

# LOCAL ANESTHETICS (LA)

LA **reversibly** block impulse conduction along nerve axons nerve and other excitable membranes that utilize  $\text{Na}^+$  channels as the primary means of action potential generation.

LA in contact with a nerve trunk can cause **both** sensory and motor paralysis in the area innervated

# **Ideal Local Anesthetics**

reduction of local irritation and tissue damage

minimization of systemic toxicity

faster onset of action

◆ longer duration of action

## Chemistry-

All LA consist of four basic componets:

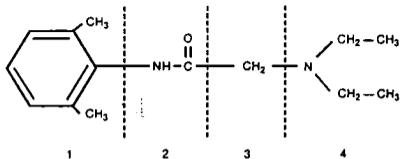
- an aromatic lipophilic ring

- the ester or amide linkage

- an intermediate hydrocarbon chain

- a hydrophilic tertiary amine terminus

The linking arrangement divides all of the LA into either an ester (-COO-) or an amide (-NH-) compound. The distinction between these two compounds lies with their different metabolic pathways and their propensity towards hypersensitivity reactions.



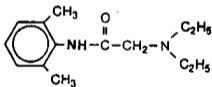
Section 1—Aromatic Ring

Section 3—Hydrocarbon Chain

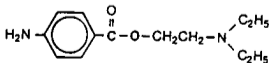
Section 2—Ester or Amide Linkage

Section 4—Tertiary Amine Group

**FIGURE 12-1.** Component structures of local anesthetics that form four distinct chemical subunits.



Lidocaine


























Procaine

**FIGURE 12-2.** Differences in structure between amide and ester local anesthetics lie in section 2, as shown in bold face type.

TABLE 17-1

## Structural formulas of some commonly used local anesthetics

Aromatic residue	Intermediate chain	Amino terminus	Aromatic residue	Intermediate chain	Amino terminus
<b>ESTERS</b>			<b>AMIDES</b>		
	$\text{COOCH}_2\text{CH}_2$			$\text{NHCOCH}_2$	
Procaine			Lidocaine		
	$\text{COOCH}_2\text{CH}_2$			$\text{NHCOCH}$ $\text{C}_2\text{H}_5$	
Propylcaine			Etidocaine		
	$\text{COOCH}_2\text{CH}_2$			$\text{NHCOCH}$	
Tetracaine			Mepivacaine		
	$\text{COOCH}_2\text{CH}_2\text{CH}$ $\text{COOCH}_3$			$\text{NHCOCH}$	
Cocaine			Bupivacaine		
	$\text{COOCH}_2\text{CH}_3$			$\text{NHCOCH}$ $\text{CH}_3$	
Benzocaine			Prilocaine		
	$\text{COCH}_2\text{CH}_2$			$\text{NHCOCH}$ $\text{CH}_3$	
Dyclonine*			Articaine		

\*Dyclonine is a lactone.

# MECHANISM OF ACTION

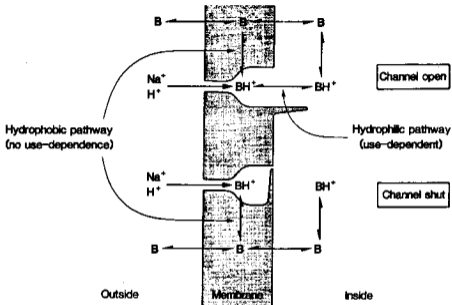
LA prevent the generation and the conduction of the nerve impulse.

The primary site of action is the cell membrane.

LA act by blocking primarily **open** and **inactive Na<sup>+</sup>** channels, preventing the influx of **Na<sup>+</sup>** during the depolarization phase of the action potential.

Both ester and amide LA reduce the discharge frequency of nerve conduction and decrease the total number of nerve fibers activated by a given stimulus.

This action prevents certain nerve fibers from firing, depending on their diameter size.



**Fig. 34.6 Interaction of local anesthetics with Na<sup>+</sup> channels.** The blocking site within the channel can be reached via the open channel gate on the inner surface of the membrane by the charged species, BH<sup>+</sup> (hydrophilic pathway), or directly from the membrane by the uncharged species, B (hydrophobic pathway).

Effects of Na Channel Block by Local Anesthetic

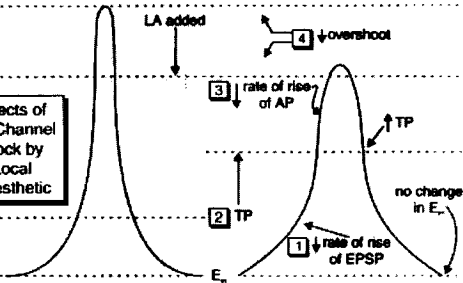


Figure 2.22

## Effect of Nerve Diameter

Fiber size affects the onset of nerve blockade. Pain and temperature sensation are carried by unmyelinated C fibers and poorly myelinated A-delta fibers.

### Order of blockade

$C < B < A\text{-delta} < A\text{-gamma} < A\text{-beta} < A\text{-alpha}$  fibers

When one installs LA near a nerve bundle, the different fibers are blocked as the concentration at the axon site increases. On unmyelinated C fibers, sodium channels reside along the entire axon, whereas in myelinated nerves, high concentrations of channels exist in the open gaps between myelin segments.

