

***Title of Lecture: Local anaesthetics***

***Date of Lecture:***

***Sheet no: 18***

***Refer to slide no. : 8***

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**Anesthesia** can be either general or local. Local anesthesia is for minor procedures like in filling and extraction of the tooth, wound sutures and in eye examination specially that the cornea is the most sensitive part for pain.

General or complete anesthesia include complete paralysis of the body including the respiratory system-like in major surgeries where we ventilate the patient.

So local anesthetics by **Definition:** Drugs that inhibit reversibly the generation and conduction of action potential in excitable membranes **(neurons)**

Chemically they are weak bases and classified into ester local anesthetics and amide local anesthetics, both of them consist of three domains:

1. Aromatic group: (aromatic ring)

 Influences the hydrophobicity of the drug. ( determine the lipid solubility of the LA)

2. Amide or Ester linkage:

 Influences the duration of action and toxicity of the drug. (toxicity is determined by this linkage which some can cause allergy other don't; Amide types can lead to malignant hyperthermia in susceptible subjects while esters don't)

3. Amine group:

 Influences the rate of onset and potency of the drug.

Regarding the onset or duration of action for both of them is very quick, the list of the DOA of the drugs in slide 4-5 are just for your information not included in the exam. In general ester type local anesthetics has shorter duration of action as compared to amide LA. Depending on the DOA and the procedure you choose the type of LA.

**Lignocaine; Lidocaine; xylocaine** all of these are generic names amide LA widely used, they were used in old types of anesthesia; regional ,topical , surface, subdural.. all the types.

Potency & toxicity of a L.A’s is proportional to their lipid solubility. ( the more lipid solubility the more potent and toxic; because lipid solubility helps the drug to get into the circulation faster that water soluble LA)

Esters LA’s e.g. Cocaine, Procaine, Tetracaine… are usually hydrolyzed in plasma by pseudo-cholinesterase. They have also differences in respect to their metabolic fate, ester types are usually metabolized very quickly by plasma by pseudo-cholinesterase. One of their by-products of metabolism is paraaminobenzoic acid (PABA), the common cause of allergic reactions seen with these agents

Amide LA’s e.g. Lidocaine, mepivicaine…are metabolized in the liver that's why duration of action is longer than the ester types.

True allergic reactions rare (especially with lidocaine) more frequent allergic reactions is by ester types

**Characteristics of an ideal L.A:**

- Quick DOA

- Proper DOA sufficient for the surgical procedure

- Should be water soluble (to bind receptors) and stable in solution ( all LA are weak bases so they can exist in the tissues in either lipid or water soluble, for the activitiy the drug should be water soluble and polar enough to bind to its receptors but for the penetration of membranes it should be lipid soluble and what determine the form of the drug is the ph of the media ( working area), there effects are usually receptor mediated however we don't have specific antagonists for LA, also LAs should be stable in solution not broken down )

- Effective when applied topically and when injected ( effective in many routes or ways of administration)

- Low systemic toxicity

No available ideal L.A .

**MOA of LAs:**

As we mentioned before LAs are believed to be receptor mediated; the LA interacts with specific receptors on the membrane of the neuron leading to a Blockade of voltage gated Na Channels which leads to inhibition of action potential generation and propagation. Following that the LA inter the cell causing the desired effects.

So basically they block Na channels which are connected to ion channels receptors.

**Differential blockade**

We have different kind of nerves mediate the sensation of pain, touch ,temperature..etc LAs don't block these nerves equally, sensory nerves are more effected but large doses can affect motor nerves (lead to the complete blockade of conduction). Usually the unmyelinated c-fibers are first affected. And the sequence of local anesthesia following the injection of the drug start pain nerves would be anesthetized first then cold, warmth, touch then deep pressure and motor nerves could be affected by large doses ( the last nerves to be affected by local anesthetics) .

