جامعة تكريت – كلية الطب البيطري

الدراسات العليا \ فرع الادوية والفسلجة والكيمياء الحياتية

ماجستير أدوية

أ د حسام الدين النجار

First Term \ 2024-2025

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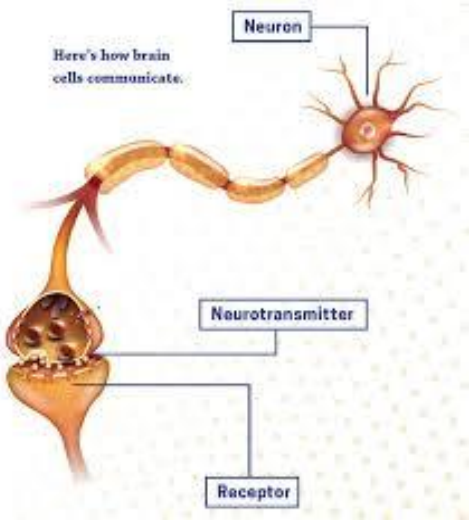
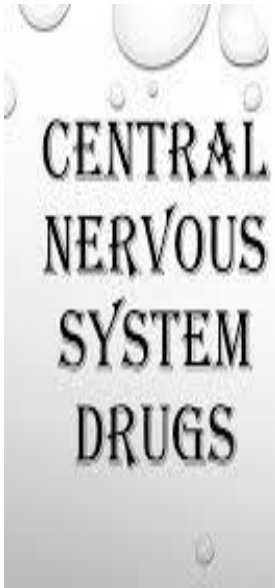
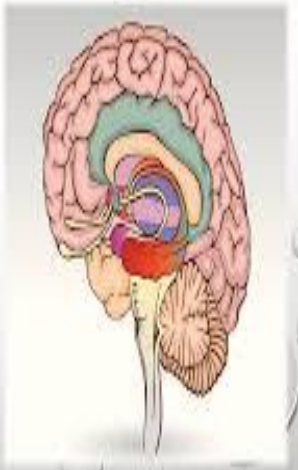


Advanced Pharmacology

LOCAL ANESTHETICS





Local anesthetic: produce loss of sensation to pain in a specific area of the body without the loss of consciousness.

History

- Coca leaves from the genus Erythroxylum
- Erythroxylum contains high concentration of alkaloid up to 0.7-1.8%
- Alkaloid has natural nitrogen bases found in the coca leaves, also known as cocaine
- Genus Erythroxylum discovered in South America, Venezuela, Bolivia, and Peru since pre-Columbian periods
- Earliest cultivation and use of the coca leaf went back to about 700 BC in Bolivia and Andes regions
- New discoveries showed humans used coca more than 5,000 years ago in Ecuador

Development of general and local anesthesia

- Took place in Western Europe from 1750 to 1850
- Chemists and physicians collected sample of coca leaves for experiments
- Isolated active principle of coca leaf, synthesized to a drug for patients to feel more relief of pain when taking surgeries
- In 1860, German chemist Albert Niemann successfully isolate the active principle of coca leaf; he named it cocaine

In 1865, Willhelm Lossen determine the correct molecular formula of cocaine ($C_{17}H_{21}NO_4$)

Niemann discovered the effect of numbness of the tongues caused by alkaloid in 1860

Based on Niemann's discovery, Russian physician Basil Von Anrep did experiments on animals, such as rats, dogs, and cats.

He injected small quantity of 1% solution to his tongue; tongue became insensitive

He concluded cocaine is a good drug for surgical anesthetic

William Steward Halsted and Richard John Hall developed the inferior dental nerve block techniques for dentistry.

physicians began to do research of cocaine in the clinic trials.

