INTRA\nVENOUS LIPID
EMULSION THERAPY

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OBJECTIVES

• Discuss background on Intravenous lipid emulsion (ILE) therapy.
• Explore proposed mechanisms of ILE.
• Review relevant animal studies and selected human case reports.
• Examine in which overdoses ILE should be considered and in what doses.

DISCLOSURES

• There are no conflicts of interest to disclose.
**INTRAVENTOUS LIPID EMULSION THERAPY**

- Basic concept of ILE involves the intravenous administration of a high concentration of lipid as a “rescue” agent for toxicity produced by lipophilic drugs.

**LIPID EMULSION THERAPY**

- Exact mechanism of action of lipid emulsion therapy not known.
- Various mechanisms of action proposed:
  1) “Lipid sink” theory
  2) Direct source of energy
  3) Increase intracellular calcium
  4) Increase production of nitric oxide

**LIPID SINK THEORY**

- Rapid increase in lipids in vascular compartment draw lipid soluble (lipophilic) drugs out of periphery and into vascular compartment.
  - Drugs move into vascular compartment down concentration gradient
- In essence, this theory has ILE reducing the volume of distribution of drug.
**CHANGE IN ENERGY THEORY**

- During normal conditions, free fatty acids are preferred substrate for myocardial ATP production, while carbohydrates are the preferred substrate in shock states.
- Local anesthetics inhibit an enzyme (carnitine acetyltransferase), which moves fatty acids across the inner mitochondrial membrane.
- ILE may provide enough FA to overcome blockade.

**CHANGE IN CALCIUM THEORY**

- *In vitro* studies demonstrate free fatty acids can open voltage-gated calcium channels in myocardial cells.
- The increase intracellular calcium may be desirable in drug-induced myocardial depression.

**HISTORY**

- 1974: Kriegstein et. al. demonstrated with *in vitro* studies lipids are storage reservoirs for chlorpromazine (Thorazine).
- 1998: Weinberg et. al. demonstrated lipid emulsion (as pretreatment or rescue) shifts dose-response curve in bupivacaine-induced asystole in rats.
HISTORY (CONT.)

• 2003: Weinberg demonstrated lipid infusion can rescue dogs in bupivacaine-induced asystole.

• 2006: First human case report describing 20% lipid emulsion as resuscitative agent from local anesthetic-induced cardiac arrest.

WHAT IS LIPID EMULSION?

• ILE used since 1961 as ingredient in TPN.

• Various commercial concentrations of ILE exist; 20% most common.

• 20% ILE contains:
  – 20% soybean
  – 1.2% egg yolk
  – 2.25% glycerin

• Not same as propofol.

PRETREATMENT WITH ILE

• Rats received 10%, 20%, or 30% ILE as pretreatment before administration of 0.75% bupivacaine.

• Doses of bupivacaine required to induce asystole parallels concentration of ILE.

<table>
<thead>
<tr>
<th>Concentration of ILE</th>
<th>Bupivacaine dose required to induce asystole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>17.6 mg/kg</td>
</tr>
<tr>
<td>10%</td>
<td>27.6 mg/kg</td>
</tr>
<tr>
<td>20%</td>
<td>49.8 mg/kg</td>
</tr>
<tr>
<td>30%</td>
<td>82 mg/kg</td>
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</table>
ILE AND BUPIVACAINE

- 12 dogs received 10 mg/kg IV bupivacaine.
- All dogs developed circulatory collapse followed by 10 minutes closed chest compressions.
- Dogs randomized to receive 4 cc/kg of 20% ILE followed by 0.5 cc/kg/min or equivalent volume of normal saline.
- All saline-treated dogs died; all ILE-treated dogs lived.


ILE AND CLOMIPRAMINE

- Clomipramine is a fat-soluble TCA.
- Authors compared sodium bicarbonate with ILE in a rabbit model of TCA toxicity.
- 2 phases:
  - First phase compared time to improvement in MAP.
  - Second phase compared survival
    - 8 cc/kg 20% ILE vs. 2 cc/kg 8.4% sodium bicarbonate.


ILE AND CLOMIPRAMINE

- Phase 1:
  - Time to improvement with ILE vs. bicarbonate vs. saline.

Phase 2:
- 0/4 rabbits treated with NaHCO₃ survived;
- 4/4 rabbits treated with ILE survived.
ILE AND VERAPAMIL

- Verapamil is a lipid-soluble calcium channel blocker.
- 30 rats given IV verapamil, followed 5 minutes later by 12.4 cc/kg of either normal saline or 20% lipid emulsion.
- ILE-treated rats survived twice as long as saline-treated rats.


