Physiology and Pharmacology

Pharmacokinetics
- Pharmacokinetics of Local Anesthetics
  - Uptake
    - Oral Route
    - Topical Route
    - Injection
  - Distribution
  - Metabolism (Biotransformation)
  - Excretion

Uptake
- Vasoactivity
  - Local anesthetics affect local blood vessels in the area injected
  - Most produce vasodilation
    - Ester anesthetics are more potent vasodilators
    - Cocaine is the only local anesthetic that consistently produces vasoconstriction
  - Initial action produces vasoconstriction (inhibition of the uptake of catecholamines (NE) into tissue binding sites, leading to xs of free NE causing a prolonged and intense state of vasoconstriction

So what?
- Vasodilation \(\Rightarrow\) Increases the rate of absorption of the local anesthetic into the blood
  - decreasing the duration of action
- Vasoactivity
  - increasing the anesthetic potential for overdose

Oral Route
- Local anesthetics (other than cocaine) are absorbed poorly from the GI tract
- Most undergo significant hepatic first-pass effect

Topical Route
- When intact skin is present, topical application does not provide anesthetic action, but if damaged or not present, it does (eg. Sunburn, mucosa)

Injection
- Uptake is dependent upon the injection site's vascularity and the drug's vasoactivity

Distribution
- Once absorbed into the blood, local anesthetics are distributed to all body tissues.
- Blood level of the local anesthetics
  - Rate of drug absorption into the cardiovascular system
  - Rate of drug distribution from the vascular component to the tissues
  - Elimination of the drug through metabolic/excretory pathways
  - Decrease in blood levels of Local Anesthetics
Ester local anesthetics are hydrolyzed in the plasma by pseudocholinesterase. Allergic reactions are usually not to the ester local anesthetic, but to PABA.

**Metabolism - Esters**

**Metabolism - Amides**

- Primary site of biotransformation is the liver
- Liver function and hepatic perfusion influence the rate of biotransformation
  - Patients with lower than usual hepatic blood flow (hypotension, congestive heart failure) or poor liver function (cirrhosis) are unable to biotransform amide local anesthetics at a normal rate
- The products of biotransformation can have clinical effects
  - Lidocaine
  - Prilocaine or Articaine

**Absolute and Relative Contraindications**

- Absolute – under no conditions may the offending drug be administered to the patient
  - eg. allergy
- Relative – it is preferable to avoid administration of the drug because of an increased risk that an adverse response will develop

**Excretion**

- Kidneys are the primary excretory organ for both the local anesthetic and its metabolites
- A percentage is excreted unchanged in urine (lower % in esters than in amides)
- Patients with significant renal impairment may be unable to eliminate the local anesthetic compound or its metabolites from the blood

**Amide vs. Esters**

- Amide-linked LA’s are relatively resistant to hydrolysis
- Ester-linked LAs are hydrolyzed in aqueous solution

**Systemic Actions**

- The central nervous system and the cardiovascular system are the most susceptible
- Systemic actions are related to the blood level (plasma level)
- The blood level of the anesthetic depends on its rate of uptake and on the rate of distribution and biotransformation
<table>
<thead>
<tr>
<th>Central Nervous System</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Local anesthetics cross the blood-brain barrier</td>
</tr>
<tr>
<td>- They cause CNS depression</td>
</tr>
<tr>
<td>- At therapeutic levels there are no significant CNS effects</td>
</tr>
<tr>
<td>- At toxic levels, there are! ➔ seizure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>preconvulsive signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signs</strong></td>
</tr>
<tr>
<td>- Slurred speech</td>
</tr>
<tr>
<td>- Shivering</td>
</tr>
<tr>
<td>- Muscular twitching</td>
</tr>
<tr>
<td>- Tremor in muscles of face and extremities</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>- Numbness of tongue and circumoral region</td>
</tr>
<tr>
<td>- Warm, flushed feeling of skin</td>
</tr>
<tr>
<td>- Pleasant dreamlike state</td>
</tr>
<tr>
<td>- Generalized lightheadedness</td>
</tr>
<tr>
<td>- Dizziness</td>
</tr>
<tr>
<td>- Visual disturbances</td>
</tr>
<tr>
<td>- Auditory disturbances</td>
</tr>
<tr>
<td>- Drowsiness</td>
</tr>
<tr>
<td>- Disorientation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Lidocaine and procaine toxicity may present initial mild sedation instead of the excitatory symptoms</td>
</tr>
<tr>
<td>- If either excitation or sedation is observed in the initial 5 to 10 minutes after administration of local anesthetic ➔ be aware</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Local Tissue Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Intraoral injection of lidocaine, mepivacaine, prilocaine and bupivacaine can produce alterations in the skeletal muscle.</td>
</tr>
<tr>
<td>- Longer-acting local anesthetics cause more localized skeletal muscle damage than shorter-acting drugs</td>
</tr>
<tr>
<td>- Reversible ➔ Muscle regeneration is usually complete within 2 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory System</th>
</tr>
</thead>
<tbody>
<tr>
<td>- At lower levels, local anesthetics have a direct relaxant action on bronchial smooth muscle</td>
</tr>
<tr>
<td>- At overdose levels, they may produce respiratory arrest as a result of generalized CNS depression</td>
</tr>
</tbody>
</table>
Clinical Manifestations of Local Anesthetic Overdose

