. (J Pediatr Surg. 2005 Sep;40(9):1446-53)

• Alwayn et al.
  – “Omega-3 fatty acid supplementation prevents hepatic steatosis in a murine model of nonalcoholic fatty liver disease. (Pediatr Res. 2005 Mar;57(3):445-52.)
What’s old is new….

1998

Iyer & Clayton


“Plant sterols (phytosterols) may be involved in the pathogenesis of parenteral nutrition-associated cholestasis”
PN-associated liver injury is due in part to the lipid components
Liver Histology
Route of Administration of Soybean Oil

Javid et al, J Ped Surg, 2005
What about switching the type of lipid?
Liver Histology

Chow

ORAL PN + Oral FOLE

PN alone

ORAL PN + IV FOLE

H&E 400X

Alwayn et al, Pediatr Res, 2005
Why weren’t other ILEs Considered….
2004 Clinical Use of FOLE in Pediatric IFALD
FOLE Compassionate Use Protocol

• Conventional fat emulsions discontinued
• FOLE dosing
  – 1 gram/kg/day for the remainder on PN
• Additional non-protein calories provided as carbohydrate
# Death and Transplants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FOLE</th>
<th>Soybean Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n (%)</td>
<td>3 (5)</td>
<td>8 (17)</td>
<td>0.11</td>
</tr>
<tr>
<td>Transplantation, n (%)</td>
<td>1 (2)</td>
<td>5 (11)</td>
<td>0.09</td>
</tr>
<tr>
<td>Death or transplantation, n (%)</td>
<td>4 (7)</td>
<td>13 (28)</td>
<td>0.007</td>
</tr>
</tbody>
</table>
Mean Direct Bilirubin Levels

FOLE patients

Soybean Controls

Ann Surg. 2009 Sep;250(3):395-402
Intravenous Fish Oil Monotherapy as a Source of Calories and Fatty Acids Promotes Age-Appropriate Growth in Pediatric Patients with Intestinal Failure-Associated Liver Disease

Kathleen Guza PharmD, BCNSP, ARNP, Muralidhar H. Premkumar MD, Kara L. Calkins MD, Mark Puder MD, PhD
Other ILE Strategies
Prevention
Impact of Soybean Lipid Dose
Pilot study n=28
Prospective RCT
Infants > 26 weeks GA on >50% total calories from PN
Compared 1g/kg/d to 3g/kg/d
Results:
- Ave PN duration 5.4 weeks
- Tot increase in dbili from baseline less in low dose group (p=0.04)
- Weight z-score increased more in 3g/kg/d group
- No EFAD
CONCLUSION:
- Markers of cholestasis rose at a slower rate using 1g/kg/d IFE
Prophylactic SOLE Lipid Restriction
1g/kg/day

• Surgical neonates (n=82) receiving 1g/kg/d retrospectively compared to control cohort (2g/kg/d) (n=132)

• Results: PNALD less in 1g/kg/d group (22% vs. 43% p=0.003)

• FOLE rescue used in 4 infants in standard dose vs. 2 infants in low dose group
Protocol:
- 1 g/kg/d twice weekly
- If EFAD develops: 1 g/kg/day 3x/week
- If the EFAD persists: 2 g/kg/day 3x/week

Preliminary results indicate IFE restriction resulted in a statistical significant reduction in total bilirubin without impacting growth or causing EFAD.
• Multicenter study RCT
• 136 neonates <48 hrs of age randomized to low (1 g/kg/d, n=67) or high dose (~3g/kg/d n=69) SO
• Results
  – no difference in PNALD (69% vs 63%; 95% confidence interval, -0.1 to 0.22; P = 0.45)
  – weight, length, and head circumference at 28 DOL, discharge, and over time were not different (P > 0.2 for all)
• Conclusion: Compared with the control dose, low-dose SO was not associated with a reduction in PNALD or growth
BCH Experience: 
SOLE Dose and Cholestasis

- Retrospective chart review: All patients who received PN/IL in the NICU at BCH between January 2007 – June 2011

- **Inclusion Criteria**
  - Age <2 months at PN/IL initiation
  - On IL for at least 3 weeks at CHB
  - No PN/IL prior to transfer to CHB
  - Gastrointestinal surgical condition as indication for PN/IL

- **Exclusion Criteria**
  - Multisystem organ failure
  - Inconsistent IL dosing

