

# Pharmacology

Modified no. 11

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# Local Anesthesia

## Color code

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Slides



Doctor



Additional info



Important

- ❑ Previously, we have talked about General anesthesia.
- ❑ **Now, we are going to talk about local anesthesia.**
- ❑ In general anesthesia, we mainly deal with brain (CNS).
- ❑ In local anesthesia, we are dealing with **free nerve endings**. Whether they are myelinated or not.
- ❑ How? **By targeting Na<sup>+</sup> channels** within nerves.
- ❑ The effect will include **Autonomic NS + Pain sensation**.
- ❑ Local anesthetics are called also: Na<sup>+</sup> stabilizers.
- ❑ **MOA:** Blocking Na<sup>+</sup> channels > decrease propagation of the signal.
- ❑ Rule: Smaller nerve fiber = better effect of drug.

# Local anesthesia

- Local anaesthetics block the initiation and spread of action potentials in nerve fibres by preventing the voltage-dependent increase in Na<sup>+</sup> conductance.
- They do this in two ways :
  - (1) By acting non-specifically to stabilise the membrane.
  - (2) by specifically plugging Na<sup>+</sup> channels. The latter mechanism is the most important for most local anaesthesia.
- Most are used with adrenaline to prolong duration of action by constricting blood vessels.

# Chemistry

All local anesthetics contain **3**  
structural components:

- an aromatic ring (usually substituted)
- a connecting group which is either an ester (e.g., novocaine) or an amide (e.g. lidocaine)
- an ionizable amino group

Chemical structure of local anesthetics

Aromatic lipophilic portion - Intermediate chain - Amine hydrophilic portion



❑ Now, let's talk about the chemistry of these drugs.

❑ They are divided into:  
Amides and Esters

- In our body, we have too much esterases. So, ester-containing local anesthetics are **short acting drugs**.

- For amides, our esterases have no access to them >>> **Long acting drugs**.

Both types have **Nitrogen** at their ends.  
Both types have **Aromatic ring**.

❑ Penetration and Lipophilicity.

- This is a very important aspect to be covered to understand the MOA of these drugs.

- **MOA:** Binding of the drug to the inactive Na<sup>+</sup> channel of the nerve from the inside (intracellular aspect) >>> So we have to penetrate. **The aromatic ring will help us in this penetration.**

- **Note:** We all know from 1st year that the membrane of cells is phospholipid bilayer.

- Also, **the ionization state of the drug** plays a key role in penetration and efficiency of the drug.

- These drugs are weak basis ( Pka = 7.4-7.9). [Weak basis are ionized in most of cases].

## Lipid solubility:

determines, **potency, plasma protein binding and duration of action** of local anesthetics

	<u>Lipid solubility</u>	<u>Relative potency</u>	<u>Plasma protein binding (%)</u>	<u>Duration (minutes)</u>
<u>procaine</u>	1	1	6	60-90
<u>lidocaine</u>	4	2	65	90-200
<u>tetracaine</u>	80	8	80	180-600

- All of them ends with **caine**.
- Lidocaine is used also in arrhythmia (B1).

- All these drugs differ in 4 things:

- It is important to know that these drugs are injectable.
- And for drug to be injected, it must be firstly water soluble >>> that's why the **nitrogen** end of the drug must be charged.
- The more lipid soluble = more duration of action. Why? >> More penetration.
- The more binding with plasma protein = more duration of action.
  - Why? Because Na<sup>+</sup> channels are proteins, and binding of drug with plasma protein can be reflected on binding with Na<sup>+</sup> channels.
- In Summary:
  - DOA (Duration of Action) is controlled mainly by 2 factors: Lipid solubility/penetration + Protein binding.
  - We try to use long-acting agents in long-acting operations [like during labor, epidural dural anesthesia is required, Long-acting drug is used (Bupivacaine)].