MORE ON ILE AND VERAPAMIL

- 14 dogs administered verapamil until a 50% reduction in MAP occurred.
- Hypotension then maintained for 30 minutes.
- 20 cc/kg saline, calcium, and atropine administered over next 15 minutes.
- Animals then received 7 cc/kg of either NS or 20% lipid emulsion.


ILE AND VERAPAMIL (CONT)

Asterisks indicate statistical significance (p < 0.05).

Kaplan-Meier curve demonstrating improved survival with ILE vs. saline (control) group.
DOSING OF ILE WITH VERAPAMIL
• Verapamil toxicity induced in 30 rats.
• After 5 minutes, 20% ILE bolus given.

<table>
<thead>
<tr>
<th>Dose of ILE (cc/kg)</th>
<th>Mean survival (minutes)</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>6.2</td>
<td>56</td>
</tr>
<tr>
<td>12.4</td>
<td>63</td>
</tr>
<tr>
<td>18.6</td>
<td>143.8</td>
</tr>
<tr>
<td>24.8</td>
<td>126.6</td>
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<tr>
<td>37.6</td>
<td>130</td>
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</tbody>
</table>

ILE AND PROPRANOLOL
• Propranolol is a highly lipophilic non-cardio-selective beta blocker.
• 22 rabbits received propranolol until 60% reduction in MAP.
• Animals then received 6 cc/kg of either normal saline or 20% lipid emulsion.

ILE AND PROPRANOLOL
• MAP restored better in ILE-treated rabbits than saline-treated rabbits.
ILE AND METOPROLOL

- Metoprolol is a relatively hydrophilic beta blocker
- 20 rabbits given metoprolol infusion until the MAP had decreased 60% of baseline
- Randomized to receive 6 cc/kg of either 20% ILE vs. normal saline


BUPIVACAINE AND ILE (AGAIN)

- Porcine model where animals received 5 mg/kg of 0.5% bupivacaine IV
- Ventilation stopped until asystole developed
- 1 minute later, CPR started
- 10 animals randomized to receive either 0.8 U/kg vasopressin and 45 mcg/kg epinephrine or 4 cc/kg of 20% ILE, beginning 2 minutes after CPR started.

BUPIVACAINE AND ILE

- Defibrillations of 3, 4, and 6 J/kg 3 minutes after each drug dosing for shockable rhythm
- 0/5 pigs treated with ILE lived; 5/5 pigs treated with vasopressors had ROSC
- Is the difference due to asphyxia?
- Is it due to the higher dose of epi?
  - Previous studies with lipid indicate worse outcomes with high dose epi and lipid vs. low dose epi and lipid


I SMELL BACON

- 19 pigs given 10 mg/kg IV bupivacaine.
- Animals randomized to receive either 4 cc/kg 20% ILE followed by infusion of 0.5 cc/kg/min or equal volume of saline.
- Primary endpoint was ROSC for at least 1 minute.


ILE AND bupivacaine

• ROSC occurred in 3/10 of ILE, and 4/9 in normal saline (p=0.65)
• Higher serum bupivacaine concentrations with ILE at 10 min (23.2 vs. 15.3; p=0.004)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>15 min</th>
<th>30 min</th>
<th>45 min</th>
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<tbody>
<tr>
<td>ILE</td>
<td>122 ± 28</td>
<td>188 ± 16.9</td>
<td>192 ± 26.8</td>
<td>184 ± 33.8</td>
</tr>
<tr>
<td>Normal</td>
<td>107 ± 20</td>
<td>138 ± 7.9</td>
<td>137 ± 16.3</td>
<td>188 ± 56.7</td>
</tr>
<tr>
<td>Mean</td>
<td>117 ± 8.2</td>
<td>169 ± 12.6</td>
<td>187 ± 17.7</td>
<td>210 ± 33.5</td>
</tr>
<tr>
<td>Orbit</td>
<td>82 ± 10.2</td>
<td>188 ± 17.4</td>
<td>183 ± 34.3</td>
<td>184 ± 63.7</td>
</tr>
<tr>
<td>Control</td>
<td>98 ± 12</td>
<td>84 ± 3.4</td>
<td>80 ± 5.6</td>
<td>74 ± 14.3</td>
</tr>
<tr>
<td>Unit</td>
<td>g/L</td>
<td>g/L</td>
<td>g/L</td>
<td>g/L</td>
</tr>
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</table>

Results are shown as mean ± SD. Data are means of measurements taken before the administration of bupivacaine. Different columns across rate rows were analyzed using Student's t-test. *p<0.05.


