

# Physiology and Pharmacology

## Pharmacokinetics

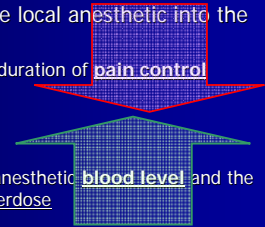
- Pharmacokinetics of Local Anesthetics
  - Uptake
    - Oral Route
    - Topical Route
    - Injection
  - Distribution
  - Metabolism (Biotransformation)
  - Excretion

## 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 anesthetic into the blood
  - decreasing the duration of **pain control**
- increasing the anesthetic **blood level** and the 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
  - 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 pseudocholinesterase



- 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 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-linked LA's are relatively resistant to hydrolysis

Ester-linked LAs are hydrolyzed in aqueous solution



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



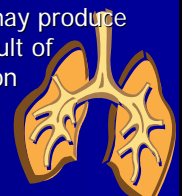
- Local anesthetic action decreases:
  - Electrical excitability of the myocardium
  - Conduction rate
  - Force of contraction
- Therapeutically advantageous in managing dysrhythmias (PVCs, ventricular tachycardia)

## 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-clonic 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 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

- $\alpha$ -receptors
  - Activation by sympathomimetic drug produces a response that includes the contraction of smooth muscle in blood vessels (vasoconstriction)
- $\beta$ -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 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 of 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-methyltransferase (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)

## 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  $\alpha$ -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  $\alpha$  receptor stimulation (75%) with some  $\beta$  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

TABLE 4-2. Effects of dose and epinephrine on local anesthetic properties

	Increased dose (concentration or volume)	Addition of epinephrine
Onset time	↓	↓ <sup>a</sup>
Degree of motor blockade	↑	↑
Degree of sensory blockade	↑	↑
Duration of blockade	↑	↑
Area of blockade	↑	↑
Peak plasma concentration	↑	↓

<sup>a</sup> Minimal effect for etidocaine.

## Maximum Dosages of Vasoconstrictor

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

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