# Weak bases

– Proportion of **free base (R-NH<sub>2</sub>)** and **salt (R-NH<sub>3</sub><sup>+</sup>)** forms depends on **pH and pK** of amino group.

$$\text{pH} = \text{pK} + \log \frac{[\text{base}]}{[\text{salt}]}$$

(Henderson-Hasselbalch equation)

– Example: Calculate the proportions of free base and salt forms of tetracaine (pK = 8.5) at pH (7.5).

$$7.5 = 8.5 + \log \frac{[\text{base}]}{[\text{salt}]}$$

$$\log \frac{[\text{base}]}{[\text{salt}]} = -1$$

$$\frac{[\text{base}]}{[\text{salt}]} = 10^{-1} = 1/10$$

∴ there is 10x more drug in the ionized than in the non-ionized form at physiological pH

- ❑ For drug to be injected, it must be ionized. But, For drug to penetrate (do its effect), it must be unionized.
- ❑ From biochemistry course, ionization depends on Pka and PH.
- ❑ **Local anesthetics are weak bases (pKa = 7.4-7.9). In acidic/hypoxic area, a huge shift will occur between Pka and PH, which results in ionization of drug >>> no effect.**
- ❑ **That's why in inflamed/hypoxic/narcotic areas, where PH is lowered (so, the unionized form of the drug decreases) >> so, the full effect of local anesthetics is not achieved.**

عشان هيك لما يكون في التهاب بأسنانك، مفعول البنج عند دكتور الأسنان ما يكون فعال

- ❑ In emergencies, to overcome this issue, some doctors give **Sodium bicarbonate, Why?**
  - It **alkalinizes** the local environment, shifting the pH towards a more basic level and this **increases the proportion of unionized anesthetic, allowing better penetration** and improved effectiveness.

❑ Question: Why not just increase the dose in inflamed area to overcome acidity? 😞

Ans: Because during inflammation, permeability increases > access of drug to the blood/heart increases > bad complications (antiarrhythmic effects on heart {Lidocaine}).



- To overcome this issue, **we give vasoconstrictor with the injection (epinephrin)**. So, in the cartilage, we have (The local anesthetic drug + vasoconstrictor).

👉 This mixture **will increase DOA of the local anesthetic drug**, the actual DOA of the drug alone = 30 mins, with addition of vasoconstrictor = 3 hours.

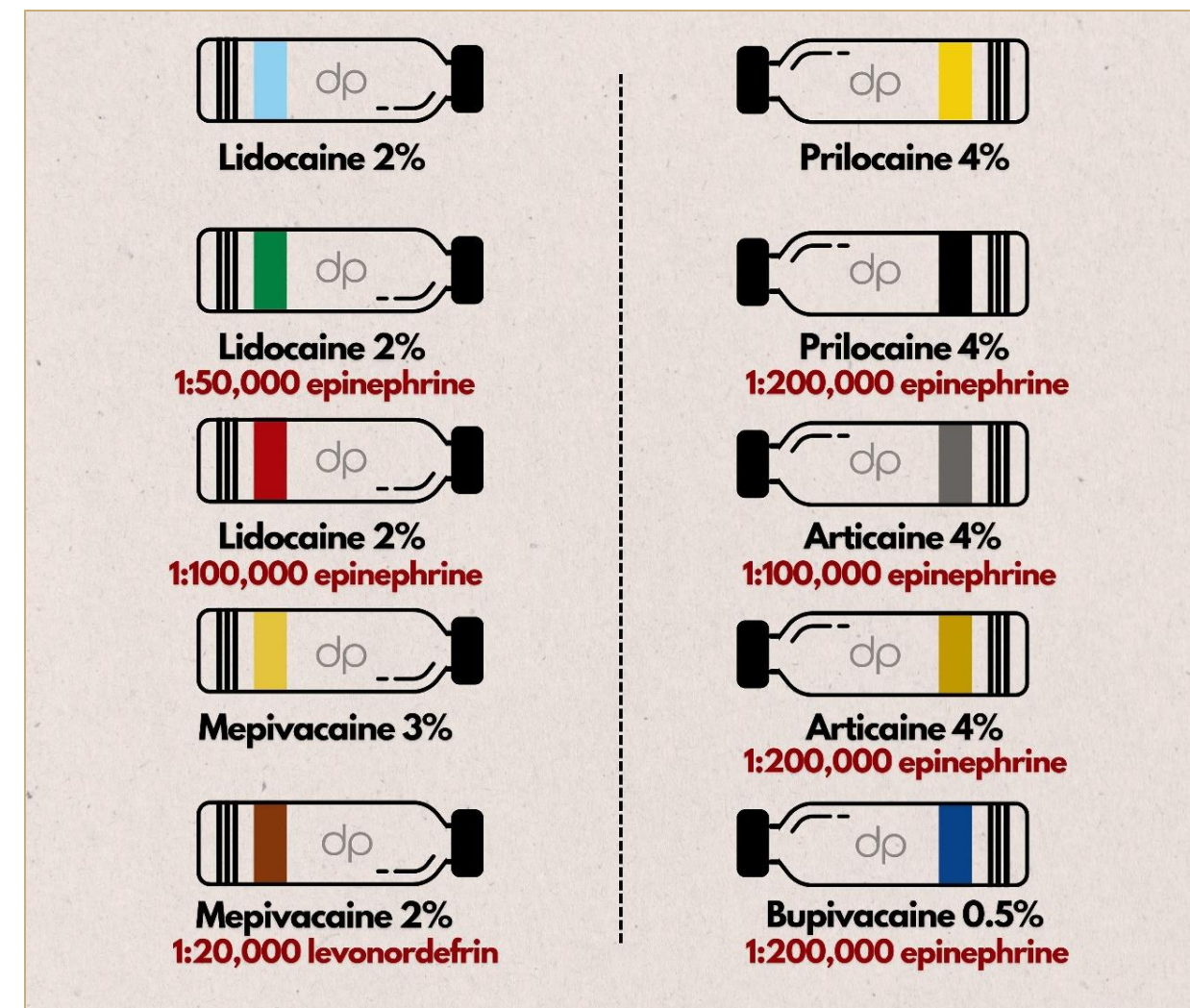
زي عند دكتور الأسنان، الدكتور بحط دوا مدته قليلة، بس بخلطه مع ابينيفرن فبضل مفعول التخدير ثلاث ساعات أو أكثر أحيانا

