



Round : Anesthesia - Lecture 4.....

Group no : B 8.....

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Local Anesthetic Drugs

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Definition

Local Anesthetic (LA) : drugs that induce a •
REVERSIBLE loss of sensation (especially the pain)
in a part of the body **WITHOUT** inducing loss of
consciousness or sleep .

Can range from blocking separate nerves to blocks and trunks

Like supraclavicular is different than infraclavicular as a dermatome.

Uses : suturing, minor surgeries as (catheterization, •
dental surgeries)

It's better to use local anesthetic drugs in these situations to avoid the development of unwanted adverse effects associated with general anesthesia

Advantages

- Pt. remains **conscious** •
- maintains **airway**
- **Aspiration** of gastric contents is **unlikely**
- Smooth recovery requiring **less skilled** nursing
- **earlier discharge** of pt. → less expensive

→ Spinal anesthesia protects the patient by allowing them to manage their own airway as they remain conscious.

Spinal anesthesia causes hypotension, if it was severe it can cause vomiting, but patients can manage it and the risk of aspiration is very low. If we use general anesthesia in severe hypotensive patients, risk of aspiration is high if we don't manage the airway so quickly

Disadvantages

- In patients with phobias or during embarrassing surgeries •
- pt. may prefer to **sleep** •
- practice and **skills required** for the best results
- some blocks need **30 min** or more to be **effective** Like epidural
- it may **not** always be **totally effective** and additional analgesics may be needed (IV/General) when we get partial block anesthesia

→ Sometimes local is not enough because patients could be highly irritated and can't handle the surgery and we need to induce hypnosis even if it wasn't that major

In emergency cases, when rapid sequence induction is required such as fatal distress in OB/GYN, we can't wait and we need to act even if she had a full stomach so we use general anesthesia instead of spinal.

- Scoline is used in rapid sequence induction to administer the tube as quickly as possible

Mechanism of action

As a **weak base**, LA exists in our bodies in 2 forms

- If abscess is present, it reduces the effectivity of anesthetic drugs

1) Uncharged free base $R-NH_2$ **“lipid soluble”**

2) Cationic salt $R-NH_3^+$ **“water soluble”**

remember : Unionized $\rightarrow$ can penetrate the cell membrane $\rightarrow$ effective “absorbed by the body”

remember : Ionized $\rightarrow$ cannot penetrate cell membrane $\rightarrow$ ineffective “cannot be absorbed”

The proportion between 2 forms depends on **the base pka** and the **tissue ph**

★ Sodium bicarbonate is administered to increase the onset of action of the drug. It does that by increasing the tissue ph, which increases the PKa and the unionized drug. Except for Bupivacaine (not affected)

$Pka = ph$ at which 50% of drug is ionized

★ PKa determines the onset of action

Mechanism of action

Main Idea : prevent pain fibers to send pain signals •
to the CNS Pain sensation is carried by A delta nerves and C dorsal nerves.

Mechanism : *block* the voltage-gated *sodium* •
channels of excitable membranes → *block*
generation and conduction of nerve *impulses* in
localized site *without* structural damage to neurons
(It Blocks sensory transmission from a limited area of •
the body to the CNS)

The *effect of LA* is *terminated* by *absorption* to
systemic circulation → *systemic adverse effects.*

the *action potential* is triggered by a brief pulse of electric current



depolarization of membrane



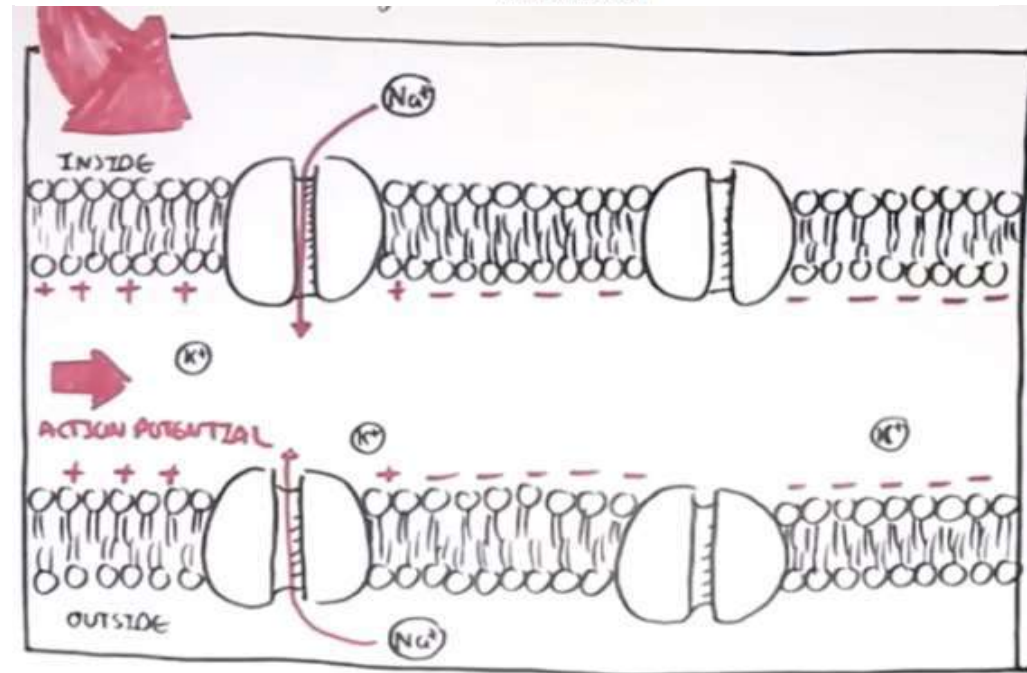
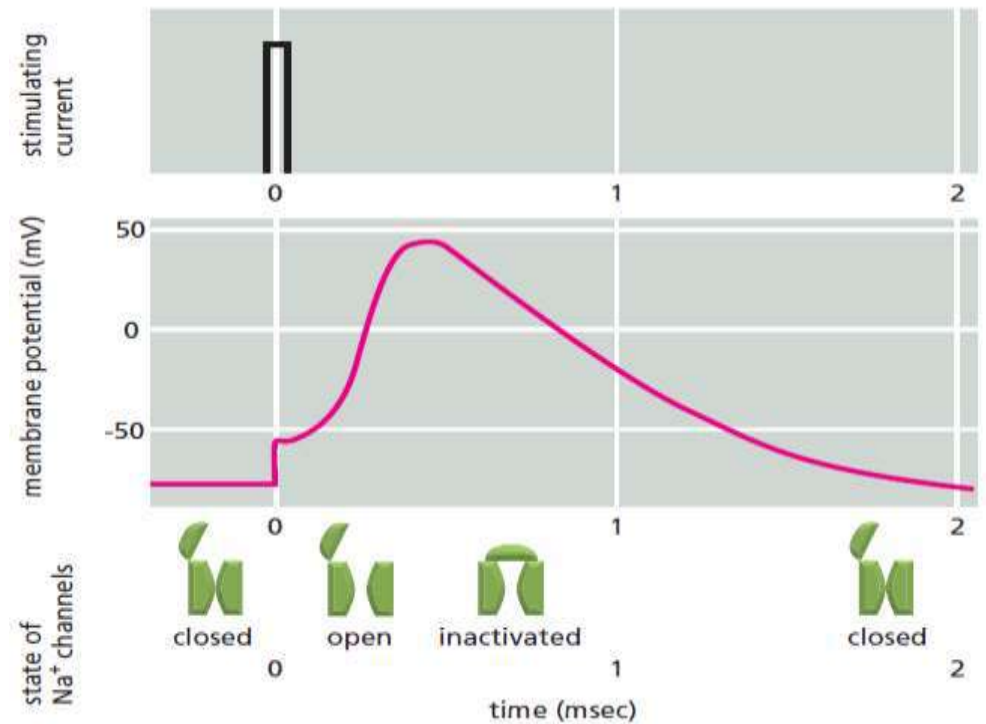
opening of voltage-gated Na^+ channels



