Pharmacology

History

- Centuries of use of the leaves of the coca plant in Andean Peru- only naturally occurring LA
  - Cocaine isolated in 1860 with multiple reports of peripheral nerve blocks
  - 1860 + - Freud uses on patients/ becomes addicted
  - August Bier- 1st spinal with cocaine in 1899
    - 1st introduced in 1885
    - 1st IV regional block in 1908

Sequence

- Procaine - 1904
- Lidocaine – 1943
- Bupivacaine – 1957
- Prilocaine – 1959
- Ropivacaine -1990's
The Na+ Channel- Site of LA Action

Specific Receptors
- Modulated receptor theory
- A specific [protein] receptor is responsible for inactivation of the Na+ channel
  - Internal gate or H gate
- Molecules can directly occlude the channel

Na+ Channels in Neuronal Cell Membranes- Modulated Receptor
- Large alpha subunit, 2 beta subunits
- Channel exists in three states
  - Resting
  - *Activated (open)
  - *Inactivated

* LA can access
Explains Differences Between LA Drugs

- Frequency dependent blockade
  - The more rapidly the nerve fires the more dense the block tends to become
- Binding is more likely to occur in open and inactivated states

Result of LA Administration

- An action potential does not occur due to block of the Na+ channel
- Threshold potential is not reached therefore the nerve does not depolarize
- Resting membrane potential alteration is minimal

Local Anesthetic Effect

Summary: LA Action

Block of Na+ channels with loss of nerve conduction
Therefore we call the result of LA action...

Conduction Block

Key Physio-chemical Properties

• Ionization
• Diffusibility
• Lipid solubility
• Protein binding
• Vasodilation

Local Anesthetics and Ionization

• Local anesthetics are weak bases
• Both ionized and non-ionized local anesthetic molecules are necessary for LA action
• Carries a charge- since they are bases-the charge is usually the result of picking up a hydrogen molecule = H+ 
Ionized/Non-ionized Pairs

**Ionization Determines Speed of Onset**

- The greater the % of local not ionized increases entry speed into the neuron
- Therefore:
  - Onset speed: \( \frac{1}{\text{ionization}} \)
- Diffusion to tissue site also important in onset (kinetic factor)

**Variables Affecting Ionization**

- \( H^+ \) Non-\( H^+ \)
- Adjuncts
- Intrinsic structure pKa
- \( \text{pH of site} \)
- \( \text{pH of solution} \)
**pKa**
- pKa is the pH at which 50% of drug is ionized & 50% nonionized
  - Or: When pKa=pH, 50% of drug is ionized, 50% is non-ionized
- Local anesthetic pKa ranges between 7-9
  - Esters usually have a higher pKa than amides

**pH of the Solution & Site**
- Local anesthetics in free, 'base' form are poorly soluble (powder)
- Commercial preparations
  - The base is made into a salt by combining it with a strong acid which makes the LA water soluble
  - Bottles of LA have a pH of 2.7-6.5 because of the acid addition

**Ionization Variables**

pH range (systemic) compatible with life = 6.8-7.8
Ionization and Onset Speed

<table>
<thead>
<tr>
<th>Agent</th>
<th>pKₐ</th>
<th>% Un-ionized (pH 7.4)</th>
<th>Relative Onset Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaine</td>
<td>9.1</td>
<td>3</td>
<td>Slow</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>8.6</td>
<td>14</td>
<td>Slow</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>8.2</td>
<td>17</td>
<td>Slow</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>8.2</td>
<td><strong>8.1</strong></td>
<td>Slow</td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td>9.3</td>
<td>2</td>
<td>Rapid</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>7.9</td>
<td>24</td>
<td>Rapid</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>8.1</td>
<td>33</td>
<td>Rapid</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>7.9</td>
<td>39</td>
<td>Rapid</td>
</tr>
</tbody>
</table>


Alkalization of Local Anesthetics

<table>
<thead>
<tr>
<th>Drug</th>
<th><strong>HCO₃⁻</strong> Dose</th>
<th>Epidural Effect</th>
<th>Axillary Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>1 ml 10 ml</td>
<td>Faster onset by 2-3min (sensory &amp; motor)</td>
<td>Faster sensory (1 min) Faster motor (7 min)</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>1 ml 10 ml</td>
<td>Faster sensory No motor diff.</td>
<td>No difference</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>0.1 ml 10 ml</td>
<td>Faster onset by 2-3min (sensory &amp; motor)</td>
<td>Faster onset by 1-2 min.</td>
</tr>
</tbody>
</table>

**8.4 % Solution.

Adapted from: Mulroy, MF Pharmacology and Toxicity of Local Anesthetics in Barash, PG (ed) ASA Refresher Courses in Anesthesiology, 1996; 24:35-24.

