Local Anesthetic (LA) — Classification and Chemistry

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Local anesthesia is required for many surgical procedures, be it minor or major. Local anesthetics act by blocking the neuronal impulses in the area they have been administered at, and this is achieved primarily by blocking voltage-gated sodium channels. Local anesthetic drugs have a variable onset and duration of action, ranging from a few minutes to a few hours. While they are generally safe, they may cause an allergy, cardiotoxicity or neurotoxicity. In this article, we will study the pharmacodynamics, pharmacokinetics, mechanism of action, important indications and toxicity of local anesthesia.

Chemistry of Local Anesthetics

Local anesthetics exist in **ionized (cation)** and **unionized forms**. Ionization of the drug affects its transportation across the **lipid plasma membrane**. The ionized form (water-soluble but lipid insoluble) of a local anesthetic is important as it is the most active at the receptor site (lipidic plasma membrane/axon). However, this form has poor penetration in the neuronal membrane (where lies the receptor site for local anesthetics).

Always remember: pKa of the drug is the pH at which the ionized and unionized forms of the drug are present in equal amounts. The ionized form of the drug is water-soluble and the non-ionized form of the drug is lipid-soluble.

Image : “Chemical structure of local anesthetics” by Murphy567. License: CC BY-SA 3.0

The **pH** and **pKa** are important in determining the ionization of the drug. In regional anesthesia, for example, when the drugs are injected into the infected tissues, the local pH is low, which leads to a more ionized form. Thus, there is reduced diffusion into the membrane and slow clinical effect. This can be facilitated by adding **bicarbonate** to the local anesthetic, thereby leading to a faster onset of action.

However, it is important to note that the action of local anesthetics is dependent on both the ionized and non-ionized forms of the drug. The ionized form of the drug is water-soluble and the non-ionized form of the drug is lipid-soluble (soluble in the plasma membrane of a cell/axon).

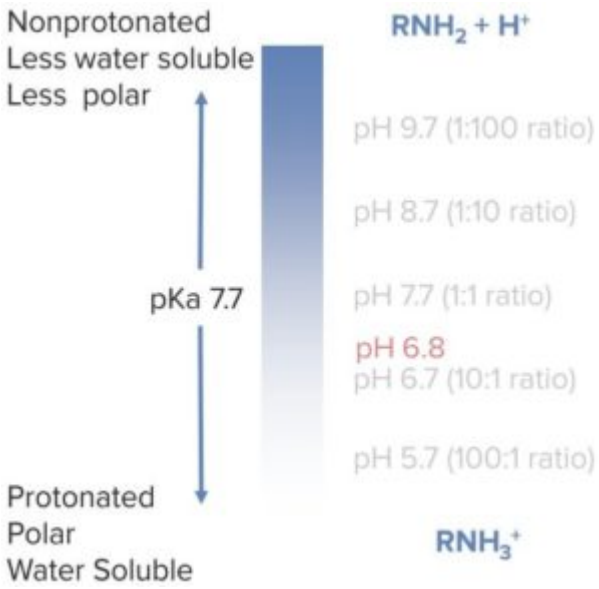
Before reaching (the non-ionized form of drug), the plasma membrane of axon (site of action), a drug (ionized form of drug) must pass through the aqueous extracellular phase.

Classification of Local Anesthetics

Structurally, local anesthetics have a lipophilic aromatic ring, which is connected to a hydrophilic group by an intermediate chain, which can be an amide or an ester.

Amides

Lidocaine (or lignocaine), prilocaine, mepivacaine, etidocaine, bupivacaine, ropivacaine and levobupivacaine.



“Local Anesthetics” Image created by Lecturio

Example: Lidocaine pKa 7.7

- Inflamed tissue may have a pH as low as 6.8 (normal tissue 7.4)
- Lidocaine is sometimes given with bicarbonate to alkalinize the area and make the drug more lipid-soluble.
- Once inside the neuron, the pH is 6.9, so it becomes more polar and water-soluble.