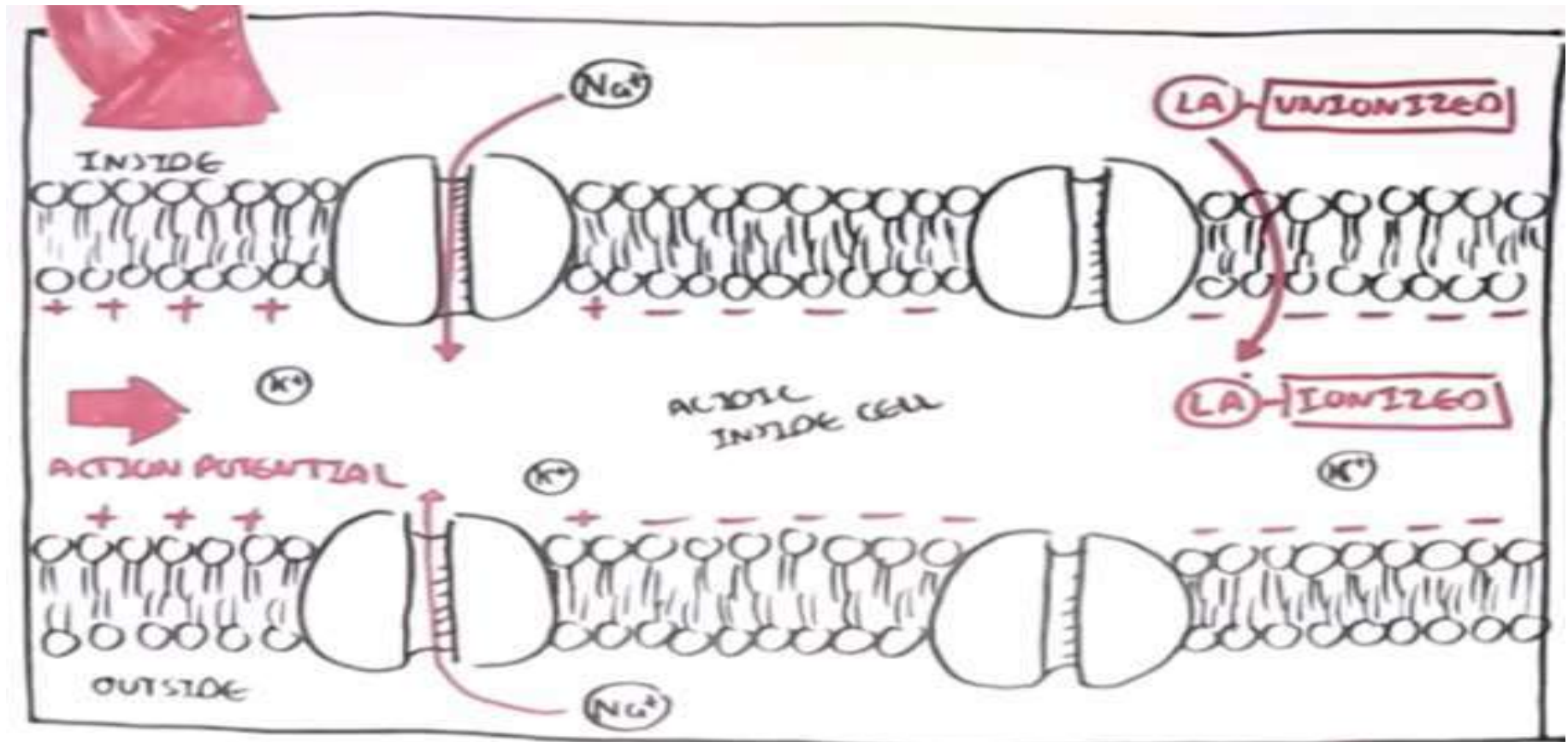
inactivation of voltage-gated Na^+ channels