The recovery go in reverse ( motor nerves would recover first and pain is the last)

**Factors affecting local anesthetic action**

**Effects of PH:**

Charged form binds to receptor site, uncharged form penetrates membrane

Lower pH solution, (more acidic) shifts equilibrium toward the ionized form (receptor binding), delaying the onset action

Inflammation increases the acidity of the medium. This leads to lesser penetration into the nerves and, therefore, lesser activity. (it takes more time)

**Effect of lipid solubility**

Highly lipophilic LA’s penetrate the nerve membrane more easily. More lipophilic agents are more potent as local anesthetics

**Effect of vasodilator activity**

Greater vasodilator activity leads to decreased potency and decreased duration of action. (Upon vasodilatation the drug inter the circulation faster) the reverse effect with vasoconstriction it increase the DOA as it limit the systemic absorption of LA.

**Absorption & distribution of L.A’s**

Absorption of L.A into systemic circulation depends on:

- The dose ( larger dose better absorption)

- Blood supply ( larger supply better absorption)

- Chemical properties of L.A (lipid solubility)

L.A’s could get into circulation even when applied topically or on mucus membranes or through faulty IV administration (Avoid IV administration due to the severe side effects of LA and the local purpose ,except in rare procedures)

L.A’s could distribute to all tissues, > 90% of dose getting into circulation is usually cleared by the lung (acts as a buffer to L.A( it's clearance depend on the lung

L.A’s could also pass through the placenta e.g. Mepivacaine crosses well ( that's why it's used in Cesarean section, its crossing isn't dangerous on the fetus ); Bubivacaine, Lidocaine and Chloroprocaine do not

Ester L.A’s are usually metabolized by plasma cholinesterase and amide L.A’s are usually metabolized by the liver.

**Methods of application & clinical uses:**

We can apply them on the skin 🡪 burns

Lozenges 🡪 throat

Suppositories 🡪 into the rectum in management of hemorrhoids

**1. Surface anaesthesia**

Application of LA to skin to relieve itching, burning, & surface pain (minor sunburns).

**2. Topical anaesthesia**

On mm of nose, mouth, eye tracheobroncheal tree (in bronchoscopy procedures) and urethra ( if you are going to insert a tube in urethra or catheter)

**3. Infiltration**

Just beneath the skin.( you need to make sure you are not inside a vein) Widely used in dentistry and minor surgical procedures e.g. suturing a cut wound. Most widely used LA’s include Lidocaine, Procaine; Bupivacaine

**3. Regional block**

\*all this procedures should be done by in expert whether in local or general anesthesia\*

Injection of LA around a nerve. Provides excellent anaesthesia for a variety of procedures: buccal surgeries, brachial plexus block (upper extremity), sciatic, femoral plexus block (for lower extremity), epidural and spinal anaesthesia..(most LA’S )

So regional block is excellent in surgeries that require the conscious patient help during it.

**- Spinal anaesthesia (subarachnoid block)**

Injection of L.A into spinal fluid leading to temporary cord transection. Separating the nerve conduction to an extent help you to perform surgeries from the upper abdomen and downward ( also in surgeries that require conscious patient such as prostate surgery with a heart problem patient so you can by spinal anesthesia to go through ur surgery without interrupting the hemodynamic of the body, although local anesthesia have side effects on the hemodynamics but less evident than in general anesthesia) . (Lidocaine & Tetracaine)

**- Lumbar epidural anaesthesia**

It's the same as in spinal anesthesia but it doesn't have a drop in the blood pressure (not significant) . Lumbar epidural anesthesia is Injection outside the dura

Covers same area as spinal anaesthesia but larger doses required (upper abdomen downward)

Widely used in obstetrics to deliver babies (cesarean section). Bupivacaine & Lidocaine are widely used

**Caudal anaesthesia**

Injection into the sacral hiatus above the coccyx( same principle as spinal anesthesia but it's used as it has less side effects on the heart and blood pressure ).Used in cases of perineal and rectal surgeries

So as a conclusion spinal, lumbar epidural and caudal are basically the same but differ in the severity of the side effects (most sever spinal least caudal but most used is epidural)

**- IV extremity block**

A tourniquet is placed on arm and the L.A is given IV (Lidocaine; Tetracaine) for surgeries in the upper or lower extremities not exceeding one hour.

**- Sympathetic block**

Blockade of sympathetic ganglia by L.A (inject the sympathetic ganglia) highly specific. We have discussed the sympathetic system previously and we mentioned that it can be combined with LA, LA can be available with or without vasoconstriction. Vasoconstrictors will lead to an extension of the DOA of the LA, Useful in certain vasospastic diseases and some pain syndromes affecting upper & lower extremities.

