Name, Title, Affiliation
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Chief, Clinical Pharmacy Services, Mississippi Baptist Medical Center
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Presentation Title
Lipid Injectable Emulsions (ILE) Do's and Don'ts

Disclosures
Speakers Bureau: Fresenius Kabi, Janssen

Presentation Overview/Summary
• In 2017, the ASPEN Parenteral Nutrition Safety Committee conducted a ILE Survey with Gap Analysis. The survey revealed a number of institutions do not filter their ILE’s and infusion times vary from published recommendations.

Learning Objectives
• Learning objectives for the presentation.

At the conclusion of the presentation, the learner will be able to:
1. Summarize the 2017 ASPEN ILE survey and gap analysis.

Key Takeaways/Fast Facts
• The results of this survey conducted in late 2016 found a wide variation in practice, particularly across patient age groups. Conclusion: These findings demonstrate the need for ongoing dissemination and education on standardized safe practices for ILE use.

Learning Assessment Questions

1. Question 2: 2-in-1 PN will have intravenous lipid emulsion (ILE) piggybacked along with the PN. What is the appropriate hang time for ILE when piggybacked with a 2-in-1 PN?
   A. 8 hours
   B. 12 hours
   C. 18 hours
   D. 24 hours

Learning Assessment Answers:
1. Answer = B; Rationale: Current recommendations state that ILE within a TNA should have a maximum hang time of 24 hours. Recommendations also state than ILE piggybacked into a 2-in-1 PN solution should have a maximum hang time of 12 hours. Tubing should also be changed every 12 hours when ILE is piggybacked with 2-in-1 PN. These recommendations also state that if ILE is to be infused separately over > 12 hours, the dose should be divided into two parts with a new container and tubing every 12 hours.

References:
Learning Objectives
Upon completion of this session, the learner will be able to….

1. Summarize the 2017 ASPEN Lipid Survey and Gap Analysis.

Lipid Injectable Emulsion Survey With Gap Analysis

Table 2. How ILE Is Administered.

<table>
<thead>
<tr>
<th>Patients</th>
<th>TNA, %</th>
<th>Separate ILE Infusion, %</th>
<th>Both TNA and Separate ILE Infusion, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult patients</td>
<td>38.4</td>
<td>43.1</td>
<td>18.5</td>
</tr>
<tr>
<td>Pediatric patients</td>
<td>17.5</td>
<td>57.1</td>
<td>25.4</td>
</tr>
<tr>
<td>Infant patients</td>
<td>5.6</td>
<td>88.8</td>
<td>5.6</td>
</tr>
</tbody>
</table>

ILE, lipid injectable emulsion; TNA, total nutrient admixture.
Table 4. Repackaging of ELT in Pediatric and Neonatal Patients.

<table>
<thead>
<tr>
<th>Repackaging Technique and Hang Time</th>
<th>Pediatric Patients, %</th>
<th>Infant Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILT repackaged into syringes and stored for a maximum of 12 hours</td>
<td>20.6</td>
<td>26.6</td>
</tr>
<tr>
<td>ILT repackaged into syringes and stored for a maximum of 24 hours</td>
<td>34.7</td>
<td>54.4</td>
</tr>
<tr>
<td>ILT drawn down to a lesser volume in the manufacturer’s original container and infused for a maximum of 12 hours</td>
<td>18.1</td>
<td>5.1</td>
</tr>
<tr>
<td>ILT drawn down to a lesser volume in the manufacturer’s original container and infused for a maximum of 24 hours</td>
<td>12.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Other techniques and hanging times</td>
<td>13.9</td>
<td>18.1</td>
</tr>
</tbody>
</table>

ILT, Lipid emulsion solution.
The Use of Alternative ILEs in the Pediatric Population

Disclosures
Pharmaceutical advisory board
- B Braun
- Baxter
Consultant
- B Braun
- Fresenius Kabi
- Pfizer Pediatric Center of Excellence
- Xellia Pharmaceuticals
- Northsea Therapeutics
- Alcresta
- Otsuka Pharmaceutical Factory
Patents/royalties for use of Omegaven

Presentation Overview/Summary
For more than 50 years, soybean oil lipid emulsions were the mainstay of therapy in the pediatric patient. In 2016 a mixed oil emulsion was approved for use in adults and 2018 a pure fish oil emulsion became available for pediatric patients with PN associated liver disease. This session will discuss the approved and unapproved uses of these ILEs in pediatric patients and discuss potential the pros and cons of each product.

Learning Objectives
At the conclusion of the presentation, the learner will be able to:
1. Understand when lipid restriction protocols can be safely used
2. Discuss the concerns of using a mixed oil IVLE in a pediatric patient
3. List which patients should not receive fish oil monotherapy

Key Takeaways/Fast Facts
1. Pure soybean oil emulsions may be an appropriate alternative to the newer lipid emulsions in certain patients with limited venous access and multiple intravenous medications.
2. Monitoring essential fatty acid status is important in patients receiving an alternative IVLE.
3. Lipid restriction protocols should not be used with alternative IVLEs.

