Lipid Rescue: What we have learned thus far

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Disclosures

No financial relationships to discuss
Will discuss off label drug use
Lipid Rescue:

- Several animal models

Bupivicaine
Verapamil
Clomipramine
Propranolol
Amiodarone
Parathion
Chlorpromazine
Thopental
Lipid Rescue:

- Multiple case reports and case series
- > 76 case reports for drug toxicity thus far
- 55 case reports for non-anesthetic drug toxicity
Lipid Rescue: What we have learned thus far

Timing

Dosing

Safety Considerations
Lipid Rescue: Cases for discussion

#1

- 70 y/o male with femoral neck fracture, receives bupivacaine femoral nerve block for analgesia for transport to another hospital.

- Becomes dizzy, disoriented.

- VS: BP 140/80, HR 105, RR 18
Lipid Rescue: Cases for discussion
#1

- Mild bupivacaine toxicity
- VS: BP 140/80, HR 105, RR 18

- Monitor, oxygen, wait for it to wear off?
- Timing of treatments? Dosing?
- Increase PR, QRS
- Decrease BP, heart block, asystole, seizure
LipidRescue™

TREATMENT FOR LOCAL ANESTHETIC-INDUCED CARDIAC ARREST

PLEASE KEEP THIS PROTOCOL ATTACHED TO THE INTRALIPID BAG

In the event of local anesthetic-induced cardiac arrest that is unresponsive to standard therapy, in addition to standard cardio-pulmonary resuscitation, Intralipid 20% should be given I.V. in the following dose regime:

- Intralipid 20% 1.5 mL/kg over 1 minute
- Follow immediately with an infusion at a rate of 0.25 mL/kg/min.
- Continue chest compressions (lipid must circulate)
- Repeat bolus every 3-5 minutes up to 3 mL/kg total dose until circulation is restored
- Continue infusion until hemodynamic stability is restored. Increase the rate to 0.5 mL/kg/min if BP declines
- A maximum total dose of 8 mL/kg is recommended

In practice, in resuscitating an adult weighing 70kg:

- Take a 500ml bag of Intralipid 20% and a 50ml syringe.
- Draw up 50ml and give stat I.V. X2
- Then attach the Intralipid bag to an IV administration set (macrodrip) and run it I.V over the next 15 minutes
- Repeat the initial bolus up to twice more – if spontaneous circulation has not resumed.

If you use Intralipid to treat a case of local anaesthetic toxicity, please report it at www.lipidrescue.org. Remember to restock the lipid. Ver 7/06
Lipid Rescue: Cases for discussion
#2

- 14 y/o female ingested amitriptyline, in PICU, intubated, on NaHCo3 for QRS 102 mSec, BP 130/80, HR 110
- 20 hours post ingestion, develops T-C seizure, wide complex dysrhythmias
- Timing of Treatments? Dosing?
Lipid Rescue: Cases for discussion
#2

- 14 y/o female, amitriptyline, OD
- Seizures, wide-complex
- Pulseless
- Timing of Treatments? Dosing?
**Lipid Dosing**

<table>
<thead>
<tr>
<th>Local anesthetic toxicity</th>
<th>Non-local anesthetic toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local anesthetic toxicity is IV</td>
<td>Usually oral</td>
</tr>
<tr>
<td>Short duration</td>
<td>Long duration</td>
</tr>
<tr>
<td>Single toxin</td>
<td>Multiple agents, unknown</td>
</tr>
<tr>
<td>Used for cardiac arrest or pre-arrest</td>
<td>Mostly pre-arrest</td>
</tr>
<tr>
<td>No other effective treatment</td>
<td>Most have antidotes</td>
</tr>
<tr>
<td></td>
<td>Longer time to onset of toxicity</td>
</tr>
<tr>
<td></td>
<td>Dose adjustment may be needed</td>
</tr>
</tbody>
</table>
Lipid Infusion: Indication

American College of Medical Toxicology
Interim Guidance for the Use of Lipid Resuscitation Therapy (LRT)

- Lipid use is solely discretionary and is based on the clinical judgment
- No standard of care requirements to use or not to use
- LRT is a reasonable consideration in serious hemodynamic, or other, instability from a xenobiotic with a high degree of lipid solubility, even if the patient is not in cardiac arrest.
Lipid Infusion: Indication

American College of Medical Toxicology
Interim Guidance for the Use of Lipid Resuscitation Therapy (LRT)

• If used, LRT should be instituted for patients with hemodynamically instability, not responsive to standard resuscitation measures

• Use of LRT instead of, or in conjunction with, other therapies that have been anecdotally reported to be effective, such as euglycemic-insulin therapy, is to be based on the clinical judgment
Lipid Infusion: The Science Behind a New Treatment Modality

Adopted by

American College of Medical Toxicology
Interim Guidance for the Use of Lipid Resuscitation Therapy
Recommended Guideline

• 1.5 ml/kg bolus of 20 % fat emulsion over 2-3 minutes

• Then 0.25 ml/kg/min of 20 % fat emulsion

• Bolus can be repeated for continued PEA/Asystole
Lipid Rescue: Cases for discussion

#3

- 36 y/o male with ischemic cardiomyopathy, AICD, ingested digoxin, carvedilol
- Intubated, OG lavage, charcoal
- VS BP 110/79 HR 70
- 6 hours post ingestion, BP 70, HR 40
- Timing of Treatments? Dosing?
- Will lipids work?
Other Support for Lipid Sink/Sponge Mechanism

