Pharmacologic Options
Peripartum Analgesia Day 2
Objectives Day 2

- Local Anesthetics
- Local anesthetic allergy
- Local anesthetic toxicity
Local Anesthetics

Amides

Esters
Local Anesthesia for Peripartum Analgesia

• Variety of methods to provide analgesia for intrapartum care, delivery and postpartum analgesia:
  - Perineal infiltration for episiotomy and repair
  - Pudendal block
  - Paracervical block
  - Labour epidural or CSE or intrathecal analgesia
  - TAP block for postpartum analgesia

• 2 classes of local anesthetic agents: amides and esters

• Local anesthetic toxicity can occur with all agents and with any mode of delivery
History of Local Anesthetics

- Cocaine isolated 1856
- 1884 cocaine used in ocular surgery
- 1880’s Regional anesthesia plexus
- 1898 cocaine used in spinal anesthesia
- 1905 1st synthetic LA (procaine) introduced
- 1943 lidocaine synthesized
- Mepivacaine (1957), Bupiv (’63), Ropiv (’96)
Local Anesthetics (LA)

• All local anesthetics are weak bases that require addition of hydrochloride salt to be water soluble and therefore injectable

• Method of action: reversible conduction blockade of nerve impulses by sodium channel blockade
  - Slow the rate of depolarization so threshold action potential never reached
  - State-dependent blockade: bind more readily to actively firing neurons as sodium channel active = open
  - Lipid solubility allows to cross membrane and bind to receptor in inactive state
Molecular Structure

Modifying the various components alters potency, lipid solubility, rate of metabolism and duration of action.

\[
\text{lipophilic} \quad \text{hydrophilic}
\]

- **Aromatic Portion**
- **Intermediate Chain**
- **Amine Group**

- **AMIDE**
- **ESTER**

\[ \text{Lipophilic} \quad \text{Hydrophilic} \]

\[ \text{CH}_{(n)} = \text{Hydrocarbon chains} \]

\[ \{\begin{align*}
\text{COO} &= \text{Ester Linkage} \\
\text{NH} &= \text{Amide Linkage}
\end{align*}\]
Local Anesthetics (LA)

- All local anesthetics are weak bases that require addition of hydrochloride salt to be water soluble and therefore injectable
- Method of action: reversible conduction blockade of nerve impulses by sodium channel blockade
  - Slow the rate of depolarization so threshold action potential never reached
  - State-dependent blockade: bind more readily to actively firing neurons as sodium channel active = open
  - Lipid solubility allows to cross membrane and bind to receptor in inactive state
Inhibiting the Action Potential

Transmembrane Resting Potential (mV)

Normal

Threshold Potential

Local Anesthetic

Resting Potential
Local Anesthetics (LA)

- All local anesthetics are weak bases that require addition of hydrochloride salt to be water soluble and therefore injectable
- Method of action: reversible conduction blockade of nerve impulses by sodium channel blockade
  - Slow the rate of depolarization so threshold action potential never reached
  - State-dependent blockade: bind more readily to actively firing neurons as sodium channel active = open
  - Can also bind to receptor when channel = inactive-closed but not resting-closed
The Voltage Gated Sodium Channel

R is the receptor site for local anesthetic binding
Clinically, this means the woman who is actively contracting has faster onset of epidural analgesia than one who is not.
Inhibiting Nerve Transmission

Access to Na channels in myelinated nerves occurs at the Nodes of Ranvier

Must block 3 sequential Nodes to successfully inhibit nerve conduction
Types of Nerve Fibres

- Concentration of LA determines degree of blockade along hierarchy of nerve fibres - myelination and size:

