Pharmacology of Local Anesthetics

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Disclosure Statement

- I do not have any relevant relationship with any commercial interests to disclose.
- The views expressed herein are those of myself and do not reflect official policy or position of the Uniformed Services University of the Health Sciences, the Department of Defense, or the United States Government.

Content Roadmap

- Anatomy
  - Physiology
  - Mechanism
  - Fiber Blockade
- Structure & Activity
  - Structure
  - Onset
  - Potency
  - Duration
- Adverse Effects
  - Allergy
  - LAST – CNS
  - LAST – CV
  - Case Report
  - LAST - Treatment
- Preparation
  - Making Additives
  - Epinephrine
  - Others
Nerve Anatomy

- Collection of Efferent and Afferent axons.
- Endoneurium = individual axon
- Fascicle = group of individual axons
- Perineurium = covers fascicle
- Epineurium = covers group of fascicles

Bottom Line: Several layers of tissue surround individual axons = barriers to local anesthetics.

Hodgkin and Huxley


1963 Nobel Prize - Physiology

Action Potential

- When an electrical impulse is applied, the protein-based membrane channels open and Na ions enter via the concentration gradient.
- Shortly after Na enters, K ion channels open and Na channels close - K leaves according to its concentration gradient.
- K channels are slower to close resulting in a hyperpolarization - a relative refractory period (one way conduction).
- Intracellular Na is actively removed by the Na/K pump (3 Na out/2 K in) and K continues to passively diffuse out - restoring the resting membrane potential.
Local anesthetics are drugs that reversibly block the conduction of impulses in electrically excitable tissue. Influenced by:
- Nerve Anatomy (size, myelination, type)
- Local tissue conditions (environmental pH)
- Local anesthetic properties (pKa, lipid solubility, protein binding, additives)
Local Anesthetics Suppress Action Potentials

- Bind to open and inactive sodium channels located inside the axon.
- Prevent influx of sodium.
- Prevent action potential firing = no transmission of “information.”

Use-Dependent Block

- The more channels that are opened, the greater the block.
- Local anesthetics preferentially bind to open sodium channels.
- Increased firing of action potentials = increased frequency of open channels.
- Therefore, increased “use” = increased block
Concentration and Volume

- Minimum Blocking Concentration
- The concentration that halts impulse propagation.
- Critical Blocking Length (volume spread)
- Myelinated Fibers: 3 nodes of Ranvier
- Unmyelinated Fibers: 3-6 mm
- Key Point: Concentration + Volume = Blockade


Barash Clinical Anesthesia 8th ed. P. 568

Key Point: Concentration + Volume = Blockade

Nerve Fiber Characteristics

<table>
<thead>
<tr>
<th>Fiber Type</th>
<th>Size (microns)</th>
<th>Function</th>
<th>Clinical Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>&lt;3</td>
<td>Preganglionic, Sympathetic</td>
<td></td>
</tr>
<tr>
<td>C*</td>
<td>0.3-1.3</td>
<td>Temperature, Dull Pain</td>
<td></td>
</tr>
<tr>
<td>A-delta</td>
<td>1-4</td>
<td>Temperature, Sharp Pain</td>
<td></td>
</tr>
<tr>
<td>A-gamma</td>
<td>3-6</td>
<td>Muscle Spindle, Muscle Tone</td>
<td></td>
</tr>
<tr>
<td>A-beta</td>
<td>8-22</td>
<td>Light pressure, Touch</td>
<td></td>
</tr>
<tr>
<td>A-alpha</td>
<td>6-22</td>
<td>Somatic, Motor, Proprioception</td>
<td></td>
</tr>
</tbody>
</table>

* Unmyelinated Fibers

Barash Clinical Anesthesia 7th ed. p. 563, 565-56

Sequence of LA Blockade

- Sympathetic (autonomic) block with vasoconstriction and warm skin.
- Loss of temperature (cold before hot).
- Loss of sharp pain (needle prick).
- Loss of touch and deep pressure sensation.
- Loss proprioception
- Motor paralysis
- Onset Summary: Autonomic > Sensory > Motor

“Differential Blockade” – block sensory, spare motor
Local Anesthetics

Anatomy
Structure & Activity
Adverse Effects
Preparation

Molecular Structure

Lipophilic

Hydrophilic

Ester Linkage
- Hydrolyzed by plasma esterases
- Rapidly inactivated
  - Chloroprocaine
  - Procaine
  - Tetracaine
  - Cocaine

Amide Linkage
- Bio-transformed by hepatic enzymes
- More stable, longer plasma half lives
  - Lidocaine
  - Bupivacaine
  - Ropivacaine
  - Mepivacaine

Barash Clinical Anesthesia 7th ed. p. 566
Some local anesthetics exist as enantiomers or optical isomers.