In experimental models, lipid soluble drugs responded to lipids

**Log P** Lipid/aqueous partition coefficient
Ratio of the concentration of a compound in an organic solution/aqueous solution
**Log D** uses pH (ionization)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Partition coefficient LogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivicaine</td>
<td>p 3.6</td>
</tr>
<tr>
<td>Verapamil</td>
<td>p 3.8</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>p 4.7</td>
</tr>
<tr>
<td>Propranolol</td>
<td>p 3.6</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>p 6.6</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>p 3.1</td>
</tr>
<tr>
<td>Thopental</td>
<td>p 2.8</td>
</tr>
<tr>
<td>Carvetalol</td>
<td>p 2.79</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>p 3.0</td>
</tr>
</tbody>
</table>

\[
\log P_{\text{oct/wat}} = \log \left( \frac{[\text{solute}]_{\text{octanol}}}{[\text{solute}]_{\text{un-ionized water}}} \right)
\]
Lipid Sink / Sponge Mechanism

Intravenous fat emulsion
Soaks up lipid soluble drug

Pulls toxin off site of toxicity, into intravascular compartment

Intravenous Fat

Intravascular

Tissue

K1

K2
Lipid Sink / Sponge Mechanism

Intravenous fat emulsion
Soaks up lipid soluble drug

IF IFE can’t pull toxin off site of toxicity, into intravascular compartment

Intravascular

K1

Tissue

K2

Intravenous Fat

K1

K2
Lipid Rescue: Cases for discussion

#3

- 36 y/o male with ischemic cardiomyopathy, AICD, ingested digoxin, carvedilol
- Intubated, OG lavage, charcoal
- VS BP 110/79 HR 70
- 6 hours post ingestion, BP 70, HR 40
- Timing of Treatments? Dosing?
Lipid Rescue: Cases for discussion

#4

- 70 y/o male ingests 30 5 mg tablets of amlodipine 1.5 hours prior
- Awake, alert, BP 85 to 79/44, HR 79, RR 20
- CaCL₂, phenylephrine, vasopressin, HIE (1u/kg bolus, then 1u/kg/hr)
- IFE 1.5 ml/kg then 0.25ml/kg/min
- Max 8ml/kg, received 40 ml/kg
- Safety?
Lipid Dose

- 2 Liters of 20 % over 4.5 hrs or 28 ml/kg
  - Clinical Toxicology. 2010 48 (4): 393-6

- Nutritional Doses 5-10, 15 ml/kg/d/6hours
  - 350-1050 ml in 70 kg

- Resuscitation 9 ml/kg(30min) or 16ml/kg(1hr)
  - 1.5 ml/kg bolus then 0.25 ml/kg/min (15 ml/kg/hr)

- Animal Models
  - 7-18.6 ml/kg
  - LD 50 in rodents 67 ml/kg
Lipid Dose

- **Animal Models of Lipid Toxicity**
  - Reg Anesth Pain Med. 2010 Mar-Apr;35(2):140-4
    - LD 50 in rodents 67 ml/kg
    - Dose range 20 – 80 m/kg
  - Myocardium, brain, pancreas, and kidneys was normal at all doses.
  - Microscopic abnormalities in lung and liver were observed at 60 and 80;
  - Histopathology in the lung and liver was worse at 1 hr than at 4 and 24 hrs
Potential Adverse Effects of Lipid Infusion

Acute Lung Injury

Fat overload syndrome
Potential Adverse Effects
Fat Overload Syndrome

May occur with large doses and rapid infusion
• Inadequate clearance of lipids
• Sludging in
  ▪ Lungs
  ▪ Brain
  ▪ Kidney
  ▪ Retina
  ▪ Liver
Lipid Infusion: The Science Behind a New Treatment Modality

Fat overload syndrome – potential adverse effect
- hyperlipemia
- fever
- hepatomegaly
- jaundice
- splenomegaly
- pancreatitis *
- lung injury *
- anemia
- leukopenia
- thrombocytopenia
- coagulation disturbances
- seizures
- coma
Potential Adverse Effects
Acute Lung Injury

2 proposed mechanism

• Conversion of linoleic acid to arachidonic acid vasoactive prostaglandins causing vasoconstriction and hypoxia

• Micro-fat emboli occlude pulmonary vasculature
Potential Adverse Effects
Acute Lung Injury

No strong evidence that lipids cause acute lung injury

Studies were inconsistent
Some studies showed changes in pulmonary artery pressures, shunting, vascular resistance

When lung injury occurs, it was mild and resolved within 3-4 hours
Lipid Rescue: Cases for discussion

#5

- 26 y/o male with status epilepticus after smoking crack. Intubated, seizures controlled with lorazepam and midazolam
- BP 85 to 79/60, HR 136, QRS 148 msec
- Sodium bicarbonate, Mg
- Timing of Treatments? Dosing?
- Will lipids work?
Lipid Rescue: Cases for discussion

#5

- 26 y/o male with status epilepticus after smoking crack, controlled with lorazepam and midazolam
- BP 85 to 79/60, HR 136, QRS 148 msec
- Midazolam log P 3.89
- Lorazepam log P 2.39
- Timing of Treatments? Dosing?
- Will lipids work?
Lipid Rescue: What we have learned thus far: Timing, dosing, safety considerations

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