Oil’s Well That Ends Well
Understanding the Differences in Lipid Emulsions

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Disclosures

• B.Braun – advisory board, consultant
• Fresenius Kabi – consultant, research support
• Pronova/BASF – advisory board, research support
• Sancilio & Company -advisory board, research support

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

I will be discussing unapproved and off labeled use of medications.
Learning Objectives

• Discuss challenges of bringing new intravenous lipid emulsions (IVLE) to the U.S. market
• Understand the what data was used to approve IVLE in the U.S.
• Describe the differences in the currently used products in the U.S.
IV Lipid Emulsions are Not New

- William Courten 17th century
  - Intravenous olive oil 1g/kg given to a dog
  - Fatal outcome
    - Severe respiratory distress
    - ? Embolism

- Edward Hodder -1873 (Canada)
  - Milk infusion in 3 patients with cholera
    - 2/3 survived “effect magical”
  - Could not be reproduced by others
    - unmodified fats could not be given IV
20th Century Lipid Research
1920-1960

Yamakawa
Nomura

Stare
Geyer
Meng
Canham
Lipid Emulsions

• Formed as artificial chylomicrons
  – Spherical form (200-500nm in diameter)
• Need an emulsifier to allow the dispersion of the oil into the water and ensure a stable emulsion
  – Emulsifiers similar to phospholipids in natural chylomicrons
Lipomul
Upjohn Co (Kalamazoo, MI)

• 15% cotton seed oil /4% soy phospholipids/0.3% ploxamer
• Numerous serious adverse effects
  – chills, fever, nausea, vomiting
  – dyspnea, hypoxia, and hypotension
• Product removed from the market after several years
• Negative US experience dampened the interest in fat emulsions worldwide
• Only dextrose available as a parenteral energy source
Arvid Wretlind
“Father of Complete Nutrition” - 1961
What’s Common to ALL IVLE Products

• Water for injection
• 1.2% egg yolk phospholipids
• 2.25%-2.5% glycerin
• Sodium hydroxide
What’s Different

- Phytosterol content
- Vitamin E content
- Inflammatory characteristics due to oil source

Typically not noted on the product label!
Phytosterols

- Plant sterols
- Typically only small amounts absorbed by GI tract
- Undergo hepatic metabolism
- IV phytosterols reduce bile acid flow

http://www.avfchem.com/images/04.gif
## Comparison of Lipid Emulsions

(10 g fat / 100 mL)

<table>
<thead>
<tr>
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<th>Intralipid</th>
<th>Omegaven</th>
<th>SMOFlipid</th>
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<tbody>
<tr>
<td>Soybean</td>
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<tr>
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<tr>
<td>Fish</td>
<td></td>
<td>100%</td>
<td>15%</td>
</tr>
<tr>
<td>Glycerol</td>
<td>2.25</td>
<td>2.5</td>
<td>2.5</td>
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<tr>
<td>Egg Phospholipid</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Phytosterols (mg/L)</td>
<td>439± 5.7</td>
<td>3.66</td>
<td>207</td>
</tr>
</tbody>
</table>
Vitamin E (alpha–tocopherol)

- Anti-oxidant
- Prevents hepatic injury (animal models)
- Prolonged use of soybean oil IFE may reduce $\alpha$-tocopherol concentrations in plasma lipoproteins
  - Soybean oil contains $\gamma$-tocopherol
    - Less bioactive than $\alpha$-tocopherol
# Comparison of Lipid Emulsions

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<tr>
<td>Vitamin E mg/L</td>
<td>38mg</td>
<td>150-296mg</td>
<td>163-225mg</td>
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OIL SOURCES
Soybean (SO)

- Oil source in first successful IFE (1961)
- 50% linoleic acid ($\omega$-6 fatty acid)
  - Must be converted to arachidonic acid
- 25% oleic acid ($\omega$-9 fatty acid)
- 10% alpha-linolenic acid ($\omega$-3 fatty acid)
  - Must be converted to EPA and DHA
- Very low Vitamin E content
- Rich in phytosterols
Intravenous Fat Dosage
Pure Soybean Oil

• neonates
  initial: 0.5 gm/kg/day
  max:  3 gm/kg/day *
• Infants
  initial: 1 gm/kg/day
  max:   2-3 gm/kg/day*
• 8-10% total calories should be provided as fat to prevent EFAD (0.5-1g/kg/day)
• Consider lipid restriction (i.e., 1g/kg/day in patients at risk for IFALD
Medium Chain Triglycerides (MCT)

- Derived from coconut oil
- Mainly caprylic and capric acids
- Readily oxidizable
- Devoid of pro-inflammatory properties
- May be protein sparing
- Does not impair hepatic function or immune function
- Resistant to peroxidation

CONTAIN NO ESSENTIAL FATTY ACIDS
Olive Oil

- Introduced in Europe 1990’s
- 5% of fatty acid profile linoleic acid (ω-6)
- “neutral” pro inflammatory properties
- Lower phytosterol content
- Higher α-tocopherol content
- Oleic acid is fairly resistant to peroxidation
- May leach more DEHP in comparison to soybean oil
Fish Oil