Structure: Local Anesthetics

- Structure of the LA molecule
  - Head
  - Tail
  - Intermediate chain
Examples of Amides and Esters

- Esters
  - Ester hydrolysis by plasma cholinesterase
  - Very rapid
  - Procaine/benzocaine
    - para-aminobenzoic acid (PABA)
    - Some people are allergic to PABA
Amide Metabolism

- N-dealkylation and hydroxylation in the liver
  - CP 450 MF oxidase system
  - Slower than esters
    - Prilocaine > lidocaine > mepivacaine > ropivacaine > bupivacaine

Enantiomers

- Substances of opposite shape
- Molecules existing in mirror image forms
  - Left and right handed
- When dissolved in solution rotate polarized light
  - Optical isomers
- **Important concept in LA toxicity**

Nerve Fibers

<table>
<thead>
<tr>
<th>Fiber Type</th>
<th>Sensitivity</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-Alpha</td>
<td>+?</td>
<td>Motor/Proprioception</td>
</tr>
<tr>
<td>A-Beta</td>
<td>++</td>
<td>Motor/Proprioception</td>
</tr>
<tr>
<td>A-Gamma</td>
<td>++</td>
<td>Muscle Tone</td>
</tr>
<tr>
<td>A-Delta</td>
<td>+++</td>
<td>Pain/Temp/Touch</td>
</tr>
<tr>
<td>B</td>
<td>+++</td>
<td>Paraganglionic ANS</td>
</tr>
<tr>
<td>C</td>
<td>+++?</td>
<td>Pain &amp; Postganglionic ANS</td>
</tr>
</tbody>
</table>

Differential Block (spinal area)

What you see clinically

B fibers > C fibers > motor

Myelinated Neurons: Critical length (CL)

Critical Blocking Length (CL)

In large motor fibers need ~ 1 cm. Need to block at least 2 Nodes of Ranvier
**Differential Blockade (core-mantle)**

Peripheral nerve: Core/mantle effect

It is harder to block core nerves.

---

**Minimum Blocking Concentration (Cm)**

- Must have an adequate concentration of LA available at the site of action.

- Many variables
  - Axon size, position, myelination
  - Blood flow
  - Use of Adjuncts

---

**Minimum Blocking Concentration (Cm)**

It is easier to block nerves on the outside
More on Differential Blockade

- Frequency dependent block:
  - Lidocaine & Bupivacaine (sensory)
  - Etidocaine: greater motor than sensory block

- ANS > Sensory > Motor

Physiochemical Characteristics

Ionization = 1/onset
Lipid solubility = duration, potency and toxicity
  - Protein binding = duration

Local Anesthetics

- Lipid solubility: potency
- Lipid solubility: toxicity

- The greater the lipid solubility the greater the potency and toxicity
  - Assessed with the octanol:water partition coefficient
Lipid Solubility: Potency

<table>
<thead>
<tr>
<th>Agent</th>
<th>Relative Clinical Potency</th>
<th>Octanol : Water Partition Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaine</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>2</td>
<td>43</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>8</td>
<td>221</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>6</td>
<td>115</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>8</td>
<td>346</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>6</td>
<td>800</td>
</tr>
</tbody>
</table>


Clinical Potency: Clinical Toxicity

<table>
<thead>
<tr>
<th>Agent</th>
<th>Relative Clinical Potency</th>
<th>Relative Clinical Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroprocaine</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>High</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Adapted from: Mulroy, MF (1996) Pharmacology and Toxicity of Local Anesthetics in Barash, PG (ed) ASA Refresher Courses in Anesthesiology, 24:193-204

Duration

Protein binding and lipid solubility
Duration

- Protein binding
  • \( \text{protein binding} = \frac{1}{\text{duration}} \)

- Lipid solubility
  • \( \text{lipid solubility} = \frac{1}{\text{duration}} \)

Lipid Solubility: Duration

<table>
<thead>
<tr>
<th>Agent</th>
<th>Lipid Solubility</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaine</td>
<td>&lt;1</td>
<td>Short</td>
</tr>
<tr>
<td>Chlorprocaine</td>
<td>&gt;1</td>
<td>Short</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>4</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>1</td>
<td>Moderate</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>80</td>
<td>Long</td>
</tr>
<tr>
<td>Eadocaine</td>
<td>140</td>
<td>Long</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>340</td>
<td>Long</td>
</tr>
</tbody>
</table>


Protein Binding: Duration

<table>
<thead>
<tr>
<th>Agent</th>
<th>Protein Binding</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaine</td>
<td>5</td>
<td>Short</td>
</tr>
<tr>
<td>Chlorprocaine</td>
<td>7</td>
<td>Short</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>65</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>75</td>
<td>Moderate</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>85</td>
<td>Long</td>
</tr>
<tr>
<td>Eadocaine</td>
<td>95</td>
<td>Long</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>95</td>
<td>Long</td>
</tr>
<tr>
<td>Remifentane</td>
<td>94</td>
<td>Long</td>
</tr>
</tbody>
</table>

Adjuncts Prolong LA Duration

- Vasoconstrictors
  - Epinephrine/Phenylephrine/Levonordefrin
    - Prolong duration
    - Minimize effect of LA vasodilatation
    - ↓ toxicity
    - ↑ intensity of block
    - ↓ bleeding