An ophthalmologist Carl Koller realized the importance of the alkaloid's anesthetic effect on mucous membranes

In 1884, he used the first local anesthetic on a patient with glaucoma

Freud, Halsted, and Koller became addicted to the drug through self-experimentation

Side Effects of Cocaine and Solutions

Minor:

- Addiction
- Intoxication

Solutions:

- Used nitrous oxide gases and ether for minor surgery in dentistry
- Give a low concentration of cocaine; it slows down the release of the drug into the bloodstream causing little side effects

Severe:

- Death

Procaine replaced cocaine

- In 1898, Professor Heinrich Braun introduced procaine as the first derivative of cocaine, also known as the first synthetic local anesthetic drug
- Trade name is Novocaine®

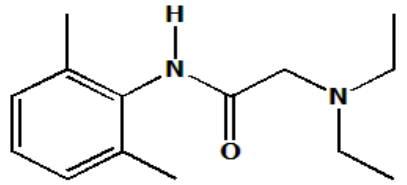
Novocaine Problems

- Took too long to set (i.e. to produce the desired anesthetic result)
- Wore off too quickly, not nearly as potent as cocaine
- Classified as an ester; esters have high potential to cause allergic reactions
- Caused high conc. of adrenaline resulted in increasing heart rate, make people feel nervous

Most dentists preferred not to used any local anesthetic at all that time; they used nitrous oxide gas.

Today, procaine is not even available for dental procedures.

Lidocaine



2-(diethylamino)-N-(2,6-dimethylphenyl) acetamide monohydrochloride "Lidocaine"

- In 1940, the first modern local anesthetic agent was lidocaine, trade name Xylocaine®
- It developed as a derivative of xylidine
- Lidocaine relieves pain during the dental surgeries
- Belongs to the amide class, cause little allergenic reaction; it’s hypoallergenic
- Sets on quickly and produces a desired anesthesia effect for several hours
- It’s accepted broadly as the local anesthetic today

