Lipid Emulsion Therapy
Objectives

• Historical perspective
• Mechanisms for lipid emulsion therapy
• Xenobiotics for which it has been reported
• Potential and reported adverse effects
• Risk-benefit ratio in acute care toxicology.
What would you do?

📅 18 years old female

- Lamotrigine and amitriptyline in unknown quantity
- Intractable seizure and wide complex tachycardia
- You start ACLS protocol
- Benzos, benzos, $\text{NaHCO}_3$, more $\text{NaHCO}_3$
- Cardioversion, CPR pulse on/off
- 60 minutes later ... is there anything you can still do????
Have you heard of “lipids”?
History

- 1970-80: lipid emulsion bind xenobiotics intravascularly?
- 1997: Unusual toxicity from bupivacaine in patient with abnormal FFA metabolism
- 1998: rats; lipid emulsion shift toxic dose upwards

*Weinberg et al. Anesthesiology 1998*
Lipid emulsions?

- Fat in parenteral nutrition
  - Glycerol
  - phospholipid
  - soybean oil
- 10-20-30% solution
How does it work?

Hypotheses:

1. Sequesters lipophilic xenobiotics inside their structures “lipid sink” or “lipid sponge” (in vitro / animal studies)
   - 🛑 xenobiotics taken away from site causing toxicity

2. Substrate for the heart in shock (in vitro / animal studies)

3. Alters favorably membranes potentials (2 in vitro studies)
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3. Alters favourably membranes potentials (2 in vitro studies)
Energy Metabolism

1 mole glucose = 38 ATP

1 mole FFA = 148 ATP

Fig. 2. Under ischemic conditions, anaerobic glycolysis in the cytosol (CYTO) is the only metabolic pathway able to produce ATP. The 5′-AMP activated protein kinase (AMPK) plays a key role, by inducing the translocation of the GLUT-4 glucose transporter and by activating the phosphofructokinase-2 (PFK-2) which in turn will stimulate the phosphofructokinase-1 (PFK-1), a potent activator of the glycolytic pathway. During reperfusion, circulating insulin in the plasma may significantly influence different steps (GLUT-4 translocation, activation of PFK-2 and PFK-1) (adapted from).^{33}
## Evidence Timeline

<table>
<thead>
<tr>
<th>Year</th>
<th>2006</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rosenblatt human bupivacaine presumed cardiac arrest with 20% IVE bolus</td>
<td>Sirianni lamotrigine buproprion Felice JMT 1st review of literature</td>
<td>Cave Systematic Review AEM Meehan Case series abstract</td>
<td>numerous case reports in human and animal poisoning Jamaty ClinTox Systematic Review</td>
<td>Cave EMA Summary of published evidence ObS</td>
<td>Taftachi RCT Levine Case series</td>
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</tbody>
</table>

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Lots of animal experiments

- 1962 Russel; thiopental
- 1974 Krielsgtein; carbamazepine
- 1987 Minton; amitriptyline
- 2006 Weinberg; bupivacaine
- 2006 Cave; propanolol
- 2006 Bania; propanolol
- 2006 Tebutt; verapamil
- 2007 Harvey; clomipramine
- 2007 Weinberg; bupivacaine
- 2008 Harvey; propanol
- 2008 Bania; verapamil
- 2008 Mayr; bupivacaine
- 2008 Medlej; verapamil
- 2008 Weinberg; bupivacaine
- 2008 Perez; verapamil (optimal dose)
- 2008 Yoav; clomipramine
- 2009 Hicks; bupivacaine (epi + VP)
- 2009 Cave; atenolol
- 2009 Chu; nifedipine
- 2009 Perez; verapamil (infusion rate)
- 2009 Di Gregorio; bupivacaine (epi + VP)
- 2010 Candela; bupivacaine
- 2010 Niiya; amiodarone
- 2010 Browne; metoprolol
- 2011 Kazemi; thiopental
- 2011 Harvey; propanolol (insulin)
- 2012 ...
- 2013 ...

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## Human case reports

- **mepivacaine**  
- **bupropion**  
- **propanolol**  
- **haloperidol**  
- **lidocaine**  
- **lamotrigine**  
- **amitriptyline**  
- **olanzapine**  
- **prilocaine**  
- **amiodarone**  
- **amlodipine**  
- **glyphosate**  
- **bupivacaine**  
- **metoprolol**  
- **nebivolol**  
- **zopiclone**  
- **cocaine**  
- **propafenone**  
- **chloroquine**  
- **quetiapine**  
- **diltiazem**  
- **dosulepin**  
- **sertraline**  
- **verapamil**  
- **flecainide**  
- **Gosselin**
Human data

- Adult and pediatric cases
- Publication bias; report successful cases
- No GI decontamination in many cases
- Variable amount lipids given
- Variable indications (cardiac arrest mostly)
- Other treatments received (what worked?)
- Intoxication model not representative “real life”
Some improvement in animals
Indications

- Cardiovascular compromise refractory to other modalities
  - liposoluble substances (L.A, CCB)
- Seizures? (marker of severe toxicity)
- No role in prophylaxis
- No role in isolated altered mental status or coma
- Not 1st line therapy ... (ABC, CPR, electricity, NaHCO₃)
- Not too early; **BUT NOT TOO LATE** ...
• Arbitrary regimen “Weinberg Protocol”
• Intralipid 20%
  – 1.5 mL/kg bolus
  – 0.25-0.5 mL/kg/min for 30-60 minutes
• No clear evidence that a infusion is needed
• Maximum total dose unclear
  – 8 mL/kg, 12 mL/kg, no limit
Can we do this in our ED? ...and look super smart?

- Yes
- We stock 20% lipid emulsion in our pharmacy +/- our ED
- We could make an intralipid kit:
  - 500 ml of 20% intralipid emulsion
  - 50 ml syringe
  - Infusion kit
  - Laminated instructions and indications
Practically....

- Draw up 50 ml syringe of intralipid – push this twice (100 ml bolus)
- Hang the rest of the 500 ml bag and run as a drip over 15 minutes
- Repeat initial 100 ml bolus if no clinical change
### Possible Adverse effects

<table>
<thead>
<tr>
<th>Bolus</th>
<th>Infusion</th>
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<tr>
<td>TG clearance rate (6mmol/L/hr) expected 80 mmol/L after one hour treatment</td>
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<tr>
<th>Lab interferences <em>(Heijboer 2010; Grunbaum 2012)</em></th>
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<td>Binding of useful medications (epinephrine, others)</td>
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<tr>
<td>Pancreatitis <em>(Levine 2012; Marwick 2009)</em></td>
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<td>Hypersensitivity</td>
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<td>Priapism (7 cases TPN)</td>
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</table>
Safety studies

   – 55% survival in case deemed fatal otherwise
   – 3/9 cases of lipemia
   – more than 10 other probable adverse effects

2. Hiller et al.
   – 9 rats
   – LD 50 = 67 mL/kg
33 year old male, ingests 30 tablets of flecainide

- 60 minutes later in hospital
- How would you manage this patient?
Case - continued

- Get Intralipids
- OR or ICU
- Best if you make a protocol to have in your crash cart
- Take big syringe and remove 150 mL from the bag, inject push
- Repeat bolus vs. infusion???
Lipid emulsion is an emerging therapy

Rescue of cardiovascular collapse

Most evidence for binding xenobiotics intravascularly

Mostly experimental evidence (conflicting)

Risk/benefit; poor information on adverse effects

Best dosing regimen unknown
Questions?