What is 1:200,000 ? = (1 gram/200,000 ml)

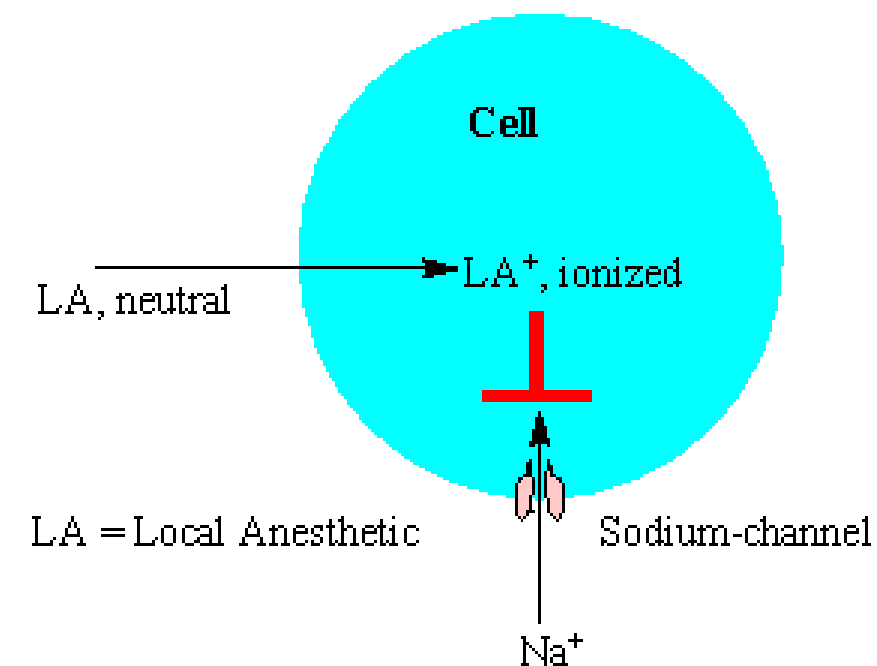
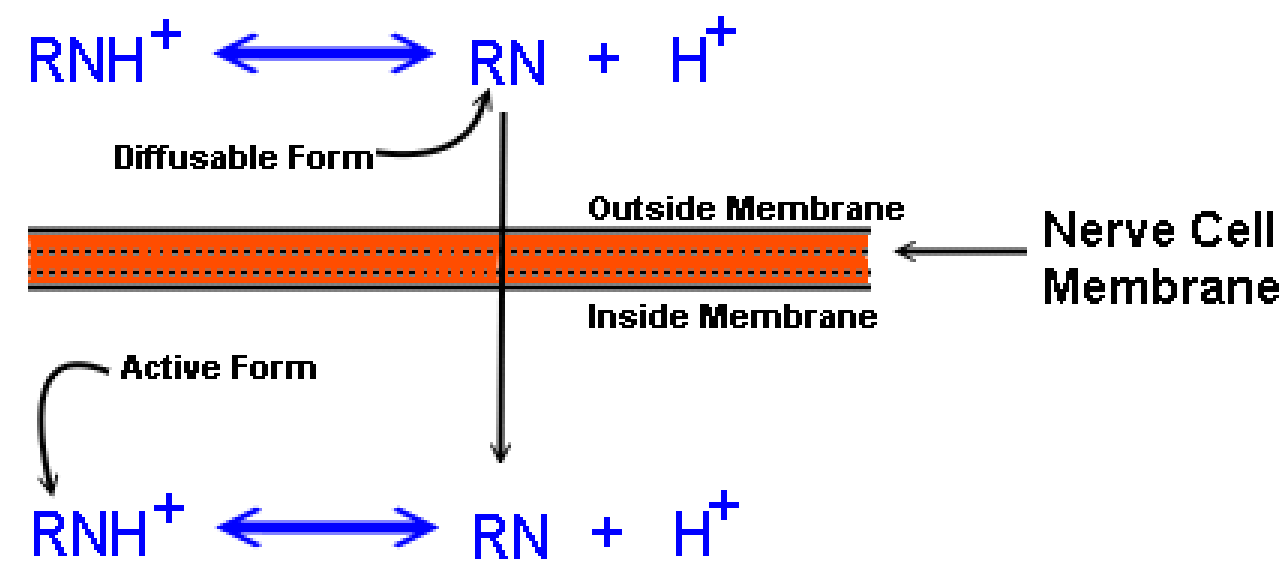
- The degree of vasoconstriction needed depends on the blood supply of the area.
- In regions with high blood flow, a greater degree of vasoconstriction is beneficial to prolong anesthesia and reduce systemic absorption. However, in areas with limited blood supply, such as the fingers, excessive vasoconstriction can lead to ischemia and necrosis.
- Local anesthetics alone can cause systemic effects like hypotension and arrhythmias due to their sodium channel-blocking properties. Therefore, vasoconstrictors are added to minimize these effects and prolong anesthesia, but in very low concentrations, such as 1:200,000, to prevent excessive constriction in vulnerable areas.