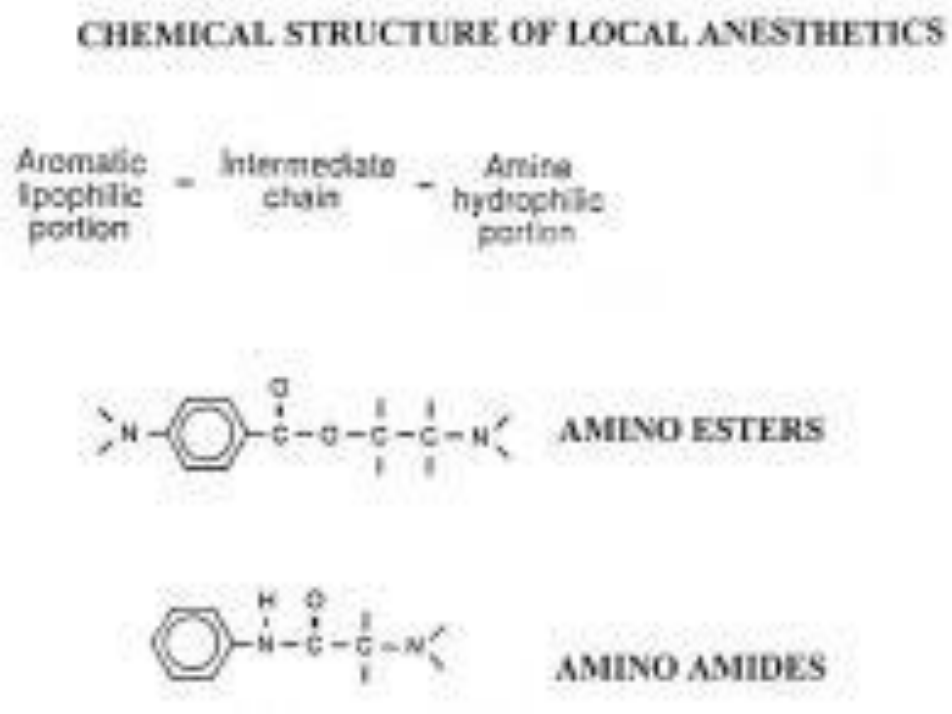
Differences of Esters and Amides

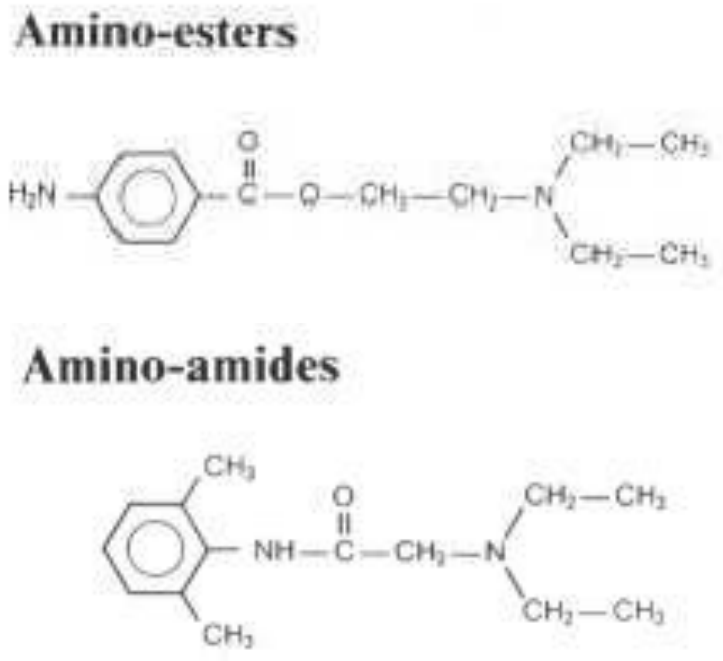
- All local anesthetics are weak bases. Chemical structure of local anesthetics have an amine group on one end connect to an aromatic ring on the other and an amine group on the right side. The amine end is hydrophilic (soluble in water), and the aromatic end is lipophilic (soluble in lipids)
- Two classes of local anesthetics are amino amides and amino esters.

Amides:	Esters:
--Metabolized in liver and very	--Metabolized in plasma through pseudocholinesterases
stable in solution	not stable in the solution
	Cause allergic reactions