Esters

Cocaine, procaine, chloroprocaine, tetracaine (amethocaine) and benzocaine

Mnemonics to remember esters :

Professional **chlo**rine, **benz**ene, and **cocaine** are **tetra** packed. It is also easy to remember that amides have names with more than one letter ‘i’ while esters have one.

Mode of Action of Local Anesthetics

Local anesthetics act primarily by inhibiting the **voltage-gated sodium channels** (they also inhibit potassium channels) on the neuronal membrane and thus block peripheral nerve conduction. They bind more to the open or inactive sodium channels than those in their resting phase.

- The effect is **concentration-dependent**: first, the impulses are slowed down and then, completely stopped.
- The binding is **reversible**.
- The higher the affinity of binding (or the lower the dissociation), the higher the potency.
- **Potassium channel blockage** further enhances the binding of the drug and, thereby, the anesthetic blockade itself.
- For **myelinated axons**, the smaller the diameter of the fiber, the greater the blockage. Thus, Aγ and Aδ fibers and type B preganglionic fibers are the most susceptible.
- The **non-myelinated C fibers** are less easily blocked. For the non-myelinated fibers, the smaller the fiber, the less susceptible it is.
- Other mechanisms by which local anesthetics may act involve **G-protein receptors**, **endothelial nitric oxide,** and **muscarinic receptors**.

Pharmacokinetics of Local Anesthetics

Absorption

Usually, local anesthetics are absorbed rapidly into the blood from the site of injection.

The duration of the action is limited but can be prolonged if the blood flood is reduced (e.g. by concomitant use of a **vasoconstrictor** such as epinephrine).

Functions of Vasoconstrictor:

Reduces systemic absorption, thus reduces the **systemic toxicity.**

Is more effective for shorter-acting drugs (e.g., lidocaine) than longer-acting drugs (e.g. bupivacaine and tetracaine).

Amides show a **biphasic absorption pattern** (initial rapid followed by a slow phase).

Distribution: a lot of factors are to be considered when analyzing the local and systemic distribution: tissue blood flow (and factors affecting that), patient position, etc.

Metabolism:

Esters are metabolized by **plasma cholinesterase (pseudocholinesterase)**. This leads

to the production of the metabolite **para-aminobenzoic acid (PABA)**, which leads to allergic or anaphylactic reactions. Metabolism is reduced in patients with pseudocholinesterase deficiency/atypical pseudocholinesterase.

Amides are mainly metabolized by the liver, and are reduced in the presence of potent CYP450 inhibitors, such as ketoconazole. Since PABA is not produced, allergic reactions are rare.

Plasma half-life: the half-life is short for esters (1–8 min) because metabolism by plasma cholinesterase is faster, whereas it is longer for amides (lidocaine and prilocaine < 2 h; others 3–4 h) because liver enzymes are relatively slower to act.

Clearance: excretion of the uncharged drug is limited because of poor water solubility.

Placental transfer: esters do not cross the placenta in significant amounts as they are subjected to rapid **hydrolysis**. For amides, the rate of transfer is dependent on protein binding: the higher the binding (e.g., bupivacaine), the lower the transfer.

Pharmacological Properties of Some Local Anesthetics

Drug	Onset	Duration
Bupivacaine	Slow	Long
Chloroprocaine	Fast	Short
Etidocaine	Rapid	Long
Lidocaine	Fast	Intermediate
Mepivacaine	Moderate	Intermediate
Prilocaine	Fast	Short
Procaine	Fast	Short
Ropivacaine	Moderate	Long
Tetracaine	Slow	Long

Toxicity of Local Anesthetics

The symptoms and signs of toxicity of local anesthetics, including the timing of onset, are somewhat unpredictable. A high level of suspicion is advised, especially in patients who have alterations in mental or cardiovascular status following the injection of a local anesthetic.

Central nervous system effects: can be of excitation or depression, and can be initially subtle and nonspecific – for example, light-headedness, sedation, restlessness, and nystagmus.

Transient neurologic symptoms: severe pain and/or dysesthesia following administration of local anesthetics (mainly lidocaine) for spinal or epidural blocks.