WHAT’S UP WITH THIS STUDY

• Why was this a negative study when so many other studies had beneficial effects?
  – Power calculation required 9 animals in each group;
    • Based on previous swine study using 5 mg/kg bupivacaine, this study used 10 mg/kg bupivacaine
  • Difference between the two groups at baseline
  • Closed chest compressions – did this account for the difference? Previous studies demonstrate decreased cardiac output with closed vs. open

FIRST CASE REPORT

• 58 year old male received 20 mL 0.5% bupivacaine and 20 mL 1.5% mepivacaine for brachial plexus block.
• 30 seconds after block → seizure.
• Additional seizure followed by asystole.
• 20 minutes into asystole, 100cc 20% Intralipid administered.
• Single sinus beat in seconds; NSR in 15 seconds.

ILE WITHROPIVACAINE
• 84 year old female received 40 cc of 1% ropivacaine via axillary plexus block.
• Dizziness and sedation developed, followed by seizure and asystole.
• 10 minutes into asystolic arrest, 100 cc 20% ILE bolused, followed by a drip of 10 cc/min.
• After 200 cc ILE administered, ROSC occurred.
• Patient made complete recovery.

ILE IN BUPROPION AND LAMOTRIGINE
• 17 year old female ingested 7.95g bupropion and 4g lamotrigine.
• Arrived in ED 6 hours post ingestion
  – Normotensive with HR 116.
  – Withdrawal to painful stimuli.
  – EKG with QRS 122 msec and QTc 485 msec
• Admitted to ICU.

ILE IN BUPROPION AND LAMOTRIGINE (CONT.)
• 10 hours post ingestion, seizure followed by PEA → VT → VF arrest occurred.
  – 18 minutes into arrest, 50 mEq NaHCO₃ administered with ROSC 2 minutes later.
• 17 minutes later, PEA arrest occurred again.
  – 52 minutes into second arrest, 20% ILE (100cc) administered with ROSC.
• Patient discharged to rehab after prolonged ICU course with only mild neurologic deficits.
RECOMMENDED DOSES

• No uniform dosing established.

• Animal models typically use higher doses than those in published human case reports.

<table>
<thead>
<tr>
<th></th>
<th>Bolus</th>
<th>Infusion</th>
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</thead>
<tbody>
<tr>
<td>Weinberg</td>
<td>1 cc/kg x3</td>
<td>0.25 cc/kg/min</td>
</tr>
<tr>
<td>Rosenblatt</td>
<td>1.2 cc/kg</td>
<td>0.5 cc/kg/min</td>
</tr>
<tr>
<td>Litz</td>
<td>2 cc/kg</td>
<td>0.2 cc/kg/min</td>
</tr>
</tbody>
</table>

• When used as TPN, maximum recommended infusion rate is 0.11 g of fat/kg/hr.

COMPLICATIONS

• Complications can be due to:
  1) Direct reactions
     • Pyrogenic
     • Fat overload
  2) Contaminated IFE solutions
     • Occurs when mixing IFE as part of TPN solution
     • Unlikely to occur when IFE used as antidote

• Prolonged, high dose infusions associated with fat overload.

COMPLICATIONS (CONT.)

• Fat overload associated with hyperlipidemia, hepatosplenomegaly, fat emboli, hemolytic anemia, and thrombocytopenia.

• Short term use (e.g. as antidote), not believed to be associated with adverse effects, except:
  – Allergic reaction to soy (theoretical)
  – Thrombophlebitis (only adverse effect described with antidotal use).
LABORATORY ABNORMALITIES

- Inadvertent administration of 2L of 20% lipid in a 71 year old amlodipine overdose resulted in uninterpretable CBC, chemistries
- Ultracentrifugation permitted analysis 3 hours later

COMPLICATIONS

- 13 year old developed cardiac arrest following amitriptyline overdose
- Treated with 1.5 cc/kg of 20% ILE, followed by 0.25 cc/kg/min.
- Blood gas, chemistries uninterpretable secondary to lipemia
- Pancreatitis developed

LABORATORY INTERFERENCE

- Possible interference with spectrophotometric measurements of methemoglobin.
POTENTIAL USES

• Animal models demonstrate benefit with:
  – Chlorpromazine
  – Local anesthetics
  – Propranolol
  – Verapamil
  – TCA

• Human case reports suggest benefit with:
  – Bupropion
  – Lamotrigine
  – Local anesthetics
  – Quetiapine and sertraline*
  – Zopiclone and venlafaxine*
  – Verapamil

  * Report describes decreased sedation

CONCLUSIONS

• ILE is emerging as a rescue agent for several lipophilic drug toxicities.

• Many unknowns still exist, including its mechanism of action and desired dose.

• Consider 100 cc bolus of 20% ILE for cardiac arrest due to suspected lipophilic drug toxicity.
THANK YOU!

REFERENCES