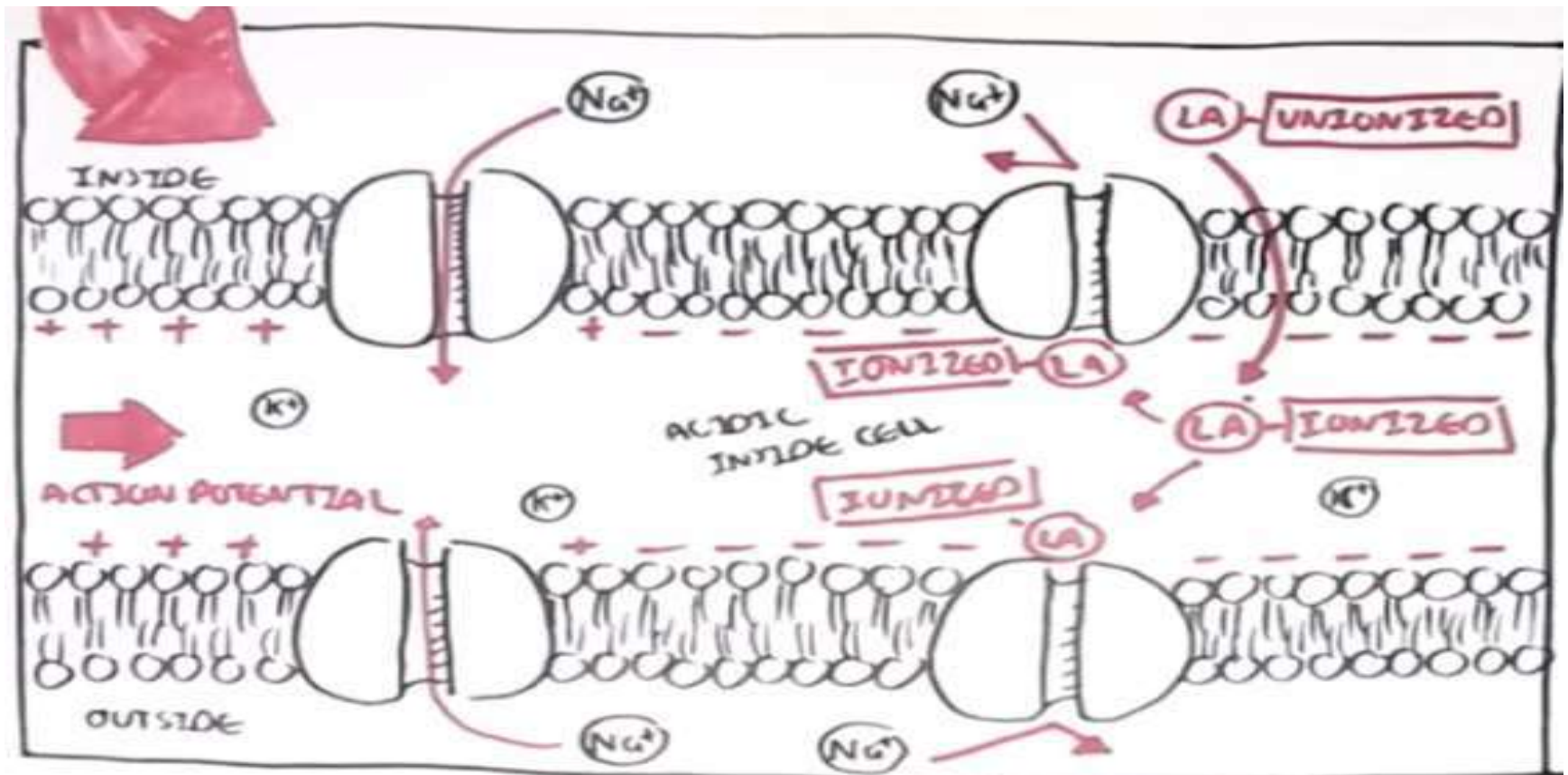
return to the *closed* conformation



- LA gain access to their receptors from the cytoplasm or the membrane.
 - the drug molecule (**nonionized, uncharged**) must cross the lipid membrane to reach the cytoplasm.



- once inside the axon, the ionized (**charged**) form block voltage-dependent sodium channels and reduce the influx of sodium ions,
 - thereby preventing depolarization of the membrane and blocking conduction of the action potential