1g/kg/day IL group

2-3 g/kg/day IL group

Nehra et al JPN 2013 Jul;37(4):498-505
Patient characteristics while on parenteral nutrition

<table>
<thead>
<tr>
<th></th>
<th>IL at ≤1g/kg/day (n=29)</th>
<th>IL at &gt;1g/kg/day (n=31)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of PN</td>
<td>61.6 ± 8.7</td>
<td>54.4 ± 6.5</td>
<td>0.5071</td>
</tr>
<tr>
<td>Dbili at start</td>
<td>0.6 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.1738</td>
</tr>
<tr>
<td>Maximum Dbili*</td>
<td>5.3 ± 0.9</td>
<td>5.1 ± 0.7</td>
<td>0.9076</td>
</tr>
<tr>
<td>Time to Max Dbili*</td>
<td>5.7 ± 0.9</td>
<td>7.1 ± 0.7</td>
<td>0.2315</td>
</tr>
<tr>
<td>Number of major operations</td>
<td>1.7 ± 0.2</td>
<td>1.5 ± 0.1</td>
<td>0.254</td>
</tr>
<tr>
<td>Patients with bacteremia</td>
<td>8 (27.6%)</td>
<td>7 (22.6%)</td>
<td>0.7685</td>
</tr>
<tr>
<td>Cholestasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dbili &gt;2 for 1 week</td>
<td>16 (55.2%)</td>
<td>17 (54.8%)</td>
<td>1.0000</td>
</tr>
<tr>
<td># pts switched to Omegaven</td>
<td>8 (27.6%)</td>
<td>7 (22.6%)</td>
<td>0.7685</td>
</tr>
</tbody>
</table>
Safety and efficacy of Fish Oil Based Lipid Emulsion in the Prevention of PNALD

a double-blind randomized controlled clinical trial to compare Soybean oil to Fish oil at 1g/kg/day

• Primary outcome:
  – Incidence PNALD

• Secondary outcomes:
  – Safety
    - Growth
    - Infection risk
    - EFA status
    - Neurodevelopment

• Inclusion Criteria:
  – <3mo at enrollment
  – Baseline d bili <1
  – Expected PN ≥ 21 days

• Exclusion criteria:
  – Shock
  – Severe hemolytic disorder
  – Baseline triglyceride >400 mg/dL
  – Prior exposure to intravenous fat emulsion

Primary Outcome: Incidence of cholestasis

Soybean Oil

Fish Oil

No difference in weekly median bilirubin values between groups

Conclusions from the pilot study . . .

No difference in the incidence of cholestasis

No adverse effects:

- Growth
- Infection rate
- Fatty acid profiles
- Neurodevelopment
Treatment
A Double-Blind Randomised Controlled Trial of Fish Oil-Based versus Soy-Based Lipid Preparations in the Treatment of Infants with Parenteral Nutrition-Associated Cholestasis

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*Department of Pediatrics and *Department of Paediatric Surgery, Department of Surgery, The Chinese University of Hong Kong, and Department of Pharmacy, Prince of Wales Hospital, Shatin, Hong Kong.

Key Words
Fish oil-based lipid preparation - Newborn infants - Parenteral nutrition-associated cholestasis - Randomised controlled trial

Abstract
Background: Infants receiving prolonged parenteral nutrition (PN) are at risk of PN-associated cholestasis (PNAC). This can progress to hepatic failure and death if PN cannot be discontinued. Fish oil-based parenteral lipid preparation (FOLP) has been shown to be beneficial in case studies. Objectives: (1) To evaluate whether FOLP could halt or reverse the progression of PNAC compared with soy-based parenteral lipid preparation (SLP), and (2) to assess the effects of FOLP on liver function and physical growth. Methods: Design: double-blind randomised controlled trial. Setting: level III neonatal intensive care unit. Participants: Infants with PNAC (plasma-conjugated bilirubin concentration ≥5 μmol/L or ≥2 mg/L) expected to be PN-dependent for 52 weeks. Interventions: To receive either FOLP or SLP at 1.5 g/kg/day. Primary outcome: treatment survival of PNAC, with 4 months after commencement of lipid treatment. Secondary outcomes: rate of change of weekly liver function tests, infant growth parameters, blood lipid profile and episodes of late-onset sepsis. Results: A total of 9 infants were randomised to the FOLP group and 7 to the SLP group. There was no significant difference in survival of PNAC at 4 months between groups. Rates of increase of plasma-conjugated bilirubin and plasma alanine transaminase in the SLP group were significantly greater than in the FOLP group (P < 0.01) per week and 9.3 vs. 2.11 μmol/L per week, respectively, P = 0.002. Increased enteral nutrition was associated with significant improvements in PNAC in infants receiving FOLP compared with SLP (P < 0.05 vs. 1.4 g/L) per 10% increase in enteral nutrition, respectively. The study was terminated prematurely. Conclusion: Progression of PNAC in PN-dependent infants can be halted by replacing SLP with FOLP and reversed by increasing the proportion of enteral nutrition in infants receiving FOLP. Replacement of SLP with FOLP in PN-dependent infants who develop PNAC may be considered.