Learning Assessment Questions

Question 1: (True/false) Pure fish oil lipid emulsions contain only omega-3 fatty acids.
A. True
B. False

Question 2: According to the Holman Index, biochemical essential fatty acid deficiency occurs then the triene:tetrane ratio is:
A. > 0.05
B. < 0.05
C. >0.2
D. >0.4

Question 3: (true/false) Pure fish oil emulsions are FDA approved for use in preventing PN associated cholestasis in children.
   A. True
   B. False

Question 4: (true/false) Under the right circumstances, soy/MCT/olive/fish oil lipid emulsions can cause EFAD.
   A. True
   B. False

Question 5: (true/false) Fish oil monotherapy has been shown to be ineffective as a treatment of acetaminophen toxicity.
   A. True
   B. False

Learning Assessment Answers:
1. Answer: B (false). Fish oil contains both omega-3 and omega-6 fatty acids and when dosed appropriately, can provide sufficient essential fatty acids to prevent deficiency.

2. Answer: C. According to the Holman Index, biochemical evidence of EFAD occurs when the triene:tetraene ratio is greater than 0.2. Physical signs occur when the ratio is greater than 0.4. Other laboratory ranges have been used to describe what is observed in healthy individuals eating a typical Western diet.

3. Answer: B (false). Pure fish oil emulsions are only FDA approved as a source of essential fatty acids and calories in children with PN associated cholestasis. It is not approved for preventing PNAC.

4. Answer: A (true). In patients who are totally PN dependent, lower doses of these mixed oil emulsions have been associated with EFAD. Monitoring of EFA status is necessary to ensuring adequate doses are being provided.

5. Answer: A (true) In animal models, fish oil monotherapy has been shown not to be effective in treating the hepatic damage seen with acetaminophen toxicity.

References


The Use of Alternative ILEs in the Pediatric Population

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Disclosures

• Pharmaceutical advisory board
  – B Braun
  – Baxter
• Consultant
  – B Braun
  – Fresenius Kabi
  – Pfizer Pediatric Center of Excellence
  – Xelilia Pharmaceuticals
  – Northsea Therapeutics
  – Alcresta
  – Otsuka Pharmaceutical Factory
• Patents/royalties for use of Omegaven

A licensing agreement exists between Boston Children’s Hospital & Fresenius Kabi for the use of Omegaven in PNALD.

I will be discussing off labeled indications and products that are currently not FDA approved.

Disclosures

Soybean Oils

Recommendation: Based on 2 level 2 studies, in critically ill patients who are not malnourished, are tolerating some EN, or when parenteral nutrition is indicated for short term use (< 10 days), withholding lipids high in soybean oil should be considered.

– insufficient data to make a recommendation about withholding lipids high in soybean oil in critically ill patients who are malnourished or those requiring PN for long term (> 10 days)


Learning Objectives

At the end of this session, participants will be able to:
• Understand when lipid restriction protocols can be safely used
• Discuss the concerns of using a mixed oil IVLE in a pediatric patient
• List which patients should not receive fish oil monotherapy

Deciding When to Use Which Lipid Emulsion When.....
Intestinal Failure (IF)

- **Definition:**
  - PN dependence > 3 mo.
- Over 60% of infants with IF develop cholestasis (direct Bilirubin > 2 mg/dL)
  - Before 2004: mortality was 37.5% due to liver failure and or sepsis (Boston Children’s Hospital)
  - 78% mortality if bilirubin > 3 mg/dL for 3 months
  - Approach 90% mortality if cholestasis and remain on PN for > 1 year
  - 1.4% of all deaths of children 4 years of age and under

Prevention of IFALD

Impact of Soybean Lipid Dose

- **Lipid Restriction 1g/kg/day**
  - 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 Lipid Restriction

1g/kg/day

- Surgical neonates (n=82) receiving 1g/kg/d retrospectively compared to control cohort (2g/kg/d) (n=132)
- Results: PNLAD less in 1g/kg/d group (22% vs. 43% p=0.003)
- Omegaven rescue used in 4 infants in standard dose vs. 2 infants in low dose group

Severe Lipid Restriction

Current Opinion in Organ Transplantation 2010, 15:330–333

- **Protocol:**
  - 1 g/kg/d twice weekly
  - If EFAD develops: 1g/kg/day 3x/week
    - If the EFAD persists: 2g/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.
Secondary Outcomes: Growth

<table>
<thead>
<tr>
<th>Week</th>
<th>Median Weight-for-age Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-2.5</td>
</tr>
<tr>
<td>1</td>
<td>-2.0</td>
</tr>
<tr>
<td>2</td>
<td>-1.5</td>
</tr>
<tr>
<td>3</td>
<td>-1.0</td>
</tr>
<tr>
<td>4</td>
<td>-0.5</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

Median Weight-for-age Z-score Week

P=0.72

Secondary Outcomes: Infection rate

<table>
<thead>
<tr>
<th></th>
<th>Soybean Oil (n=10)</th>
<th>Fish Oil (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total # positive blood cultures</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Total # positive stool cultures</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total # positive sputum cultures</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Secondary Outcomes: Neurodevelopment

<table>
<thead>
<tr>
<th>Soybean Oil</th>
<th>Fish Oil</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 month Bayley Cognitive</td>
<td>95</td>
<td>93</td>
</tr>
<tr>
<td>24 month Bayley Language</td>
<td>100</td>
<td>111</td>
</tr>
<tr>
<td>24 month PARCA-R Cognitive</td>
<td>99</td>
<td>101</td>
</tr>
<tr>
<td>24 month PARCA-R Linguistic skills</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>24 month PARCA-R Composite Score</td>
<td>59</td>
<td>98</td>
</tr>
</tbody>
</table>

*PARCA-R: Parent Reports of Child’s Abilities

Conclusions from the pilot study...