Classification of LA

**Based on
delivery
option**

*Based on
potency and
duration*

*Based on
chemical
structures*

Topical

Creams and ointments

**Injectable
(infiltrative)**

perineural

Also called the nerve block

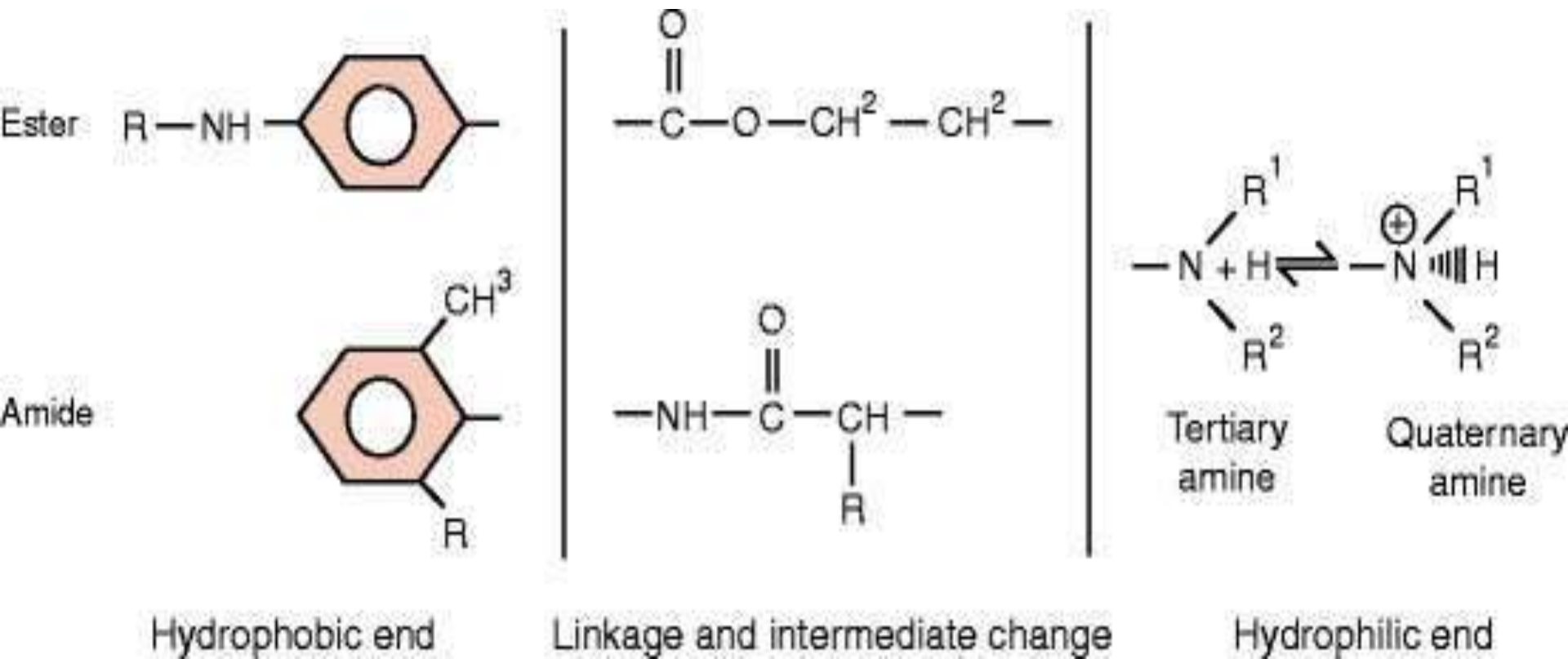
**Neuraxial
(spinal , caudal , epidural)**

- Caudal (low epidural) is used in pediatric patients for groin/urological surgeries like circumcision and hernia repair. Mainly the purpose of it is pain management where we inject the drug into the sacrococcygeal ligment through the sacral area. It's NOT done in adults as it's very difficult.

- **Injectable anaesthetic:**
 - *Low potency, short duration* – **Procaine** and Chlorprocaine
 - *Intermediate potency* – **Lidocaine (Lignocaine)** and Prilocaine
 - *High potency and long duration* – **Tetracaine, Bupivacaine,** Ropivacaine, Etidocaine, Mepivacaine and Dibucaine (Cinchocaine)
- **Surface anaesthetic:**
 - **Soluble** – **Cocaine**, Lidocaine, Tetracaine and Benoxinate
 - **Insoluble** – Benzocaine, Butylaminobenzoate and Oxethazine

According to chemical structure

- all LA are **weak bases**
- All LA share 3 structures :
 - Hydrophilic** amine group (tertiary amine)
 - intermediate group** (either *esters* or *amide*)
 - Lipophilic** aromatic group (Aromatic Ring)



☆ Drugs in this family have only one I in their names and are NOT metabolized in the liver.

Esters

A- Esters of benzoic acid

☆ Esters are metabolized in plasma as they are degraded by plasma pseudocholine esterase EXCEPT cocaine which is metabolized in the liver. All esters cause hypotension EXCEPT cocaine.

-Benzocaine: used **only** in **surface** anesthesia

-Procaine:

- **first synthetic injectable LA**
- **slow onset (slow penetration) → not used for surface anesthesia**
- Greatest vasodilation
- **used for soft tissue (e.g. dentistry) → max dose 1000 mg**
- **rapidly destroyed → systemic toxicity is negligible**

-Cocaine

B-Esters of PABA (PARA-AMINO-BENZOIC ACID)