<table>
<thead>
<tr>
<th>Fiber Type</th>
<th>Function</th>
<th>Diameter (μm)</th>
<th>Myelination</th>
<th>Conduction Velocity (m/s)</th>
<th>Sensitivity to Block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha</td>
<td>Proprioception, motor</td>
<td>12–20</td>
<td>Heavy</td>
<td>70–120</td>
<td>+</td>
</tr>
<tr>
<td>Beta</td>
<td>Touch, pressure</td>
<td>5–12</td>
<td>Heavy</td>
<td>30–70</td>
<td>++</td>
</tr>
<tr>
<td>Gamma</td>
<td>Muscle spindles</td>
<td>3–6</td>
<td>Heavy</td>
<td>15–30</td>
<td>++</td>
</tr>
<tr>
<td>Delta</td>
<td>Pain, temperature</td>
<td>2–5</td>
<td>Heavy</td>
<td><strong>12–30</strong></td>
<td>+++</td>
</tr>
<tr>
<td>Type B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsal root</td>
<td>Pain, temperature</td>
<td>0.4–1.2</td>
<td>None</td>
<td><strong>0.5–2.3</strong></td>
<td>Slow and unmyelinated</td>
</tr>
<tr>
<td>Sympathetic</td>
<td>Postganglionic</td>
<td>0.3–1.3</td>
<td>None</td>
<td>0.7–2.3</td>
<td>++++</td>
</tr>
</tbody>
</table>

- Order of LA effect: C ≈ B ➔ A delta ➔ A beta ➔ A alpha

Sharp pain

Dull pain

Table 2. Relative size and susceptibility to block of types of nerve fibers.
# Types of Nerve Fibres

<table>
<thead>
<tr>
<th>Fiber Type</th>
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<td>2–5</td>
<td>Heavy</td>
<td>12–30</td>
<td>+++</td>
</tr>
<tr>
<td>Type B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preganglionic autonomic</td>
<td>&lt;3</td>
<td>Light</td>
<td>3–15</td>
<td>+++</td>
<td></td>
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<tr>
<td>Type C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsal root</td>
<td>Pain</td>
<td>0.4–1.2</td>
<td>None</td>
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<td>++++</td>
</tr>
</tbody>
</table>

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*Table 2: Relative size and susceptibility to block of types of nerve fibers.*
Types of Local Anesthetics

Esters
- procaine
- chloroprocaine
- tetracaine
- cocaine

Amides
- bupivacaine
- lidocaine
- ropivacaine
- mepivacaine
- levobupivacaine
## Esters vs Amides

<table>
<thead>
<tr>
<th>PROPERTIES</th>
<th>AMINOESTERS</th>
<th>AMINOAMIDES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism</td>
<td>rapid by plasma cholinesterase</td>
<td>slow, hepatic</td>
</tr>
<tr>
<td>Systemic toxicity</td>
<td>less likely</td>
<td>more likely</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>possible - PABA derivatives form</td>
<td>very rare</td>
</tr>
<tr>
<td>Stability in solution</td>
<td>breaks down in ampules (heat, sun)</td>
<td>very stable chemically</td>
</tr>
<tr>
<td>Onset of action</td>
<td>slow as a general rule</td>
<td>moderate to fast</td>
</tr>
<tr>
<td>pKa's</td>
<td>higher than PH = 7.4 (8.5-8.9)</td>
<td>close to PH = 7.4 (7.6-8.1)</td>
</tr>
</tbody>
</table>
Local Anesthetics - Activity

- Activity of local anesthetics is a function of:
  - lipid solubility
  - diffusability
  - protein binding affinity
  - percent ionization at physiologic pH (pKa)
  - vasodilating properties
LA Activity Characteristics

- Potency is related to lipid solubility, because 90% of the nerve cell membrane is composed of lipid
  - High solubility = improved transit into the cell membrane
  - High potency means fewer LA molecules needed to block the Na channel
- Diffusability influences the speed of onset
  - pKa determines ion state and therefore diffusability
- Protein binding is related to duration of action
  - High protein binding = longer duration of action
  - Also affects availability of drug: specifically the fetus
    - Lidocaine less protein bound than bupivacaine = more crosses the placenta
LA Site of Action: Epidural and Spinal

- Epidural:
  1. Dural Cuff
  2. Spinal nerve root exiting intervertebral foramina
  3. Spinal Cord

Degree and extent of block depends on the dose of LA:
- Concentration: density of block
- Volume: spread of block especially epidural
pKa

- Degree of LA ionization dictates movement across the tissues to site of action
- pH of tissue vs pKa of drug determines ratio ionized: unionized
- Tissue buffering produces more un-ionized LA allowing for membrane diffusion; repeated injections use up buffer pool
- Transfer across tissue membranes dictates:
  - Onset
  - Duration
  - Toxicity: local and systemic
  - In obstetrics: ion-trapping in the acidotic fetus
- The pKa of amides ranges from 7.6 to 8.1. At physiologic pH (7.4), most of the local anesthetic is in the ionized state = active state BUT transfer across membranes SLOW
Importance of pKa
Ion-trapping in the Fetus

