LOCAL ANESTHETICS

Blanton

SLIDE 1:
Local Anesthetics have been in use since the 1860s. As was the general practice at the time pharmaceutical chemists noticed among other things that cocaine caused a numbness of the tongue when tasted. All of the currently used local anesthetics were developed as a result of these early observations.

Local anesthetics produce numbness by blocking nerve conduction. They block both sensory and motor nerves. Fortunately, their actions are completely reversible and therefore have valuable therapeutic uses.

SLIDE 2:
Their mechanism of action is to block voltage dependent Na channels and thus inhibit action potential generation.

As I imagine you have covered many times: In order for a nerve impulse to be propagated, a slight influx of Na causes a slight depolarization to occur. When the neuron is depolarized enough to reach threshold potential, voltage dependent Na channels open and Na rushes in. This influx of Na is responsible for generating an action potential. When the Na channel is open, the local anesthetic can enter. Its site of action is near the intracellular end of the Na channel pore. When the local anesthetic occupies this site, Na influx is reduced. If the Na influx is reduced over a sufficient length of the nerve, then impulse is blocked altogether.

SLIDE 3:
Because it is a noncompetitive antagonist, and more specifically a **pore blocker**, the local anesthetic's actions are frequency/use dependent. It can't enter the pore unless the channel is open. Therefore a nerve that is firing more frequently will be more susceptible to local anesthetic block.

Na channels rapidly inactivate. This inactivated state is a desensitized state that cannot result in action potential generation. The channel must cycle back to the resting state to be available for Na entry. Local anesthetics

stabilize the inactivated state, making it less likely to resensitize and become available again for stimulation.

SLIDE 4:

-The actions of local anesthetics are also voltage dependent because voltage is the regulator of the channel in the first place.

-Conditions that change the resting membrane potential alter the probability that the channel will be opened and thus the probability that the local anesthetic can reach its site of action.

-For instance, depolarizing conditions enhance the probability of opening and hyperpolarizing conditions decrease the probability of opening.

SLIDE 5:

Most local anesthetics are **weak bases** with pka's of 8-9. They are poorly water soluble as the free base, so they are typically marketed as a salt in a slightly acid pH, for example tetracaine HCL. In the body, they primarily exist as the ionized cationic form. This can be calculated from the Henderson Haselbach equation.

For instance, a LA with a pKa of 9, the protonated form exists at a 100x fold excess at pH 7.

pKa-pH = log P/NP 9-7 = 2 ; 2= log of 100/1

SLIDE 6:

Lipophilicity and conversion of the charged to the uncharged form are the rate limiting steps for entry into the nerve. Studies have shown that the local anesthetic must cross the membrane and then enter the channel pore from the cytosolic side. The binding site for the local anesthetic is near the cytoplasmic end of the channel. Small size and lipophilicity are characteristics that make the local anesthetic bind to the Na channel more rapidly.

-l**ipophilicity allows LA to cross membrane**

- charged form binds to sodium channel

Uncharged form- cross membrane Charged form- binds and blocks sodium channel

SLIDE 7:
Local anesthetic block can occur in any nerve. However, the susceptibility of block is generally viewed as how fast it occurs in a given nerve type.

-Diameter, length, and frequency of firing all contribute to the rate at which block occurs.

- Type C fibers are inhibited more quickly than Type B which are inhibited more quickly than Type A.

-In general, pain is blocked first, then sensory functions. Motor function is the last to disappear. Recovery occurs in the reverse order.

-The location of a nerve in a bundle can affect its sensitivity. For instance, if a motor nerve is located at the periphery of a bundle, it may be deadened before a sensory nerve that is located more centrally in the bundle.

SLIDE 8:
The basic structure of the majority of the local anesthetics is simple: A lipophilic group, an intermediate chain, and a hydrophilic group that is ionizable.
-There must be some hydrophilicity for the drug to be water soluble and to be capable of diffusing into its site of action. The intermediate chain usually contains an amide or esther linkage to the lipophilic moiety.

- Ester linkages are more susceptible to hydrolysis than are amide linkages.