- Chlorprocaine
- Propoxycaine
- Tetracaine

 This causes allergy

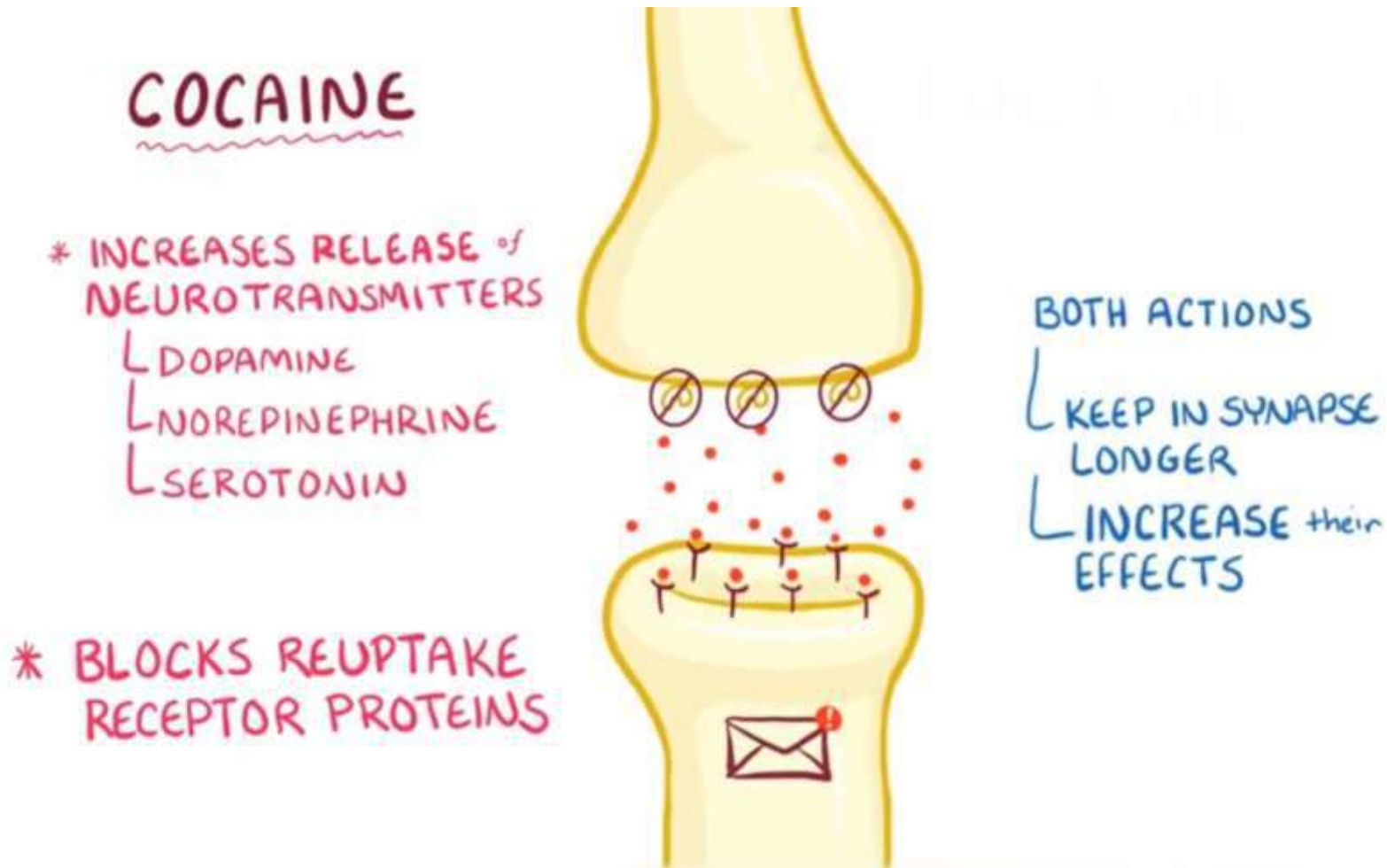
Cocaine (Esters of benzoic acid)

- **block** norepinephrine **reuptake** at sympathetic neuroeffector junctions → **prevents** its **vasodilation** effect → gives **vasoconstricting** actions So it elevates the blood pressure and heart rate, causing tachycardia
- It's an **excitatory** drug. (blocks dopamine reuptake)
- It's easily soluble , so if it is absorbed too quickly , serious side effects can occur .
- Also , some patients maybe sensitive to it .

Note: using of cocaine as a local anesthetic is not likely to cause psychological dependence or other serious side effects .



Mechanism of cocaine



Amides

☆ Since amides have an I in their name, so they have an extra I in drug names that belong to this family. So amide drugs have TWO I in their names

-Lidocaine :

☆ Amides have an I in their name so they are metabolized by the liver (i for an i)

- **most widely used as local , Nerve block and topical**
- Rapid penetration → **1st choice of surface anesthesia**

Can be used as an anti-arrhythmic drug too

-Bupivacaine :

☆ The most cardio- depression causing agent

- used when anesthesia **is desired postoperative pain is anticipated**
- **not** recommended for **children or handicapped patients** because of the increased risk of postoperative injury (chewing on a numb lip).

NOTE : IT'S THE MOST CARDIOTOXIC DRUG IN HIGH DOSES Long duration

- Mepivacaine
- Prilocaine
- Ropivacaine

Others

- QUINOLONE

- Centbrucidine

- KETONE

- Dyclonine

Bupivacaine is also known as Marcaine. We have two forms of it, heavy and light depending

Heavy marcaine (bupivacaine) is mainly used during spinal anesthesia as we inject the drug into the CSF, so when it is heavy this prevents it from reaching the CNS and causing toxicity. However, this heavy form has a longer duration of action and it is more potent than the light form.

Light marcaine (bupivacaine) on the other hand is used in epidural anesthesia, give 0.5ml.

Saddle anesthesia is similar to spinal so we can only administer heavy marcaine. We administer 1 ml but without fentanyl. We target S2-S4 to numb the area. The patient needs to stay still for 5 mins after the injection, it numbs the area but vital functions remain intact along with motor function. It is mainly used in cases of perianal abscess and hemorrhoids

*** When we have hypotensive anesthesia (patients who are expected to experience bleeding, like during nasal adenoidectomy), we manage them by targeting the mean arterial pressure. We can lower it until 60mmHg to activate the physiological autoregulation. In these cases we use remifentanyl since it is quick, causes vasodilation and reduces the risk of bleeding. Remifentanyl is quicker and different than fentanyl since it's metabolized by plasma pseudocholine esterase while fentanyl is metabolized in the liver. So it is the drug of choice in these cases.

AMIDES

- **longer** lasting analgesia.
- Produce **more** intense analgesia.

Higher lipid solubility so more potent than esters

- **Rarely** cause hypersensitivity reactions

If amides caused allergy, which is rare, it's due to the substances that are added to the drug for safety measures

- **Not** hydrolyzed by Plasma Cholinesterase, more slowly destroyed by **liver microsomal P450 enzymes**.