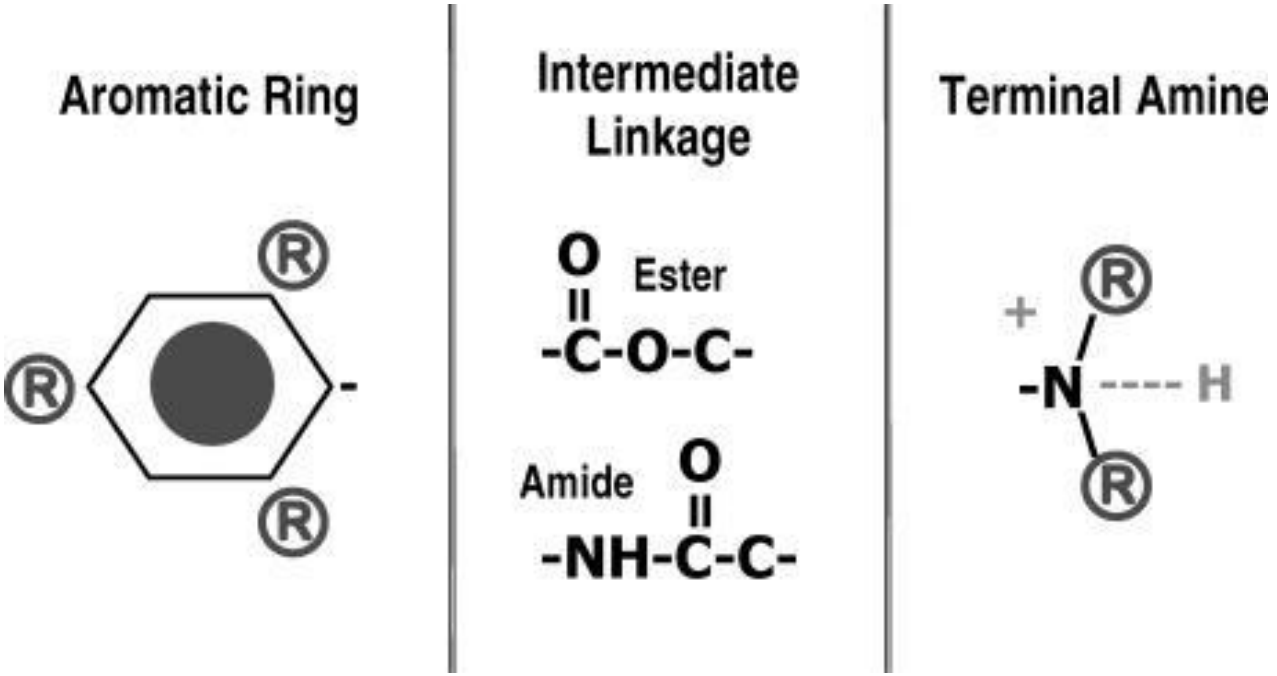
Structures of Amides and Esters

- The amine end is hydrophilic (soluble in water), anesthetic molecule dissolve in water in which it is delivered from the dentist's syringe into the patient's tissue. It's also responsible for the solution to remain on either side of the nerve membrane.
- The aromatic end is lipophilic (soluble in lipids). Because nerve cell is made of lipid bilayer it is possible for anesthetic molecule to penetrate through the nerve membrane.
- The trick the anesthetic molecule must play is getting from one side of the membrane to the other.





Structure



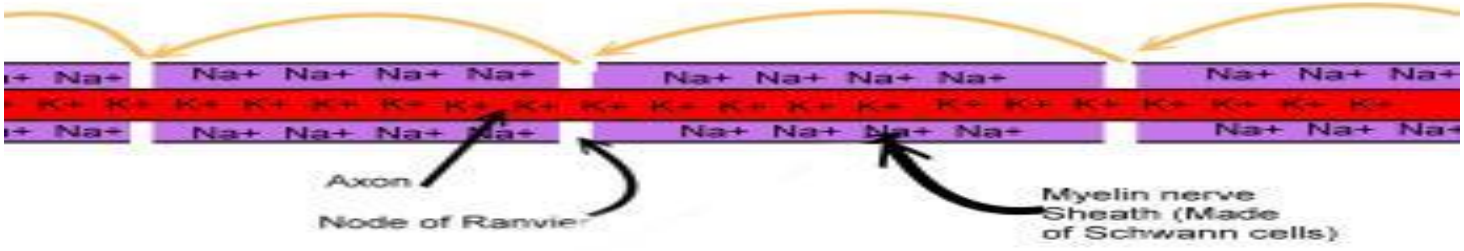
- Aromatic Ring – fat soluble (hydrophobic)
- Terminal Amine – water soluble (hydrophillic)
- Ampophoteric character

Amides and Esters

Esters	**Potency**	**Onset**	**Duration (min)**
Procaine	1	Slow	45-60
Chloroprocaine	4	Rapid	30-45
Tetracaine	16	Slow	60-180
Amides			
Lidocaine	1	Rapid	60-120
Etidocaine	4	Slow	240-480
Prilocaine	1	Slow	60-120
Mepivicaine	1	Slow	90-180
Bupivicaine	4	Slow	240-480

Mechanism

- The mechanism of local anesthetics connects with the ion channels, nerve, and depolarization.
- Local anesthetics block the conduction in peripheral nerves that inhibited the nerve to excited and created anesthesia.
- The sodium influx through these channels depolarizes the nerve cell membranes. It also created high impulses along the way.
- LAs Prevent transmission of nerve impulses
- Stabilization of closed inactivated Na^+ Channels
- Prevents Na^+ permeability from increasing slowing the rate of depolarization and preventing the threshold potential from being reached
- No action potential is propagated
- No alteration of resting potential occurs
- The anesthetic is a reversible reaction. It binds and block the sodium channels.
- As a result, the nerve loses depolarization and the capacity to create the impulse, the patient loses sensation in the area supplied by the nerve.



