Intravenous Lipid Emulsions (IVLE)

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Disclosures

- I have no disclosures to make
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Objectives

• To provide pharmacists with an understanding of the background of Intravenous Lipid Emulsions (IVLEs) approved for use by Health Canada and on the Alberta Health Services Drug Formulary
• Recognize IVLE bags
• Provide indications and contraindications for use
• Discuss key safety issues relating to PN IVLEs
Fatty Acids

• Fatty acids are:
  o Individual components of fat
  o Chains of Carbon and Hydrogen
    • Short, medium and long chains
  o Saturated, monounsaturated and polyunsaturated (highly unsaturated)

• Purpose of IVLEs:
  o Source of essential fatty acids (EFAs)
  o Alternative source of calorie provision
Metabolic Pathway of n-6 and n-3 Fatty Acids

Le et al. PLEFA, 2009.
Background

- Intravenous Lipid Emulsions (IVFE) first used in practice in 1961
  - Composed solely of Soybean oil (SO) based IVLE
- Since then, 3 alternative IVLEs have been made available in Europe and other parts of the world
- Creation of alternative IVLE largely motivated by desire to reduce the intake of Omega-6 Fatty Acids (n-6)
- Alternative IVLE to SO may have greater clinical benefits
Current Recommendations

Canadian Clinical Practice Guidelines, March 2009/2013

“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. There are 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). Practitioners will have to weigh the safety and benefits of withholding lipids high in soybean oil on an individual case-by-case basis in these latter patient populations.”

www.criticalcarenutrition.com 10.2
Strategies to Optimize Parenteral Nutrition and Minimize Risks: Use of lipids, Mar 2013
“When parenteral nutrition with intravenous lipids is indicated, IV lipids that reduce the load of omega-6 fatty acids/soybean oil emulsions should be considered. However, there are insufficient data to make a recommendation on the type of lipids to be used that reduce the omega-6 fatty acid/soybean oil load in critically ill patients receiving parenteral nutrition.”
“Many patients who require IVFEs are already in a compromised state. Such patients could potentially have better clinical outcomes when receiving one of the alternative IVFEs to diminish the intake of the potentially pro-inflammatory ω-6 fatty acid - linoleic acid - which compromises more than 50% of the fatty acid profile in SO.”

Vanek et al. 2012
European Society for Parenteral and Enteral Nutrition (ESPEN), 2009

“Statement: Lipid emulsions should be an integral part of PN for energy and to ensure essential fatty acid provision in long-term ICU patients. (Grade B).”

“Recommendation: Addition of EPA and DHA to lipid emulsions has demonstrable effects on cell membranes and inflammatory processes (Grade B). Fish oil-enriched lipid emulsions probably decrease length of stay in critically ill patients. (Grade B).”

Current Recommendations- cont’d

European Society for Parenteral and Enteral Nutrition (ESPEN), 2009

“The optimal PN regimen for critically ill surgical patients should probably include supplemental n-3 fatty acids (Grade C). The evidence-base for such recommendations requires further input from prospective randomised trials.”

Systematic review of 6 RCTs in ICU patients
Evaluating the effects of PN Fish oil-based strategies

Conclusions:
- "FO containing emulsions may be associated with a tendency to reduce mortality and ventilation days in the critically ill."
- No effect on infectious complications or ICU LOS
- Due to lack of clinical data there is inadequate evidence to recommend the routine use of FO-containing IVLEs in PN and EN
- Further research is required
Parenteral Fish Oil Lipid Emulsions in the Critically Ill: A Systematic Review and Meta-Analysis

William Manzanares, MD, PhD; Rupinder Dhaliwal, RD; Brian Jurewitsch, PharmD; Renee D. Stapleton, MD, PhD; Khurshed N. Jeejeebhoy, MD, FRCP(C), PhD; and Daren K. Heyland, MD, FRCP, MSc.

Figure 1. Effects of fish oil lipid emulsion strategies on mortality (n = 5). CI, confidence interval; LCT, long-chain triglyceride; MCT, medium-chain triglyceride.

Figure 3. Effects of parenteral fish oil lipid emulsions on ventilation days (n = 5). CI, confidence interval.
Secondary analysis of data from a prospective multicentered study.