ESTERS

- **Short** duration of action
- **Less** intense analgesia
- **Higher** risk of hypersensitivity because

Very important note

the **metabolism of most ester produce PABA**

Least hepatic clearance (only cocaine)

- Hydrolyzed by Plasma Cholinesterase in blood.

Makes them less stable and of a shorter duration

- **Rarely** used for Infiltration anesthesia
- But useful **for topical anesthesia on** mucous membranes.

Important clinical properties of LA

- **Physiologic activity of LA depends on their :**

- 1. lipid solubility.** ☆ Lipid solubility determines the potency of the drug.

- Lipid solubility determines the drug's ability to cross the blood brain barrier, and its absorption. The higher lipid solubility the higher the absorption so less doses needed to produce an effect

- 2. Diffusibility.**

- It is also affected by lipid solubility of the drug

- 3. affinity for protein binding.** ☆ Protein binding determines the duration of action.

- The higher the affinity the more it binds to plasma proteins, the longer it takes to clear it out so less number of doses needed and longer duration of action.

- 4. percent ionization at physiologic pH.**

- The active drug is the unionized part of the drug. So less ionization, the more active

- 5. vascularity and vasodilating properties.**

- **Lipid Solubility $\leftrightarrow$ Potency :**
Higher solubility can use a *lower concentration* and *reduce* potential for *toxicity* [LA] , because 90% of the nerve cell membrane is composed of lipid
- **Diffusibility :**
Diffusibility of the local anesthetic through tissue other than nerve tissue also influences the *speed of action onset*.
- **Protein Binding $\leftrightarrow$ Duration :**
The more firmly the local anesthetic *binds* to the protein of the sodium channel, the *longer* the duration of action.

Bupivacaine 95%	Lidocaine 65%
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- **PH and Pka :**

- they control the forms by which LA exists in the body
*the more **acidic the tissue** → the **ionized** form presents.*

- **Pka ↔ Onset :**

- Pka: pH at which the **ionized** and **non-ionized** forms are present at **equilibrium** , it ranges from **7.4-8.5**
- The **more closely** the equilibrium pH (**pka**) for a given anesthetic approximates the **physiologic pH** of tissues (ie, 7.35-7.45), the **more rapid** the **onset** of action.

Extracellular pH

Like in cases of abscess

- **Infections** → ↑ extracellular acidity → ↑ extracellular ionized form of LA → ↓ LA crossing → ↓ **activity**.
- Adding NaHCO_3 to LA solution → ↑ **activity** (rapid onset). Except bupivacaine

Intracellular pH

- **Carbonated solutions of LA** are saturated with CO_2 which readily enters nerve cells → ↑ intracellular acidity → ↑ intracellular ionized (active) form available to block Na^+ channel → ↑ **activity**.

- **Tissue Vascularity :**

- Nasal mucosa, oral mucosa, the scalp, and the skin of the head and neck have a tremendous blood supply.
 - *High vascularity* → *rapid absorption* of LA into serum → may precipitate an *adverse reaction*
 - *inject* the area *more slowly* and *wait longer* between injections
- IV is highest vascularity >> least is SC

- **Vasodilation properties of LA & the need of vasoconstrictors :**

- All clinically effective **injectable L.A** have some degree of **vasodilating activity**.

- A* ↑ **absorption** of L.A into CVS → **removal** from injection site

- B* Rapid **diffusion** of L.A from injection site → ↓ **duration** of action & **depth** of anesthesia.

- C* Higher **plasma** level of L.A → ↑ risk of **toxicity**

- D* ↑ **bleeding** at injection site.

- **Addition of vasoconstrictor to L.A : (WHY???)**

- A* constricts BV → ↓ **perfusion** → slow absorption → ↓ toxicity

- B* Higher **volume** of L.A **around nerve** → ↑ **duration** of action

- C* ↓ **bleeding** at injection site

Except for cocaine we don't give vasoconstrictor with

Because it is a vasoconstrictor itself we don't want to result in ischemia

Effects of LA on nerves

– Factors that influence nerves sensitivity to LA :

– **fiber diameter**

- ***smaller** fibers are **blocked more** easily than larger ones.*

– **myelination** - *myelinated fibers are **blocked more** easily than unmyelinated ones*

– Critical length of the nerve must be blocked to induce LA → **2-3 Ranvier nodes** in myelinated neurons

– **physiologic firing rate**

- *Use dependence - activated pain fibers fire **rapidly** - **selectively blocked***

– **anatomic location**

- *fibers located in the **periphery** of a thick nerve bundle are **blocked sooner** than those in the core - exposed earlier to higher concentrations of the anesthetic – sensory*



According to myelination and diameter, A delta and B are fastest to be blocked.

According to diameter alone, C is fastest to be blocked

- - **Autonomic fibers** are more susceptible than somatic ones
 - Myelinated and smaller diameter fibers are blocked faster
- Order of blockage in general : All A fibers are myelinated, B are some myelinated, C are unmyelinated
 - type B & C → type A δ → type A β → type A γ → A α
 - Pain → temperature → touch → deep pressure
 - We can test if LA started working by testing with a pinprick for pain, alcohol swab for temperature..etc
 - (start from the *fastest to block* and the *slowest to recover*)
 - The fastest to be blocked, the slowest to recover
 - ★ In general, the order of blockage is as it follows:
Sympathetic block > Sensory block > Motor block
- All LAs have effects on Na⁺ channel of :  Often dose dependent so in epidural motor block takes much time while in spinal motor blockade occurs rapidly

Sensory nerve endings

Nerve trunks

NM junctions

Ganglion

Receptors

Effects of LA on other tissues

- class I antiarrhythmic agents**. Ex : lidocaine
- Most local anesthetics also have ***weak blocking*** effects on ***skeletal muscle*** neuromuscular transmission, but these actions have no clinical application
- The mood elevation induced by cocaine** – CNS effect by ↑ dopamine

Uses & Administration

1. Surface anesthesia (for minor surgeries):

- Applied to skin & mucous membranes of nose, mouth & cornea as a solution, jelly or cream.