Introduction
Advances in neonatal intensive care [1] have reduced morbidity and mortality of infants with severe hyperbilirubinemia and intraventricular hemorrhage. These infants often remain PN-dependent. A recent systematic review [2] showed that fish oil-based lipid preparations are safe and effective in PNAC. This is the first study to evaluate the effects of fish oil-based lipid preparations on PNAC in a randomised controlled trial setting.
Hong Kong RCT
Neonatology 2014;105:290-296

- 1.5 g/kg/day for both IFE
- 16 infants (FO n=9, SO n=7)
- no significant difference in reversal of IFALD at 4 months between groups
  - Rates of increase of Dbili & ALT in SO group > FO group
    - 13.5 vs.0.6 µmol/l/wk and 9.1 vs. 1.1 IU/l/wk (p = 0.03)
  - ↑ EN associated with significant improvement of IFALD in FO group compared to SO
  - Rate of increase of direct bilirubin in the SO group significantly higher than in the FO group (p = 0.03)
  - ALT significantly worsened, increasing by 9.1 IU/l per week in the SO group (p < 0.01) but not in the FO group (1.1 IU/l per week, p = 0.71)
  - Rate of increase of ALT in the SO group significantly greater than in the FO group (p = 0.02).
Omegaven isn’t a wonder drug..

"It’s called a miracle drug because it'll be a miracle if it's covered by your insurance."
## Independent Predictors of Treatment Failure

PELD = 4.8[ln(TB)] + 18.57[ln(INR)] – 6.87[ln(albumin)] + 4.36 (if age <1 yr) + 6.67 (if growth failure)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Reversed (n=128)</th>
<th>Treatment failure (n=20)</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline PELD score ≥ 15</td>
<td>30 (23%)</td>
<td>13 (65%)</td>
<td>0.005</td>
<td>4.7 (1.6, 13.9)</td>
</tr>
<tr>
<td>History of GI bleed</td>
<td>22 (17%)</td>
<td>9 (45%)</td>
<td>0.006</td>
<td>4.6 (1.5, 13.8)</td>
</tr>
<tr>
<td>Patient age ≥ 16 weeks at FO initiation</td>
<td>47 (37%)</td>
<td>14 (70%)</td>
<td>0.004</td>
<td>5.5 (1.7, 17.5)</td>
</tr>
<tr>
<td>Ventilator at FO initiation</td>
<td>16 (13%)</td>
<td>7 (35%)</td>
<td>0.002</td>
<td>6.8 (2.1, 22.5)</td>
</tr>
</tbody>
</table>


Other Approaches

• SOLE/MCT/Olive/FOLE
• 50/50 blend FOLE + SOLE
• Reduced dose SOLE
• Olive oil/SOLE blend
SOLE/MCT/Olive/FOLE

- Birmingham (UK) Children’s
- Case series infants/children with PNALD while on SO & switched to alternative ILE (n=8)
- 1 patient died, 1 listed for transplant
- Remaining 6: “sudden, often dramatic and sustained fall in bilirubin 1-3 months after switching”

Source: Protheroe/Murphy
SOLE/MCT/Olive/FOLE
Dose Makes a Difference!

