LIPID EMULSION FOR LOCAL ANESTHESIA TOXICITY

Brian D. Berry Jr., CRNA, MS
Adjunct Faculty
University of Pittsburgh

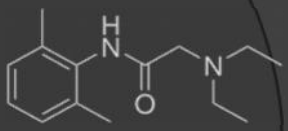
UPMC Staffing Network, Nurse Anesthesia
University of Pittsburgh Medical Center
Department of Anesthesia

Objectives

- Discuss and Review the pharmacodynamics/pharmacokenetics 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

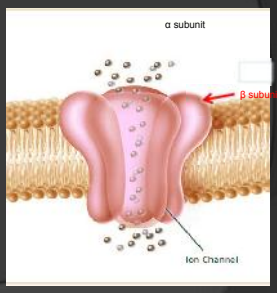
Pharmacodynamics

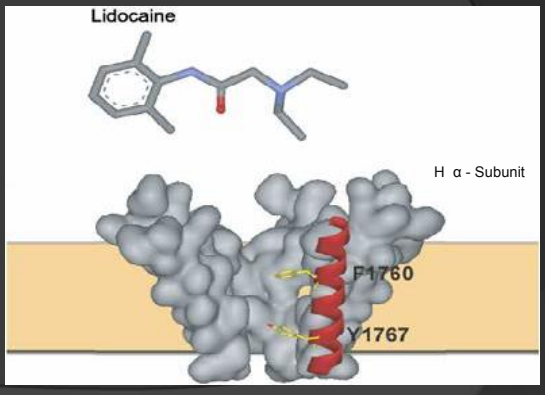
- Locals have 3 basic components
  - Amine group
  - Aromatic group
  - Linkage group
- Adding carbons = ⇧ lipophilicity, duration of action, and protein binding
- Reversibly block conduction of impulses along central and peripheral nerve pathways (autonomic, somatic sensory and somatic motor)

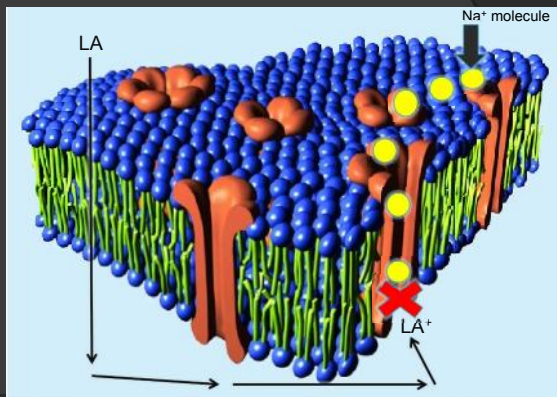


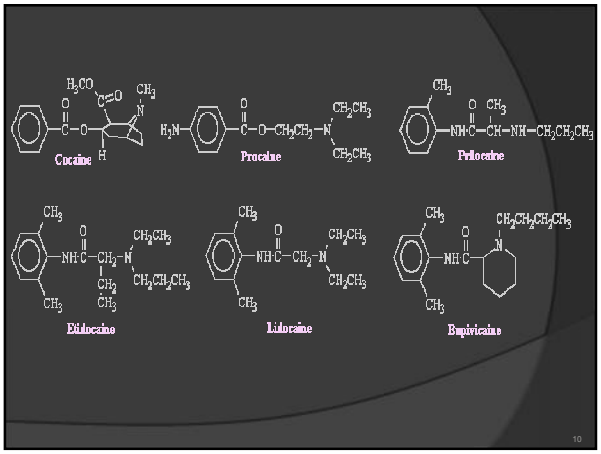
LAs pharmadynamics (cont)

- Weak bases
- Increased affinity for open Na^+ channels and 75% of channels must be blocked for effect
- H type alpha subunit binds to local anesthetics









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
- Saftey has ↑ d/t
  - Aspiration
  - Knowledge (i.e. local toxic doses)
  - Divided doses
  - Test dose with epi

