Physiology and Pharmacology

Pharmacokinetics

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

Uptake

- Vasoactivity
  - Local anesthetic 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 vasodilation (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

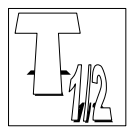
So what?

- Vasodilation → Increases the rate of absorption of the local an) the blood
  - decreasing the duration of
  - increasing the anesthetic and the potential for overdose

- Oral Route
  - Local anesthetics (other than cocaine) are absorbed poorly from the GI tract
  - Most undergo significant hepatic fist-pass effect
- Topical Route
  - Where 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 blood levels of Local Anesthetics

Metabolism - Esters

- Ester local anesthetics are hydrolyzed in the plasma by psuedocholinesterase
- Allergic reactions are usually not to the ester local anesthetic, but to PABA

Metabolism - Amides

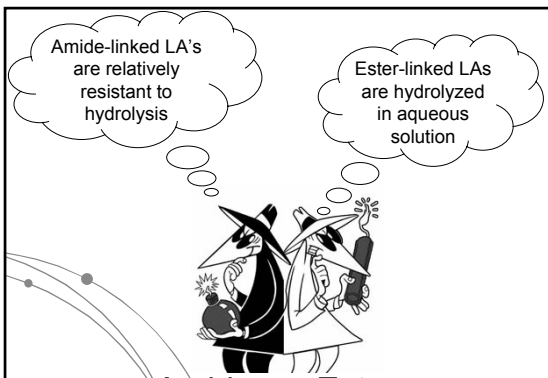
- Primary site of biotransformation is the liver
- Liver function and hepatic perfusion influence the rate of biotransformation
  - Patients with lower than usual hepatic blood flow (hypotension, congestive heart failure) or poor liver function (cirrhosis) are unable to biotransform amide local anesthetics 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 tan 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

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

Central Nervous System

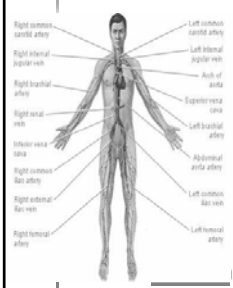
- Local anesthetics cross the blood-brain barrier
- They cause CNS depression
- At therapeutic levels there are no significant CNS effects
- At toxic levels, there are! ➔ seizure

preconvulsive signs and symptoms

- Signs
  - Slurred speech
  - Shivering
  - Muscular twitching
  - Tremor in muscles of face and extremities
- Symptoms
  - Numbness of tongue and circumoral region
  - Warm, flushed feeling of skin
  - Pleasant dreamlike state
  - Generalized lightheadedness
  - Dizziness
  - Visual disturbances
  - Auditory disturbances
  - Drowsiness
  - Disorientation

- Lidocaine and procaine toxicity may present initial mild sedation instead of the excitatory symptoms
- If either excitation or sedation is observed in the initial 5 to 10 minutes after administration of local anesthetic → be aware

Cardiovascular



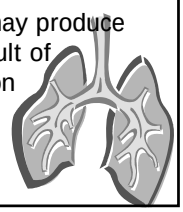
- Local anesthetic action decreases:
  - Electrical excitability of the myocardium
  - Conduction rate
  - Force of contraction
- Therapeutically advantageous in managing dysrythmias (PVCs, ventricular tachycardia)

Local Tissue Toxicity

- Intraoral injection of lidocaine, mepivacaine, prilocaine and bupivacaine can produce alterations in the skeletal muscle.
- Longer-acting local anesthetics cause more localized skeletal muscle damage than shorter-acting drugs
- Reversible ➔ Muscle regeneration is usually complete within 2 weeks

Respiratory System

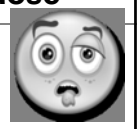
- At lower levels, local anesthetics have a direct relaxant action on bronchial smooth muscle
- At overdose levels, they may produce respiratory arrest as a result of generalized CNS depression



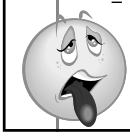
Clinical Manifestations of Local Anesthetic Overdose

- Signs
  - Low to moderate overdose levels
    - Confusion, talkativeness, apprehension, excitedness, 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

Clinical Manifestations of Local Anesthetic Overdose



- 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
- Added to local anesthetic solutions to oppose vasodilating actions
- 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

- 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 sympthomimetic 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 sympthomimetic 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
  - eg. 1 to 1000 (1:1000)
- Maximum doses presented in miligrams
- 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-dependents 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

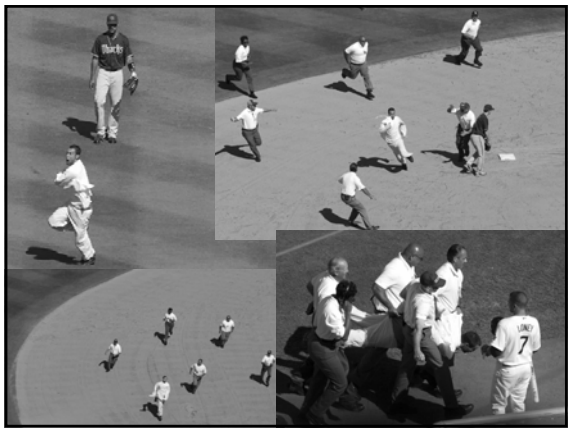
- Termination of action and Elimination
  - Primarily by reuptake by the adrenergic nerves
  - The remaining epi is inactivated in the blood by enzymes
    - Catecho-O-methlytransferase (COMT)
    - Monoamine oxidase (MAO)
  - Small amounts are excreted unchanged in the urine

Epinephrine – Maximum Doses

- Normal, healthy patient: 0.2 mg per appointment
  - 10 mL of a 1:50,0000 dilution (5 cartridges)
  - 20 mL of a 1:100,000 dilution (11 cartridges)
  - 40 mL of a 1:200,000 dilution (22 cartridges)

Epinephrine – Maximum Doses

- 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 (eg. Thyroid dysfunction, diabetes, and sulfite sensitivity
  - Patients receiving MAO inhibitors, tricyclic antidepressants and phenothiazines

Adding Epinephrine

Maximum Dosages of Vasoconstrictor

TABLE 16-3. *Maximum recommended dose of vasoconstrictors (70 kg)*

	Healthy	ASA II	ASA III
Epinephrine 1:100,000	3 mcg/kg 200 mcg max (11.1 cart)	1.5 mcg/kg 100 mcg/kg (5.5 cart)	0.75 mcg/kg 40 mcg/kg (2.22 cart)
Levonordefrin 1:20,000	7 mcg/kg (5.4 cart)	3.5 mcg/kg (2.7 cart)	1.5 mcg/kg (1.2 cart)

Maximum Dosages of Vasoconstrictor

Based on 70kg person

****Healthy patient - 0.2 mg**

****Cardiac patient - 0.05 mg**

Dose		Cartridges
▪ Epinephrine	1:50,000 -	5 (H), 1 (C)
▪ Epinephrine	1:100,000 -	10 (H), 2 (C)
▪ Epinephrine	1:200,000 -	20 (H), 4 (C)

Maximum Dosages of Local Anesthetic

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

* with epinephrine

Maximum amount of local anesthesia

- **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: 3mcg/kg x 70 kg = 0.21 mg (11 carpules)**
- **Limited by epinephrine dose**

Epinephrine Overdose

Symptoms

- Anxiety
- Restlessness
- Headache
- Tremor
- Dizziness
- Sweating
- Pallor
- Palpitations
- Respiratory difficulty

Signs

- Elevated BP (systolic)
- Increased HR
- Abnormal rhythm
- Cardiac conduction abnormalities
- Cardiac dysrhythmias
- Cardiac arrest