Figure 7-7. Fetal-maternal arterial (FA/MA) lidocaine ratios are greater during acidemia compared with a normal pH. (From Blehl D, Shnider SM, Levinson G, et al. Placental transfer of lidocaine: effects of fetal acidosis. Anesthesiology 1978;48: 409–412; with permission.)
Calculating ionized:unionized

\[ \text{pKa} - \text{pH} = \log \left[ \text{ionized/non-ionized} \right] \]

\[ \text{ionized:unionized} = \log_{10} \left( \text{pKa}\text{-pH} \right) \]

Example: lidocaine pKa 7.9, fetus 7.0
\[ \text{ionized: unionized} = 10^{0.9} = 7.9 \]

The resulting ratio of 8:1 ionized to non-ionized indicates a poorer penetration into the nerve tissue but also will trap the lidocaine on the fetal side.
# pKa and Onset

<table>
<thead>
<tr>
<th>AGENT</th>
<th>Pot.</th>
<th>Onset</th>
<th>pKa</th>
<th>%PB</th>
<th>P. coef</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaine 0.5-1% (Novocain)</td>
<td>1</td>
<td>Rap</td>
<td>8.9</td>
<td>5.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Chloroprocaine 2-3% (Nesacain)</td>
<td>4</td>
<td>Rap</td>
<td>8.7</td>
<td>?</td>
<td>0.14</td>
</tr>
<tr>
<td>Tetracaine 0.1-0.5% (Pontocain)</td>
<td>16</td>
<td>Slow</td>
<td>8.5</td>
<td>75.6</td>
<td>4.1</td>
</tr>
<tr>
<td>Lidocaine 1-5% (Xylocaine)</td>
<td>1</td>
<td>Rap</td>
<td>7.9</td>
<td>64.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Mepivacaine 1.5% (Carbocaine)</td>
<td>1</td>
<td>Mod</td>
<td>7.6</td>
<td>77.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Bupivacaine 0.25-0.75% (Marcaine Sensorcaine)</td>
<td>4</td>
<td>Slow</td>
<td>8.1</td>
<td>95.6</td>
<td>27.5</td>
</tr>
<tr>
<td>Etidocaine 0.5-1.5% (Duranest)</td>
<td>4</td>
<td>Rap</td>
<td>7.7</td>
<td>94</td>
<td>141</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>1</td>
<td>Rap</td>
<td>7.9</td>
<td>55</td>
<td>0.9</td>
</tr>
<tr>
<td>Ropivacaine 0.75% (Naropin)</td>
<td>4</td>
<td>Mod</td>
<td>8.1</td>
<td>94</td>
<td>2.9</td>
</tr>
</tbody>
</table>

**pKa near 8 means only 3% of LA available in lipid soluble form: tissue buffering needed**
Manipulating pH to enhance effect

- Alkalinization, by adding sodium bicarbonate, increases amount of unionized (= lipid soluble) drug available
  - Enhances onset by 3-5 min
  - Enhances intensity of block both sensory and motor
  - Enhances spread in epidural space
- Lidocaine: can add 1mL 8.4% NaHCO$_3$ to 10 mL
- Bupivacaine: can only add 0.1 mL 8.4% NaHCO$_3$ to 10mL before precipitation occurs
Onset in Obstetrics: warming

A comparison of warmed Bupivacaine and lidocaine for epidural top up for C/S
BJA 1994 72 221-3
Warming improved onset for lidocaine to pin prick
Test dose lidocaine and epinephrine time 0
Inadequate anesthesia bupiv x2, warmed B 1 and warmed L x 2

<table>
<thead>
<tr>
<th></th>
<th>Bupiv 0.5% 20°C N=27</th>
<th>Lidocaine 2% 20°C N=28</th>
<th>Bupiv 0.5% 38°C n=29</th>
<th>Lidocaine 2% 38°C N=27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset to T6</td>
<td>29.9 (7.1)</td>
<td>27.0 (6.9)</td>
<td>29.8 (6.7)</td>
<td>24.4 (7.6)**</td>
</tr>
<tr>
<td>Pt ready for Sx 15 min</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Volume</td>
<td>23.9</td>
<td>22.6</td>
<td>22.4</td>
<td>21.1</td>
</tr>
<tr>
<td>Use of entonox/opioid</td>
<td>10</td>
<td>11</td>
<td>14</td>
<td>8</td>
</tr>
</tbody>
</table>