SLIDE 9:
Injection of local anesthetics are made into the desired site of action. Their ability to provide blockade of nerve conduction is limited by their systemic absorption. In other words, the greater the rate of removal from the injection site, the faster the offset of anesthetic action.
Several factors determine systemic absorption. These include: 1) the intrinsic properties of the drug itself, 2) the site of administration, 3) the intrinsic degree of vasodilator activity, and 4) drug tissue binding.

As for **drug physicochemical properties**, amides are rapidly taken up and distributed. Esters are so prone to immediate hydrolysis that their absorption is of little consequence.

-Lipophilicity related sequestration into fat would be another example of a drug property.

-The site of injection has to do with vascularity and fat content.

- The more vasodilatory activity that the drug has the more it is likely to be absorbed.

- Vasoconstrictors reduce the absorption.

SLIDE 10:
Vasoconstrictors are very important with regard to local anesthetic pharmacology. By eliminating blood flow to and from the injection site, they can increase the duration of effect of intermediate acting drugs by 50%.

They also reduce any toxicity of the local anesthetic, because they reduce blood levels. The local anesthetics are all vasodilators to varying degrees. The only exception is cocaine, which is a vasoconstrictor because of sympathomimetic activity.

Most commonly epinephrine is co administered with the local anesthetic. Other vasoconstrictors that are used are norepinephrine, phenylephrine, and vasopressin. Too much vasoconstrictor can lead to local hypoxia, so care must be taken.

Avoid use of vasoconstrictors at extremities- fingers, toes, penis,etc

SLIDE 11:
-Butyrlcholinesterase rapidly metabolizes ester linked local anesthetics.

-Amide linked local anesthetics are metabolized by the hepatic microsomal system, so impaired liver function predisposes an individual to toxicity.

SLIDE 12:
The number of local anesthetics on the market makes it impossible to cover them all. I have selected a few from both ester and amide categories. Let's first consider the ester category.

Ester type Local Anesthesthetics

Procaine (1905) was the 1st synthetic local anesthetic. It is of low potency, exhibits slow onset, and has a very short duration of action. It as well as other esters can produce hypersensitivity reactions in some individuals.

Chlorprocaine is a chlorinated analog of procaine and has an even shorter t1/2. These 2 are made for injection and may be used for infiltration or nerve block or spinal anesthesia.

Both procaine and chlorprocaine are inefficiently absorbed through mucous membranes.

SLIDE 13:
Tetracaine (1938) has a longer duration. It is available in both topical and injectable forms. Because of its slow metabolism it can cause toxicity, but slow metabolism results in reduced risk of hypersensitivity comparted to procaine . It is frequently used in spinal anesthesia.

SLIDE 14:
Cocaine is used less and less because of its abuse liability and its potential for producing toxicity. It was used at one time as an ophthalmic anesthetic, but it produces mydriasis (excessive dilation of pupil) and corneal sloughing. Currently it is only used as a respiratory tract anesthetic in a topical form.

Side Effects:
-It can produce severe CNS side effects at high dosage which include tonic clonic seizures and pyrexia.

- CV side effects are due to local anesthetic action on the heart and sympathetic stimulation. Anesthetic actions range from arrythmias to cardiac failure. Sympathetic activity is due to the blockade of catecholamine transport.

SLIDE 15:
Benzocaine is a topically used ester that is available in ointments and creams.

Amide type Local Anesthesthetics

SLIDE 16:
Lidocaine (1948) is a widely used amide LA. It has several advantages over the ester compounds because it is longer lasting and does not produce hypersensitivity. It is efficiently absorbed from the mucous membranes, and it can be used in every route except ophthalmic.

SLIDE 17:
Bupivacaine is an amide that has a very long duration of action. It is useful by injection, but is ineffective locally.

SLIDE 18:
Toxicity profile of local anesthetics is related to 3 main areas: immune system, CV, and central nervous system.

Immune system: The allergic reaction only occurs with some of the esters. It is a result of metabolic production of paraaminobenzoic acid.

SLIDE 19:
CV effects occur because of excessive concentrations being absorbed. Direct inhibitory actions on the heart muscle include decreased conduction velocity and inotropic effect. CV collapse and death may result from cardiac arrest due to arrhythmia or depression of pacemaker activity. Cocaine has the added CV toxicity profile because it has sympathomimetic activity.