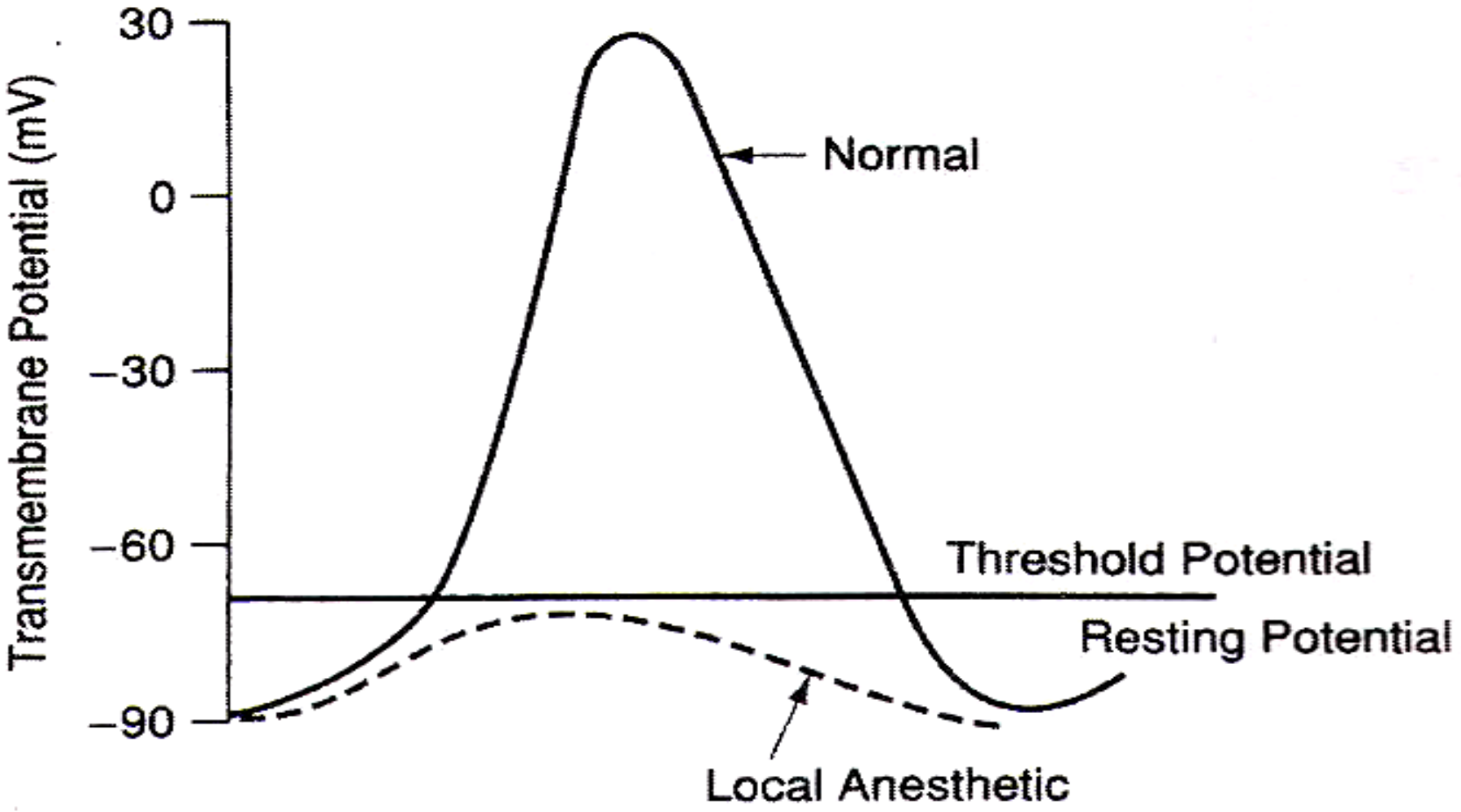


Figure 7-3. Local anesthetics slow the rate of depolarization of the nerve action potential such that the threshold potential is not reached. As a result, an action potential cannot be propagated in the presence of local anesthetic, and conduction blockade results.