  **Coloring system:** local anesthetic Cartridge can help doctors identify the correct anesthetic formulation and **epinephrine concentration**, as even slight increase or decrease of epinephrine can causes significantly impact vasoconstriction, anesthesia duration, and systemic effects.

- However, it is important to note that the color-coding system for local anesthetics is different from that used for other drug classes. The colors are used to differentiate particular drug class. For example, blue labels are used to indicate opioids. This helps a lot in people who don't have knowledge in drugs thinking they are taking a new drug according to trade names, but actually they are taking same drug.



local anesthetic enters nerve fibre as neutral free base and the cationic form blocks conduction by interacting at inner surface of the  $\text{Na}^+$  channel



inflammation → reduced susceptibility to anesthesia (lowered local pH increases proportion of anesthetic in charged form that cannot permeate nerve membrane).

Why the ionization happened inside the cell? Because PH intracellular is lower than PH extracellular.

# Functional consequences of Na<sup>+</sup> channel blockade by local anesthetics:

- **nerves**: decrease or abolition of conduction.
- **vascular smooth muscle**: **vasodilatation** similar to diuretics (thiazide).
- **heart**: decreased excitability (reduced pacemaker activity, prolongation of effective refractory period) **like lidocaine**.
- **central nervous system**: increased excitability, followed by generalized depression.

For instance, the first inhibition of inhibitory neurons causing excitation (neg- x neg- = pos+). However, on the long term causes depression and may lead to respiratory depression

# vasoconstrictor

Adrenaline is the conventional vasoconstrictor included in commercial local anesthetic preparations.

The concentration of adrenaline in these preparations can vary and is expressed as grams/ml (e.g. 1:100,000 = 1 gram/100,000 ml).