- Rich in ω-3 fatty acids
  - Primarily DHA, EPA
- Contains some arachidonic acid
- Little to no phytosterols
- Rich in Vitamin E
- Considered to have nutritional as well as therapeutic benefits
- Potential MOA in IFALD: GPR120 agonist
  - mediates anti-inflammatory effects

(J Hepatology 2014:60:625–632)
Function of Each Oil Type

- **Soybean oil**: provides essential fatty acids
- **MCT**: source of rapidly available energy, spares larger amounts of essential fatty acids for incorporation into cell membranes
- **Olive oil**: indirect anti-inflammatory effect by replacing omega-6 fatty acids with oleic acid and is less prone to peroxidation than PUFAs
- **Fish-oil**: influence inflammatory reaction
  - inhibit inflammatory gene induction, cytokine release and adhesion molecule, source of DHA
Rationale for Reducing Soybean Oil Intake

• Decreases linoleic acid load
• 2 ways to achieve this
  – Dilute with another inert oil
  – Partially replace some soybean oil with another type of oil that has different inflammatory properties
Proposed Benefits of a Mixed Oil ILE

• Favorable omega-6/omega-3 fatty acid ratio
  – ratio 2.5:1 (Intralipid 7:1)
  – Mixing four different oils optimizes the fatty acid profile

• Emulsions enriched with alpha-tocopherol maintain an adequate antioxidant status
  – avoids lipid peroxidation
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### EFA % by weight

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<tr>
<td>Linoleic</td>
<td>50</td>
<td>4.4</td>
<td>21.4</td>
</tr>
<tr>
<td>α-Linolenic</td>
<td>9</td>
<td>1.8</td>
<td>2.5</td>
</tr>
<tr>
<td>EPA</td>
<td>0</td>
<td>19.2</td>
<td>3</td>
</tr>
<tr>
<td>DHA</td>
<td>0</td>
<td>12.1</td>
<td>2</td>
</tr>
<tr>
<td>Arachidonic acid</td>
<td>0</td>
<td>1 -4</td>
<td>0.15-0.6</td>
</tr>
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EPA: Eicosapentaenoic Acid; DHA: Docosahexaenoic Acid
BRINGING IV LIPID EMULSIONS TO THE UNITED STATES
Intralipid
1962 (Sweden)

• Soybean oil based
  – Linoleic acid (52%), linolenic acid (8%), and oleic acid (22%).

• Vitrum Company
  – Swedish a family-owned enterprise committed to PN

• Numerous generics quickly followed but *not in US*
  – European PN: 50% calories as lipid emulsion and the remainder as dextrose (i.e., the fat system)
  – Dudrick 1968 US PN: high dextrose / **NO FAT** (i.e. dextrose system)
IVLE Development Challenges

• IVLEs have been approved based on ability to provide calories and essential fatty acids

• To date, IVLE trials have been underpowered to show statistically significant changes in clinical outcomes

• Original product goals:
  – provide concentrated ENERGY
  – To secure delivery of ESSENTIAL FATTY ACIDS
  – … and do it SAFELY

No product has been approved based on therapeutic efficacy
“The oils contained in these emulsions are ones found in diet, and the fatty acid distribution is similar to that found in dietary vegetable oils. It seems that the efficacy is really that of a nutrient source of calories. **Clearance of triglycerides** is probably an acceptable measure of effective use of the fat for energy in muscle or storage in adipose tissue.”
Intralipid in the U.S.

10% Intralipid approved by FDA (1975); 20% (1981) 30% (1993)

After the first application for 20% Intralipid in January 1980:

- FDA requested data collected by the US Army & Riker Laboratories in the 1960’s

US Army data:

- 47 patients
  - 500 ml Intralipid 20%/day - 6 – 21 days (596 infusions)

- Parameters measured:
  - Hematology, Coagulation, LFTs, TG, Cholesterol, phospholipids

US Army and Stockholm data:

- Liver and spleen biopsies (after Intralipid infusions)

- Data collected from other centers: 664 patients/1850 infusions
Intralipid: Pediatric Data for Approval

- Children < 4 years of age
- No adolescents studied
Liposyn

• Developed by Abbott Laboratories
• 3 products
  – Liposyn 10%  – 100% safflower oil (77% LA /0.1% ALA)
  – Liposyn II -  50/50 soybean – safflower oil blend
  – Liposyn III 100% soybean oil
Liposyn (original)

- 10% approved 1979; 20% 1981
- Approval based on:
  - Prevent S&S of EFAD in PN patients
  - Source of calories
  - T/T ratio used to assess EFA status
  - Studies:
    - Adult
      - 50 patients 14-28 days duration (566 infusions) 15 trials/5 protocols
      - Used LA dosing as variable
    - Pediatric
      - 5 patients, up to 28 days
- Discontinued in 1984

FDA Workshop October 29th, 2013
Liposyn

Liposyn 20%
– Administration of Liposyn 20% providing about 1/3 to half of caloric requirements will maintain or improve nutritional status without causing undue side effects
  – Provide calories in smaller fluid volume
  – Two week duration
  – Hematology, chemistry, urinalysis
• Adults
  – 2 protocols; n=116, 1907 infusions
• Pediatrics, 1353 infusions
  – Infants/children n=43
  – Premature infants n=17