Differential Conduction Blockade

- B-fibers are affected at the lowest concentrations
- Small C-fibers
- C-fibers and small and medium A-fibers
- Result
  - Loss of pain and temperature
  - Touch, propioception and motor preserved
- High concentrations all can be blocked

Order of Blockade

1. pain
2. cold
3. warmth
4. touch
5. deep pressure
6. motor

- Recovery is in reverse

Factors Affect the Reaction of Local Anesthetics

Lipid solubility

- All local anesthetics are weak bases. Increasing the lipid solubility leads to faster nerve penetration, block sodium channels, and speed up the onset of action.
- The more tightly local anesthetics bind to the protein, the longer onset of action.
- Local anesthetics have two forms, ionized and nonionized. The nonionized form can cross the nerve membranes and block the sodium channels. So, the more nonionized presented, the faster the onset action.

pH influence

- Usually at range 7.6 – 8.9
- Decrease in pH shifts equilibrium toward the ionized form, delaying the onset action.
- Lower pH, solution more acidic, gives slower onset of action

Factors Affect the Reaction of Local Anesthetics (cont.)

Vasodilation

- Vasoconstrictor is a substance used to keep the anesthetic solution in place at a longer period and prolongs the action of the drug
- vasoconstrictor delays the absorption which slows down the absorption into the bloodstream
- Lower vasodilator activity of a local anesthetic leads to a slower absorption and longer duration of action
- Vasoconstrictor used the naturally hormone called epinephrine (adrenaline). Epinephrine decreases vasodilator.

Side effects of epinephrine

- Epinephrine circulates the heart, causes the heart beat stronger and faster, and makes people feel nervous.

Toxicity

- Toxicity is the peak circulation levels of local anesthetics
- Levels of local anesthetic concentration administered to patients are varied according to age, weight, and health.
- Maximum dose for an individual is usually between 70mg to 500mg
- The amount of dose also varied based on the type of solution used and the presence of vasoconstrictor.

Example:

---For adult whose weight is 150lbs and up, maximum dose Articaine and lidocaine is about 500mg

---For children, the dosage reduced to about 1/3 to ½ depending on their weight.

The doses are not considered lethal.

Some common toxic effects:

--light headedness ---shivering or twitching --seizures

--hypotension (low blood pressure) --numbness

Factors of circulation levels

Factors of circulation levels are the rates of absorption, distribution, and metabolism.

- Absorption depends on the speed of administration and levels of the doses.
- Distribution allows absorption to occur in three phases. First, the drug occurs at highly vascular tissues in the lungs and kidneys. Then it appears in less vascular (muscle and fat). Then the drug is metabolized.
- Metabolism involves in the chemical structure based on two classes, amide and ester as discussed earlier.

Clearance

- Clearance = amount of plasma volume cleared of drug in given time (volume/time)
- Relatively little LA is cleared without metabolism
- Amides
  - Liver cytochromes (Cyp 1A9 and Cyp 3A4)
- Esters
  - plasma esterases and to lesser degree liver esterases
- Clearance is affected by hepatic blood flow
  - Propanolol has been shown to reduce clearance of LA's (bupivcaine best evidence)
  - Thought to be due to reduction in hepatic blood flow
- Renal clearance is limited due to solubility

Clearance and Drug-Drug Interactions?

- Cytochrome P450 3A4
  - **Inhibitors**:Amiodarone, cimetadine, clarithromycin, clotrimazole, cyclosporin, diltiazem, ethinylestradiol, erythromycin, fluconazole, fluoxetine, fluvoxamine, itraconazole, ketoconazole, metronidazole, norfloxacin.
- Cytochrome P450 1A9
  - Variable expression – small portion of population has non-functional enzyme
  - Inducers: caffeine and smoking
  - Inhibitors: fluoxetine