# Clinical Applications

**nerve block**: injected locally to produce **regional anesthesia** (e.g., dental and other minor surgical procedures).

- Local anesthesia is injected subcutaneously around sensory nerve endings. Useful in minor surgery.
- **Infiltration anesthesia can produce with 0.25–0.5% aqueous solution of lidocaine or procaine (usually with co-administration of adrenaline).**
- Patches can be used for VZV that can help anesthetize the pain by sustained release of lidocaine for example and inhibiting the inactive Na<sup>+</sup> channels or active Na<sup>+</sup> channels.

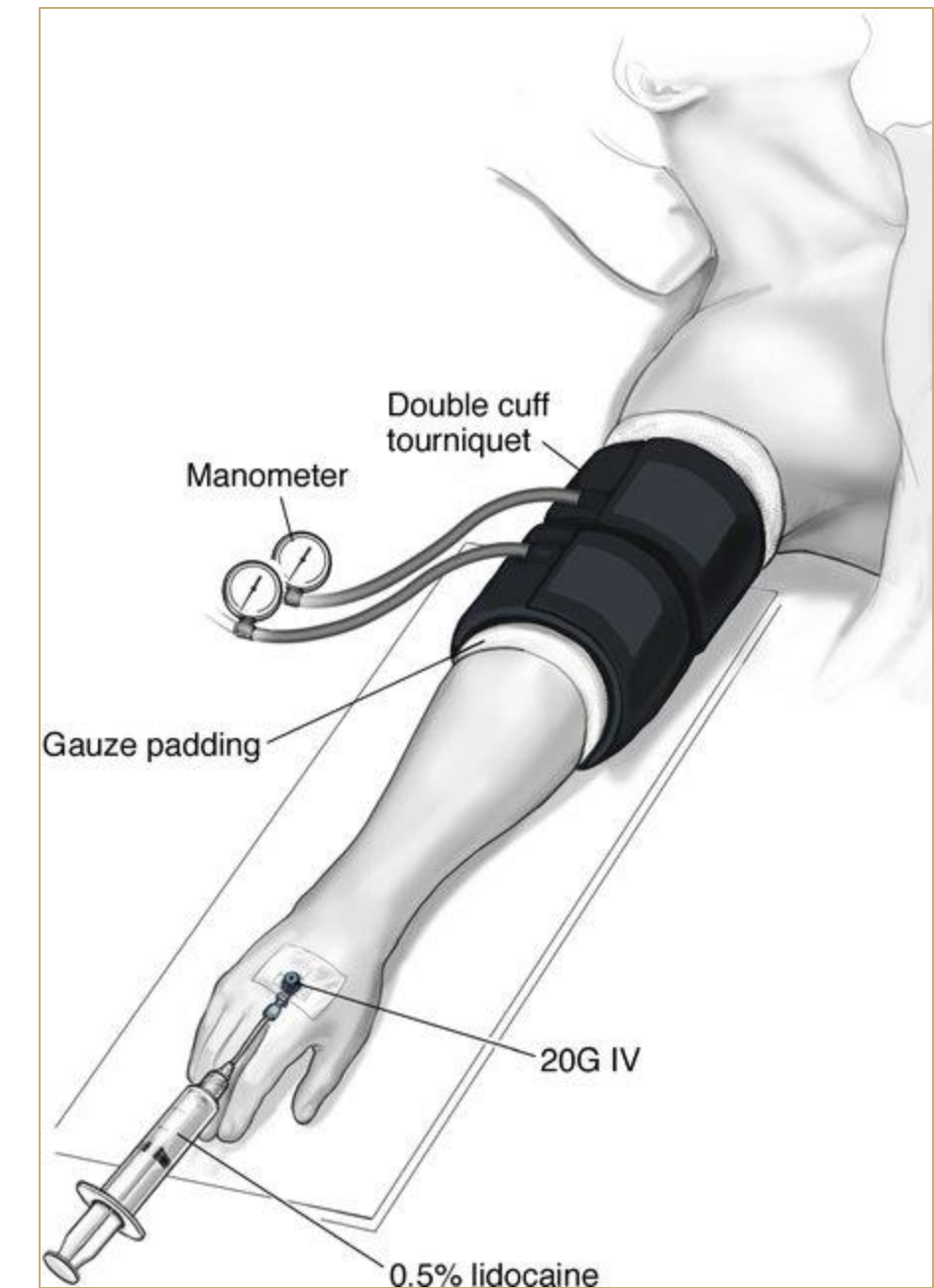
- In some cases, vasoconstrictors are avoided, particularly in patients with arrhythmias, as epinephrine can cause complications for the patient. However, using local anesthetics alone carries risks, such as hypotension and potential proarrhythmic effects due to their sodium channel-blocking properties, so it is very complex regarding both the presence and absence of epinephrine.
- Therefore, coloring systems are crucial in ensuring the most effective anesthetic with the lowest possible dose of epinephrine.