No adverse effects:
- Growth
- Infection rate
- Fatty acid profiles
- Neurodevelopment

No difference in the incidence of cholestasis

Treatment of IFALD

Fish Oil Monotherapy

- Dose: 1g - 1.5 g/kg/day
- All soy containing IFE discontinued
- Efficacy:
  - Boston (historical controls)
  - LA (historical controls)
  - Texas (historical controls)
  - Hong Kong (prospective RCT)
Hong Kong RCT

- 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/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

How long should you remain on fish oil monotherapy?

Results of Pair Matching

- Resolution of Cholestasis
- Mortality Rates between Groups

Average time-to-resolution (days)

Boston Experience
Pair-Matching Analysis
Methodology

- Parameter # 1: direct bilirubin; 80-125% of the value of the potential pair was tolerated
- Parameter # 2: Age at baseline; ± 28-day range was accepted for the potential pair
- Parameter # 3: Gestational age; 90-110% of the value of the potential pair was accepted

31 patients were included in the analysis and matched according to the above mentioned criteria

- 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/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)
**Long-Term Outcomes in Children With Intestinal Failure-Associated Liver Disease Treated With 6 Months of Intravenous Fish Oil Followed by Resumption of Intravenous Soybean Oil**

(JPEN J Parenter Enteral Nutr. 2018 Nov 8)

- Children treated who resumed SO after FO; prospectively followed for 4.5 years or until death, transplant, or PN stop
- 1° outcome cumulative incidence rate IFALD return
- 48 subjects
  - 71% IFALD resolution after 6 mo.
  - 27 resumed SO
  - IFALD 26%
  - Transplant 6%

**Predictors of Intravenous Fish Oil (Omegaven®) Failure in the Treatment of Parenteral Nutrition-Associated Liver Disease**


- Study Design
  - Retrospective review of prospectively collected data for patients started on FO (Omegaven®) therapy at BCH from January 2004 to December 2014.
  - Inclusion criteria:
    - All patients with PNALD who received at least 1 dose of FO therapy from January 1, 2004 to December 31, 2014
  - Exclusion criteria:
    - Patients who started FO at outside institution
    - Patients who are still cholestatic (only included patients who have either failed or reversed)

- Results
  - 85.7% cholestasis reversed (156/182)
  - 14.3% failed FO therapy (26/182)
    - 8 transplants (6 multivisceral, 2 liver)
    - 18 deaths
  - 16.9% of pts transferred from OSH with PNALD vs. 9.4% of pts who developed PNALD at BCH failed FO therapy.
    - 20/118 [16.9%] vs. 6/64 [9.4%], P=0.16

**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.”

**Study Design**

- Retrospective review of prospectively collected data for patients started on FO (Omegaven®) therapy at BCH from January 2004 to December 2014.
  - Inclusion criteria:
    - All patients with PNALD who received at least 1 dose of FO therapy from January 1, 2004 to December 31, 2014
  - Exclusion criteria:
    - Patients who started FO at outside institution
    - Patients who are still cholestatic (only included patients who have either failed or reversed)

- Results
  - Patients who failed therapy had more advanced biochemical liver disease at time of FO initiation:
    - Lower GGT, platelets; Higher DB, INR, PELD
  - Patients who failed therapy had higher rates (than patients whose cholestasis resolved) of:
    - History of GI bleeding
    - Mechanical ventilation &/or sepsis at time of FO initiation
    - Neurologic, genetic/chromosomal, or endocrine comorbidity at FO initiation
Independent Predictors of Treatment Failure

<table>
<thead>
<tr>
<th></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>8.8 (2.1, 22.5)</td>
</tr>
</tbody>
</table>

Regressed equation:

\[ \text{PELD} = 4.8(\ln(TB)) + 18.57(\ln(INR)) - 6.87(\ln(albumin)) + 4.36 \text{ (if age <1 yr)} + 6.67 \text{ (if growth failure)} \]

Lessons learned...

- Patients who failed therapy were older and had more advanced biochemical and clinical liver disease at FO initiation.
  - However, many patients with similar labs and acuity responded to FO therapy.
- Early initiation of FO therapy once biochemical cholestasis is detected in PN-dependent patients is recommended.
  - 85 pts since 2011: 3 deaths, 1 LTx
- Reversibility of PNALD cannot be reliably determined.

Acetaminophen Toxicity

Animals fed a fish oil-based diet were more susceptible, rather than resistant, to APAP-induced hepatotoxicity.

