بسم الله الرحمن الرحيم

DOPAMINE SCIENTIFIC TEAM

Local anesthesia

FINAL | Lecture 6

﴿إِنِّي تَوَكَّلْتُ عَلَى اللَّهِ رَبِّي وَرَبِّكُمْ ۚ مَّا مِن دَابَّةٍ إِلَّا هُوَ آخِذٌ بِنَاصِيَتِهَا ۚ إِنَّ رَبِّي عَلَىٰ صِرَاطٍ مُّسْتَقِيمٍ﴾

Written by: Raneem AH
Sarah Mahasneh

Reviewed by: Deema Nasrallah

PHARMACOLOGY

Local anesthesia

- Local anaesthetics block the initiation and spread of action potentials in nerve fibres by preventing the voltage-dependent increase in Na+ conductance.
- They do this in two ways :

(1) By acting non-specifically to stabilise the membrane.

(2) By specifically plugging Na+ 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

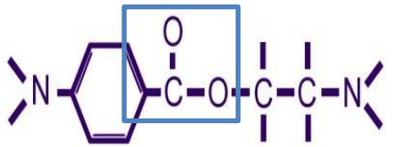
All local anesthetics contain **3 structural components**:

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

- Both are weak basis pKa=8
- Amino group is the one thāt gains or loses a hydrogen, so it's the ionizable group. Therefore, they could be uncharged (non-ionized) or charged (ionized).

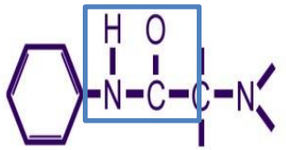
Chemical structure of local anesthetics

Aromatic lipophilic portion - Intermediate chain - Amine hydrophilic portion



AMINO ESTERS

Ester bond

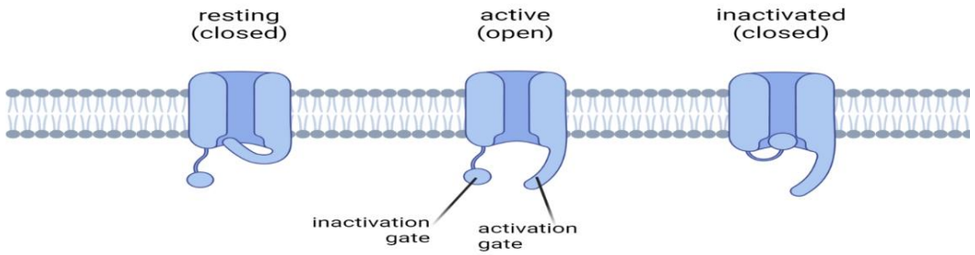


AMINO AMIDES

Amide bond

Mechanism Of Action:

- All anesthetics have the same MOA, they all must enter to the neuron by crossing cell membrane. To cross this membrane, they must be in a **non-ionized.**
- Once inside the neuron, the lower pH (compared to the outside) causes the drug to become **ionized**. Recall: This ionization occurs as the environment moves further from the drug's pKa, giving the drug a positive charge.
- Inside the neuron, they block **sodium channel** in its **inactive state** by binding to it and so there is no propagation for the signal (Pain, temperature, pressure).
- Increasing the dose, increases the signal block. **Pain** is the **first signal** to be blocked because it’s fibers are thinner and have a lower intensity of sodium channel opening, making them easier to block.Temperature is blocked next, followed by pressure.



Lipid solubility:

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

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

weak bases

– proportion of free base (R-NH2) and salt (R-NH3+) forms depends on pH and pK of amino group

pH = pK + log [base]/[salt]

(Henderson-Hasselbalch equation)

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

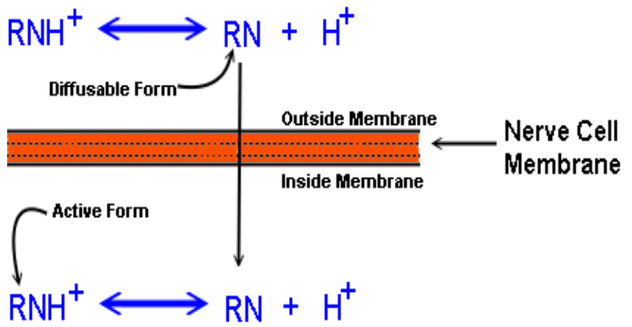
7.5 = 8.5 + log [base]/[salt]