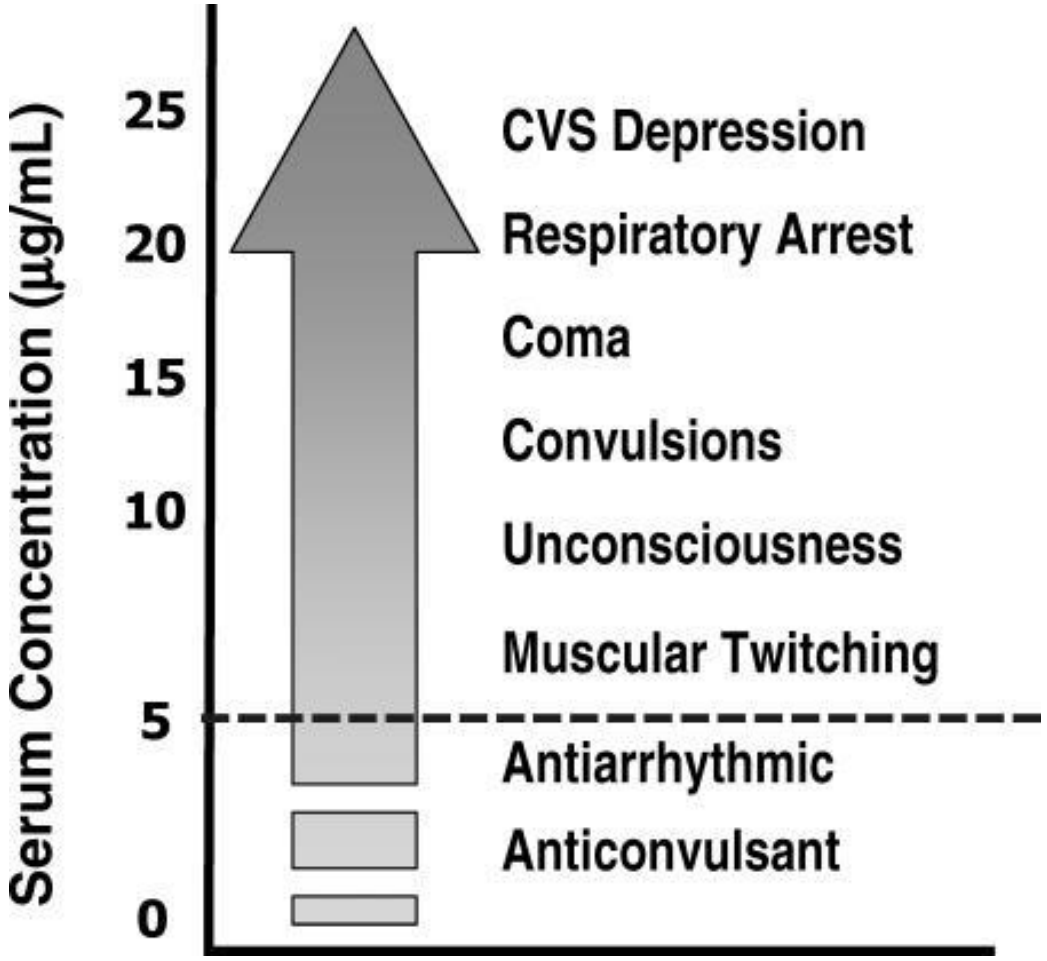
Side Effects - Allergy

- Rare Events
- <1% of all adverse reactions
- Often systemic toxicity is attributed to allergy
- Esters are more likely to cause allergy
  - PABA
- Allergy is usually due to preservatives
  - methyl paraben (structurally similar to PABA)
  - Sodium metabisulphite
- Antibodies are made to preservatives not LA
- Known allergies to Ester LA do not preclude use of Amide LA
- Epi – can cause hypotension and sometimes syncope following LA administration is actually intravascular injection

Systemic Toxicity

- Too much LA in plasma
  - Rate of absorption versus distribution
  - Drug
  - Where it is injected
    - IV
    - Depot
- Low $PaCO_2$ increases likelihood of seizures
- Hyperkalemia increases toxicity
- High serotonin levels may increase likelihood of seizures (SSRI's, MAOI's – little research)

Systemic Toxicity - Lidocaine



"Thanks for Listening"