Other Approaches

- SMOFlipid
- 50/50 blend FO + SO
- Reduced dose SO

SMOFlipid

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

Patients who shouldn’t be treated with Omegaven....
Concerns with SMOFlipid

- Not FDA approved in children
- Dosing important
- Low doses
  - Cause EFAD
- Higher doses
  - no hepatoprotective benefits

### Authors Study Design Cohort Lipid dose Length

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Cohort</th>
<th>Lipid dose</th>
<th>Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diamond et al</td>
<td>Pilot, multicenter, double-blind randomized trial comparing SMOFlipid to SOLE</td>
<td>60 premature neonates (age 3-7 days, gestational age ≤ 34 weeks, birth weights 1000-2500 g) on PN</td>
<td>2 g/kg/day</td>
<td>7-14 d</td>
</tr>
<tr>
<td>Repa et al</td>
<td>Prospective, randomized, double-blind study</td>
<td>28 children (5 month - 11 years) on PN</td>
<td>1-3 g/kg/day</td>
<td>8 wks</td>
</tr>
<tr>
<td>Goulet et al</td>
<td>Single-center, prospective, randomized, double-blind trial</td>
<td>230 ELBW infants (birth weight 500-2000g) on PN</td>
<td>3 g/kg/day day 5</td>
<td>7-14 d</td>
</tr>
<tr>
<td>Tomsits et al</td>
<td>Prospective, double blind, randomized trial comparing SMOFlipid to SOLE</td>
<td>60 premature neonates (age 3-7 days, gestational age ≤ 34 weeks, birth weights 1000-2500 g) on PN</td>
<td>2 g/kg/day</td>
<td>7-14 d</td>
</tr>
<tr>
<td>Rayyan et al</td>
<td>Double-blind trial comparing SMOFlipid to SOLE</td>
<td>53 neonates (&lt;34 week gestation, birth weights 1000-2500 g) on PN</td>
<td>3.5 g/kg/day day 6-14</td>
<td>35 d</td>
</tr>
</tbody>
</table>

*No studies were longer than 8 weeks*

**No studies looked at EFAD**

SMOFlipid failed to reverse IFALD

- Korea
- Case reports (n=2)
  - Received 2-3 g/kg/d SMOFlipid
  - IFALD developed
- IFALD reversed upon discontinuing SMOFlipid and switching to Omegaven monotherapy


- 4 infants receiving SMOFlipid® as their IV lipid source
  - essential fatty-acid status, triglycerides, and dosing strategy reviewed
- Conclusions
  - May render infants at risk for EFAD.
  - Hypertriglyceridemia and cholestasis are known adverse effects and require monitoring

*Safe and well tolerated,* *Incidence of IFALD not of progressive IFALD in children with intestinal ROP, no difference in hypertriglyceridemia*
SOY LIPID RESTRICTION

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

Pros and Cons
Soybean Oil ILE

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

- Cons
  - High 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

- Cons
  - Need at least 1g/kg/day to prevent EFAD
  - 10% emulsion
  - Little compatibility information

Putting it all together....

50/50 FO + SO

- Canada
- 12 patients with PNALD
- 1g/kg/d SO + 1g/kg/d FO
- 5 cases, hepatic dysfunction while on the blended regimen progressed until Intralipid® stopped and Omegaven® was given alone
- Complete resolution of PNALD occurred in 9 patients (75%)
Pros and Cons
Soy-MCT-Olive-Fish ILE

Pros
-20% emulsion
-can use to reduce GIR
-contains MCT – more stable TNAs

Cons
-3g/kg/d = 1g/kg/day soybean ILE
-not approved for use in pediatric patients
-limited compatibility data
-dose low: EFAD, dose high: IFALD

Gura’s Thoughts

• New start
  – Intralipid or SMOFlipid at age appropriate doses (i.e., 3g/kg/day if neonate)
• Limited vascular access/lots of IV meds
  – Intralipid 1g/kg/day
• Need to reduce GIR, no IFALD present
  – SMOFlipid
• IFALD
  – Omegaven

4 Lipid Emulsions Oil Red-O

PN + ClinOleic
PN + OM
PN + SMOF

There is no ideal ILE
Monitoring is essential!

Never assume….

WHEN YOU ASSUME
YOU MAKE AN OUT OF AND
References


References


References

Presentation Title
ILE: Does and Don’ts- The Utility of Alternative ILEs in the Adult Population

Disclosures
I have a commercial relationship with Fresenius Kabi as a consultant. I will not include any practice recommendations and will address only evidence-based science in my presentation.

Presentation Overview/Summary
- Data and recommendations for use of mixed oil intravenous lipid emulsion (IVLE) in adults are not clear. A large portion of the currently available data is based on investigations of formulations that were previously only available in Europe. In addition, the heterogeneity between published investigations further complicates evaluation of clinical use. Multiple meta-analyses have been conducted to evaluate the clinical utility of mixed oil IVLE and have reported conflicting results. Mixed oil IVLE has been reported to have a positive impact on a variety of important clinical outcomes. This case report will focus on the use of mixed oil IVLE in a critically ill patient with impaired triglyceride clearance.

