Objectives

- Discuss and Review the pharmacodynamics/pharmacokinetcs of local anesthetics
- Differentiate between local anesthetics and their potential to cause local toxicity
- Discuss the mechanism of action of local toxicity
- Discuss current literature regarding lipid emulsion therapy
Pharmacokinetics

- Absorption, Distribution, Metabolism, and Excretion
  - Absorption influenced by site, dose, and use of epi
  - Redistribution from vessel rich group to vessel poor group
  - Amide LAs metabolized by CYP3A4
  - Ester broken down my plasma cholinesterase
  - Renal excretion

Toxicity

- Good News...incidence has decreased
  - 7.5-20 per 10,000 peripheral nerve blocks
  - 4 per 10,000 epidurals
- Toxicity most often to intravascular injection and not accumulation
- Safety has ↑d/t
  - Aspiration
  - Knowledge (i.e., local toxic doses)
  - Divided doses
  - Test dose with epi

Factors influencing LA toxicity

- Site
- Speed
- Total amount
- Route
  - Remember, vasculature directly affects systemic absorption
Toxicity (cont’d)

- From increasing to decreasing order of absorption:
  1. Inhalational/Intravenous
  2. Intercostal
  3. Caudal
  4. Paracervical
  5. Epidural
  6. Brachial Plexus/Femoral
  7. Spinal
  8. Sciatic
  9. Subcutaneous

Toxicity (cont’d)

- LA binds to the Na⁺ in the heart (maybe on the Ca²⁺ and the K⁺ channels) inhibits cAMP.
- Cardiac LA toxicity is very difficult to manage and treat
  - Resuscitation – well documented as very difficult
- Bupivacaine is the most cardiotonic of Las.

Signs and Symptoms of Toxicity

- **Early** – agitation, light headedness, altered mental state, vision Δ’s, slurred speech, HTN, ↑HR
- **Moderate** – CNS excitation, cardiac arrhythmias, contractile depression, conduction blockade
- **Severe** – ↓BP, ↓HR, ventricular arrhythmias, seizures, cardiac collapse

Lipid Emulsion

- Discovered by Weinberg et al.
- **Components**
  - 20% soybean oil
  - 1.2% egg yolk phospholipids
  - 2.25% glycerin
  - water

<table>
<thead>
<tr>
<th></th>
<th>Intralipid</th>
<th>Liposyn III</th>
<th>Medialipid</th>
<th>Clinoleic</th>
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<tbody>
<tr>
<td><strong>Oils</strong></td>
<td>100% soybean oil</td>
<td>100% soybean oil</td>
<td>50% soybean oil and medium chain triglycerides</td>
<td>80% olive oil and 20% soybean oil</td>
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<tr>
<td><strong>Triglycerides (g/L)</strong></td>
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<tr>
<td><strong>Glycerol (g/L)</strong></td>
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<td>25</td>
<td>25</td>
<td>22.5</td>
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</table>
Lipid Emulsion (cont’d)

- **Pharmacodynamics**
  - "Lipid Sink" theory
    - Creates 2 compartments within the blood
      - Lipid Compartment
      - Aqueous Compartment
    - Lipophilic LAs are drawn into the lipid compartment or lipid "sink" portion of blood
    - LAs in the aqueous compartment of plasma

- **Pharmacokinetics**
  - Lipolysis
    - Remaining particles to liver or internalized into endothelial cells

Lipid Emulsion Contraindications

- Patients allergic to soybean protein, egg yolks, or egg whites
- Individuals with compromised fat metabolism
- No complications with Lipid Emulsion when administered to patient suspected to have local toxicity

Local Anesthesia Injected in Blood

After Lipid Emulsion
**Past (where we’ve been)**
- Pt had a carnitine deficiency and was extremely sensitive to Bupivacaine
- Carnitine is component necessary for transport of fatty acids into mitochondria
- Fatty acids supply the majority of cardiac energy needs
- Initial theory = Bupivacaine inhibits carnitine. Thus, decreasing fatty acid uptake
- Pretreating with lipid infusion would potentiate cardiac arrhythmias