Objective: Examine the effects of different IV Fat emulsions on clinical outcomes in critically ill patient.

Patients admitted to ICU for >72 hrs, mechanically ventilated within 48 hrs, received PN for ≥5 days and did not change IVLE.

n=451,

- 70 Lipid Free
- 223 SO (Soybean oil)
- 65 MCT (Medium Chain Triglycerides)
- 74 OO (Olive Oil)
- 19 FO (Fish Oil)
• **Results:**
  - When compared to lipid free PN provision patients who received FO IVLE had faster time to ICU discharge.
  - When compared with SO IVLE, patients who received OO or FO had shorter termination of mechanical ventilation alive and shorter time to ICU discharge alive.

• **Use of IV fat emulsions in PN, especially Olive and Fish Oils were associated with improved clinical outcomes.**

  Edmonds et al 2014
Background

• 3 IVLEs approved for use on AHS Provincial Drug formulary:
  1. Intralipid® 20%
  2. ClinOleic® 20%
  3. SMOFlipid® 20%
Background - Intralipid®

Intralipid® 20%

Product supplied by Fresenius Kabi
Background - Intralipid®

Intralipid® 20%

- Lipid source: 100% refined soybean oil
  - n-6 fatty acid rich IVLE
- Used in North America for years
- Only IVLE approved in Canada for pediatric and neonate populations
Background - Alternative IVLEs

Newer Alternative IVLEs
(ClinOleic® 20% and SMOFlipid® 20%)

- Anti-inflammatory, antioxidant properties, lower risk of intestinal failure associated liver disease (IFLD)
- Approved by Health Canada for use in adults
Background - ClinOleic®

ClinOleic® 20%

Product supplied by Baxter
Background - ClinOleic®

ClinOleic® 20%

- Lipid Source: 80% olive oil; 20% soybean oil
  - From soybean oil: Contains 18.5% n-6 and 2% n-3 fatty acids
- Meets needs of most adult patients
- May meet needs of pediatric and neonatal patients
  - Off-label use
  - Based on patient needs and clinical judgement of prescribing health professional
Background - ClinOleic®

ClinOleic® 20%

• Immune neutral
  – Contains olive oil, less n-6 fatty acids
  – Less pro-inflammatory and immune suppressive in sepsis and more antioxidant effects vs. Intralipid

• Is currently the default IVLE for adult patients only in some AHS Zones
Background - SMOFlipid®

SMO Flipid® 20%

Product supplied by Fresenius Kabi
Background - SMOFlipid®

SMOFlipid® 20%

- 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%
- Only IVLE with n-3 fatty acids: EPA and DHA
- May be a better energy source for the critically ill who would benefit from the addition of n-3 fatty acids
- Off-label use for high risk neonate and pediatric patients
Why have 3 IVLEs available?

- Limited evidence for one IVLE that is beneficial to all patient populations
  - Heterogeneity in existing literature
  - Benefit comparisons of ClinOleic® vs. SMOF® needed
    - Presence or absence of sepsis
    - Incidence of IFLD
  - Limited information of dose-dependent effects of different levels of SMOFlipid® 20%
    - Varied concentrations of EPA and DHA
    - Not studied across neonate, pediatric and adult populations – Higher doses need to be monitored
Why have 3 IVLEs available? (Cont’d)

• Each IVLE has a unique source of fat blend - provides clinicians the ability to select the IVLE that best meets the clinical and metabolic needs of patient

• IVLE choice based on patient needs and clinical judgment of prescribing health professional
Intralipid® 20%

Pros and indications for use:

• Home PN patients, on 3-in-1 PN solutions, that require product with long term shelf stability
• Smaller adults and adults with high BMI at risk for essential fatty acid deficiency (EFAD)
• Local drug toxicity
Contraindications:

- Hypersensitivity to fat emulsion or excipients
- Hypersensitivity to egg or legume (soybean). Cross allergic reactions observed between soybeans and peanuts
- Severely disordered fat metabolism
- Consult AHS parenteral monograph prior to administration
ClinOleic® 20%

Pros for use of ClinOleic compared to Intralipid® 20%:

- Improved fatty acid balance (PUFA intermediates)
- Improved vitamin E status and peroxidation markers
- Improved lipid profile (total-cholesterol, LDL)
ClinOleic® 20% (Cont’d)