Learning Objectives
At the conclusion of the presentation, the learner will be able to:
1. Summarize current evidenced based considerations for use of alternative IVLE in adult patients who require PN support
2. Explain the role of a 4-oil IVLE formulation in a critically ill adult patient with hypertriglyceridemia

Key Takeaways/Fast Facts
- Data and recommendations for use of mixed oil intravenous lipid emulsion (IVLE) in adults are not clear
- Data from previous investigations of alternative IVLE in patients requiring PN support have demonstrated a positive effect on triglyceride clearance

Learning Assessment Questions
1. Four-oil intravenous lipid emulsions have been investigated for potential clinical advantages including
   a. Stabilization of 3-in-1 PN solutions
   b. Prevention of micronutrient deficiencies associated with injectable soybean emulsions
   c. Improved triglyceride clearance
   d. Enhance carnitine metabolism in pediatric patients
2. Factors contributing to conflicting recommendations for routine clinical use of alternative IVLE in adults include
   a. Lack of comparative studies between specific IVLE formulations
   b. Inconsistent sources & doses of omega-3 fatty acids utilized in investigations
   c. Lack of heterogeneity between published investigations
   d. All of the above

Learning Assessment Answers:
1. Answer = C; SMOF lipid has demonstrated improved triglyceride clearance which is thought to be related to the medium chain triglyceride component
2. Answer = D; Clinical use of alternative IVLE in adults is not clear for a variety of reasons but primarily due to lack of heterogeneity between published investigations, lack of comparative studies between specific IVLE formulations and inconsistent sources and doses of omega-3 fatty acids utilized in investigations.

References
The Utility of Alternative ILEs in the Adult Population

ILE: Does and Don’ts

Todd W Mattox, PharmD, BCNSP
Medicine/Surgery Clinical Pharmacist
Moffitt Cancer Center
Tampa, Florida

Disclosures

• I have a commercial relationship with Fresenius Kabi as a consultant. I will not include any practice recommendations and will address only evidence-based science in my presentation.

Learning Objectives

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

1. Summarize current evidenced based considerations for use of alternative ILE in adult patients who require PN support
2. Explain the role of a 4-oil ILE formulation in a critically ill adult patient with hypertriglyceridemia

Clinical Use of Mixed IVLE in Adults

• IVLE provide a source of concentrated calories and essential fatty acids (FA)
• The oil source of IVLE influences cellular FA content which impacts a variety of metabolic processes such as essential FA status, cytokine production, triglyceride clearance and liver function in pts receiving PN
• The clinical relevance of oil-dependent metabolic changes associated with IVLE use in adult pts receiving PN is not clear

Clinical Use of Mixed IVLE in Adults

• Lack of comparative studies between specific formulations
• Heterogeneity between published investigations
• Patient populations; Small sample sizes
• Types of controls
• Sources & doses of omega-3 FA
• Biochemical and clinical end points
• Conflicting recommendations from a variety of sources
• International Professional Nutrition Societies acknowledge a role for lower ω-6: ω-3 IVLE
  • ASPEN, ESPEN, Canadian Critical Care Nutrition

Clinical Use of Mixed IVLE in Adults

• Areas Investigated for Clinical Advantages
  • Mortality & ventilation days in critically-ill
  • Infectious complications
  • ICU length of stay
  • Effect on Markers of Inflammation
  • PN associated liver disease
  • Serum triglyceride clearance
Clinical Use of Mixed IVLE in Adults

- Areas Investigated for Clinical Advantages
  - Mortality & ventilation days in critically-ill
  - Infectious complications
  - ICU length of stay
  - Effect on Markers of Inflammation
  - PN associated liver disease
  - Serum triglyceride clearance

MCC Criteria for Use: SMOF Lipid

- Critically ill patients requiring PN
- Patients who require PN support after HSCT
- Patients receiving SO-IVLE who develop hypertriglyceridemia
- Patients receiving SO IVLE who develop severe liver dysfunction

Patient Case Study: Adult Critical Care

52 yo woman with recurrent metastatic mucinous adenocarcinoma of sigmoid colon cancer with peritoneal involvement admitted for cytoreductive surgery, hyperthermic intraperitoneal chemotherapy (HIPEC), bilateral ureteral stent placement and hernia repair.

- Pts cytoreductive surgery included greater omentectomy, multiple peritonectomies for tumor removal, splenectomy and distal pancreatectomy, capsular lesion resections, small bowel resection and subsequent heated mitomycin intraperitoneal chemotherapy
- POD 2 Transfer to ICU for further management of hypoxia requiring heated high flow nasal cannula oxygen

Patient Case Study: Adult Critical Care

- POD 8 Development of intra-abdominal abscesses and peritonitis requiring return to the operating room for exploratory laparotomy, abdominal washout, and adhesiolysis at multiple sites.
- Post operatively, patient developed hypoxia and respiratory failure requiring mechanical ventilation and hypotension requiring vasopressor support
- Dexmedetomidine was initiated for ICU sedation, which was later changed to propofol

<table>
<thead>
<tr>
<th>Days of PN Therapy</th>
<th>Triglyceride Level mg/dL</th>
<th>LE Source</th>
<th>Notes</th>
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<tbody>
<tr>
<td>1</td>
<td>292</td>
<td>SO-IVLE</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>181</td>
<td></td>
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<tr>
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<td>215</td>
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<tr>
<td>33</td>
<td>269</td>
<td>SO-IVLE</td>
<td>Return to OR; decantacholade</td>
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<tr>
<td>46</td>
<td>152</td>
<td>SO-IVLE + propofol</td>
<td>Dexmedetomidine changed to Propofol</td>
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<td>48</td>
<td>211</td>
<td>Propofol</td>
<td>SO-IVLE held</td>
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<tr>
<td>50</td>
<td>162</td>
<td>Propofol Sc x; SMOFlipid 20% 250 mL added to PN Regimen</td>
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<tr>
<td>Days of PN Therapy</td>
<td>Triglyceride Level (mg/dL)</td>
<td>IVLE Source</td>
<td>Notes</td>
</tr>
<tr>
<td>------------------</td>
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<tr>
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<td>IVLE</td>
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<td>IVLE</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>215</td>
<td>IVLE</td>
<td>Return to OR, Dexmedetomidine changed to Propofol</td>
</tr>
<tr>
<td>51</td>
<td>298</td>
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</tr>
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<td>52</td>
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<td>IVLE</td>
<td></td>
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<tr>
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<td>230</td>
<td>IVLE</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>243</td>
<td>IVLE</td>
<td></td>
</tr>
</tbody>
</table>