- Mirror image of chemical structure & not superimposable (chiral molecules)
- Referred to as S (sinister, left) or R (rectus, right) isomers (e.g. S-bupivacaine or levobupivacaine)
- Chiral molecules can have different physiochemical and biologic properties.
- Racemic solutions are equal concentrations of S and R isomers.
- Typically, the S isomer has less toxicity and maintains local anesthetic potency.

Bupivacaine
- Racemic – a mixture of both S & R.
- Levobupivacaine is the S isomer of bupivacaine (less vasodilation, less toxicity).

Ropivacaine
- Only the S isomer form.
- Less potent than bupivacaine.
- Less toxic – leaves sodium channel more rapidly.
Basic Properties
Local Anesthetics

- Weak bases – tertiary amines
- Poorly water soluble
- Prepared as water-soluble HCL salts that are strongly acidic (pH < 6)
- Commercially prepared local anesthetics containing epinephrine often have sodium bisulfite added to lower pH to 3-4 (epinephrine is unstable in an alkaline pH).

Local Anesthetic Activity Factors

Onset of Action
Potency
Duration of Action

- pKa = Speed of Onset
- Local Anesthetics are weak bases.
- Exist in ionized (charged) and unionized forms (uncharged).
- The percentage of ionized vs. unionized form is dependent upon pH.
- When the pKa of a drug = pH, the LA is 50% ionized: 50% unionized
- The unionized form (uncharged) crosses the lipid bilayer.
- However, the ionized (charged) form binds to the sodium channel.

pKa = Speed of Onset

Barash, Clinical Anesthesia 8th ed. p. 569
Crossing the lipid bilayer

- Base and ionized forms: $B + H^+ \leftrightarrow BH^+$
- Penetration of phospholipid membrane = $B$
  (unionized, uncharged)
- Binding to receptor = $BH^+$  (ionized, charged)

Intracellular pH = 7.2

Onset of Action

<table>
<thead>
<tr>
<th>Lidocaine</th>
<th>$pK_a = 7.9$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$pH$ of environment</td>
<td>% unionized (uncharged)</td>
</tr>
<tr>
<td>7.9</td>
<td>20</td>
</tr>
<tr>
<td>7.6</td>
<td>33</td>
</tr>
<tr>
<td>7.4</td>
<td>55</td>
</tr>
<tr>
<td>7.2</td>
<td>75</td>
</tr>
</tbody>
</table>

Does infected tissue at site of local administration affect onset of action?
Sodium Bicarbonate Alkalization

- The addition of sodium bicarbonate to a local anesthetic (especially commercially prepared epinephrine containing) speeds onset of action.
- Alkalization increases the % of unionized (free base) drug to cross the nerve membrane = speeds onset of action.
- Used clinically with epidural blocks or to reduce pain of subQ infiltration.
- Ineffective in acidic infected tissue.

1mL of 8.4% sodium bicarbonate \( \rightarrow \) 10mL local anesthetic (except bupivacaine).

Potency

- Increased lipid solubility = increased potency of the local anesthetic.
- The axon and myelin sheath are composed of lipid membranes.
- Potency (lipid solubility) is increased by adding large alkyl groups.

![Chemical structures](Barash Clinical Anesthesia 8th ed. p. 308)

Bupivacaine Potency = 8
Mepivacaine Potency = 0.3

Duration of Action

- Directly related to protein binding and lipid solubility.
- High lipid solubility = slow diffusion from lipid rich environment to aqueous bloodstream.
- Protein binding = efficient binding of the LA to the sodium channel (a protein).

Protein Binding = Duration of Action
### Duration of Action

<table>
<thead>
<tr>
<th>Duration</th>
<th>2-chloroprocaine</th>
<th>Lidocaine</th>
<th>Bupivacaine</th>
<th>Mepivacaine</th>
<th>Ropivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short (45-90 minutes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate (90-180 minutes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long (5-18+ hours)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Vasomotor Action

- Local Anesthetics are vasodilators (except cocaine and ropivacaine).
- ↑ blood flow to site = ↑ absorption = ↑ risk for systemic toxicity = ↓ duration
- Epinephrine additive = vasoconstrict, ↓ systemic uptake, and ↑ duration
- Will not prolong ropivacaine (inherent vasoconstrictor and strong protein binding).
- Epinephrine can serve as a vascular marker (HR > 20 bpm, BP > 15 mmHg).