**Signs**
- Low to moderate overdose levels
  - Confusion, talkativeness, apprehension, excitement, slurred speech, stutter
  - Muscular twitching, tremor of the face/extremities, nystagmus
  - Elevated blood pressure, heart rate and respiratory rate
- Moderate to high blood levels
  - Generalized tonic-clinic seizure, followed by:
    - Generalized CNS depression
    - Depressed blood pressure, heart rate and respiratory rate

**Symptoms**
- Headache
- Lightheadedness
- Dizziness
- Blurred vision, unable to focus
- Ringing in ears
- Numbness of the tongue and perioral tissues
- Flushed or chilled feeling
- Drowsiness
- Disorientation
- Loss of consciousness

Vasoconstrictors

- Drugs that constrict blood vessels → control tissue perfusion
  - Decrease blood flow (perfusion to the site of injection)
  - Absorption is slowed
    - Lower blood levels
    - Decreased risk of toxicity
    - More remains in and around the nerve → increases duration of action
    - Decreased bleeding at injection site
- Added to local anesthetic solutions to oppose vasodilating actions

**Chemically identical or similar to the sympathetic nervous system mediators epinephrine and norepinephrine**

**Action is similar to response of adrenergic nerves to stimulation and therefore they are classified as sympathomimetic or adrenergic drugs**

Modes of Action

- Direct acting drugs
  - Act directly on the adrenergic receptors
- Indirect acting drugs
  - Act by releasing norepinephrine from adrenergic nerve terminals
- Mixed-acting drugs
  - Act both directly and indirectly

Adrenergic Receptors

- α-receptors
  - Activation by sympathomimetic drug produces a response that includes the contraction of smooth muscle in blood vessels (vasoconstriction)
- β-receptors
  - Activation produces smooth muscle relaxation and cardiac stimulation
Dilution of Vasoconstrictors

- Usually a ratio
  - e.g. 1 to 1000 (1:1000)
- Maximum doses presented in milligrams
- 1:1000 means that there is 1 gram (1000mg) of solute (drug) contained within 1000mL of solution → a 1:1000 dilution contains 1000 mg in 1000mL or 1.0mg/mL of solution

Dilution for dental local anesthetics

- Significantly lower concentrations than 1:1000
  - For epinephrine 1:100,000 or 1:200,000
  - 1:100,000 = 0.01 mg/mL = 10 μg/mL
  - 1:200,000 = 0.005 mg/mL = 5 μg/mL

Epinephrine

- Absorbed from the site of injection
  - Measurable blood levels are obtained
  - Resting plasma levels are doubled following the administration or one cartridge of lidocaine with epi 1:100,000
  - The elevation of epi plasma level is dose-dependent and may persist for 30 min

Epinephrine

- Cardiovascular dynamics – overall → direct stimulation
  - Increased systolic and diastolic pressures
  - Increased cardiac output
  - Increased stroke volume
  - Increased heart rate
  - Increased strength of contraction
  - Increased myocardial oxygen consumption
  
  These actions lead to an overall decrease in cardiac efficiency

Epinephrine

- Metabolism
  - Epinephrine increase oxygen consumption in all tissues
  - Stimulates glycogenolysis in the liver and skeletal muscle
  - Elevates blood sugar levels
  - The equivalent of four dental anesthetic cartridges of 1:100,000 epinephrine will elicit this response

Epinephrine

- Termination of action and Elimination
  - Primarily by reuptake by the adrenergic nerves
  - The remaining epi is inactivated in the blood by enzymes
    - Catecho-O-methyltrasferase (COMT)
    - Monoamine oxidase (MAO)
  - Small amounts are excreted unchanged in the urine
Epinephrine – Maximum Doses

