Regional Anesthesia: How Do We Make It Last?

Sarah Tweedy DNP, CRNA, ARNP
I have no conflicts of interest and nothing to declare

*Many of these adjuncts are considered to be off-label use*
Objectives

- Understand the basic pharmacology of local anesthetics
- Understand previously used medications and why they are no longer recommended
- Understand currently used medication adjuncts for peripheral nerve blocks
- Understand the future direction of adjuncts for peripheral nerve blocks
Local Anesthetics: How Do They Work Again?
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- **Duration of Action**: Determined by *protein binding and lipid solubility*
  - Drugs with high affinity for protein and lipids = firm attachment to those substances
  - Local anesthetic receptor on the neural membrane is composed of protein
  - Site of injection: speed of absorption changes based on location
    - Local anesthetics cause vasodilation (except cocaine and ropivacaine)

- **Onset of Action**: Determined by ionization
  - Charged form will not penetrate membranes well
  - Dreaded pKa (Lower pKa = faster onset; except chloroprocaine which is concentration based)

- **Potency**: Determined by the lipid solubility of the local anesthetic
  - Axolemma and myelin sheath are composed of lipids (i.e. lipid soluble drugs can pass easily through the nerve membrane)
  - Increased lipid solubility correlates with increased protein binding
    - Also correlates with increased likelihood of cardiac toxicity (bupivacaine)
Local Anesthetics: How Do They Work Again

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Drug</th>
<th>Common Name</th>
<th>Relative Potency</th>
<th>Onset</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low potency; short duration of action</td>
<td>Procaine</td>
<td>Novocaine</td>
<td>1</td>
<td>Slow</td>
<td>60-90</td>
</tr>
<tr>
<td></td>
<td>Chloroprocaine</td>
<td>Nesacaine</td>
<td>1</td>
<td>Fast</td>
<td>30-60</td>
</tr>
<tr>
<td>Intermediate potency; intermediate-long duration of action</td>
<td>Mepivacaine</td>
<td>Carbocaine</td>
<td>2</td>
<td>Fast</td>
<td>120-240</td>
</tr>
<tr>
<td></td>
<td>Prilocaine</td>
<td>Citanest</td>
<td>2</td>
<td>Fast</td>
<td>120-240</td>
</tr>
<tr>
<td></td>
<td>Lidocaine</td>
<td>Xylocaine</td>
<td>2</td>
<td>Fast</td>
<td>90-200</td>
</tr>
<tr>
<td>High potency; long duration of action</td>
<td>Tetracaine</td>
<td>Pontocaine</td>
<td>8</td>
<td>Slow</td>
<td>180-600</td>
</tr>
<tr>
<td></td>
<td>Bupivacaine</td>
<td>Marcaine, Sensorcaine</td>
<td>9</td>
<td>Intermediate</td>
<td>180-600</td>
</tr>
<tr>
<td></td>
<td>Etidocaine</td>
<td>Duranest</td>
<td>6</td>
<td>Fast</td>
<td>180-600</td>
</tr>
<tr>
<td></td>
<td>Ropivacaine</td>
<td>Naropin</td>
<td>10</td>
<td>Slow</td>
<td>180-600</td>
</tr>
</tbody>
</table>
## Local Anesthetics: How Do They Work Again?

<table>
<thead>
<tr>
<th>Local Anesthetic</th>
<th>Manufacturers’ Recommended Single-Injection Max Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorprocaine</td>
<td>11 / (14)</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>4 / (7)</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>4 / (7)</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>7 / (8.5)</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>2.5 / (3.2)</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>6 / (8)</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>3 / (3.5)</td>
</tr>
</tbody>
</table>

*Drug alone / (drug with epinephrine)
History of Local Anesthetic Adjuncts

- **Adenosine**
  - No additional benefit\textsuperscript{19}

- **Dextran**
  - Needs high powered studies; currently inconclusive for any benefit\textsuperscript{19}

- **Fentanyl**
  - No benefit when compared to other routes\textsuperscript{19}

- **Hydromorphone**
  - No benefit when compared to other routes\textsuperscript{19}

- **Ketamine**
  - No benefit when compared to other routes\textsuperscript{19}
  - Unacceptably high incidence of adverse effects (psychotomimetic)\textsuperscript{19}
History of Local Anesthetic Adjuncts

- **Midazolam**
  - Neurotoxic in animal models\(^\text{19}\)
  - Not recommended for use\(^\text{19}\)

- **Morphine**
  - No benefit when compared to other routes\(^\text{19}\)

- **Neostigmine**
  - No benefit\(^\text{19}\)
  - Causes adverse side effects that increase with increased doses\(^\text{19}\)
  - Neurotoxic when injected perineural\(^\text{19}\)