# Topical Agents

- Local anesthesia is applied directly to mucous membranes such as those of the conjunctiva, nose, throat, or urethra.
- Agents of choice is Tetracaine, Lidocaine and Proparacaine.
- Onset of anaesthesia takes about 20 seconds and duration of action is about 8 minutes.
- **high concentrations (2–5%).** To increase penetration.
- Given without Local anesthesia and its taste like strawberry.

# Injection Agents

- Intravenous Regional Anaesthesia.
- Local anesthesia injected intravenously distal to a pressure cuff to arrest blood flow.
- Remains effective until the circulation is restored. Used for limb surgery. **Mainly Lidocaine (Lignocaine) and Prilocaine.**
- To anesthetize the limb, you need to apply a cuff above the site you wish to anesthetize and constrict blood flow. Vasoconstrictors should not be used, as they would cut off blood supply to the entire limb.

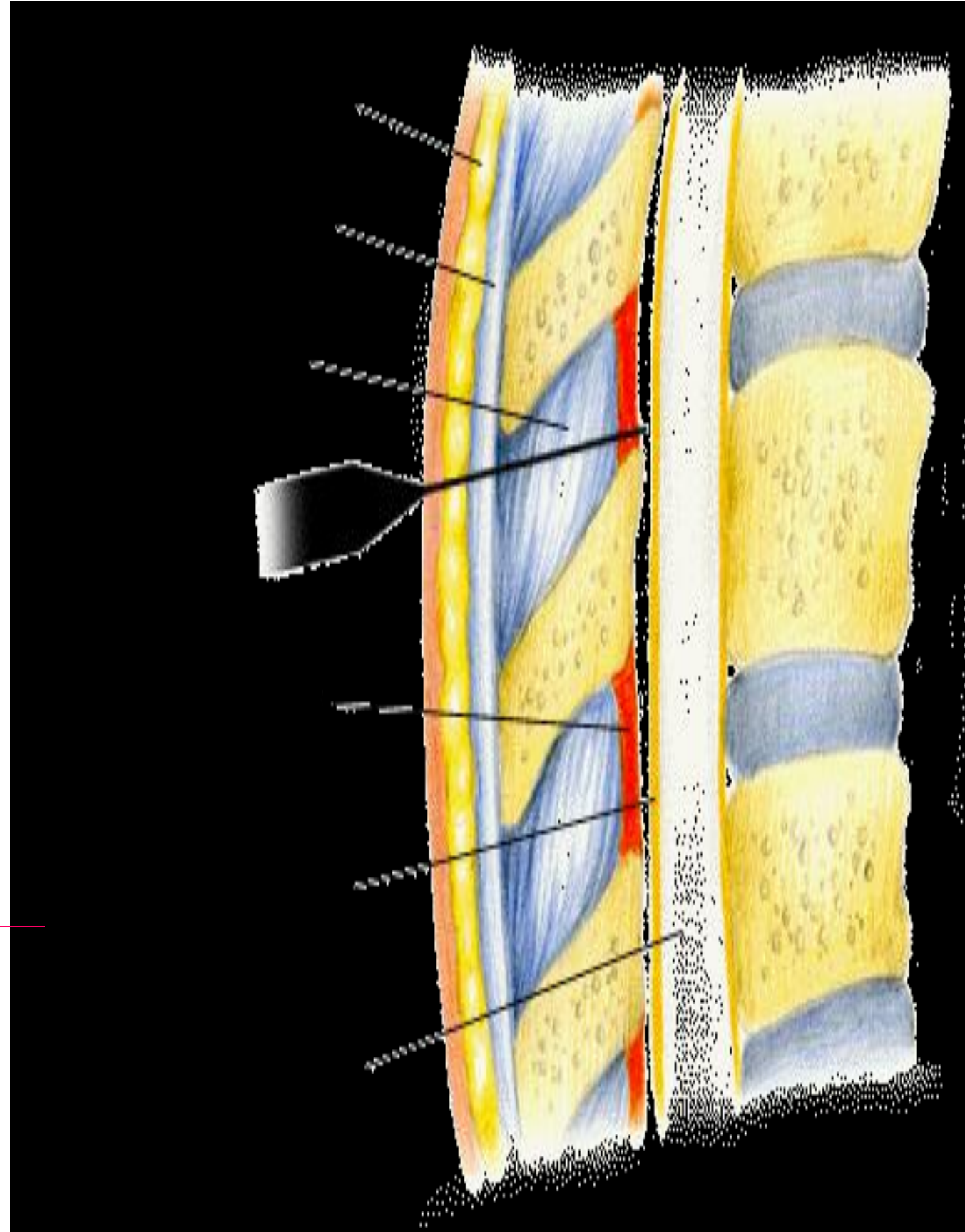


Extra Pic

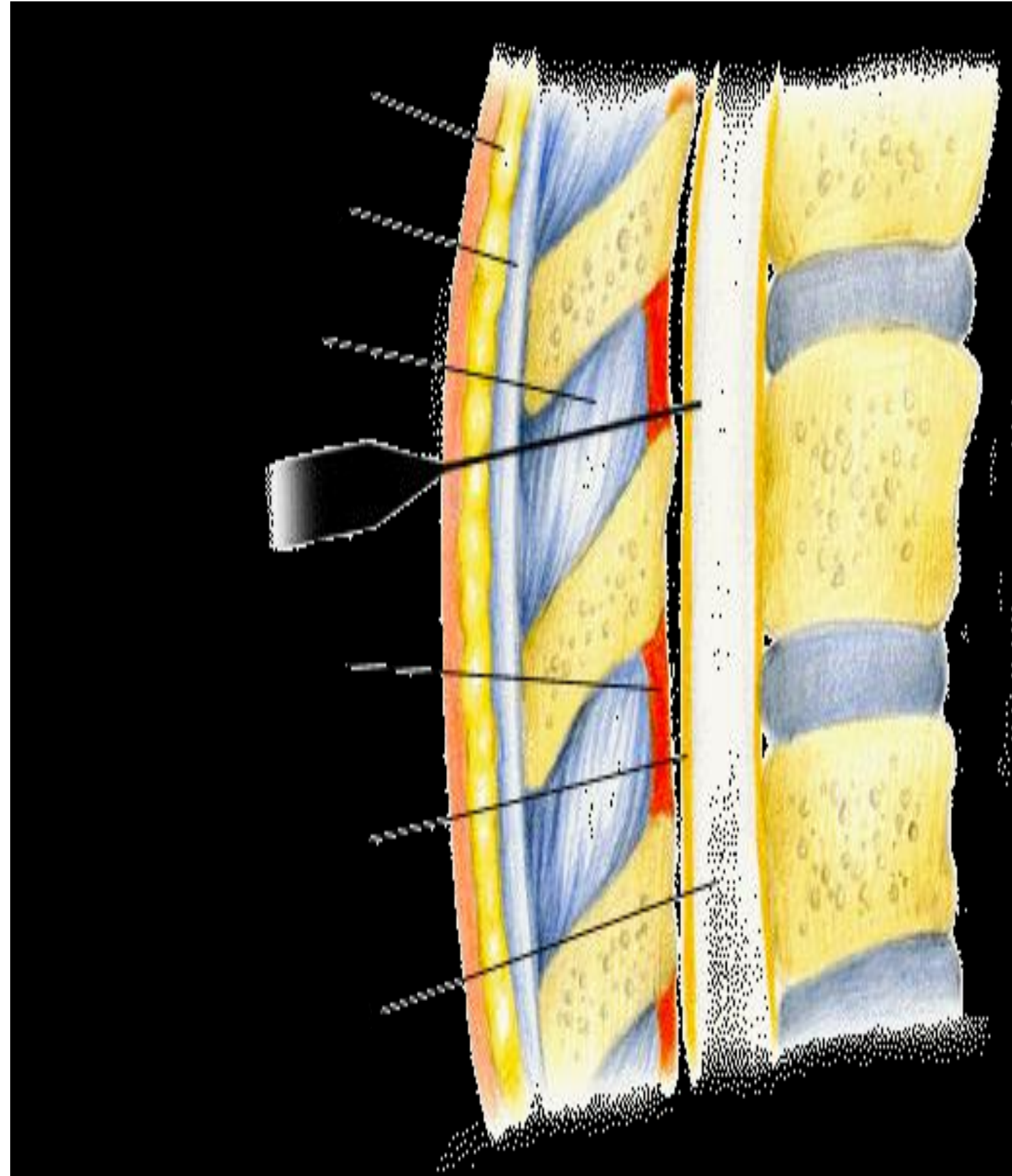
# Spinal & Epidural

- **Spinal Anaesthesia**
  - Local anaesthesia injected intrathecally into the CSF of the subarachnoid space to act on spinal roots and spinal cord.