FDA Workshop October 29th, 2013
Liposyn II and Liposyn III

• Liposyn II
  – Clearance studies and prior approvals of Liposyn original

• Liposyn III
  – No clinical trials on 10% and 20% concentrations
  – 2 uncontrolled studies on Liposyn III 30%
Nutrilipid (B. Braun)

- 10% and 20% approved May 1993
  - Was discontinued but reintroduced in 2014
- Approved based on noninferiority studies to Intralipid and Liposyn III
Pharmacopeial Specifications

• Helps determine embolic risk and assists in determining beyond use dating
  – Larger (> 5 μm) particles can become trapped in the lungs
  – Values that outside USP 729 established ranges suggest an unstable emulsion

• USP 729
  – Mean Droplet Diameter
    • <500 nm (0.5 μm)
  – Large globule content (% fat-residing globules) >5 μm (PFAT$_5$)
    • Must not exceed 0.05%
NEW LIPID EMULSIONS IN THE US
What’s Different with FDA Approval Process

• Nutrition noninferiority study endpoints still used
  – Weight gain
  – Weight maintenance
  – Serum levels of free fatty acids/triglycerides

• Other studies may be needed if deemed absolutely necessary
  – ? Phytosterol content
  – PFAT₅ if packaging changes
  – Pediatric specific studies
WHAT’S APPROVED
Clinolipid (Baxter)

- Newest IFE product approved in US (2013)
- Lower % PUFAs but still providing an adequate amount of EFAs
  - 80% refined olive oil and 20% refined soybean oil
- Lower soybean oil content in order to ↓ LA levels
- Contains the same 5 major fatty acids, including the same EFA components as the soybean oil
- Approved as a non-inferiority product to Intralipid

FDA workshop October 29, 2013
Clinolipid

- No pediatric indication (black box warning can be fatal in premature infants)
  - Increase risk of essential fatty acid deficiency (EFAD)
- Only available in 1000mL containers
  - Not listed as pharmacy bulk package
  - Provides 200 grams fat (typical adult dose 67 g/day)
- **Must** be administered with 1.2 micron inline filter
- Cannot be used with some PN compounding devices
  - Increases particle generation
SMOFlipid (Fresenius Kabi)

• Approved in Europe 2000; US July 13, 2016
• Lipid Source: 30% soybean oil; 30% medium chain triglyceride (MCT) oil; 25% olive oil; 15% fish oil
• May provide anti-inflammatory, immune protection and pro-oxidant properties compared to Intralipid 20%
• May be a better energy source for the critically ill who would benefit from the addition of n-3 fatty acids
SMOFlipid® - Composition

Fatty Acid Pattern of Lipid Emulsions vs. Human Umbilical Cord Blood and Human Breast Milk

- **Human Umbilical Cord Blood**
- **Human Breast Milk**
- **SMOFlipid®**
- **Soybean oil** (100%)
- **Olive oil/Soybean oil** (80%/20%)
- **MCT/LCT** (50%/50%)

**Legend**
- Saturated fatty acids (SFA)
- Monounsaturated fatty acids (MUFA)
- Essential fatty acids (EFA)

References:
- Oliveira OR, Santana MG, Santos FS et al. Lipids Health Dis 2012;11:157
Current Approval

SMOFlipid approved in **adults**
- as a source of calories and essential fatty acids

Pediatric indication
- submission of postmarketing pediatric studies deferred to 2019

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/207648Orig1s000ltr.pdf
Pediatric Dosing

• SMOFlipid **NOT suitable** for lipid restriction protocols
• Recommended dosing:
  – 2-4 g/kg/day (Goulet O, et al. JPEN 2010; 34:485-495)
WHAT’S BEING USED INVESTIGATIONALLY/COMPASSIONATE USE
Omegaven
(Fresenius Kabi)

• Approved in Europe
• 100% fish oil (10% IVLE)
• Typically used in combination with Intralipid
• Max labeled dose 0.2g/kg/day
• Dose used in PNALD: 1g/kg/day as monotherapy
• Not indicated for use in children
• Not intended to be used as monotherapy
• Not FDA approved
July 2002

- 16 year old male s/p BMT with a soy allergy requiring PN/lipids
- Developed essential fatty acid deficiency
- Treated with Omegaven® as monotherapy for 50 days until able to resume enteral feeds
- No adverse events associated with its use despite having several listed contraindications (hypertriglyceridemia, hyperglycemia)

Omegaven Compassionate Use Protocol

- Conventional fat emulsions are discontinued
- Omegaven® dosing: advanced to 1 g/kg/day for remainder of time on PN
- Additional non protein calories provided as carbohydrate
Comparison of 4 IVLEs

- Chow
- Intralipid
- Clinoleic
- Omegaven
- SMOFlipid

Boston Children's Hospital
Until every child is well

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Conclusions

- New products are currently only approved for use in ADULTS
- There is still no perfect IVLE
- Progress is being made
- We still have a long way to go
THANK YOU!
Thank you!
References

References