Contraindications:

- Hypersensitivity to egg, soybean proteins, olive or soybean oil, excipients, or components of the container
- Severe hyperlipidemia or lipid metabolism disorders
- Hypertriglyceridemia-associated acute pancreatitis
- Consult AHS parenteral monograph prior to administration
SMOFlipid® 20%

Pros (vs. Intralipid® and ClinOleic®):

• Liver enzyme improvement
• Improved fatty acid ratio and n-3 fatty acid intake (EPA, DHA)
• Improved vitamin E status and peroxidation markers
SMOFlipid® 20% (Cont’d)

Indications for use:

• Select surgical and critically ill patients with or without sepsis
• Patients in ICU greater than 2 weeks, persistent inflammatory catabolic syndrome (PICS) and not tolerating the IV lipid
• Non-ICU patients: intestinal failure and hepatobiliary disease
• Home PN patients not tolerating Intralipid® 20%
Contraindications:

- Hypersensitivities to eggs, peanuts, soy or fish proteins, active ingredients or excipients
- Severe hyperlipidemia, liver insufficiency, blood coagulation disorders, renal insufficiency (without access to hemofiltration or dialysis)
- Acute shock
Contraindications (Cont’d):

- **General contraindications to infusion therapy**
- **Unstable conditions** (examples include: severe post-traumatic conditions, uncompensated diabetes mellitus, acute myocardial infarction, stroke, metabolic acidosis)
- **Consult AHS parenteral monograph prior to administration**
# Fatty Acid Composition - IVLEs

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Intralipid® 20%</th>
<th>ClinOleic® 20%</th>
<th>SMOFlipid® 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFA (%)</td>
<td>18</td>
<td>15</td>
<td>40.6</td>
</tr>
<tr>
<td>MUFA (%)</td>
<td>22</td>
<td>65</td>
<td>30</td>
</tr>
<tr>
<td>PUFA (%)</td>
<td>61</td>
<td>20</td>
<td>26.4</td>
</tr>
<tr>
<td>n-3 (%)</td>
<td>8.0</td>
<td>2.8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.8 g/L ALA</td>
<td>ALA = 2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EPA = 3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DHA = 2.0</td>
</tr>
<tr>
<td>n-6 (%)</td>
<td>52</td>
<td>18.5</td>
<td>21.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37.2 g/L LA</td>
<td></td>
</tr>
<tr>
<td>n-9 (%)</td>
<td>22</td>
<td>62</td>
<td>27</td>
</tr>
</tbody>
</table>
## Cost

<table>
<thead>
<tr>
<th>IVLE Name</th>
<th>Package size</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intralipid® 20%</td>
<td>500 mL</td>
<td>$11.25</td>
</tr>
<tr>
<td>ClinOleic® 20%</td>
<td>500 mL</td>
<td>$12.51</td>
</tr>
<tr>
<td>SMOFlipid® 20%</td>
<td>500 mL</td>
<td>$13.50</td>
</tr>
</tbody>
</table>
Not considered for formulary

- Contains very long chain n-3 fatty acids
  - EPA and DHA
- Requires Health Canada special authorization
- Considered experimental in Canada
- Possible indications:
  - Treatment and/or prevention of IFLD
  - Oral or enteral therapy is not possible and poor outcome with other PN IVLE
Safety and Efficacy

- All 3 IVLEs have been used widely in Europe with a strong safety record
- Lipids generally not compatible with many drugs
  - Emulsion can break quite easily
  - No drug compatibilities have been done
- Do not mix PN lipid emulsion with any drug or any drugs in the same IV line
- Consult AHS parenteral monograph
Safety

Safe storage

• Store in protective over pouch at room temperature (15-30°C)
• Do not freeze
• Stock different PN lipid emulsions separately
PN IVLE Administration

Common blood work

• Site specific routine PN monitoring
• Baseline, then weekly and monthly (once stable):
  – Liver function, including ALT, AST, AP, t-bili, albumin, CRP, pre-albumin
  – Lipid panel, including TG
• Monthly coagulation or earlier if indicated
• Essential fatty acid (EFA) monitoring, especially long-term usage
IVLE dosing recommendations (general)