2. Infiltration (for minor surgery):

- Injected SC & in submucosal tissues to reach nerve branches & terminals. Do NOT give vasoconstrictors when numbing terminal nerves to avoid ischemia

3. Nerve block (for dentistry & surgery): We can use ultrasound to guide the needle.

- Injected close to nerve trunks (e.g. dental nerves - brachial plexus).

4. Spinal anesthesia:

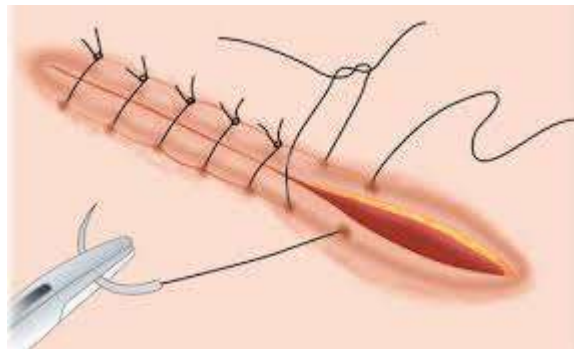
- Injected in subarachnoid space below L2, acts on spinal roots & spinal cord.
- Used for **surgery of abdomen, pelvis & legs** when general anesthesia is contraindicated.

5. Epidural anesthesia:

- Injected outside the dura, blocks spinal roots.
- Same **uses as spinal anesthesia** with decrease risk of side effects.
- Commonly used in obstetrics **for painless labor**

Uses

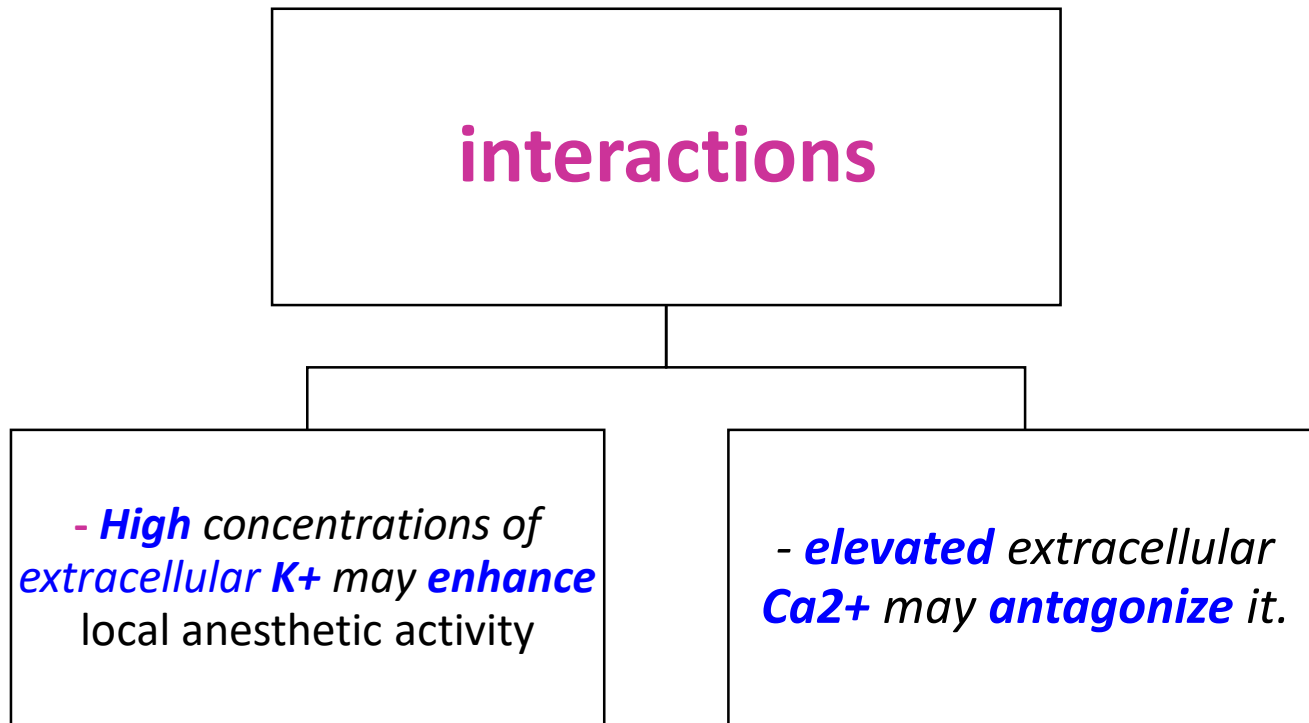
- Excision
- Minor surgery stitching
- Dentistry
- Podiatry
- Skin trauma & surgery
- Labor pain [Epidural injection](#)
- Post op. pain (**Bupivacaine**)



Contraindication & Interactions

- **Contraindications :**

- sepsis
- coagulopathy
- drug allergy
- Lack of informed consent or unwilling patient



Side Effects (Undesired, Local, Systemic)

❖ Undesired :

- Mild ***bruising, redness, itching***, or swelling where the medication was injected
- mild ***dizziness, nausea & numbness*** in places where the medicine is accidentally applied.