SLIDE 20:
CNS toxicity is usually due to the inadvertent injection of the anesthetic intravascularly.

-Generalized excitation is thought to be due to suppression of inhibitory pathways (GABAARs and GlyRs).

- Restlessness proceeds to convulsions, coma, and cardiorespiratory arrest.

Time and dose- Excitation- Depression- Coma- Death

SLIDE 21:
Long lasting motor and sensory deficits have been associated with overdose of chlorprocaine in spinal anesthesia.

Now we'll briefly cover some of the clinical uses for local anesthetics.

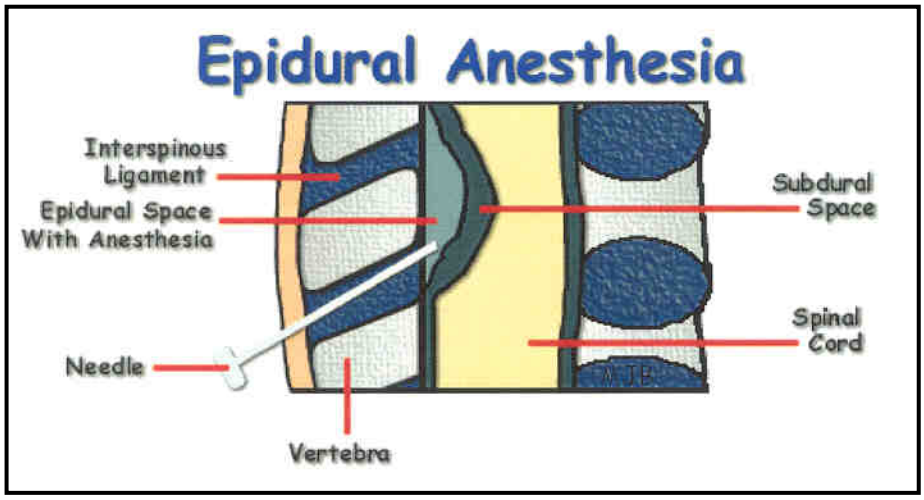
SLIDE 22:
Surface anesthesia is provided by aqueous salts of a number of anesthetics, including benzocaine and lidocaine. There are formulations for use on all body surfaces including the eye. Benzocaine is particularly good for burns and other conditions of denuded flesh, because it isn't absorbed.

SLIDE 23:
Infiltration anesthesia is simply the injection of the local anesthetic in a region without regard to the cutaneous route of the nerves. This can be used for superficial tissues or intraabdominal organs.

SLIDE 24:
Nerve Block is an injection of local anesthetic into or about peripheral nerves or nerve plexuses. Both sensory and motor nerves are affected.

SLIDE 25:

Epidural anesthesia is commonly used for laboring women. The local anesthetic is injected into the epidural space which is bounded by the ligamentum flavum, dura, and spinal periosteum. It can be injected in the sacral hiatus, or in lumbar, thoracic, or cervical regions. The spinal nerve roots are chiefly affected. A large amount is needed because diffusion is required. [*However if an opiate like fentany is also onboard, the amount of LA can be reduced substantially*]



SLIDE 26:

Spinal anesthesia is an injection of the local anesthetic around the nerve routes within the subarachnoid space in the lumbar region. The entire lower body can be deadened in such a fashion. Positioning of the patient and the use of an appropriate specific gravity of the anesthetic produces the deadening of the desired region. Autonomic nerves are extremely sensitive to local anesthetics, so CV function is usually depressed. Hypotension and poor venous return must be treated aggressively to reduce the possibility of brain damage or kidney failure.

Headache: can also occur because of the presumed leak of CSF from the hole in the dura.

SLIDE 27:
As for a study guide for this section, know the MOA of local anesthetics. What are the main differences between ester and amide drugs? In the drug list (those listed in lecture script and ppt), which are esters and which are amides? How long acting are they? What if any are the distinguishing properties? e.g., cocaine- vasoconstrictor, sympathomimetic benzocaine- only useful topically

SLIDE 28:
What is the utility of the vasoconstrictors?

Study Guide: handouts, ppts, lecture script; First Aid Basic Sciences Organ Systems, 2nd Edition: Chapters 5.