Second Semester (2020-2021)

Pharmaceutical Chemistry I

Topic 3

The Local Anesthetics

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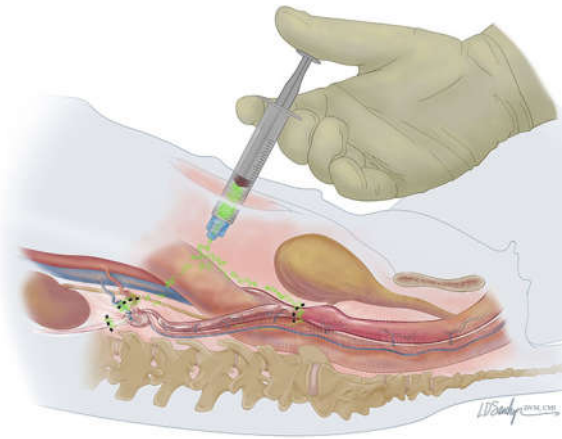
Pharmaceutical Chemistry and Drug Control



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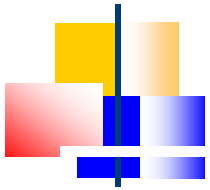


The Local Anesthetics (LA)

- Drugs inhibit the conduction of action potentials in all afferent and efferent nerve fibers.

- الأدوية التي تثبط توصيل كمونات العمل في جميع الألياف العصبية الواردة والصادرة.

- Thus, pain and other sensations are not transmitted effectively to the brain, and motor impulses are not transmitted effectively to muscles.

- وبالتالي، لا ينتقل الألم والأحاسيس الأخرى بشكل فعال إلى الدماغ، ولا تنتقل النبضات الحركية بشكل فعال إلى العضلات.

- Local anesthetics have various clinical uses:

  - to treat acute or chronic pain
  - to prevent the sensation of pain during procedures.

Mechanism of Action of LA

The mechanism of action of the local anesthetics is believed to be via their sodium channel blocking effects.

- When the local anesthetic binds:

It blocks sodium ion passage into the cell → *blocks the formation and propagation of the action potential* → *blocks the transmittance of the message of "pain" or even "touch" from getting to the brain*

- The ability of a local anesthetic to block action potentials depends on:
  - the ability of the drug to penetrate the tissue surrounding the targeted nerve
  - the ability of the drug to access the binding site on the sodium channel

Mechanism of Action of LA

- Local anesthetics **do not access** the binding site by entering into the sodium channel from the exterior of the neuron. The molecules are too big to pass by the selectivity filter.
- The local anesthetic molecule is believed to bind to the binding site (at α subunit) in its ionized form.

3 proposed pathways for access of local anesthetics to the binding site:

Hydrophobic pathway (A)

- The anesthetics pass through the membrane in their uncharged form
- In the axoplasm (سيتوبلاسما محور العصبون), they re-equilibrate with their cationic species

Mechanism of Action of LA

Hydrophobic pathway (B)

Before passing all the way through the lipid membrane, the anesthetic may be able to directly access the local anesthetic binding site

Hydrophilic pathway (C)

- The anesthetic molecule may access the binding site via a hydrophilic pathway by entering into the sodium channel from the interior of the pore, when the channel is open.

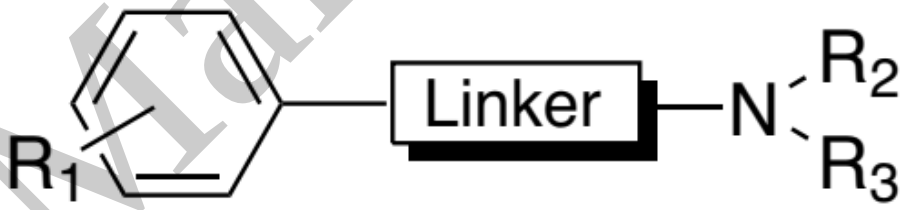
SARs of Local Anesthetics

The structure of most local anesthetic agents consists of three parts:

(a) **Lipophilic ring** that may be substituted

(b) **Linker** of various lengths that usually contains either an ester or an amide

(c) **Amine group** that is usually a tertiary amine with a pKa between 7.5 and 9.0



1 The Aromatic Ring

1. Adds lipophilicity to the anesthetic and helps the molecule penetrate through biological membranes.
2. It is also thought to have direct contact with the local anesthetic binding site on the sodium channel: (π–π interaction or a π -cation interaction).

- *Substituents on the aromatic ring may increase the lipophilic nature of the aromatic ring*

2 The Linker

- The linker is usually an ester or an amide group along with a hydrophobic chain of various lengths (2 carbons mostly)
- ↑ the number of carbon atoms in the linker ⟶ ↑ lipid solubility, ↑ protein binding, ↑ duration of action, and ↑ toxicity
- Esters and amides are bioisosteres having similar sizes, shapes, and electronic structures.