Lam (2018)

– ILE doses 2.2 g/kg/day
– Improved hepatic function in comparison to controls receiving mixed oil ILE
– Children receiving mixed oil ILE had significantly lower CB levels
– Prolonged exposure (≥4 weeks) to mixed oil ILE associated with decreased liver injury in comparison to SOLE
SOLE/MCT/Olive/FOLE: Dose and EFAD

- Cary et al. (2018)
- Case series of 4 children receiving mixed oil ILE for IFALD who developed EFAD
- All 4 were switched to FOLE and had resolution of EFAD
- The authors suggested that in order to prevent EFAD in neonates, it is necessary to dose mixed oil ILE at 3g/kg/day to provide the same EFA content as 1g/kg/day of SOLE.
Impact of Higher SOLE/MCT/Olive/FOLE Doses

• May blunt the hepatoprotective response
• Repa et al (2018)
  – ELBW randomized to mixed oil ILE or SOLE
  – Both dosed up to 3 g/kg/d
  – Found no significant difference in the rate of IFALD (10% versus 16%)
• Canada
• 12 patients with PNALD
• 1g/kg/d SO + 1g/kg/d FO
• 5 cases, hepatic dysfunction while on the blended regimen progressed until SOLE stopped and FOLE was given alone
• Complete resolution of PNALD occurred in 9 patients (75%)
Control: 3 g/kg/d,
Intervention: 1 g/kg twice weekly, n = 31 each group

Results:

42% resolution (fat reduction)

10% resolution control group

Cober et al, J Pediatr 2012;160:421-7
Olive Oil/Soybean Oil ILE

- Pawlik et al
- Prospective RCT
- Retinopathy of prematurity primary outcome
- Infants BW <1250 g
  - 60 received Clinoleic + Omegaven
    - 3.5 g of lipids/kg BW per day (proportional dose = 1.2 g of Omegaven and 2.3 g of ClinOleic)
  - 70 given Clinoleic alone
    - 3.5 g/kg ClinOleic

Olive Oil/Soybean Oil ILE

• Results:
  – 9 infants in the fish oil supplemented group required laser therapy for ROP vs. 22 infants in the Clinoleic alone group (risk ratio [RR], 0.48; 95% confidence interval [CI], 0.24-0.96)
  – 3 infants in the fish oil group developed IFALD vs. 20 infants in the Clinoleic group (RR, 0.18; 95% CI, 0.055-0.56)

• Conclusion:
  – Infants receiving fish oil had less ROP and less IFALD than those receiving a standard lipid emulsion.
Olive Oil/Soy Oil Blends

- OO/SO 4:1; high ratio of n-6 to n-3 fatty acids (9:1)
- 5 premature neonates with SBS – treated with a 1:1 combination of FOLE and olive/soybean-based ILE for periods ranging between 7 and 17 months
- 4/5 patients normalized DB during their first year of life; 5/5 all recovered with normal liver function

Key Points
Pros and Cons
Soybean Oil ILE

- **Pros**
  - 50+ years of experience
  - 1g/kg/day does not cause EFAD
  - Lots of compatibility information

- **Cons**
  - Higher risk of IFALD
  - Rich in phytosterols, omega-6 fatty acids
  - Low in alpha-tocopherol
Pros and Cons
Fish Oil ILE

• Pros
  – Improves hepatic function in IFALD
  – Rich in omega-3 fatty acids, alpha-tocopherol
  – Low in phytosterol content
  – No black box warning!

• Cons
  – Need at least 1g/kg/day to prevent EFAD
  – 10% emulsion
  – Little compatibility information
Pros and Cons
Soy-MCT-Olive-Fish ILE

• Pros
  - 20% emulsion
  - can use to reduce GIR
  - contains MCT – more stable TNAs
  - contains DHA, ARA; less soybean oil

• Cons
  - 3g/kg/d = 1g/kg/day soybean ILE
  - not FDA approved for use in pediatric patients
  - limited compatibility data
Pros and Cons
Olive-Soy ILE

• Pros
  - 20% emulsion
  - can use to reduce GIR
  - contains less pro-inflammatory oils (80% olive oil)

Cons
  - cannot use in soy restriction protocols
  - limited US studies
  - limited compatibility data
  - not FDA approved for use in pediatric patients
“Even When the Wound Is Healed, the Scar Remains”

So what should you use????
Gura’s Rules for ILE Selection

• Use all of them – none can be used for everything!

• To prevent IFALD
  – 1g/kg/day soybean oil monotherapy
    • Fluid restricted patients
    • Limited access, lots of parenteral medications
  – Age appropriate dose soy/MCT/olive/fish or olive/soy
    • To reduce carbohydrate load provided by PN
  – ? Olive oil/SOLE – European literature

• To treat IFALD
  – Encourage enteral nutrition when safe to do so
  – 1 -1.5 g/kg/day fish oil monotherapy
    - 1.5g/kg/day when needing to decrease GIR
Any Questions?????

Clear as mud!!!!