- No more than 30% total energy from fat
- No more than 10% total energy from saturated fat
- At least 2-4% total calories should be EFA (linoleic) to prevent EFAD
- 0.25 to 0.5% total calories as alpha-linolenic acid
IVLE dosing recommendations (specific)

- **Intralipid®**
  - Not to exceed 2 g/kg body weight/d (1-2 mL/minute or 500 mL over 5-9 hours)

- **ClinOleic®**
  - 1-2 g/kg/d
  - Never exceed 0.15 g lipids/kg/h (0.75 ml/kg/h)
PN IVLE Administration (Cont’d)

IVLE dosing recommendations (specific)

- SMO Flipid®
  - 1-2 g fat/kg body weight/d corresponding to 5-10 mL/kg body weight/d
  - Recommended infusion rate: 0.125 g fat/kg body weight/h
  - Not to exceed 0.15g fat/ body weight/hr corresponding to 0.75 mL/kg body weight/h
  - Caution with hyperlipidemia (serum triglycerides (TG))
    - Reduce or stop infusion if TG greater than 3 mmol/L
    - Prevention of fat overload syndrome
Adverse Effects

• Consult AHS parenteral monograph

• Frequent (more than 2%)
  o Nausea, vomiting and muscle effects

• Less frequent/rare (less than 2%)
  o Abdominal pain or distension, back pain, inadequate diabetes control
  o Cholestasis, abnormal liver function, increased bilirubin and hepatic enzymes
  o Hypersensitivity reactions
Fat overload syndrome with lipid products

- Impaired ability to eliminate triglycerides
- Characterized by hyperlipidemia, fever, jaundice, fat infiltration, hepatosplenomegaly, hypoxia with or without respiratory insufficiency, anemia, leukopenia, coagulation disorders and coma
- Usually reversible when lipid emulsion is stopped
Essential Fatty Acid Deficiency (EFAD)

• Inadequate intake of linoleic (n-6, more common) and alpha-linolenic (n-3) fatty acids
• Higher risk for long-term usage of ClinOleic® IVLE
• Lower risk for SMOFlipid® or Intra lipid® IVLEs
• Some populations at risk:
  – Short bowel syndrome, Crohn’s, chronic pancreatitis
  – Biliary atresia with hepatic stents, patients on ECMO
EFAD signs and symptoms:

- Dermatitis, poor wound healing, fatty liver
- Increased liver function tests, hyperlipidemia, increased infections
- Hemolytic anemias, thrombocytopenia
EFAD Monitoring and treatment

EFAD Monitoring

- Biochemical evaluation triene:tetraene ratio
  - Triene acid production increased when linoleic and arachidonic fatty acids are low
- Ratio greater than 0.2 suggests EFAD

EFAD Treatment

- Provide appropriate dose of chosen IVLE to meet EFA requirements
- Monitor patient clinical and physical status for resolution of EFAD markers
EFAD and Carnitine’s role

- Transports long chain fatty acids into mitochondria to be oxidized and produce energy
- Not routinely in PN formulas
  - Risk for deficiency in long term PN patients
- If possible, evaluation is warranted in long-term PN patients with hypertriglyceridemia or signs of fatty liver disease
  - Carnitine panel
- Treatment: Carnitine supplementation
Summary

• 3 IVLEs approved by Health Canada and are available for use in AHS
• More supportive evidence is becoming available regarding the benefits of alternative IVLE.
• Further research still required to determine which IVFES and/or combinations of IVFES may be most clinically useful for specific patient populations.
Abbreviations

**IVLE** = intravenous lipid emulsions

**PN** = parenteral nutrition

**PICS** = persistent catabolic syndrome

**IFLD** = intestinal failure associated liver disease

**MCT** = medium chain triglyceride

**EPA** = eicosapentaenoic acid

**DHA** = docosahexaenoic acid

**ALA** = alpha-linolenic acid

**LA** = linoleic acid

**EFA** = essential fatty acid

**EFAD** = essential fatty acid deficiency

**PUFA** = polyunsaturated fatty acid

**SO** = Soybean oil

**LDL** = low-density lipoprotein

**SFA** = saturated fatty acids

**MUFA** = monounsaturated fatty acids

**ECMO** = extracorporeal membrane oxygenation

**RCT** = randomized control trial

**LOS** = Length of Stay

**TG** = Triglycerides
References