** p<0.05 to all other groups
Duration of Action

- Dependent upon:
  - Agent used: protein binding, lipid solubility
  - Dose: concentration and volume depending on route
  - Route: related to tissue reabsorption and offset of effect
  - Site injected: nerve fibre characteristics
  - Adjuvants used: epinephrine, phenylephrine
  - Vascularity: if vascular area then LA is quickly absorbed and removed from the site
# Duration of Local Anesthetics

<table>
<thead>
<tr>
<th>Block type</th>
<th>Lidocaine 1-2%</th>
<th>Bupivacaine 0.25-0.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltration</td>
<td>30-60 min</td>
<td>120-240 min</td>
</tr>
<tr>
<td>Infiltration with epi</td>
<td>90-120 min</td>
<td>360-480 min</td>
</tr>
<tr>
<td>Epidural</td>
<td>30-90 min</td>
<td>180-300 min</td>
</tr>
<tr>
<td>Epidural with epi</td>
<td>90-120 min</td>
<td>180-300 min</td>
</tr>
<tr>
<td>Pudendal</td>
<td>60-120 min</td>
<td>180-240 min</td>
</tr>
<tr>
<td>TAP block</td>
<td>120-240 min</td>
<td>360-720 min</td>
</tr>
</tbody>
</table>
Minimum Effective Concentration

- MLAC is the equivalent of MAC for inhaled anesthetics
  - Minimum concentration necessary to produce conduction blockade of nerve impulses in 50% of people

- Influenced by:
  - Nerve fibre diameter (C, B, A - α B γ δ)
  - Tissue pH (if ↑ then MLAC decreases)
  - Access to neural tissue
  - Frequency of nerve stimulation: small sensory fibres transmitting pain fire more rapidly than motor fibres

- Each LA has unique MLAC reflecting different drug potency
- MLAC motor fibres 2X MLAC sensory fibres
- MLAC epidural bupivacaine for labour analgesia in dystocia > MLAC for SVD!!
Differential Conduction Blockade

- Used intentionally to provide analgesia of varying degrees vs anesthesia with local anesthetics i.e. labour analgesia vs anesthesia for CD with an epidural
- Selective blockade of small nerve fibres with low concentrations of LA: preserving touch (A-β), proprioception (A-α) and motor function (A-α)
Comparative Pharmacology LA agents

<table>
<thead>
<tr>
<th>Classification</th>
<th>Potency</th>
<th>Onset</th>
<th>Duration after Infiltration (mins)</th>
<th>Maximum Single Dose for Infiltration (mg)</th>
<th>Toxic Plasma Concentration (µg/ml)</th>
<th>pK</th>
<th>Protein Binding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procaaine</td>
<td>1</td>
<td>Slow</td>
<td>45-60</td>
<td>500</td>
<td>8.9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td>4</td>
<td>Rapid</td>
<td>30-45</td>
<td>600</td>
<td>8.7</td>
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<td></td>
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<tr>
<td>Tetracaine</td>
<td>16</td>
<td>Slow</td>
<td>60-180</td>
<td>100 (topical)</td>
<td>8.5</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Amides</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Lidocaine</td>
<td>1</td>
<td>Rapid</td>
<td>60-120</td>
<td>300</td>
<td>&gt;5</td>
<td>7.9</td>
<td>70</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>4</td>
<td>Slow</td>
<td>240-480</td>
<td>300</td>
<td>&gt;5</td>
<td>7.7</td>
<td>94</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>1</td>
<td>Slow</td>
<td>60-120</td>
<td>400</td>
<td>&gt;5</td>
<td>7.9</td>
<td>55</td>
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<tr>
<td>Mepivacaine</td>
<td>1</td>
<td>Slow</td>
<td>90-180</td>
<td>300</td>
<td>&gt;5</td>
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<tr>
<td>Bupivacaine</td>
<td>4</td>
<td>Slow</td>
<td>240-480</td>
<td>175</td>
<td>8.1</td>
<td>9%</td>
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<tr>
<td>Levobupivacaine</td>
<td>4</td>
<td>Slow</td>
<td>240-480</td>
<td>175</td>
<td>&gt;4</td>
<td>8.1</td>
<td>&gt;97</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>4</td>
<td>Slow</td>
<td>240-480</td>
<td>200</td>
<td>&gt;4</td>
<td>8.1</td>
<td>94</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Classification</th>
<th>Fraction Nonionized (%) at pH 7.2</th>
<th>Fraction Nonionized (%) at pH 7.4</th>
<th>Fraction Nonionized (%) at pH 7.6</th>
<th>Lipid Solubility</th>
<th>Volume of Distribution (liters)</th>
<th>Clearance (liters/min)</th>
<th>Elimination Half-Time (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esters</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>0.6</td>
<td>65</td>
<td>9</td>
<td>9</td>
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<td>Procaaine</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>11</td>
<td>35</td>
<td>7</td>
<td>7</td>
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<tr>
<td>Chloroprocaine</td>
<td>5</td>
<td>7</td>
<td>11</td>
<td>80</td>
<td></td>
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<tr>
<td>Amides</td>
<td>17</td>
<td>24</td>
<td>28</td>
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<td>Lidocaine</td>
<td>24</td>
<td>28</td>
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<td>17</td>
<td></td>
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</tr>
</tbody>
</table>
Safety Issues Related to Local Anesthetics