Summary

- Data from previous investigations of alternative IVLE in patients requiring PN support have demonstrated a positive effect on triglyceride clearance.

- This case illustrates an association with use of an alternative IVLE containing Soybean oil, MCT oil, Olive oil and Fish oil with improvement in triglyceride concentrations in a complicated critically ill patient receiving PN.

Questions?

Todd.Mattox@Moffitt.org

References

4. Zaloga GP. Phytosterols, lipid administration, and liver diseases during parenteral nutrition. JPEN J Parenter Enteral Nutr. 2015;39(suppl):1S-21S.
Name, Title, Affiliation
Jay M Mirtallo, MS, RPh, BCNSP, FASHP, FASPEN, Clinical Practice Specialist, The American Society for Parenteral and Enteral Nutrition and Professor Emeritus, The Ohio State University, College of Pharmacy

Presentation Title
Overview and History of ILEs Available in the United States

Disclosures
I have a commercial relationship with Fresenius Kabi as a member of speaker’s bureau and consultant. I also consult with Coram Home Infusion, MedEdicus and Wolters Kluwer. I will provide practice recommendations that are based on formal structured review of the literature and will state inclusion and exclusion criteria.

Presentation Overview/Summary
Clinicians have had over 4 decades experience with Soy based ILE. Along this journey, there have been many issues with ILE use that needed to be addressed. ILE is a complex formula that has physico-chemical properties that present issues with stability and compatibility. Although an excellent source of essential fatty acids, Soy ILE is scrutinized for its usefulness as an energy source and its role in physiologic processes related to immunity, infection, coagulation and stress. The safety of Soy ILE is dependent on daily dose, infusion rate, duration of therapy and administration method. This led to the evolution of ILE products not commercially available in the United States until recently. In our quest to find ILE that have a lower content of omega-6 fatty acids, a reliable source of omega-3 fatty acids and an efficient energy source, we now have ‘alternative’ ILE available to consider. Its an exciting time for PN therapy due to the approval of the ‘alternative’ ILEs and the discussion of if, when and how these will be put into use.

Learning Objectives
At the conclusion of the presentation, the learner will be able to:
1. Discuss the variables to consider when selecting ILE products for use in practice
2. State the advantages of ILE over dextrose as a PN calorie source
3. Describe the characteristics of the various oils used in ILE products
4. Compare the compositional difference in ILE products available in the US

Key Takeaways/Fast Facts
Variables to consider when selecting ILE products for use in practice
- Cost
- Stability
- Compatibility
- Metabolism
- Oxidized for energy
- Free radical production
- Triglyceride clearance
- Administration: as TNA or separate infusion, multi-chamber product
- Physiologic impact on immunity, infection, coagulation and stress response

Learning Assessment Questions
1. ___________________ is an advantage of ILE use as a calorie source in PN
   A. Reduced fluid volume due to caloric density
   B. Reduced glucose load
   C. Increased carbon dioxide production
   D. Decreased in-use contamination

2. The infusion rate of ILE associated with a lower rate of hypertriglyceridemia is______________ g/kg/d.
   A. < 1.5
   B. 2.0
   C. > 1.5
D. >2.5

3. A characteristic of _____________ oil is its reliable triglyceride clearance
   A. Soy
   B. Olive
   C. Medium Chain Triglycerides (MCT)
   D. Fish

4. An important compositional difference of the new ‘Alternative’ ILE products as compared with Soy ILE is _____________.
   A. The inclusion of fish oil
   B. The particle size of the emulsion
   C. Reduced omega-6 fatty acid content
   D. The inclusion of medium chain triglycerides

Learning Assessment Answers:
1. Answer = B: Although oral fat is more calorically dense than dextrose, because the concentration of lipid in ILE (20%) is lower that dextrose (50-70%) before admixture in PN, it is not always more calorically dense. Fat oxidation has a lower amount of carbon dioxide produced than carbohydrate and ILE. ILE due to its lower osmolality and oil characteristic may support microbial growth better than dextrose based PN if inadvertently contaminated.
2. Answer = A: in the study by Liop, ILE infusion rate was correlated with hypertriglyceridemia with the frequency being lower at a rate of <1.5 g/kg/d (24.9% compared with 54.5% at rates > 1.5 g/kg/d). A rate >2.5 g/kg/d should not be exceeded according to all ILE package inserts.
3. Answer = C: MCT is also efficiently oxidized, soy oil is useful for essential fatty acids, olive oil is not metabolized to active biproducts and fish oil provides a rich source of omega 3 fatty acids
4. Answer = C: Although fish oil and medium chain fatty acids are positive additions to ILE formulations, not all ILEs contain fish oil and/or MCT but the ‘alternatives all have a lower content of omega 6 fatty acids.