- **Sufentanil**
  - No benefit when compared to other routes\(^\text{19}\)
  - Increased side effect profile\(^\text{19}\)
Current Local Anesthetic Adjuncts

- Alpha 2 adrenoreceptor agonists
  - Clonidine
  - Dexmedetomidine
- Buprenorphine
- Epinephrine
- Liposomal Bupivacaine
- Steroid
Clonidine

- Mechanism of action: α-2 receptor agonist; hyperpolarization of nucleotide gated cation channels
- Dosing: 0.5µg/kg (max 150µg)
- Wide range of results
  - One meta analysis showed duration was prolonged by 2 hours
  - Best used with intermediate acting local anesthetics
  - Upper extremity blocks had more success than lower extremity blocks
  - Adverse effects increased with increased doses
- More extensive research needs to be completed before routine use is recommended
Dexmedetomidine

- Mechanism of action: $\alpha$-2 receptor agonist (7 times more selective than clonidine); hyperpolarization of nucleotide gated cation channels$^{19}$
- Dosing: 1-2$\mu$g/kg$^{13,19}$
  - Lower dose = less side effects
- Increased duration of motor block, and prolonged time to first request for analgesia for brachial plexus blocks$^{19}$
- Increased duration of sensory block by 3 hours and reduction of pain scores for 4 hours$^{18}$
- Low incidence of adverse effects, can see hypotension/bradycardia as seen with IV administration$^{19}$
Buprenorphine

- **Mechanism of action**: decreased potassium conduction and increased calcium conduction; inhibits release of Substance P
  - Substance P is a proinflammatory polypeptide secreted by nerves and inflammatory cells that is thought to be involved in the synaptic transmission of pain
- **Dosing**: 0.3mg or 0.3µg/kg
- **Duration of action**: prolonged 1.5- to 3-fold for brachial plexus and sciatic nerve blocks
  - Some studies included epinephrine + buprenorphine
  - Perineural addition extended block longer than IM
  - Increased risk of PONV, no other adverse effects increased
    - Recommended to provide polymodal antiemetics
Epinephrine

- Proposed mechanism of action: constricts vessels in surrounding area\textsuperscript{19}
  - Some antinociceptive properties through α-2 agonism
- Dosing: 0.5-1µg/kg or 5-10µg/mL\textsuperscript{19}
- Does not prolong the duration to the same extent with all locals\textsuperscript{19}
  - Best with short and intermediate acting local anesthetics
  - Recent study showed no longer than 60 minutes extra\textsuperscript{21}
- Can increase the risk for neurotoxicity\textsuperscript{3}
  - Current recommendations are against use of epinephrine unless ultrasound is unavailable or tip of needle is not visualized
Liposomal Bupivacaine

Bupivacaine encapsulated in DepoFoam
Liposomal Bupivacaine

- **Mechanism of action**: microscopic lipid vesicles ranging in size from 0.02-40 µm act as reservoirs for drugs with low bioavailability\(^\text{19}\)
- **FDA approved for** hemorrhoidectomy, bunionectomy, fascial plane blocks and recently interscalene nerve blocks\(^\text{11}\)
  - Dentistry as well
- **Mixed results of efficacy depending on the study you read**\(^\text{11}\)
  - Some state no statistical difference in outcome
  - Some state 1st day specifically a reduction in opioid use
  - Some state up to 72 hours of relief
  - Detected in plasma up to 96 (infiltration)-120 (interscalene) hours after injection
- **Potential side effects**\(^\text{11}\)
  - Avoid additional local anesthetic for 72 hours*
  - Nausea, vomiting or constipation
  - Always risk of local anesthetic side effects
Liposomal Bupivacaine

**Pharmacokinetics: Exparel 266 mg**

- **Initial peak (1-2 h):** 3% extra-liposome bupivacaine
- **Second peak (24-48 h):** slow release of bupivacaine from DepoFoam
Liposomal Bupivacaine

Administration:

- Comes in a 10 or 20mL vial at 1.3% concentration (max dose is 20mL or 266mg for infiltration; 10mL or 133mg for brachial plexus blocks)\(^1\)
- Not verified for use in <18ya\(^1\)
- Dilution with sterile saline up to 300mL\(^1\)
  - May also *admix* bupivacaine HCl- do not exceed 1:2 (bupi HCL:liposomal bupi)
    - Example: 0.5% Bupi HCl: max 133mg (26mL) with 20mL liposomal bupivacaine
  - Wait at least 20 minutes after lidocaine infiltration to administer
- Do not mix liposomal bupivacaine with anything except the above mentioned\(^1\)
  - Possibility of reducing the efficacy of DepoFoam to encapsulate bupivacaine
Steroid (Dexamethasone)