- Toxicity from local anesthetics an ongoing concern
- Toxicity can be local (to neural tissue) or systemic
- Determining factors:
  - Drug
  - Dose
  - Site of administration (vascular absorption)
  - Use of epinephrine
  - Condition of the patient
- Peak plasma concentration occur with: intercostal > epidural > major nerve > infiltration > spinal
- Perineum and cervix richly vascularized in the parturient
- Pregnant women require less bupivacaine to evoke toxic effects
Toxicity Potential of LA agents

The higher the potency, the less drug needed to induce CNS toxicity
Pregnancy Effects on Toxic Dose

Likely secondary to decreased protein binding (lower levels of albumin and alpha-1 acid glycoprotein) so more free drug available.
Typically seen before cardiovascular toxicity

Excitatory signs/symptoms then depressant ones:
- Numbness: circumoral and tongue
- Tinnitus (ringing ears)
- Lightheaded
- Visual changes
- Muscle twitching
- Convulsions
- Coma
- Respiratory depression

Peak plasma concn after epidural lidocaine 400 mg (20 mL 2%): 3-4µg/mL
(Cardiovascular) CVS Toxicity

- All LA inherently depress cardiac muscle
- Sodium channel binding in cardiac conduction and muscle tissues causes:

![Cardiovascular Toxicity Diagram](image-url)
Agent Specific Cardiac Toxicity

Cardiac Toxicity
Inotropy-Potency Relationship

- Bupivacaine
- Tetracaine
- Cocaine
- Lidocaine
- Chloroprocaine
- Procaine

Relative Negative Inotropy vs. Relative in vivo Anesthetic Potency
Treatment of Systemic Toxicity

When there is CVS collapse:
- ACLS
- A B C’s
- Defibrillation
- Benzodiazepines for seizures
- Epinephrine
- Vasopressin
- Lidocaine?
- Amiodarone

Lipid rescue - infusion of Intralipid
- May sequester free bupivacaaine in plasma
Neurotoxicity

- All local anesthetics at sufficiently high concentration can cause direct neural tissue damage
  - Lidocaine and chloroprocaine worst offenders: 10-30% depending upon concentration
  - Bupivacaine 0.75% (spinal dose) incidence <5%
  - “TNS” or “TRI” to describe the transient radicular dysfunction associated with spinal lidocaine and (daycare) surgery
True Allergy to Local Anesthetics

- Most reports of allergy due to absorption of epinephrine
- Amides cause less than 1% of LA allergy
- Para-amino benzoic acid (PABA) well known allergen
  - Ester LA metabolite = PABA

Cross-allergen with PABA are sulfonamides (sulfa antibiotics) but NOT sulfites
Treatment of LA Allergy