Sustained Release

- Local anesthetics can be incorporated into:
  - Liposomes
  - Lipid drug carriers
  - Polymer matrices or microspheres

- Benefits are prolonged duration of effect

Intra-Articular Local Anesthetic/Opioid

- Intra-articular local anesthetics are associated with opioid sparing effects in a variety of orthopedic procedures

- Evidence is conflicting with respect to the efficacy of intra-articular morphine in providing post-operative pain relief
Local Anesthetics - Esters

- Types of esters:
  - Procaine (Novocaine)
  - Chloroprocaine (Nesacaine)
  - Tetracaine (Pontocaine)
  - Cocaine
  - Benzocaine

Procaine (Novocaine)

- Uses - Local infiltration, e.g. dental
  - Concentration - 0.5-1%
  - Onset - relatively slow
  - Duration - short (25-30 minutes)
  - Potency - low
  - Toxicity - low

Chloroprocaine (Nesacaine)

- Uses - local infiltration, nerve blocks
  - Epidural reactivation for delivery
    - Concentration - 1-3%
    - Onset - very rapid
    - Duration - short (25-30 minutes)
    - Potency - low
    - Toxicity - low
Tetracaine (Pontocaine)

- Uses - spinal anesthesia
  - Concentration - 0.5-1%
  - Onset - slow
  - Duration – can be as long as 2-5 hours
  - Potency - high
  - Toxicity - moderate

Cocaine

- Used as a topical agent in ENT
  - 4 (10)%
  - Significant systemic absorption occurs

- Both LA effect and local vasoconstriction
  - Blocks NE reuptake at adrenergic nerve terminals
  - Works in the CNS

Benzocaine

- Benzocaine is the ethyl ester of p-aminobenzoic acid (PABA)
- Most commonly used topical anesthetic primarily
- Not typically water soluble- very lipid soluble
- pKa = 2.5 (very different)
# Amino Amides

- Lidocaine (Xylocaine)
- Mepivacaine (Carbocaine, Polocaine)
- Bupivacaine (Marcaine, Sensorcaine)
  - L- Bupivacaine (Chirocaine)
- Etidocaine (Duranest)
- Prilocaine (Citonest)
- Ropivacaine (Naropin)
- Dibucaine
- Articaine (Septocaine)

## Lidocaine (Xylocaine)

- **Uses** - local anesthetic, all types of regional
  - Most commonly used
    - Concentration - 0.5-10%
    - Onset - rapid
    - Duration - moderate (0.5-2 hours)
    - Potency - moderate
    - Toxicity - moderate

## Mepivacaine (Carbocaine)

- **Uses** - local infiltration, nerve blocks & epidural
  - Similar to lido, lacks vasodilator properties
    - Concentration - 1-2%
    - Onset - moderate
    - Duration - moderate (0.5-1 hour)
    - Potency - moderate
    - Toxicity - moderate
Bupivacaine (Marcaine, Sensoricaine)

- Uses - all types of local & regional anesthesia
  - Sensory block > motor block
  - Bound to alpha 1 acid glycoprotein
    - Concentration - 0.25-0.75%
    - Onset - slow
    - Duration - long (1.5-3 hours)
    - Potency - high
    - Toxicity - high; potential cardiac toxicity

Levo-bupivacaine (Chirocaine)

- Uses:
  - Epidural, other blocks, local infiltration
    - Up to 0.75% can be used – even in OB
    - Has replaced bupivacaine in many practices
    - L isomer of bupivacaine
      - Less cardiotoxic, similar efficacy
    - Pharmacology is very similar to bupivacaine

Etidocaine (Duranest)

- Uses - nerve blocks & epidurals
  - Motor block > sensory block
    - Concentration - 0.5-1.5%
    - Onset - Rapid
    - Duration - long (1.5-3 hours)
    - Potency - high
    - Toxicity - moderate
Prilocaine (Citonest)

- Uses - IV regional, infiltration, epidural
  - Danger of methemoglobinemia (>600mg)
  - Rx - methylene blue 0.5-1 mg/kg
- Concentration - 0.25-4%
- Onset - rapid
- Duration - moderate
- Toxicity - low
- Potency - moderate

Ropivacaine (Naropin)

- S-isomer formulation (unique chiral structure)
- Otherwise similar to Bupivacaine without the cardiac toxicity
  - Not quite as potent
  - Cleared more rapidly
  - Slightly shorter duration and pain block (a-delta & C) may be better than bupivacaine

Dibucaine

- Used in the lab to assess for pseudocholinesterase deficiency
  - Normally 80% of pseudocholinesterase is inhibited by dibucaine, # would be 80 and patient is normal
  - Heterozygous atypical is 40-60
  - Homozygous atypical is 20
- Also used in cream preparations for rectal itching....
Articaine (Septocaine)

- Uses:
  - Effective for periosteal stimulation and surgery
  - 4% solution used for dental blocks
  - Comes premixed with 1-2:100,000 epinephrine
- Onset/Duration: intermediate
- Solution contains sodium metabisulfite; use with caution in patients with a history of allergy to sulfites


This Concludes the Pharmacology Presentation