- Mechanism of action: Current theory - local action on nerve fibers\textsuperscript{19}
  - Not the same as its anti-inflammatory effect
- Dosing: 4, 8, & 10mg all used; no dose-response relationship noted\textsuperscript{7}
- 37\% increase in prolongation of upper and lower extremity blocks when used with ropivacaine\textsuperscript{5}
  - Decreased pain for 24 hours
- A meta-analysis showed reduction of pain scores at 2, 6 and 12 hours and reduced pain medication intake for 24 hours\textsuperscript{4}
- Some studies have shown no statistical difference between intravenous and perineural administration\textsuperscript{8}
  - Cochrane review showed perineural prolonged sensory block 3 more hours; no difference in pain intensity/pain medications taken\textsuperscript{15}
Future Local Anesthetic Adjuncts

- Bupivacaine-collagen implant
- Liposomal adjuncts
- Magnesium
- SABER-bupivacaine
- Tramadol - old & new
Bupivacaine-Collagen Implant

- **Mechanism of Action:** Collagen matrix that is biodegradable and fully resorbable, impregnated with bupivacaine that is released as the collagen is degraded\(^\text{11}\)
- **Dosing:** Currently varying concentrations\(^\text{11}\)
  - Bi-phasic peaks such as that with liposomal bupivacaine
  - Initial research shows 30 minutes to 20 hours
- **One study showed** decreased pain scores at 24 & 48 hours with no change in opioid intake and another showed no change in pain scores but opioid intake was reduced\(^\text{11}\)
  - More studies needed!
- **Side effects:** Constipation, nausea & headache\(^\text{11}\)
Liposomal Adjuncts

- **Duration of Action:** Extended duration of action due to liposomes surrounding medication\(^{16}\)

- **Animal studies showing positive results for both liposomal dexamethasone and liposomal dexmedetomidine when added with liposomal bupivacaine\(^{16}\)**
  - Increased block 2.9-fold
  - Duration of time increased 16.2 +/- 3.5 hours
    - Single adjunct addition extended 8-10 hours
  - Decreased tissue inflammation as well

- **Addition of unencapsulated adjuvants prolong duration by 25 +/- 6.3 hours\(^{16}\)**
  - Accompanied with systemic side effects
Magnesium

- Mechanism of action: NMDA receptor antagonist, voltage-gated calcium channel inhibition\textsuperscript{19}
- Doubled the analgesic effect of lidocaine interscalene block with 500mg MgSO\textsubscript{4} in one study\textsuperscript{19}
  - Has been shown to add $\sim$2 hours to bupivacaine/epinephrine ISB
  - *Study completed outside of U.S.\textsuperscript{1}
- Lack of well defined neurotoxicity studies; therefore, it is currently not recommended for routine use\textsuperscript{19}
- Side effects: bradycardia, hypotension, sedation, headache\textsuperscript{19}
SABER-Bupivacaine

- Sucrose Acetate Isobutyrate Extended Release-Bupivacaine\(^{11}\)
- Mechanism of Action: bioerodible injectable depot system (able to deliver drugs over days to 3 months)\(^{11}\)
  - Linear pharmacokinetics; location of block can disrupt how long medication lasts
- One study showed this medication decreased pain up to 3 days\(^{11}\)
- Again, more studies necessary before approval\(^{11}\)
Tramadol

- Proposed mechanism of action: some inhibition of voltage gated potassium and sodium channels\textsuperscript{10}
- Previously contradictory results\textsuperscript{17}
- 2017 meta-analysis of brachial plexus blocks +/- tramadol\textsuperscript{17}
  - 100mg prolonged sensory block by 61.5 minutes for axillary block (not ISB or SCB)
  - 100mg prolonged motor block by 65.6 minutes
  - 100mg prolonged analgesia by 125.5 minutes
  - Did not increase chance of adverse effects
- Likely more research to come- not yet recommended for routine use
LAST but not least....

Know your signs/symptoms of Local Anesthetic Systemic Toxicity (LAST)\textsuperscript{12}:

- Vertigo
- Tinnitus
- Ominous Feelings
- Circumoral numbness
- Garrulousness
- Tremors
- Myoclonic Jerks
- Convulsions
- Coma
- Cardiovascular Collapse
Treatment of LAST

Local Anesthetic Systemic Toxicity

CALL FOR HELP

Support Ventilation

Life Support
- Initiate cardiovascular life support protocols
- Alert nearest cardiovascular pulmonary bypass facility

Stop Seizures
- Midazolam

Lipid Emulsion Therapy
- BOLUS 1.5 mL/kg
- INFUSE 0.25 mL/kg/min

ASSESS
- Cardiovascular Instability
- Repeat Bolus 1.5 mL/kg
- Hypotension
- Double Infusion 0.5 mL/kg/min

Cardiovascular Stability
- Continue Infusion 10'
- Monitor 12 Hours
References


References