 **Use of vasoconstrictors**

-Extend DOA of L.A (50% prolongation of action

-Limit systemic toxicity or delay absorption of L.A (30% reduction in blood level) and hence reduce the anaesthetic toxicity syndrome

-Limit bleeding ( like using epinephrine in the extraction of the tooth)

* **Epinephrine**

Widely used. An α & β adrenergic drug → side effects

2% Lidocaine produces similar anaesthesia to 1% Lidocaine + vasoconstrictor

The concentration of LA in drug combined with vasoconstrictor is lower (lower doses) than a drug without vasoconstrictor that produce the same anesthetic effect (because vasoconstrictors increase the DOA

* **Levonorderfin**

Has α1 agonistic activity with little β activity

Widely used in some dental cartridges and causes less hypertension and tachycardia as compared to epinephrine

* **Phenylephrine**

Pure α agonist and has little direct cardiac effects

Widely used with procaine in dentistry and for subarachnoid block

* **Fellypressin**

Very widely used nowadays in dentistry. ADH-like (ADH has two major activities first reabsorption of water from kidney tubules and vasoconstriction "it's also known as vasopressin") Fellypressin is with sole vasoconstrictor activity selective to certain types of receptors that mediate the vasoconstriction activity of ADH associated with less side effects as compared to epinephrine and alpha agonists

**Side effects to L.A’s**

- Allergy (appear very quickly)

Range from mild to severe allergic reactions and it is more frequent with the ester type L.A’s (due to PABA)

You can't terminate the action of already injected drug but you don't go further and you give antihistamine directly

\*\*Question: the drug that is used in all types of local anesthesia is Lidocaine

- Cardiac toxicity

Due to direct depression of conduction in heart leading to decreased excitability, conductivity and contractility ( some have good effect on the heart and it's rhythm like Lidocaine we'll discuss later)

- Systemic **vasodilatation (except Cocaine), ↓ BP & cardiac arrest** which add to the severity of the drop of the conductivity of the heart

Most of LA lead to vasodilatation (little vasoconstriction but mainly vasodilatation) except caciane is a sole vasoconstrictor.

**- CNS manifestations:**

Restlessness, tremors, disorientation, convulsions (with large doses), CNS depression, respiratory failure and death

- Malignant hyperthermia

Reported with the use of certain amide L.A’s (along with succinylcholine and halothane those three are most dangerous drugs leads to this fatal condition drug of choice for it is dantrolene; spasticity and elevation of body temp recorded for certain amide LA)

**Lidocaine=Lignocaine=Xylocaine**

The most widely used L.A in all types of local anaesthesia

Also, highly effective in the management of ventricular tachyarrhythmias "drug of choice due to its good inhibition of conductivity in the heart" (in this case should be given IV)

Has a medium action & more intense & more prolonged duration of action than Procaine

 **Bupivacaine**

Widely used in epidural anaesthesia and obstetrical procedures to relieve labor pain (it's not very likable in natural labors as pain drives and keep it going that if there is no pain we induce it with oxytocin and prostaglandin we can use pethedine as it has less effect on the fetus and its respiration "narcotic analgesic used routinely 50mlg without alleviating all the pain", while in Caesarean cases it's much more acceptable).

It relieves the pain of labor at concentrations of 0.125% while permitting some motor activity of abdominal muscles to aid in expelling the fetus

Approved for spinal anesthesia and it is 4 times more potent and more toxic than Mepivacaine and Lidocaine

**Prilocaine**

Less toxic than Lidocaine, widely used in dentistry ± Felypressin

Produces unique side effect: methemoglobinemia where iron is reduced from ferrous to ferric which make the hemoglobin capacity lower for carrying oxygen

**Cocaine**

Good vasoconstrictor. Used in nasal and oral surgeries. CNS stimulant. Leads to addiction

Don't need the addition of vasoconstrictor

Readily absorbed from mm’s reaching the brain very quickly

Used only topically due to above toxicities

**Procaine**

Ineffective when applied topically. Used in obstetric epidural anaesthesia, infiltration, nerve block and spinal anaesthesia