  - Used for surgery to abdomen, pelvis or leg when general anaesthesia not appropriate. Mainly Lidocaine and Tetracaine.
- **Epidural anaesthesia** (injection of the Local anaesthesia to the spinal column but outside the dura mater **in the dura sac**), used in obstetrics.
- **Hypotension** is a major side effect in these operations.

# Epidural



# Spinal



# Conclusion

**The table is not  
for  
memorization**

<b>Anesthetic</b>	<b>pKa</b>	<b>Onset</b>	<b>Duration (with Epinephrine) in minutes</b>	<b>Max Dose (with Epinephrine)</b>
<b>Procaine</b>	<b>9.1</b>	<b>Slow</b>	<b>45 - 90</b>	<b>8mg/kg – 10mg/kg</b>
<b>Lidocaine</b>	<b>7.9</b>	<b>Rapid</b>	<b>120 - 240</b>	<b>4.5mg/kg – 7mg/kg</b>
<b>Bupivacaine</b>	<b>8.1</b>	<b>Slow</b>	<b>4 hours – 8 hours</b>	<b>2.5mg/kg – 3mg/kg</b>
<b>Prilocaine</b>	<b>7.9</b>	<b>Medium</b>	<b>90 - 360</b>	<b>5mg/kg – 7.5mg/kg</b>
<b>Articaine</b>	<b>7.8</b>	<b>Rapid</b>	<b>140 - 270</b>	<b>4.0mg/kg – 7mg/kg</b>

**Causes  
methemoglobinemia**

- Length of time from induction until the reversal process is complete.