## Action of local anesthetics (LAs)

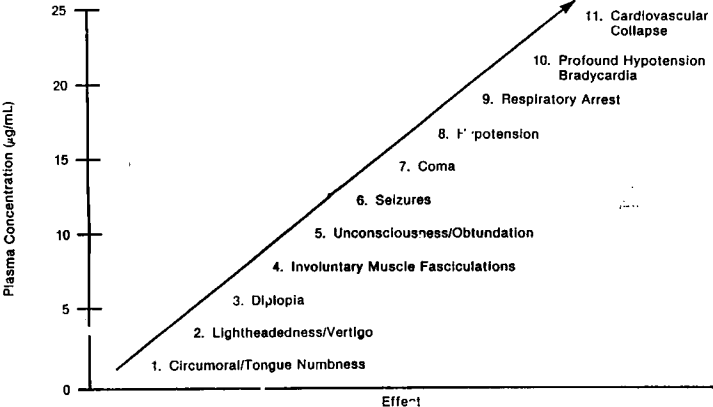
- LAs block action potential generation by blocking  $\text{Na}^+$  channels.
- LAs are amphiphilic molecules, with a hydrophobic aromatic group, and a basic amine group.
- LAs probably act in their cationic form, but must reach their site of action by penetrating the nerve sheath and axonal membrane as unionized species; they therefore have to be weak bases.
- Many LAs show use-dependence (depth of block increases with action potential frequency). This arises:
  - because anesthetic molecules gain access to the channel more readily when the channel is open
  - because anesthetic molecules have higher affinity for inactivated than for resting channels.
- Use-dependence is mainly of importance in relation to antiarrhythmic and anticonvulsant effects of LAs.
- LAs block conduction in the following order: small myelinated axons, non-myelinated axons, large myelinated axons. Nociceptive and sympathetic transmission is thus blocked first.

**Table 34.1 Pharmacokinetic properties of local anesthetics**

<b>Drug</b>	<b>Rate of onset</b>	<b>Duration</b>	<b>Tissue penetration</b>	<b>Plasma <math>t_{1/2}</math> (approx)</b>
<b>Procaine</b>	Moderate	Short	Slow	30 min
<b>Lidocaine</b>	Rapid	Moderate	Rapid	2 h
<b>Tetracaine</b>	Slow	Long	Moderate	1 h
<b>Dibucaine</b>	Moderate	Long	Moderate	3 h
<b>Bupivacaine</b>	Slow	Long	Moderate	3 h
<b>Prilocaine</b>	Moderate	Moderate	Moderate	2 h

## Unwanted effects and pharmacokinetics of LAs

- LAs are either esters or amides. Esters are rapidly hydrolyzed by plasma cholinesterase, and amides are metabolized in the liver. Plasma half-lives are generally short, about 1–2 hours.
- Unwanted effects are due mainly to escape of LAs into systemic circulation.
- Main unwanted effects are:
  - CNS effects, agitation, confusion, tremors progressing to convulsions and respiratory depression
  - cardiovascular effects, namely myocardial depression and vasodilatation, leading to fall in blood pressure
  - occasional hypersensitivity reactions.
- LAs vary in the rapidity with which they penetrate tissues, and in their duration of action. Lidocaine penetrates tissues readily, and is suitable for surface application; bupivacaine has a particularly long duration of action.



**FIGURE 12-6.** Relationship between rising plasma concentrations and toxic effects.

Table 34.2 Methods of administration, uses and adverse effects of local anesthetics (LAs)

Method	Uses	Drugs	Notes and adverse effects
<b>Surface anesthesia</b>	Nose, mouth, bronchial tree (usually in spray form), cornea, urinary tract Not effective for skin*	Lidocaine, tetracaine, dibucaine, cocaine	Risk of systemic toxicity when high concentrations and large areas are involved
<b>Infiltration anesthesia</b>	Direct injection into tissues to reach nerve branches and terminals Used in minor surgery	Most	Epinephrine often added as vasoconstrictor (not with fingers or toes, for fear of causing ischemic tissue damage) Only suitable for small areas; otherwise, serious risk of systemic toxicity
<b>Intravenous regional anesthesia</b>	LA injected intravenously distal to a pressure cuff to arrest blood flow; remains effective until the circulation is restored Used for limb surgery	Mainly lidocaine, prilocaine	Risk of systemic toxicity when cuff is released prematurely. Risk is small if cuff remains inflated for at least 20 minutes
<b>Nerve-block anesthesia</b>	LA is injected close to nerve trunks (e.g. brachial plexus, intercostal or dental nerves) to produce a loss of sensation peripherally Used for surgery, dentistry, analgesia	Most	Less LA needed than for infiltration anesthesia. Accurate placement of the needle is important Onset of anesthesia may be slow  Duration of anesthesia may be increased by addition of vasoconstrictor Highly specialized use
<b>Spinal anesthesia</b>	LA injected into the subarachnoid space (containing CSF) to act on spinal roots and spinal cord Used for surgery to abdomen, pelvis or leg, mainly when general anesthesia cannot be used	Mainly lidocaine, tetracaine	Main risks are bradycardia and hypotension (due to sympathetic block), respiratory depression (due to effects on phrenic nerve or respiratory center). Avoided by minimizing cranial spread Postoperative urinary retention (block of pelvic autonomic outflow) is common
<b>Epidural anesthesia<sup>†</sup></b>	LA injected into epidural space, blocking spinal roots Uses as for spinal anesthesia; also for painless childbirth	Mainly lidocaine, bupivacaine	Unwanted effects similar to those of spinal anesthesia, but less probable, because longitudinal spread of LA is reduced Postoperative urinary retention common

\* Surface anesthesia does not work well on the skin, though recently a non-crystalline mixture of lidocaine and prilocaine (eutectic mixture of local anesthetics or EMLA) has been developed for application to the skin, producing complete anesthesia in about 1 hour.

<sup>†</sup> Intrathecal or epidural administration of LA in combination with an opiate (see Ch. 31) produces more effective analgesia than can be achieved with the opiate alone. Only a small concentration of LA is needed, insufficient to produce appreciable loss of sensation or other side effects. The mechanism of this synergism is unknown, but the procedure is proving useful in pain treatment.