Cardiovascular effects: most local anesthetics (except cocaine) are vasodilators. (Mepivacaine has low to no vasodilator activity.) They may exacerbate existing heart conditions and lead to heart block or other electrical conducting system dysfunctions of the heart.

Cardiac toxicity is somewhat enhanced in the presence of **hyperkalemia** as there is increased depolarization, which means that more channels are in the inactive state.

Management of **serious systemic toxicity** includes the following:

- Airway, breathing, circulation support
- Control of seizures (tonic-clonic convulsions), if any
- Administration of 20 % lipid emulsion (lipid rescue therapy)

- Cardiopulmonary resuscitation, if needed

Dosage in the elderly (of the drug, as well as of the concomitant epinephrine) should be somewhat reduced as they usually have a slightly compromised liver function.

Individual Local Anesthetics

Drug	Properties	Use	Toxicity
Bupivacaine	The duration of effect is 6—18 hours. Causes more sensory than a motor block. One of the longest acting local anesthetics (half-life, 3.5 h).	Not recommended for regional anesthesia procedures that require a high volume. Agent of choice for postoperative/labor epidural analgesia (liposome injectable suspension can provide postoperativeanalgesia lasting ≥ 24 h).	Considerable risk of cardiotoxicity; accidental IV injection can cause pronounced cardiotoxicity.
Chloroprocaine	Its effect lasts 45 min. Minimal transplacental passage.	Initial drug for extradural labor block (followed by bupivacaine or ropivacaine).	Paraplegia after intradural use (probably due to sodium metabisulphite in the solution) à not recommended intradurally.
Cocaine	It has significant surface local anesthetic activity. It is the only local anesthetic with intrinsic vasoconstrictor activity; this helps reduce intraoperative bleeding.	Preferred in head, neck and pharyngeal surgery	
Etidocaine	More motor blockade.	Motor block makes it unsuitable for use during labor.	Less toxic than bupivacaine and more toxic than lidocaine.
Levobupivacaine	S(–) enantiomer of bupivacaine.		Slightly lower cardiotoxicity than the racemic mixture.
Mepivacaine	Not metabolized by neonates. Anti-arrhythmic properties.	Not recommended in obstetric anesthesia.	Rapid placental transfer.
Prilocaine		Most useful for high-dose blocks (pudendal and head–neck–face blocks).	Can cause methemoglobinemia when doses > 600 mg (because of the metabolite ortho-toluidine).
Procaine	It is metabolized very rapidly by pseudocholinesterase (half-life, 1—2 min).	Agent of choice when there is a history of malignant hyperpyrexia. Used in patients with an allergy to amides.	Relatively nontoxic.
Ropivacaine	One of the longest acting local anesthetics (half-life, 4.2 h). Causes more sensory than a motor block.	High-dose peripheral blocks. Postoperative/labor epidural analgesia.	Less toxic than bupivacaine.
Tetracaine	Has some surface activity.*	Intradural blocks.	Can cause cardiac asystole or ventricular fibrillation.
Lidocaine	Has some surface activity. Metabolized by the liver; plasma clearance is dependent on hepatic blood flow The onset of action: 2—5 min. Duration: 30 min to 2 hours without epinephrine and up to 3 hours with epinephrine.	**Routes of administration:** intravenous or intramuscular; it is never given orally because of high first-pass effect and also because the metabolites are more cardiotoxic **Use:** Local anesthetic Type 1B antiarrhythmic—useful in acute ischemic ventricular arrhythmias (by reducing abnormal automaticity) Useful in digoxin-induced arrhythmias Topical 5 % patch form is useful in postherpetic neuralgia.	Cardiovascular and neurotoxic effects (usually CNS stimulation, including seizures) Cardiotoxicity can be enhanced in the presence of hyperkalemia Rashes, but overt allergy is rare High incidence of transient neurologic symptoms **Important/other remarks:** Cimetidine reduces lidocaine clearance, and can thus increase its toxicity.

Notes:

**ability to act on the superficial nerves when applied to the mucous membrane.*

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