References
Overview and History of ILEs Available in the United States

Jay M. Mirtallo, MS, RPh, BCNSP, FASHP, FASPEN
Professor Emeritus, The Ohio State University, College of Pharmacy
Clinical Specialist, American Society for Parenteral and Enteral Nutrition

Learning Objectives

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Role of Lipid (ILE) in Parenteral Nutrition

Prevention of Essential Fatty Acid (EFA) deficiency
Dose:
- Linoleic acid 2.5% of calories
- Linolenic acid 0.5% of calories
Energy source
- Reduce dextrose load/dose
- Precursor to biochemical products of immunity, coagulation and stress response

20% Lipid Emulsion Composition: A Complex Pharmaceutical Formulation

<table>
<thead>
<tr>
<th>Product</th>
<th>Soy ILE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil</td>
<td>Soybean</td>
</tr>
<tr>
<td>Egg yolk phosphatide</td>
<td>1.2%</td>
</tr>
<tr>
<td>Glycerin</td>
<td>2.25%</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>290</td>
</tr>
<tr>
<td>pH</td>
<td>6.4-6.9</td>
</tr>
<tr>
<td>Fat particle size</td>
<td>0.8</td>
</tr>
<tr>
<td>Size</td>
<td>100, 250, 500, 1000</td>
</tr>
</tbody>
</table>
PN Pulmonary Complications: Hypercapnea

- Dextrose dose > 5 mg/kg/min
- Caloric dose > 150% of Needs

Lungs

\[ \uparrow \text{Carbon dioxide production} \]

- Respiratory failure in Pts with limited pulmonary reserve
- Prolonged mechanical ventilation

\* Less CO\(_2\) produced per molecule of fat than per molecule of dextrose
\* Respiratory quotient (RQ) dextrose = 1
\* RQ fat = 0.7

ILE: Limitations to Use

- Limitations to use as a Calorie Source
  - Cost
  - Stability
  - Contamination
  - Metabolism more complicated than dextrose

ILE: Cost Effective Nutrition Support

- Lipid emulsions 15 x more expensive than dextrose
- Restricted use: savings of $75,000 per yr
  - Diabetes or diabetes of stress
  - Impaired pulmonary function
    - CO\(_2\) retention
  - TPN-induced liver disease
- Hold Lipid for 3 weeks for EFAD prevention

ILE: Stability Concerns

- Emulsion destabilization
  - Aggregation
  - Creaming - reversible
  - Coalescence - irreversible
  - Oiling out
    - Excess particle size
    - > 6 microns

IV Lipid Emulsions: Stability Concerns

- Adverse effects of Administration
  - Particle size > 6μ
    - Fat embolism
    - Acute reactions
    - Hypotension
    - Pulmonary hypertension
    - Acidosis
    - More rapid clearance by RES in liver, spleen and lungs

ILE: In-Use Contamination

- Microbial growth characteristics
  - Lipid emulsion alone
    - Intermittent infusion separate from PN
    - Characteristics supporting microbial growth
      - Iso-osmotic
      - High pH
      - Glycerol
  - As TNA
ILE: In-Use Contamination

- Malassezia furfur
  - Dependent on exogenous fatty acids
  - Sebaceous glands and surrounding tissues
  - Propofol
    - Hang time
    - Aseptic technique
    - Contaminated equipment in preparation

Soy ILE: Metabolic Fate of IV Lipid

ILE: Factors affecting Clearance

- Phospholipid content
  - Phospholipid:Tg ratio
    - 4 X greater in 10% vs 20% emulsion
- Particle size
  - Increase size hastens clearance
- Infusion rate
  - Amount: >1.5 g/kg/d
  - Continuous
    - Fewer fluctuations in serum Tg
    - Improved fat oxidation
    - Immune function

Hypertriglyceridemia

- Plasma clearance
  - Phospholipid concentration: 10 vs 20%
    - Phospholipid:triglyceride ratio
- Infusion rate: exceed lipolytic capacity of endothelial lipases
  - Influence of critical illness
  - Accumulation of TG in RES
  - Displacement of bilirubin from albumin by FFA

Hypertriglyceridemia

- Side effects of lipids - rapid administration
  - Rate not to exceed
    - 0.11 g/kg/hr healthcare environment (continuous)
    - 0.15 g/kg/hr homecare (cyclic)
- Caution to prevent
  - Pancreatitis in adults
  - Hyperlipidemia and fat overload in neonates

Hypertriglyceridemia (6-30%)

- Infusion rate (g/kg/d)
  - < 1.5: 62/249 (24.9%)
  - > 1.5: 6/11 (54.5%)
- Risk factor: 62/215 (28.8%)
  - Renal failure
  - Gluc > 180
  - Prednisone
  - Pancreatitis
  - sepsis
- No Risk Factor: 6/45 (13.3%)
  - Important to monitor triglycerides at baseline and periodically thereafter

Fat Overload Syndrome

- Acute onset:
  - Fever
  - Jaundice
  - Inflability
  - Spontaneous hemorrhage
  - Hyperlipidemia