3 The Nitrogen

- Most local anesthetics contain a **tertiary nitrogen** with a pKa between 7.5 and 9.5
- Represents the hydrophilic part where amine group binds to receptor in charged Quaternary form
- Therefore, at physiological pH, both the cationic and neutral form of the molecule exists.
- At physiological pH, the ionized to unionized form of the anesthetic can be calculated using the *Henderson-Hasselbalch equation*

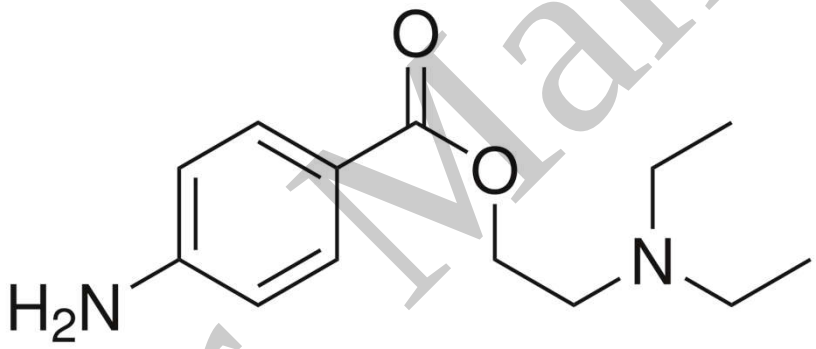
$$pH = pK_a + \log ([B]/[BH^+])$$

The Ester Local Anesthetics

1- Cocaine

- One of the most prominent surgeons at Johns Hopkins University, Dr. William Halsted, read about this account and began investigations with cocaine for general surgery.
- They successfully used cocaine during surgery, but unfortunately Dr. Halsted and several colleagues became addicted.
- Today, cocaine is used for topical anesthesia of mucous membranes using a 4% to 10% solution. If the solution remains on the membrane for 5 minutes, anesthesia and vasoconstriction of the area will occur.

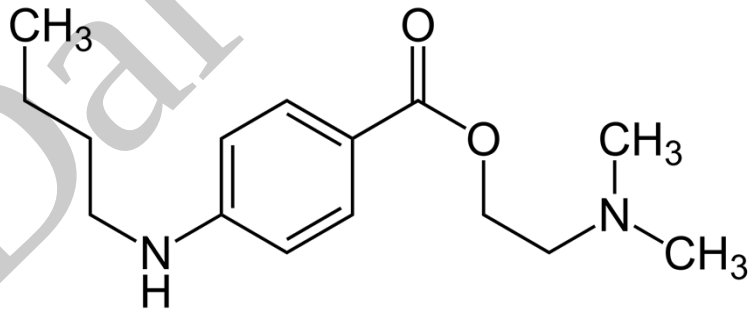
2- Procaine (Novocain)



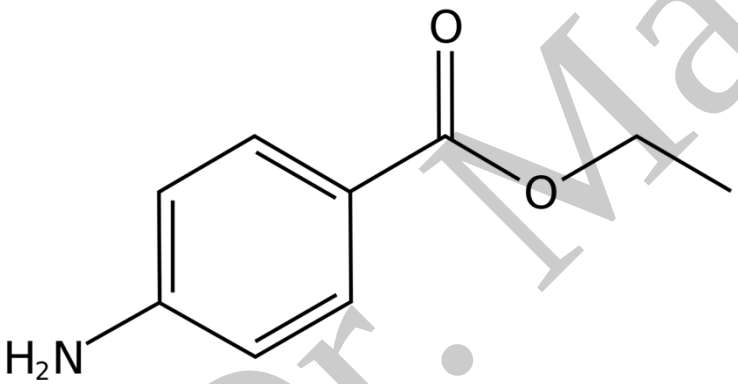
The Ester Local Anesthetics

4- Tetracaine

- The addition of the butyl side chain on the para nitrogen increases the lipid solubility of the drug and enhances the topical potency of tetracaine.



5- Benzocaine



The Amino Amide Local Anesthetics

1- Lidocaine

- When lidocaine is formulated premixed with epinephrine the pH of the solution is adjusted to between 2.0 and 2.5 to prevent the hydrolysis of the epinephrine.

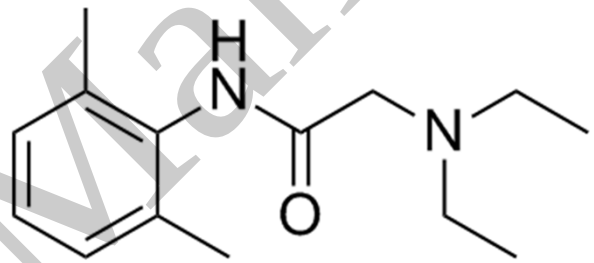


Table 2–1. Properties of Local Anesthetics

Anesthetic	Lipid Solubility	Protein Binding (%)	pKa (Unionized Fraction pH 7.4)	Molecular Weight	Potency	Speed of Onset	Duration of Action	UV/MV ratio
Chloroprocaine	0.14	~0	8.7 (5%)	271	Low	Very rapid	Short	~0
Procaine	0.02	6	8.9 (3%)	236	Low	Rapid	Short	N/A
Lidocaine	2.9	64	7.7 (35%)	234	Medium	Rapid	Medium	0.5–0.7
Mepivacaine	0.8	78	7.6 (39%)	246	Medium	Medium	Medium	0.7–0.8
Bupivacaine	8.2	96	8.1 (15%)	288	High	Slow	Long	0.2–0.4
Ropivacaine	8.0	92–94	8.1 (15%)	274	High	Slow	Long	0.2

Lipid solubility: Heptanol or octanol/buffer partition ratio; UV/MV ratio=ratio of concentration in umbilical vein to maternal vein; total concentration, not free drug concentration, is shown in the table (see text for details); N/A = not available.