❖ Local toxicity :

1) Neurotoxicity: ***Direct*** injection of LA's into ***nerve*** will result in immediate ***sever pain*** and ***pathologic damage*** to the nerve → if happened, stop injection & reposition the needle

2) Myotoxicity: Injection of LA into the ***muscles*** will result in ***histological changes*** in the tissues but it is ***insignificant***

Systemic side effects

1. CNS Toxicity :

A) Premonitory signs (initially) :

manifest as **sedation, lightheadedness, slurred speech, sensory disturbances** (metallic taste, tinnitus) , restlessness, nystagmus . ☆ Earliest signs of local anesthetic toxicity are **perioral numbness + dizziness**

If local anesthetic reaches the brain it results in convulsions

B) Stimulation followed by depression :

in **higher blood levels** → may result in **tremor, muscle twitching, tonic-clonic convulsions**. Severe convulsions may be followed by **coma** with **respiratory** and **cardiovascular depression**.

Cocaine → euphoria (unique)

Lidocaine → sedation (even at non toxic doses)

2. CVS toxicity :

1) arrhythmias

2) Hypotension

- **ARRHYTHMIAS:** direct effect
(More resistant than CNS)

- Decrease cardiac excitability and contractility
- Decreased conduction rate
- Increased refractory rate (bupivacaine)
- ALL can cause arrhythmias if conc. is high enough

Note: cocaine is exception it stimulates heart

★ It stimulates the heart since it inhibits the reuptake of catecholamines which results in tachycardia and hypertension

- **HYPOTENSION:** Arteriolar dilation is a result of:

- Direct effect (procaine and lidocaine have most effect)
- Block of postganglionic sympathetic fiber function
- CNS depression
- Avoid by adding vasoconstrictor to the preparation

- **Cocaine is exception:** produces vasoconstriction, blocks catecholamine reuptake

Treatment for CVS/CNS toxicity

❖ Treatment :

- **oxygenation** with mask
- treatment of **convulsions** – **diazepam** i.v. or thiopental
- in **hypotension** due to the vasodilation – **noradrenaline** i.v.
- in **cardiac arrest** – **adrenalin**
- **lipid emulsion injections** (commercially available preparation) as rescue therapy/**antidote** in **severe intoxications** It is a specific antidote for local anesthetic toxicity

In cases of LA toxicity, we deal with it as an emergency. First we do ABC, maintaining the airway is the most important step, if needed we perform CPR.

After that, we administer whatever drugs that are needed depending on the symptoms experienced by the patient. Then give lipid emulsion which is the drug of choice.

3. Methemoglobinemia :

- Some LA *metabolites* have significant *oxidizing properties* → *conversion* of hemoglobin into methemoglobin and *compromise* ability to carry oxygen
- e.g. *prilocaine* ^{Most important} / *benzocaine* / *lidocaine*
- treatment : *oxygen and* ^{Drug of choice.} *methylene blue* (converts methemoglobin to hemoglobin).

Again, we deal with it as an emergency, assess ABC then give methylene blue

4. Allergy : *Benzocaine causes both. + procaine causes allergies too (short name for short name)*

- rare (<1%) in amides & more often in *ester* subclass – *PABA* (*para amino benzoic acid*) metabolites are responsible for it.
 - Rashes, angio-edema, dermatitis and rare anaphylaxis. -
- Treatment: *of anaphylactic shock* – *adrenaline, corticoids, oxygen...*

ABC then give these drugs

5. Neurotoxic action :

- in **high concentration** , LA can cause nerve **damage** to central and peripheral NS.
- **Mechanism(s) not clear.**
- Permanent neurological injury is rare.
- May account **for transient neurological symptoms.**

Complications of spinal and epidural (cauda equina syndrome)

How to avoid adverse effects of LA

Those are the steps to reduce systemic effects and risks of toxicity

Inject *slowly*

Aspirate to *check* for *intravascular entry*.

Adding *a vasoconstrictor* like epinephrine to retard vascular absorption.

Don't exceed the maximum *recommended dosage*

Mainly importance of epinephrine administration, mostly dilute it with

It's important for many reasons:

1. Localizes the drug at the targeted area.
2. Increases the quality of the block by elevating the concentration remaining at the target as it would be less likely to become washed out to the circulation.
3. Increases the duration of action by slowing down its absorption to the circulation.
4. Decreases bleeding tendency.

For example, lidocaine dosing ranges from (1-1.5 ml per kg), so we use the minimum dose possible for safety measures.

The maximum dosing in LA infiltration is 5ml per kg without epinephrine.

Maximum dosing in LA infiltration without epinephrine is 7ml per kg.

- If a patient is 70kg, and we want to administrate epinephrine and LA how much do we administrate?

$7 \times 70 = 490 \text{ ml}$

EMLA (eutectic mixture of local anesthetics)

EMLA cream

- **Eutectic** = **two** solid substances **mixed** together in **equal** quantities by weight form a eutectic mixture.

E.g. Lidocaine + prilocaine → oily mixture

- the **melting point** of the **mixture** is **lower** than the **melting points** of the **individual** components.

Used as analgesic for pain which applied over the needle



Note :Many drugs classified in other groups, have significant local anesthetic effects eg, antihistamines and beta-blockers

When we want to do Bier's block, which is a method used for upper or lower limb surgeries. We use Lidocaine (3-5ml per kg) The procedure is as the following, we apply a tourniquet with double cuff, one cuff proximally and the other one distally. Then we connect a distal canula. we elevate the arm to insure it is emptied from any blood. Then we inflate the proximal, the pressure needs to be higher than systolic pressure (250-300mmHg). For a normal weighed patient, we often administrate 250-300 ml in a volume of 40 normal saline. Then we take 20 in a syringe and inject it to the patient proximally which will cause anesthesia to that limb for a period of 1 hour. However, the minimum time i can wait before releasing the tourniquet is 20 mins. Even if the surgeon finished after 5 min of starting the procedure i need to wait until 20mins has passed to avoid systemic toxicity of LA. Maximum is 60mins



Thank you