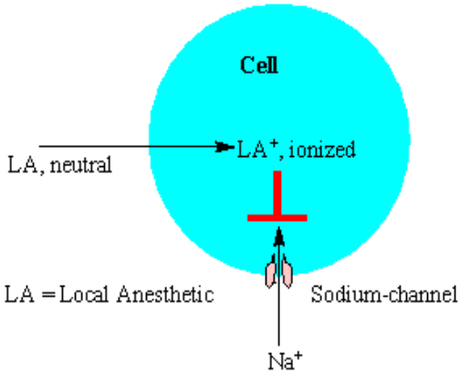
log [base]/[salt] = -1

[base]/[salt] = 10-1 = 1/10

Factors Reducing Anesthetic Efficacy:

local anesthetic **enters** nerve fibre as **neutral free base** and the **cationic form blocks conduction** by interacting at inner surface of the Na+ channel





inflammation → **reduced** susceptibility to anesthesia (lowered local pH increases proportion of anesthetic in charged form that cannot permeate nerve membrane). Same applies for hypoxic conditions (lower PH).

- Recall, that for the anesthetic to **enter** the neuron, it must first be **non-ionized** (uncharged) to cross the cell membrane. Ionization is required ***inside*** the neuron to block the sodium channel. In both of these conditions the lowered pH occurs ***outside*** the neurons. Consequently, less anesthetic is able to enter the neuron and efficacy is reduced.
- We usually wait for the inflammation to be resolved. If we can't wait, to overcome this issue, we give the anesthetic with **bicarbonate** in same syringe to neutralize the acidity of the environment and promote anesthetic function.

Conclusion

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

- Local anesthetics, originate from cocaine which is local anesthetic as well, but it enters the brain and stimulates the CNS by increasing dopamine. It highly increases the sympathetic outflow and causes many adverse effects.
- Alpha 1 receptors agonist cause vasoconstriction. We give with anesthetics a vasoconstrictor to prevent the systemic effects of local anesthetics on body.

See next slide for more details...

Functional consequences of Na+ channel blockade by local anesthetics:

- Recall the role of Na+ channels in initiating the action potential and maintaining cellular excitability.

- **Nerves:** decrease or abolition of conduction, this is the **primary therapeutic objective** of local anesthesia.

- **vascular smooth muscle:** vasodilatation. While smooth muscle contraction primarily depends on Ca^{2+}, sodium channels contribute to overall excitability and tone, also due to the CNS depressing activity of local anesthetics, on the long term it reduces sympathetic activity.

- **heart:** decreased excitability (reduced pacemaker activity, prolongation of effective refractory period) This is due to a **reduction in the slope of phase 0 depolarization**. Example: Lidocaine acts as an antiarrhythmic by reducing abnormal Na^+ influx in ischemic myocardial cells (e.g., post–myocardial infarction).

- **central nervous system:** increased excitability, followed by generalized depression.This occurs because inhibitory neurons are affected first, leading to transient excitation, followed by overall CNS suppression with continued drug exposure.

Role of Vasoconstrictors in local anesthesia

- When local anesthetics (e.g., lidocaine, Articaine) are administered **without** a vasoconstrictor, they are rapidly absorbed into the systemic circulation.

This leads to:

- Increased risk of systemic adverse drug reactions (ARDs).
- Rapid distribution to highly vascularized or lipid-rich tissues (brain/heart).
- Short duration of action, reduced time for adequate nerve penetration.

Addition of a vasoconstrictor:

- Prolongs the duration of action (Vasoconstriction slows drug absorption, allowing more time for nerve penetration and significantly extending the anesthetic effect).
- Reduces systemic absorption.
- Limits distribution to highly perfused organs such as the brain and heart.

Vasoconstrictors (Cont.)

- Common α_1-agonists: Phenylephrine, Ephedrine, Epinephrine (strongest), and Norepinephrine.
- **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).
- Dosage Guidelines: Typically used in dilutions of **1:50,000**, **1:100,000**, or **1:200,000**.
- Caution: High concentrations of epinephrine can be toxic (must be used very carefully) ; it is primarily indicated for local infiltration.

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 (the injection of anesthetic directly into the tissue across the area to be anesthetized, targeting terminal nerve endings) **can produce with 0.25–0.5% aqueous solution of lidocaine or procaine (usually with co-administration of adrenaline).**

- Lower concentrations of adrenaline (e.g., 1:200,000–1:250,000) are used when prolonged action is not required(e.g., dental and minor procedures).
- Higher concentrations (e.g., 1:100,000 or stronger) increase the intensity and duration of action.

Clinical applications (cont.)

- **Dental procedures**, if a patient is given a local anesthetic containing epinephrine (e.g., 1:50,000) and still experiences pain, **the second injection should consist of lidocaine alone** (without epinephrine).
- Accidental administration of epinephrine in such cases may lead to tissue **hypoxia** and **necrosis**.