- Fat Overload Syndrome
  - Excessive accumulation of serum lipids
  - Other symptoms
    - Lethargy
    - Tachycardia
    - Headache
    - Nausea, vomiting, abdominal pain
    - Hepatosplenomegaly
    - Cough with hemoptysis

Fat Overload Syndrome

- Children
  - 10 month to 9 years
  - Large daily doses: 3.3-5.4 g/kg/day
  - Long duration: 28-114 days
- Extreme effects when administered beyond the recommended daily dose and infusion rates

ILE: Cholestatic Jaundice

- Excessive dosage: 3 g/kg/day
- Long-term use: Mean duration 45 days
- Significant increase:
  - Alkaline phosphatase
  - Bilirubin
  - Cholesterol
- Liver biopsy:
  - Periportal, mixed inflammatory infiltrates
  - Bile duct proliferation in portal triads
  - Canalicular bile plugs
- Improvement with lower dose or PN discontinued

Parenteral Nutrition Associated Liver Disease (PNALD)

- Prevalence increases with duration of PN therapy
- Role of fat emulsions
  - Fat source
  - Phytosterol content
  - Dose
    - > 1g/kg/day in long term PN patients

Lipid Peroxidation

- Alterations in various organs as a result of tissue peroxidative damage
  - ‘Free radicals’
    - React with all cellular components:
      - Proteins
      - Nucleic acids
      - Lipids
    - α-tocopherol inhibits lipid peroxidation
ILE: Systems Issues

- TNA vs separate intermittent infusion
- Look alike-sound alike
- Safety
  - Infusion rate
  - Duration
  - Medication errors

Safety of System: Lipid Emulsions

- Medication errors occur with fat emulsions
  - Separate administration from PN
- Nodes involved
  - Order
    - Lack of standard method of ordering IVFE
  - Administration
    - Misinterpretation of the rate on the IVFE order
    - Improper programming of infusion pump

ILE: PN Ordering Practices

- g/kg/d
- g/d
- g/L of PN
- % final concentration
- g/total volume of PN
- Kcal/kg
- Volume of % concentration to be added to or infused separate from PN
- ml/d
- ml/L of PN
- G per total PN volume
- Nonprotein kcal

ILE: Clinical Implications

Soy IVE are relatively safe when used according to manufacturer best practice recommendations

- Dose < 2.5 g/kg/d
- Infusion rate < 0.11 g/kg/h
- Tg levels may be improved with use of 20% vs 10% product
- Use of Soy IV ILE require careful monitoring of triglycerides and other organ systems affected from long term use.

Evolution of ILE Products

Objective

- “Dilution” of ω-6 fatty acid content
  - Oils that are easily metabolizable and do not exacerbate inflammatory stress
    - MCT, Olive Oil
  - Add ω-3 fatty acids from fish oil
- Ultimately achieve a ratio of ω-6:ω-3 of 2:1-4:1
Oil Characteristics

- Soybean
  - Rich source of Essential fatty acids
    - Omega 6 fatty acids – more proinflammatory
- Medium chain triglycerides
  - Efficient energy source
  - Reliable triglyceride clearance
- Olive oil (Oleic acid)
  - Reduce polyunsaturated fatty acid load (peroxides)
  - Neutral end product
- Fish oil
  - Omega 3 fatty acids

U.S. Lipid Product Composition

<table>
<thead>
<tr>
<th>Brand</th>
<th>Intralipid®</th>
<th>Nutralipid®</th>
<th>Smoflipid®</th>
<th>Clinolipid®</th>
<th>Omegaven®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil Source</td>
<td>Soybean 100%</td>
<td>Soybean 30%, Medium Chain 30%, Olive Oil 25%, Fish Oil 15%</td>
<td>Soybean 20%, Olive Oil 80%</td>
<td>Fish Oil</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Fat Composition (% Mean Value(Range))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linoleic acid</td>
</tr>
<tr>
<td>Linolenic acid</td>
</tr>
<tr>
<td>Oleic acid</td>
</tr>
<tr>
<td>Eicosapentanoic acid (EPA)</td>
</tr>
<tr>
<td>Docosahexaenoic acid (DHA)</td>
</tr>
</tbody>
</table>

Summary

- Variables to consider when selecting ILE products for use in practice
  - Cost
  - Stability
  - Compatibility
  - Metabolism
    - Oxidized for energy
    - Free radical production
    - Triglyceride clearance
  - Administration: as TNA or separate infusion, multi-chamber product
  - Physiologic impact on immunity, infection, coagulation and stress response

Conclusion

- Safety and efficacy of Soy ILE has been shown to be dependent on infusion rate, daily dose (g/kg) and duration.
- Current guidelines for use in the US address the problems from Soy ILE that limits dose and use in particular patient populations
- Issues concerning the efficacy as a calorie source, triglyceride clearance and physiologic effects on immunity, coagulation and stress response led to an evolution in ILE products not commercially available in the US until recently
- Its an exciting time for PN therapy due the approval of ‘alternative’ ILEs and the discussion of if, where and how these will be put into use

Learning Assessment Questions

1. _______________ is an advantage of ILE use as a calorie source in PN
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Learning Assessment Questions

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Learning Assessment Questions

4. An important compositional difference of the new ‘Alternative’ ILE products as compared with Soy ILE is ____________
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References