**Past (Discovery)**
- Accidental
- Weinberg pretreated rats w/ infusion of lipids
- Measured the dose of bupivacaine require to induce asystole
- Rats that were pretreated were able to tolerate more bupivacaine
- Rats that were pretreated were more easily resuscitated (survivability)

**PAST (Dog Trial)**
- 12 dogs subjected to isoflurane anesthesia
- Toxic Dose of bupivacaine given
- After asystole occurred, cardiac massage for 10 minutes
- 6 dogs got lipids, 6 dogs got saline
- Results: 6 dogs in lipid group converted to NSR in 5 minutes. After 30 minutes BP, HR, and ECG normal. 6 dogs in saline group never converted to NSR
- Lipid therapy had a restorative effect on pH and O² of myocardial tissue
**Past (Rat trial)**
- 1st part of Study
  - Bupivacaine infused to a final concentration of 500 μmol/L in the heart (asystole)
  - 20% IVLE (intravenous lipid emulsion) was infused, buffer solution to control group
  - 30% reduction in time to first heart beat in the lipid emulsion group
  - IVLE hearts had a faster return to 90% of their baseline rate pressure

- 2nd part of study
  - Bupivacaine was radiolabled
  - Myocardial tissue samples from LV
    - before bupivacaine infusion
    - after bupivacaine infusion
    - 30 seconds to 2 minutes thereafter
  - Bupivacaine was extracted from myocardial tissue
    - 37 seconds for IVLE group
    - 83 seconds for the control group

- 3rd part of study (no clinically significant data)
  - [http://www.youtube.com/watch?v=b70Li9r3pL8](http://www.youtube.com/watch?v=b70Li9r3pL8)

**Past (1st Human Case)**
- 58y male for right shoulder rotator cuff repair
  - Interscalene block with 20ml of 0.5% bupivacaine and 20ml of 1.5% mepivacaine
  - s/s of local toxicity ensued
  - CPR initiated (3mg epi, 2mg atropine, 300mg of amiodarone, 40u vasopressin, Defibrillation according to ACLS protocol
  - 30min into unsuccessful CPR, member of the code team suggested lipids
  - 100ml of 20% lipid emulsion IV

**Past (1st Human Case Cont’d)**
- 360J defib, 1mg epi, 1mg atropine, 15 seconds pt in NSR
- Lipids for 2hrs at 0.5ml/kg
- 2hrs later extubated, discharged following day
- Successful!

**Past (1 month later)**
- 84y female for correction of dupytren contracture under brachial plexus block
- Medication error: 40ml of 1% ropivacaine instead of 0.5% ropivacaine
- 15 min pt lost consciousness/seizures. Intubated.
  - 100mg thiopental
  - Few minutes later bradycardia then asystole
  - CPR (including 3mg of epi in divided doses)
    - 10 minutes all ACLS failed
  - 100ml of 20% lipid emulsion → continuous infusion 10ml/min
  - chest compression continued
- After 200ml of lipids, wide complex tachyarrhythmias to NSR

**Past (Not so fast)**
- In 2006 a nineteen question survey was sent to 135 Academic Anesthesia departments in the US regarding use of Lipid Emulsions
  - 74% of the respondents said their institutions would not consider using lipid emulsions

"You’re too skeptical. Think of all those heads out there—how LCNW them for only 60c an oz?"
**Present (Lipid Mania)**

**4 case reports in May 2008 issue in Anesthesia & Analgesia**

1. Thirteen year old girl for meniscectomy L knee
   - Received lumbar plexus block (11ml of 1% lidocaine and 11ml of 0.75% ropivacaine)
   - V-tach and widening QRS patterns. Altered BP, pulse ox to 92%.
   - Local toxicity suspected 150ml of 20% lipid emulsion. 2 minutes later NSR, pulse ox to 99%, BP stable.
   - Surgery completed with no further complications

2. Ninety-one year old man for olcranon bursitis surgery
   - Infraclavicular brachial plexus block (30ml of 1% mepivacaine)
   - Incomplete ulnar nerve block.
   - Dizziness, nausea, agitation, unresponsive to verbal stim
   - LA toxicity suspected → 50ml of 20% fat emulsion, repeat dose of 50ml 3 minutes later.
   - Continuous fat emulsion drip at 0.25ml/kg/min
   - Regained consciousness after 5 minutes of drip and after total dose of 200ml arrhythmias disappeared.