"Cartridges" are color Coding of Anesthetic Preparations.
Combined anesthetic solutions are color-coded according to their epinephrine concentration (e.g., 1:50,000, 1:100,000). This system facilitates selection of the appropriate preparation; for example, red indicates a higher concentration of epinephrine.

Use of Anesthesia in Digits in cases such as **fungal infection** under the nail, local anesthesia may be required.

- Vasoconstrictors **must be avoided** because the blood supply in digits consists of end arteries with limited collateral circulation.
- Administration of epinephrine in these areas may result in ischemia and gangrene. Instead, a safer technique known as "**ring anesthesia**" is used.

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%).**

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.

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 anesthesia (injection of the Local anesthesia to the spinal column but outside the dura mater), used in obstetrics.

Spinal & Epidural

Spinal Anesthesia (Subarachnoid Block)

The local anesthetic is injected directly into the subarachnoid space (containing cerebrospinal fluid), passing **through** the dura mater.

- **Bupivacaine:** Preferred for procedures requiring a **long duration** of action (approximately 4–8 hours).
- **Prilocaine**: An alternative for **shorter durations**; however, it is generally avoided during pregnancy due to potential **fetal toxicity** (risk of methemoglobinemia).

Epidural Anesthesia

The anesthetic is deposited into the **epidural space**, which is located **outside** the dura mater.

- **Bupivacaine**: Frequently utilized in epidural blocks due to its potent sensory blockade and prolonged duration.
- **Prilocaine**: Not typically indicated for epidural use in obstetric patients due to safety concerns and the risk of placental transfer.

➢ They are often the technique of choice for labor analgesia and major lower-body surgical procedures.

Conclusion

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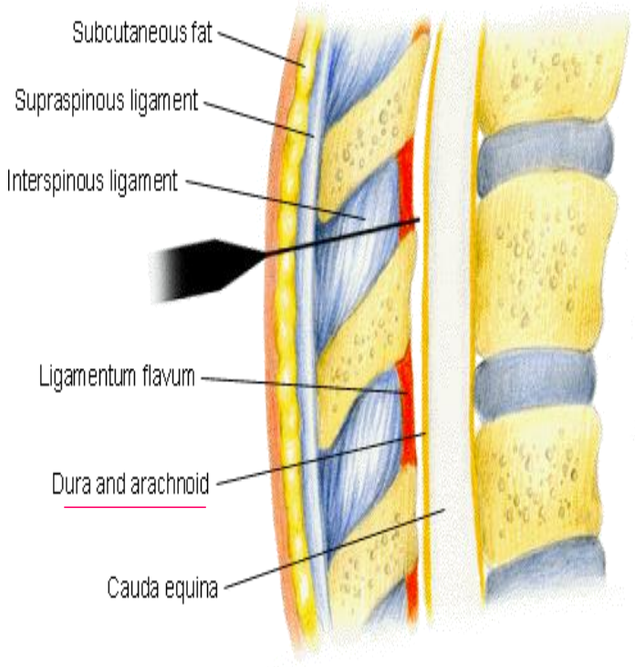
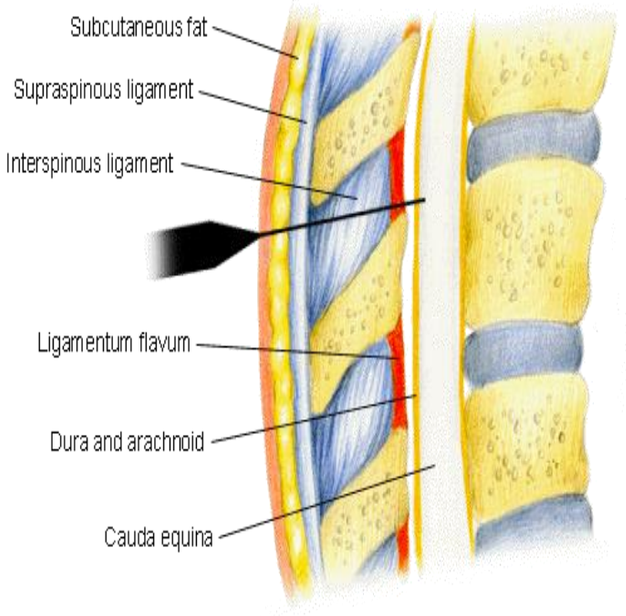
Epidural



Spinal



- When performing spinal or epidural anesthesia, the doctor aspirates to confirm correct needle placement. In spinal anesthesia, cerebrospinal fluid (CSF) is encountered as confirmation of correct placement. In epidural anesthesia, CSF should not be present. Removing a small amount of CSF also helps avoid a sudden increase in intracranial pressure that could occur with fluid injection. The most common complication is **post-dural puncture headache**, caused by CSF leakage and decreased intracranial pressure, typically lasting for up to two weeks. If the doctor removes too much CSF, this can worsen the decrease in intracranial pressure, disrupting CSF equilibrium. The key concern is avoiding dural puncture and maintaining CSF integrity. Hitting a nerve is possible but occurs very rarely.