LA	Potency	Onset	Duration of Action (min)	Max Dose (mg)	Max Dose (mg/kg)
Cocaine	14	Rapid	n/a	200	1.5-3
Procaine	1	Slow	45-60	500	8
Chloroprocaine	4	Rapid	30-45	800-1000	10
Tetracaine	16	Slow	60-180	100	1.5
Lidocaine	1	Rapid	60-120	300-400	4-5
Prilocaine	1	Slow	60-120	500	5-7
Bupivacaine	4	Slow	240-480	150-175	1-2.5
Ropivacaine	4	Slow/Medium	240-480	225	2.5-3
Levobupivacaine	4	Slow	240-480	150	2-2.5
Etidocaine	4	Slow	240-480	200-300	2-5

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 Ca^{++} and the K^+ channels) inhibits cAMP.
- Cardiac LA toxicity is very difficult to manage and treat
  - Resusictation – well documented as very difficult
- Bupivicaine is the most cardiotoxic of Las.

Signs and Symptoms of Toxicity

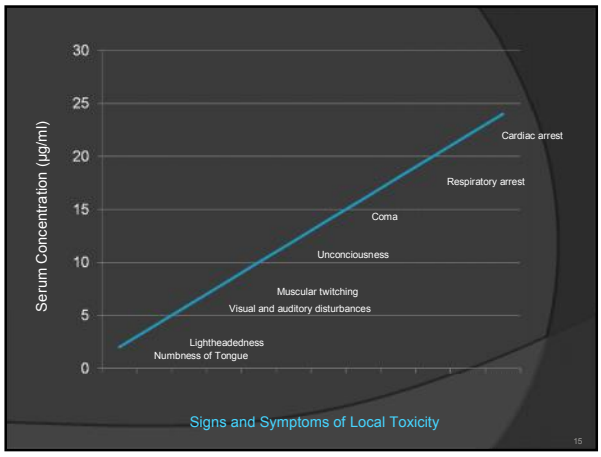
Early – agitation, light headedness, altered mental state, vision Δ's, slurred speech, HTN, ↑HR

Moderate – CNS excitation, cardiac arrythmias, contractile depression, conduction blockade

Severe - ↓BP, ↓HR, ventricular arrythmias, seizures, cardiac collapse

Lipid Emulsion

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



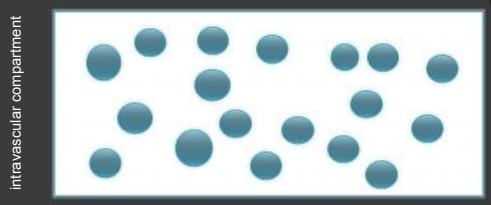
Signs and Symptoms of Local Toxicity

	Intralipid	Liposyn III	Medialipid	Clinoleic
Oils	100% soybean oil	100% soybean oil	50% soybean oil and medium chain triglycerides	80% olive oil and 20% soybean oil
Triglycerides (g/L)	200	200	200	200
Phospholipids (g/L)	12	12	12	12
Glycerol (g/L)	22	25	25	22.5

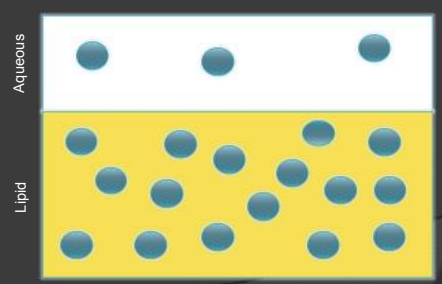
Lipid Emulsion (cont'd)

- 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

Local Anesthesia Injected in Blood



After Lipid Emulsion



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

Past (where we've been)

- Pt had a carnitine deficiency and was extremely sensative 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

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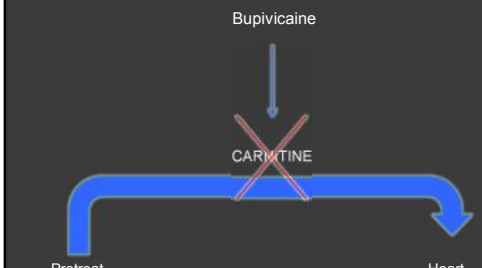

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Past (Discovery)

- 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)