- **Short-acting:**
  - Local anesthetic agent lasts less than 30 minutes.
- **Intermediate-acting:**
  - Local anesthetic agent lasts about 60 minutes.
- **Long-acting:**
  - Local anesthetic agent lasts longer than 90 minutes.

وَقَالَ رَجُلٌ مُؤْمِنٌ مِّنْ آلِ فِرْعَوْنَ يَكْتُمُ إِيمَانَهُ أَتَقْتُلُونَ رَجُلًا أَنْ يَقُولَ رَبِّيَ اللَّهُ وَقَدْ جَاءَكُمْ بِالْبَيِّنَاتِ مِنْ رَبِّكُمْ وَإِنْ يَكُ كَذِبًا فَعَلَيْهِ كَذِبُهُ وَإِنْ يَكُ صَادِقًا يُصِيبْكُمْ بَعْضُ الَّذِي يَعِدُكُمْ إِنَّ اللَّهَ لَا يَهْدِي مَنْ هُوَ مُسْرِفٌ كَذَّابٌ ﴿٢٨﴾

وَقَالَ رَجُلٌ مُؤْمِنٌ مِّنْ آلِ فِرْعَوْنَ يَكْتُمُ إِيمَانَهُ أَتَقْتُلُونَ رَجُلًا أَنْ يَقُولَ رَبِّيَ اللَّهُ وَقَدْ جَاءَكُمْ بِالْبَيِّنَاتِ مِنْ رَبِّكُمْ

قد أثنى الله على رجل مؤمن من آل فرعون كتم إيمانه وأسرره، فجعله الله تعالى في كتابه، وأثبت ذكره في المصاحف لكلام قاله في مجلس من مجالس الكفر، وأين هو من عمر بن الخطاب- رضي الله عنه- جرد سيفه بمكة، وقال: «والله لا أعبد الله سرا بعد اليوم».

ابن عطية: ٤ / ٥٥٥.

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1 → V2			
V2 → V3			



امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!