- Normal, healthy patient: 0.2 mg per appointment
  - 10 mL of a 1:50,000 dilution (5 cartridges)
  - 20 mL of a 1:100,000 dilution (11 cartridges)
  - 40 mL of a 1:200,000 dilution (22 cartridges)

- Patient with clinically significant cardiovascular disease (ASA III or IV): 0.04 mg per appointment
  - 2 mL of a 1:50,000 dilution (1 cartridge)
  - 4 mL of a 1:100,000 dilution (2 cartridges)
  - 8 mL of a 1:200,000 dilution (4 cartridges)

Other vasoconstrictors

- Norepinephrine (Levarterenol)
  - Produces significant peripheral vasoconstriction and possible elevation of blood pressure
  - Side effect ratio 9x higher than epinephrine
  - Phenylephrine (Neo-Synephrine)
    - Pure α-adrenergic agonist
    - In clinical trials, peak blood levels of lidocaine were higher with phenylephrine 1:20,000 than with epi 1:200,000
  - Lefonordefrin (Neo-Cobefrin)
    - Effects similar to norepinephrine
    - Octapressin (Felypressin)
      - Effects similar to epinephrine

Levonordefrin (Neo-Cobefrin)

- Acts through direct α receptor stimulation (75%) with some β activity (25%)
- Less cardiac and CNS stimulation than epinephrine
- Similar side effects to epi, but to a lesser degree
- Available with mepivacaine or propoxycaine/procaine in a 1:20,000 dilution

Levonordefrin (Neo-Cobefrin)

- Maximum doses
  - At one sixth (15%) the vasopressor effectiveness of epinephrine, it is used at a significantly lesser dilution (1:20,000)
  - For all patients the maximum dose should be 1mg per appointment or 20mL of a 1:20,000 dilution *limited by the local anesthetic, not the vasoconstrictor
Few contraindications to vasoconstrictor administration in the concentrations in which they are found in dental local anesthetics.

Weigh the benefits and risks of including the vasopressor in against the benefits and risks of using a “plain” anesthetic solution.

Especially with certain groups:
- Patients with more significant cardiovascular disease (ASA III and IV)
- Patients with certain noncardiovascular diseases (e.g., Thyroid dysfunction, diabetes, and sulfite sensitivity)
- Patients receiving MAO inhibitors, tricyclic antidepressants and phenothiazines

Adding Epinephrine

<table>
<thead>
<tr>
<th>Maximum Dosages of Vasoconstrictor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TABLE 16-3. Maximum recommended dose of vasoconstrictors (70 kg)</strong></td>
</tr>
<tr>
<td><strong>Healthy</strong></td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>Epinephrine</td>
</tr>
<tr>
<td>1:100,000</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Levonordefrin</td>
</tr>
<tr>
<td>1:20,000</td>
</tr>
</tbody>
</table>

**Maximum Dosages of Local Anesthetic**

- 2% Lidocaine 4.5 mg/kg (300 mg max)
- 2% Lidocaine* 7.0 mg/kg (500 mg max)
- 3% Mepivicaine 5.5 mg/kg (400 mg max)
- 0.5% Bupivacaine* 1.3 mg/kg (90 mg max)
- 4% Articaine 7 mg/kg (500)

* with epinephrine

**Maximum Dosages of Local Anesthetic**

- 2% Lidocaine with 1:100,000 epi in a healthy 70 kg male
  - Lidocaine: 7 mg/kg x 70 kg = 490 mg (13.6 carpules)
  - Epinephrine: 3 mcg/kg x 70 kg = 0.21 mg (11 carpules)

- Limited by epinephrine dose
### Epinephrine Overdose

<table>
<thead>
<tr>
<th><strong>Symptoms</strong></th>
<th><strong>Signs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Elevated BP (systolic)</td>
</tr>
<tr>
<td>Restlessness</td>
<td>Increased HR</td>
</tr>
<tr>
<td>Headache</td>
<td>Abnormal rhythm</td>
</tr>
<tr>
<td>Tremor</td>
<td>Cardiac conduction abnormalities</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Cardiac dysrhythmias</td>
</tr>
<tr>
<td>Sweating</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>Pallor</td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td></td>
</tr>
<tr>
<td>Respiratory difficulty</td>
<td></td>
</tr>
</tbody>
</table>