Utility of Intravenous Fat Emulsion in Overdose

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Disclosure

- I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

Objectives

- Describe the proposed mechanisms of action of intravenous fat emulsion (IFE) in overdose
- Recognize the medication classes in which IFE has demonstrated efficacy in overdose
- Synthesize a dosing strategy based on current literature and guidance for the administration of IFE for an overdose patient

What the Fat?

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Saline</th>
<th>10% IFE</th>
<th>20% IFE</th>
<th>30% IFE</th>
<th>40% IFE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean serum concentration of bupivacaine @ asystole (mcg/mL)</td>
<td>93.3 ± 7.6</td>
<td>115 ± 15</td>
<td>177 ± 31</td>
<td>212 ± 45*</td>
<td></td>
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<tr>
<td>Median lethal dose of bupivacaine (mg/kg)</td>
<td>17.8 (13.2-20.3)</td>
<td>27.4* (22.2-31.7)</td>
<td>49.8* (41.3-57.8)</td>
<td>82* (71.3-101)</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant difference from saline (p < 0.001)

- "Sought to confirm a chance observation that intravenous lipid treatment increases the dose required to produce asystole in rats" (Weinberg, et al. Anesthesiology. 1998; 88: 1071-5.)

- "LD50 of bupivacaine increased by 48% with IFE"

- "Statistically significant increase in survival at 15 mg/kg bupivacaine with IFE"

Proposed Mechanisms

The Lipid Sink

Enhanced Lipid Metabolism

The Lipid Sink

- Equal volume of 30% IFE
- ~25% bupivacaine

Lipid Sink

- ~75% bupivacaine

The Lipid Sink

- AKA ‘partitioning’
- IFE forms an emulsion of small lipid droplets
- Phospholipids around a triglyceride core
- Medication binds in serum lipid phase → less medication binding at site of toxicity
  - bupivacaine
  - bupropion
  - lamotrigine
  - clomipramine
  - amiodarone

Enhanced Lipid Metabolism

- Toxicity due to alteration of intracellular metabolism of lipids
  - Repair/circumvent with IFE
  - Overcome blocked/inhibited enzymes
- Inhibition of fatty acid oxidation decreases effect of IFE
  - Rats pretreated with CVT-4325
- Inhibition of carnitine palmitoyl transferase decreases effect of IFE
  - Dogs pretreated with astenine

Medications Amenable to IFE Rescue

- Medications that alter intracellular energy metabolism
  - bupivacaine, verapamil, amitriptyline, propranolol
- Medication Properties
  - Lipophilic (log P > 2)
  - Large volume of distribution
  - Medications with successful use (incomplete)
    - bupivacaine
    - mepivacaine
    - ropivacaine
    - verapamil
    - clomipramine
    - propranolol
    - bupropion
Interference with laboratory assays

Fat Overload Syndrome
Acute Respiratory Distress Syndrome

Infusion - 0.25 mL/kg/min 20% IFE
Bolus - 1.5 mL/kg 20% IFE over 2-3 minutes
Half-life of IFE ~ 30-60 minutes

Hyperlipemia, fever, fat infiltration, hepatomegaly, jaundice, splenomegaly, anemia, leukopenia, thrombocytopenia, coagulation disturbances, seizures, coma
Inference with laboratory assays

In Summary
IFE can be used as salvage therapy in symptomatic patients that have overdosed on a medication that:
- Has known severe toxic effects
- Properties known or expected to be amenable to IFE
- Does not have sufficient antidotal therapy/ patient failed antidotal therapy
- IFE can be used for treatment of Local Anesthetic Systemic Toxicity (LAST)
- Use in conjunction with Basic and Advanced Cardiac Life Support

Indications
- For patients with hemodynamic or other instability, not responsive to standard resuscitation measures...in consultation with a medical toxicologist
- Local Anesthetic Systemic Toxicity 'LAST' checklist
- Used successfully to treat CNS depression, seizures and dysrhythmias from local anesthetic toxicity

Contraindications
- Soybean allergy
- Myocardial infarction

Administration & Dosing

Dosing
- Bolus - 1.5 mL/kg 20% IFE over 2-3 minutes
- Can repeat bolus for patients with asystole or pulseless electrical activity
- Persistent cardiovascular collapse
- Infusion 0.25 mL/kg/min 20% IFE
- Can consider increasing rate of infusion if hemodynamic instability recurs
- ASRA recommends doubling infusion rate for persistent hypotension
- Continue infusion for 10 minutes once stable
- Half-life of IFE ~ 30-60 minutes
- Maximum dose = 10 mL/kg

Administration & Monitoring
- Central or peripheral access
- Hemodynamic parameters every 15 minutes during infusion
- Infusion should be terminated within 1 hour
- Monitor for Acute Respiratory Distress Syndrome
- Monitor for Fat Overload Syndrome
- More likely to occur with prolonged administration

Adverse Effects
- Acute Respiratory Distress Syndrome
- No reports of development after rescue therapy
- 2 proposed mechanisms of pulmonary toxicity
- Micro-fat emboli
- Unlikely acid conversion to arachidonic acid
- Fat Overload Syndrome
- Hyperlipemia, fever, fat infiltration, hepatomegaly, jaundice, splenomegaly, anemia, leukopenia, thrombocytopenia, coagulation disturbances, seizures, coma
- Interference with laboratory assays

Systemic Toxicity 'LAST' checklist
- Local Anesthetic
- Toxicologist
- responsive to standard resuscitation measures...in consultation with a medical toxicologist
- Does not have sufficient antidotal therapy/ patient failed antidotal therapy

Properties known or expected to be amenable to IFE
- Has known severe toxic effects

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