- ABCs (airway edema, bronchospasm)
- Epinephrine
- Fluids
- H₁ H₂ blockers
- Steroids
Testing for LA Allergy

Test the parturient at >36 weeks in LDR: be prepared to deliver if suffers severe allergic reaction

- R/O Syncopal
- Establish Nature of Reaction
- R/O Epinephrine Rx
  - Drug Known
    - Use Alternative Amide Free of Epinephrine and Preservative
  - Drug Unknown
    - Skin Test & Challenge

- SC Challenge 0.1mL Full Strength Drug
- SC Challenge 1mL Full Strength Drug
  - If Neg.
- Prick Test Using Drug, + & - Controls Intradermal .02mL Drug Diluted 1:100,
  + & - Controls
    - + Control = 1.8mg/mL Histamine Base
    - - Control = Phosphate-buffered saline

To Physician
Local Anesthetics - Amides

- Most commonly used class of LA
- Hepatic metabolism: Cytochrome P450
  - Complex and slower than ester metabolism
  - Systemic toxicity therefore more likely once hepatic pathway fully saturated: plasma concentrations will rise if repeated injections given
  - Must be aware of individual LA maximum doses and elimination half-life to avoid toxicity
Lidocaine

- Principle metabolite (monoethylglcineyxlidide) has 80% of cardiac dysrhythmia protection activity of lidocaine
  - Prolonged $T_{\frac{1}{2}}\beta$ hence prolonged protective effect
- Changes in hepatic blood flow or function affect lidocaine metabolism significantly: pre-eclampsia
Bupivacaine

- Different metabolism than lidocaine, still hepatic based
- High lipid-solubility = high potency
- Highly protein bound = long duration
- Crosses placenta less easily than lidocaine: inherently safer for fetus during labour epidural analgesia
- Epinephrine adds little to effect outside protection from systemic toxicity when injecting into vascular area
- Attempts to find a safer LA led to:
  - Levobupivacaine (racemic L isomer of bupivacaine)
  - Ropivacaine
Ropivacaine

- Higher clearance rates than for bupivacaine
- Slightly less protein bound and less lipid soluble
- Less potent than bupivacaine @ 0.6
  - In obstetrics this seems to not be important determinant of labour analgesia
  - Provides inherent increased safety as can use less for same effect
  - Less motor block (block C and A-δ fibres more)
- Better cardiovascular safety during systemic toxic reactions than bupivacaine
- Slower onset and good duration of action compared to lidocaine
## Typical Concentrations and Doses for Peripartum Analgesia and Anesthesia

<table>
<thead>
<tr>
<th>Local Anesthetic</th>
<th>Clinical Use</th>
<th>Concentration %</th>
<th>Onset</th>
<th>Duration (min)</th>
<th>Maximum Single Dose mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lidocaine</strong></td>
<td>Topical Infiltration</td>
<td>4</td>
<td>Fast, Fast</td>
<td>30-60</td>
<td>300 (4-5mg/kg)</td>
</tr>
<tr>
<td></td>
<td>Peripheral Nerve Block</td>
<td>1.2</td>
<td>Fast</td>
<td>60-240</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epidural</td>
<td>1.2</td>
<td>Fast</td>
<td>60-180</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spinal</td>
<td>2</td>
<td>Fast</td>
<td>60-120</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;2</td>
<td>Fast</td>
<td>30-60</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fast</td>
<td></td>
<td>300 or 500 (7mg/kg) with epi</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fast</td>
<td></td>
<td>300 or 7mg/kg with epi</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fast</td>
<td></td>
<td>5mg/kg or 7mg/kg with epi</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fast</td>
<td></td>
<td>40 mg</td>
</tr>
<tr>
<td><strong>Bupivacaine</strong></td>
<td>Infiltration</td>
<td>0.25</td>
<td>Fast, Slow</td>
<td>120-480</td>
<td>175 or 225 with epi</td>
</tr>
<tr>
<td></td>
<td>Peripheral Nerve Block</td>
<td>0.25-5</td>
<td>Fast</td>
<td>240-960</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epidural</td>
<td>0.0625-0.5</td>
<td>Slow</td>
<td>120-300</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spinal</td>
<td>0.25-0.75</td>
<td>Moderate</td>
<td>60-240 (60-75 for cesarean)</td>
<td>2.5mg/kg or 3mg/kg with epi</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fast</td>
<td></td>
<td>2.5mg/kg or 3mg/kg with epi</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fast</td>
<td></td>
<td>20 (9-12 mg typical for cesarean)</td>
</tr>
<tr>
<td><strong>Ropivacaine</strong></td>
<td>Peripheral Nerve Block</td>
<td>1.2</td>
<td>Slow, Slow</td>
<td>300-600</td>
<td>200 or 3 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Epidural</td>
<td>0.08-2</td>
<td>Slow</td>
<td>120-300</td>
<td>250 or 4 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Spinal</td>
<td>2</td>
<td>Fast</td>
<td>90-240</td>
<td>unknown</td>
</tr>
<tr>
<td><strong>Chloroprocaine</strong></td>
<td>Epidural</td>
<td>2</td>
<td>Fast</td>
<td>30-60</td>
<td>800 or 1000 with epi (15 mg/kg)</td>
</tr>
<tr>
<td></td>
<td>Spinal</td>
<td>2</td>
<td>Fast</td>
<td>30-45</td>
<td>Preservative free! 80 mg</td>
</tr>
</tbody>
</table>
Local Anesthetics - Esters