Weinberg et al., *Anesthesiology,* 1998

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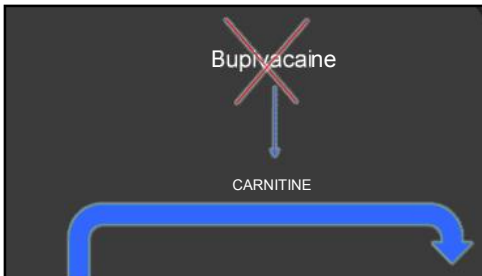

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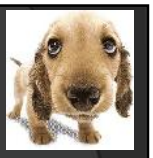
PAST (Dog Trial)



- 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 0^2 of myocardial tissue

Weinberg et al., *Reg Anes Pain Med, 2003*

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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 bupvicaine infusion
    - after bupivacaine infusion
    - 30 seconds to 2 minutes thereafter
  - Bupvicaine 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

Weinberg et al., *Reg Anesth Pain Med, 2006*

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% mepivicaine
- s/s of local toxicity ensued
- CPR initiated (3mg epi, 2mg atropine, 300mg of amiodarone, 40u vasopressin, Defribillation 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
- 2.5hrs later extubated, discharged following day
- Successful!!

Rosenblatt et al., *Anesthesiology, 2006*

PAST (1 month later)

- 84y female for correction of duputytren contracture under brachial plexus block
- Medication error: 40ml of 1% ropivacaine instead of 0.5% ropivacaine
- 15 min pt lost conciousness/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

Litz et al., *Anaesthesia,*

PAST (Not so fast)

- In 2006 a nineteen question survey was sent to 135 Academic Anesthesia departments in the US regarding use of Lipid Emulsion
- 74% of the respondents said their institutions would not consider using lipid emulsions

Corcoran et al., *Anesth Analg,* 2006




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 anesthestic
- 10 minutes after sciatic. VS deteriorated.
  - Bradycardia (30-40bpm) 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 at el., *AANA Journal,* 2010

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

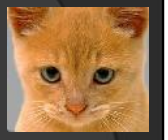
Present

- 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

2. Ninety-one year old man for olcranon bursitis surgery
   - Infraclavicular brachial plexus block (30ml of 1% mepivacaine.
   - Incomplete ulnar nerve block.
     - Additional 10ml of prilocaine
   - 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 conciousness after 5 minutes of drip and after total dose of 200ml arrhythmias disappeared.

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

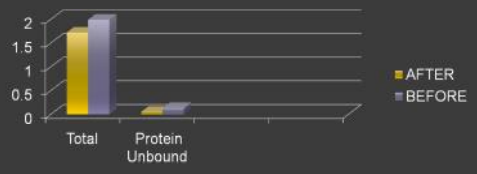
O'Brien, et al., *J Am Vet Med Assoc,* 2010

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 conciousness in 5 Minutes

Mizutani et al., *J Anesth,* 2011

Present (Case cont'd)



1.99 and 0.13 µg/mL

BEFORE LIPID EMULSION

1.72 and 0.05 µg/mL

AFTER LIPID EMULSION

"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

FUTURE

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

Boegevig et al., *Clinical Toxicology,* 2011

FUTURE

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

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

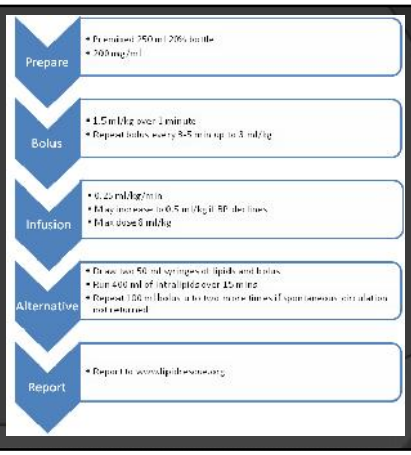
Future

- 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 –reoccurance of symptoms
- Discontinued when LE started again
- S/S dissipated. No adverse effects

McAllister et al., *Am J of Emerg Med*, 2011

"the point is to spread the word – by then we can save lives."

Guy Weinberg



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