### Maximum Single Injection Dosages

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine (plain)</td>
<td>4.5 mg/kg</td>
<td>300 mg</td>
</tr>
<tr>
<td>Lidocaine (epi)</td>
<td>7 mg/kg</td>
<td>300 mg</td>
</tr>
<tr>
<td>Mepivacaine (plain)</td>
<td>4.5 mg/kg</td>
<td>300 mg</td>
</tr>
<tr>
<td>Mepivacaine (epi)</td>
<td>7 mg/kg</td>
<td>500 mg</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>3 mg/kg</td>
<td>250 mg</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>3 mg/kg</td>
<td>175 mg</td>
</tr>
</tbody>
</table>
**Local Anesthetic Activity Summary**

- **pKa**
- **Lipid Solubility**
- **Protein Binding**

**Working Together for Total Activity**

- **Onset**
- **Potency**
- **Duration**

**Local Anesthetics**

**Anatomy** → **Structure & Activity** → **Adverse Effects** → **Preparation**

- **Allergy**
  - LAST – CNS
  - LAST – CV
  - Case Report
  - LAST – Treatment

**Allergic Reactions**

- Type I (IgE) or Type IV (T cell mediated)
- Type I is anaphylactic, immediate, and probably life-threatening.
- 1% of all reported cases - rare
- Type IV are delayed 12-48 hours after exposure.
  - Contact dermatitis
  - Ester metabolism to Para-aminobenzoic acid (PABA) → Allergen
  - Amide Methylparaben and metabisulfite preservatives → Allergen
  - Cross Sensitivity between esters and amides is unlikely

*Barash Clinical Anesthesia 8th ed., p. 580*
Pathophysiologic Factors

- ↓ CO
  - ↓ Vd and ↓ clearance

- Liver disease
  - ↓ Vd and ↓ clearance

- Advanced age
  - ↓ Vd
  - ↓ clearance
  - ↓ protein binding

= Dose Reduction

Local Anesthetic Systemic Toxicity - LAST

- Severity is proportional to the rate of delivery to the central circulation:
  - Dose
  - Vascularity
  - Use of Vasoconstrictor
  - Toxicity of drug

- Rate of redistribution and metabolism (Elimination)
  - Faster = better
  - Slower = not good (i.e. bupivacaine)

LAST - Site of Injection

- Systemic absorption = vascularity & total dose.
- ↑ vascularity = ↑ absorption

- Blood > Intercostal > Caudal > Epidural > Brachial Plexus > Sciatic
  - B - I - C - E - P - S
LAST- Central Nervous System

- Toxicity = plasma concentration
- Highly potent, lipid-soluble agents (i.e. bupivacaine) cause CNS toxicity at lower doses

<table>
<thead>
<tr>
<th>Lidocaine Plasma Concentration (μg/mL)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5</td>
<td>Analgesia</td>
</tr>
<tr>
<td>5-10</td>
<td>Lightheadedness, Tinnitus, Numbness of tongue, Palpitations</td>
</tr>
<tr>
<td>10-15</td>
<td>Seizures, Unconsciousness</td>
</tr>
<tr>
<td>15-25</td>
<td>Coma, Respiratory Arrest</td>
</tr>
<tr>
<td>&gt; 25</td>
<td>Cardiovascular depression</td>
</tr>
</tbody>
</table>

LAST- Cardiovascular System

- Requires greater plasma concentrations than needed for CNS symptoms.
- Initial signs: ↑ heart rate & ↑ blood pressure (co-occurring CNS signs)
- Dysrhythmias
- Heart Block
- Hypotension, bradydysrhythmia
- Reduced cardiac contractility
- Asystole

LAST - Prevention

- Vascular Marker (epinephrine)
- Small, incremental dosing
- Early recognition, stop LA administration
- Stop progression of CNS effects, raise seizure threshold (benzodiazepines, propofol*)
- Maintain oxygenation and ventilation

Anoxia and Systemic Acidosis are LETHAL.
LAST: Case Report

- 31 y.o. male
- Untreated HTN
- Work related trauma to L hand
- NPO x 9h
- Planned debridement/tendon repair of fingers

Plan:
- supraclavicular block with 20-30mL 0.5% bupivacaine with 1:200K epinephrine.
- Monitors, oxygen
- Midazolam 2mg after consent

Case Report: During Injection

What symptoms or signs might we have seen prior to this?

Initial treatment?

Case Report: Treatment

- Midazolam 2 mg (Propofol?)*
- Oral airway
- Positive Pressure ventilation with 100% oxygen.
- Crash cart – ACLS
- Amiodarone, Vasopressors
- N:O: CCB, Beta Blockers, Lidocaine
- 12-lead
- ABG: pH 7.01, PO2 111, PCO2 90, HCO3 23. BE - 10.
- Consider intubation
- Patient regained consciousness after 1 hour 15 minutes of supportive care.
Case Report: Treatment & Resolution

LAST: Treatment

- Early Recognition is Key
- Stop LA administration
- Oxygenation
- Raise seizure threshold (BNZ)
- Maintain Ventilation
- CPR – ACLS
- Epinephrine, Amiodarone
- Avoid: Propofol (large doses), Calcium channel blockers, beta antagonists, Lidocaine
- Supportive care
- Lipid Rescue