• Metabolized by plasma cholinesterase: hydrolysis (except for cocaine - hepatic)
• Metabolites all pharmacologically inactive
• No esterase activity in cerebrospinal fluid, therefore offset of action is by reabsorption into circulation
• Patients with atypical plasma cholinesterase activity ("succ apnea") at risk for ester LA toxicity
Chloroprocaine

- Halogenation of procaine makes chloroprocaine
  - This structure change increases hydrolysis X 4
    - Shortens duration of action
    - Limits likelihood of systemic toxicity
- Available in Canada only as 2% concentration which limits utility (3% better motor block for CS)
- Typically used for short duration procedures such as cervical cerclage (epidural or spinal)
- “Rescue” LA when used maximum dose of lidocaine at CS
  - Safety margin for systemic toxicity due to rapid metabolism of plasma active drug
Adjuncts to Local: Epinephrine

- The addition of vasoconstrictors, such as epinephrine or phenylephrine can prolong duration of action of local anesthetics, decrease their absorption (and the peak plasma level) and enhance the blockade (direct alpha$_2$-receptor effects)
- Epinephrine effect influenced by the specific LA and the site of injection:
  - Lidocaine more than bupivacaine
  - Highly vascularized areas more than intrathecally
Topical Local Anesthetic Agents

- Typically local anesthetics poorly absorbed by intact skin (mucosa is different - highly absorbent)
- Useful for skin preparation prior to minor procedures or needle puncture i.e. local anesthetic effect prior to further infiltration with local anesthetic or venipuncture/arterial line
- A few different products now available:
  - EMLA
  - Ametop
  - ELA-max (lidocaine 5% in liposomal delivery system)
  - S-caine (lidocaine 2.5%, tetracaine 2.5% in unique delivery system)
EMLA

- **Eutectic Mixture of Local Anesthetics**
- Eutectic mixtures are liquids and melt at lower temperatures than any of their components, permitting higher concentrations of anesthetics
- EMLA represents the first major breakthrough for dermal anesthesia on intact skin:
  - Topical anesthesia for IV starts
  - Initial skin analgesia prior to epidural insertion in those with extreme needle phobia
- Contents: 25 mg per mL of lidocaine, 25 mg per mL of prilocaine, adjusted to a pH level of 9.4
- Requires optimally 1-2 hr skin contact protected by transparent dressing, minimum 45 min
- May cause vasoconstriction of blood vessels making IV cannulation challenging: add nitroglycerin ointment
- Contraindicated in susceptible to methemoglobinemia

Not recommended for use on mucous membranes
Ametop

- 4% tetracaine gel
- Ester local anesthetic therefore contraindicated in pseudocholinesterase deficiency
- Shorter minimum application time than EMLA: 30 minutes
- Duration longer than EMLA: 4-6h
- Erythema of skin see vs blanching from vasoconstriction
- In randomized trials in pediatric ER, no apparent clinical differences
- Can likely get away with only 10-15min of application time if plan to use skin infiltration with LA pre-procedure (i.e. epidural)
- Not for application on muscosal membranes