- Length of time from induction until the reversal process is complete.

- **Short-acting:**
  - Local anesthetic agent lasts less than 30 minutes.

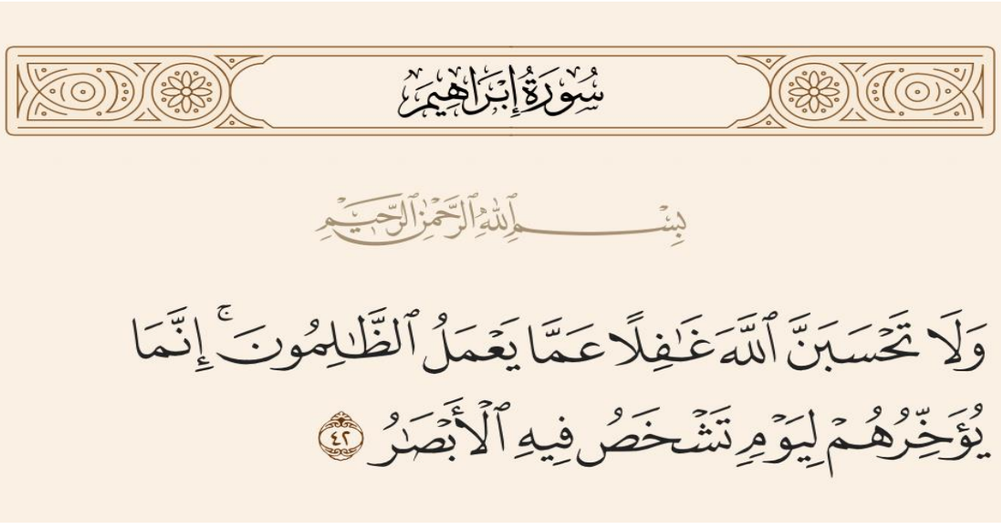
- **Intermediate-acting:**
  - Local anesthetic agent lasts about 60 minutes.

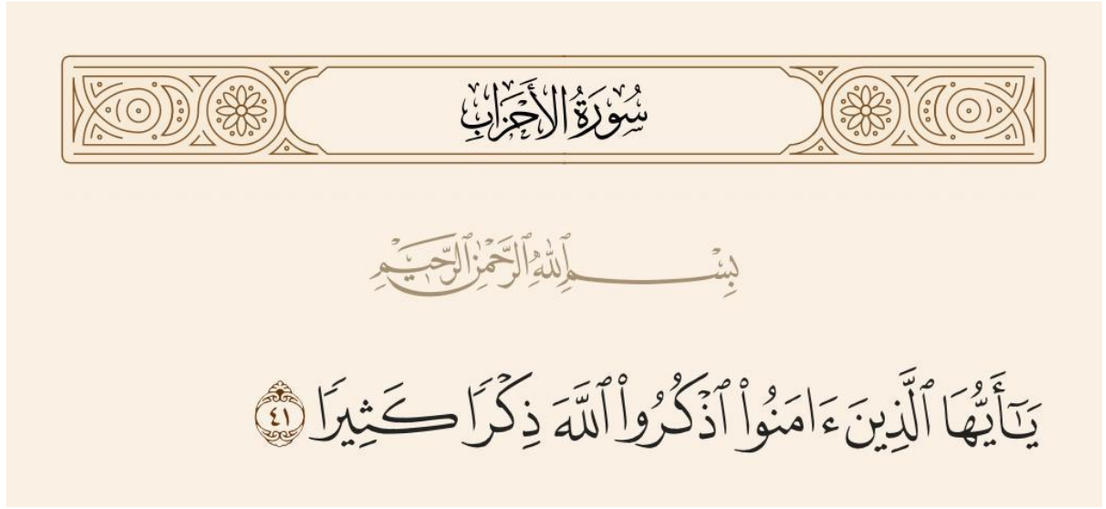
- **Long-acting:**
  - Local anesthetic agent lasts longer than 90 minutes.

PHARMACOLOGY QUIZ LECTURE 6

External Resources

رسالة من الفريق العلمي





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أن تحفظ أسرانا ومسرانا من أذى الصهاينة اللهم رد
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كل شيء قدير

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقِه من فتنة القبر وعذاب النار، أنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم.

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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			