**Present**

**83yr old woman for total knee arthroplasty**
- Healthy, lived independently

**Anesthesia Management**
- Femoral and sciatic block for post-op pain. Spinal for intra-op anesthesia management!
  - Fem block – (15ml of 0.5% bupivacaine w/ epi, 15ml of 1% ropivacaine)
  - Sciatic block consisted of the exact same local anesthetic

**10 minutes after sciatic, VS deteriorated.**
- Bradycardia (30-40bmp) to wide complex v-tach, BP (60-70mmHg systolic)
- 5 minutes of ACLS
- 250ml of 20% lipid emulsion over 30 minutes, followed by another 250ml
- 4-5 minutes patient converted to NSR

Varela et al., AANA Journal, 2010

**Present**

**69yr woman presented to ER w/ femoral neck fracture**
- Received bupivicaine femoral nerve block for pre-op analgesia
- Seizure and cardiovascular collapse developed immediately after LA
- 20% lipid emulsion was successful in normalization in hemodynamics parameters

Harvey et al., Emerg Med Australas, 2011

**Present**

**5yr old castrated male domestic short hair cat**
- Received 140mg lidocaine (20mg/kg) to facilitate closure of wound on L pelvic limb
- Severe lethargy, resp distress, poor erratic pulses, decreased BP
- Oxygen, LR, 20% LE @ 1.5ml/kg over 30 min
- Cardiovascular & behavior restored
- No adverse effects

Present

- 24 yr old surgery for fx L clavicle
- Interscalene Brachial Plexus Block
  - Received 40ml of 0.5% ropivicaine
- General anesthesia was induced
- Operation completed uneventful
- Pt restless and twitching upon emergence
  - Toxicity was suspected
- 100ml of 20% LE
- S/S disappeared
- Full recovery of consciousness in 5 Minutes

“Revolution creates relevancy”

“If you wait to do everything until you’re sure its right, you’ll probably never do much of anything.” — Win Borden

Present (Case cont’d)

- 36 yr old inhaled 5.25g of dosulepin
- Widening QRS, HR 113, BP↓
- LOC deteriorated and seizures
  - Bicarb administered
- Cardiac instability continued
- LE therapy
- BP stabilized, seizures and CNS symptoms subsided

FUTURE

- Intentional overdose in a 50yr old woman of Lamotrigine
- Lost consciousness and ECG arrhythmias
- Sodium Bicarb, no effects
- Recovery of cardiac conduction was achieved w/ 20% lipid emulsion
- Lamotrigine is Na⁺ channel blocker prescribed for seizure disorder
- Tox screening consistant w/ lipid sink theory

Boegevig et al., Clinical Toxicology, 2011

Castanares-Zapotero et al., Am Emerg Med, 2010
**Future**

- 4yr old presents to ER w/ tachycardia & agitation
  - Followed by somnolence after presumed accidental olanzapine ingestion (1-3 hrs before)
- Lipid emulsion ameliorated symptoms
- When LE stopped – reoccurrence of symptoms
- Discontinued when LE started again
- S/S dissipated. No adverse effects


**Conclusion**

- Lipid Emulsion should be considered among first lines of treatment for local anesthesia toxicity and seriously considered for lipid soluble drug overdose
- Anesthesia providers should be trained in LE rescue therapy
- LE rescue kit should be available where LA are regularly administered

“the point is to spread the word – by then we can save lives.”
Guy Weinberg