LAST: Lipid Rescue

- Exogenous lipid provides an alternate source of binding for the lipid soluble LA - “plasma sink”
- 20% Lipid emulsion: 1.5 mL/kg/h bolus
- Continuous infusion: 0.25 mL/kg/min for at least 10 min after return after cardiac function
- Max: 10 mL/kg over 30 min for initial dosing
ASRA guidelines: Lipid Rescue

Lipid Emulsion 20%
_POSTFIELDS

<table>
<thead>
<tr>
<th>Patient Weight</th>
<th>Lipid Emulsion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than 70 kg</td>
<td>Bolus 100 ml Lipid Emulsion 20% rapidly over 2-3 minutes</td>
</tr>
<tr>
<td>Less than 70 kg</td>
<td>Bolus 1.5 ml/kg Lipid Emulsion 20% rapidly over 2-3 minutes</td>
</tr>
</tbody>
</table>

- Lipid emulsion infusion 200-250 ml over 15-20 minutes
- Lipid emulsion infusion 0.25 ml/kg/min (ideal body weight)

If patient remains unstable:
- Re-bolus once or twice at the same dose and double infusion rate; be aware of dosing limit (2ml/kg)
- Total volume of lipid emulsion can approach 1 L in a prolonged resuscitation (e.g., > 24 minutes)

LAST: Lipid Rescue Website

- http://www.lipidrescue.org
- Blog
- Case Registry
- Latest Publications

Local Anesthetics

Anatomy
- Structure & Activity
- Adverse Effects
- Preparation
- Mixing Additives
- Epinephrine
- Others
Local Anesthetic Concentration

- Look at the % on the label
- Move the decimal point one value to the right
- This will equal the mg / mL concentration
- For example:
  - 0.5% Ropivacaine = 5 mg/mL concentration.
  - 20 mL = 100 mg total
  - 0.25% Bupivacaine = 2.5 mg / mL
  - 20 mL = 50 mg

Epinephrine "Ratio" (1:200K)

- 1:200,000
- 1 gram of epinephrine dissolved in 200,000 mL of solution

\[
\begin{align*}
\text{1 gram} & \Rightarrow \frac{1,000 \text{ mg}}{200,000 \text{ mL}} = \frac{0.005 \text{ mg}}{1 \text{ mL}}
\end{align*}
\]

Milligrams – to - Micrograms

- 0.005 mg/mL = 5 μg/mL
  - 3 decimal places to the right
Local Preparation

Prepare 30 mL of 0.5% Ropivacaine + 1:200K epinephrine

30 mL + __________ mL

Local Preparation: What you need to know

- Total volume of local anesthetic solution: ________ mL
- Epinephrine Ratio Calculation:

\[
\frac{1 \text{ gram}}{200,000 \text{ mL}} = \frac{1,000 \text{ mg}}{200,000 \text{ mL}} = \frac{0.005 \text{ mg}}{1 \text{ mL}} = 5 \mu g \text{ of epinephrine}
\]

Local Preparation

Prepare 30 mL of 1:200,000 epinephrine solution:

_______ mL x ________ µg/mL = 150 µg of epinephrine
So.....

- How do you get 150 μg of Epinephrine from the stock solution?
- Remember: 1:1000 = 1 mg in 1 mL
- Same as: 1000 μg in 1 mL
- Therefore: 100 μg per 0.1 mL
- So..... 150 μg = 0.15 mL

Common Epinephrine Additions

- 1:100K: 10 μg
- 1 mL
- 1:200K: 5 μg
- 1 mL
- 1:400K: 2.5 μg
- 1 mL of local anesthetic

Local Preparation Question

- You have a 20 mL vial of 2% Lidocaine
- What volume stock epinephrine (1:1000) must you add to the 20 mL vial of Lidocaine to make a 1:200,000 solution?
Local preparation question

\[
\frac{1}{200K} \quad 5 \, \mu g \\ 1 \, mL
\]

So...

\[
20 \, mL \times 5 \, \mu g/mL = 100 \, \mu g = 0.1 \, mL
\]

Adjuvants

- Additives that may increase the duration of action of local anesthetics – **Not approved by the FDA for perineural use.**
  - Dexamethasone (4-8 mg) perineural vs IV – no difference
  - Clonidine (75-100 mcg)
  - Dexmedetomidine (20-100 mcg)
  - Buprenorphine (150 mcg)
  - Magnesium (100-150 mg)
- Considerations: Length of blockade, neurotoxicity concerns, systemic side effects (bradycardia, hypotension, pruritis)
- Read the literature! Support your rationale with evidence.

Questions
References: