



Local Anesthetics (LAs)

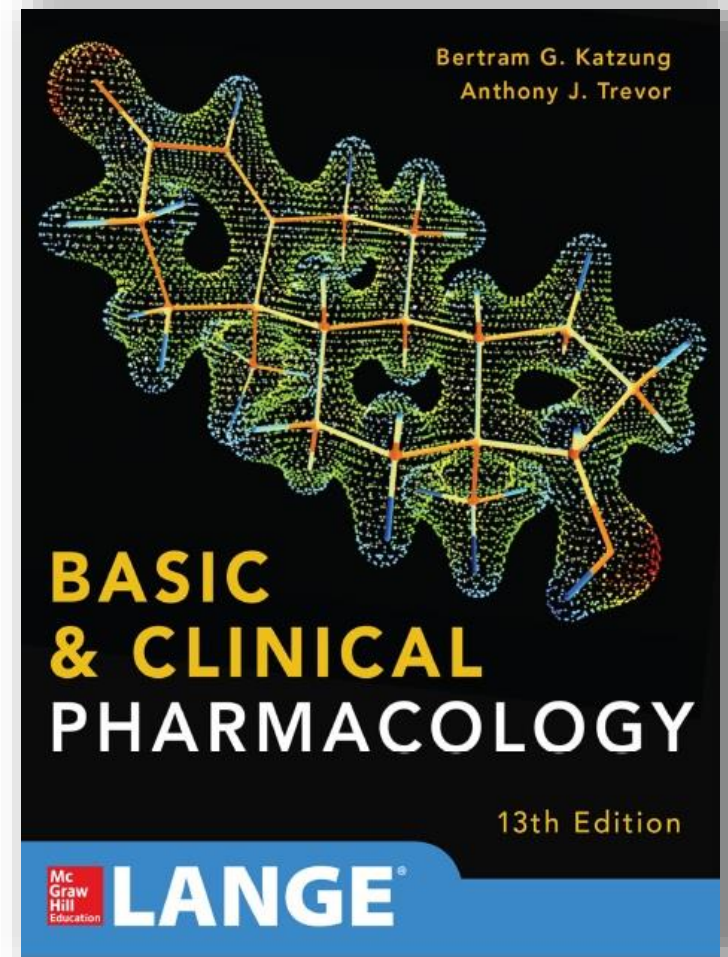
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Basic & Clinical Pharmacology

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Chapter 26



Outlines

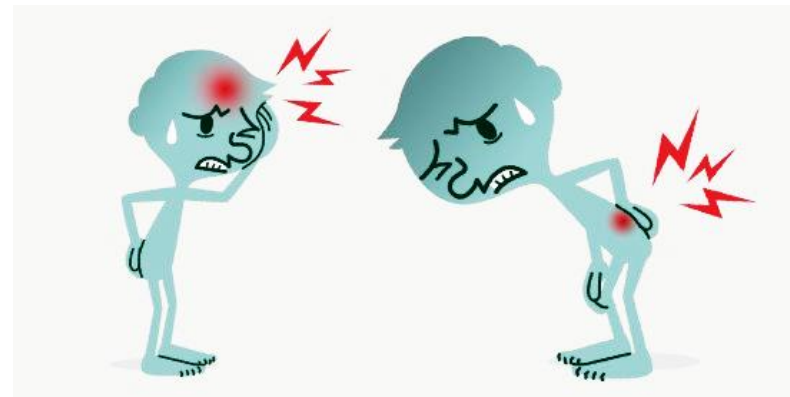
Local anesthetic drugs

- History
- Classification
- Pharmacokinetics
- Mechanism of pharmacological action
- Clinical indications
- Side effects



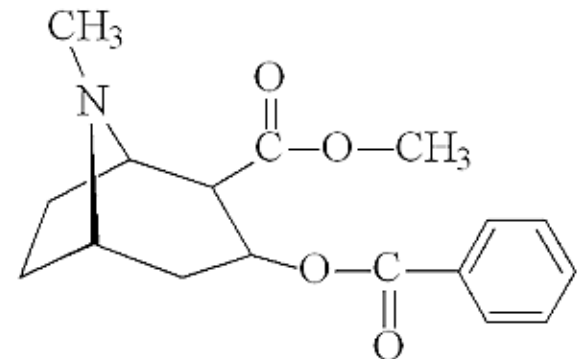
Local anesthesia

- Loss of sensation in a limited region of the body
- Disruption of afferent neural traffic via inhibition of impulse generation or propagation
 - Loss of pain sensation
 - Muscle paralysis
 - Block of autonomic nerves
 - Suppression of somatic or visceral reflexes
- Local anesthetics are often used as analgesics



Historical development of LA

- The numbing properties of cocaine were recognized for centuries
 - Used in ophthalmological process
- In 1884, cocaine used as first surgical LA
- Cocaine had significant CNS and cardiac toxicity
- Its structure has served as the template for the development of modern LAs



Chemical structure of LA

- Most local anesthetic agents consist of
 - A lipophilic portion (an aromatic ring)
 - An ionizable portion (a tertiary amine)
 - A connector chain (an ester or amide)

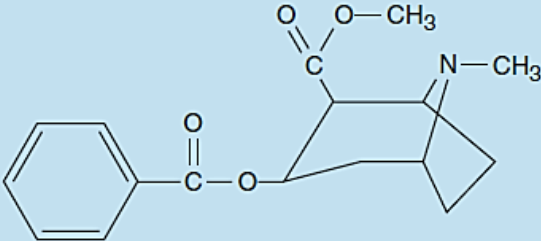
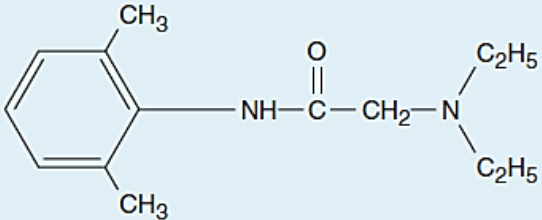
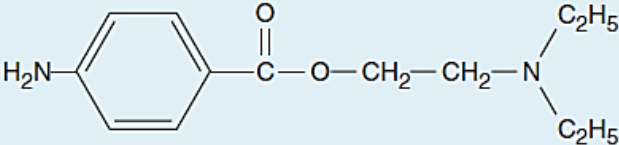
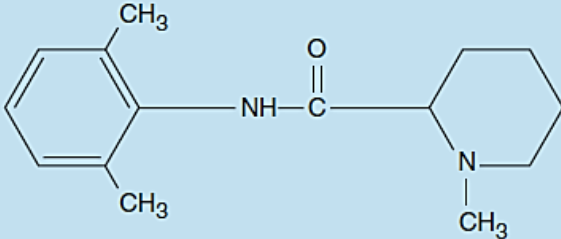
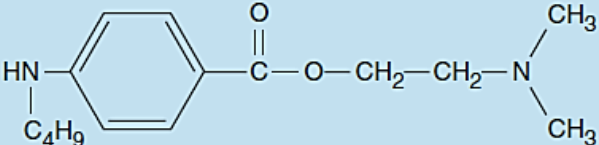
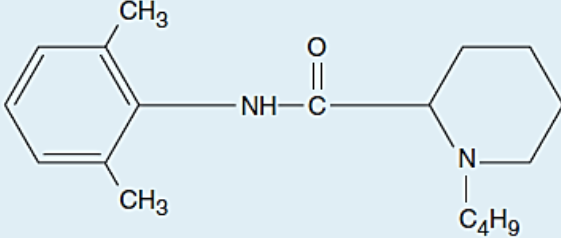
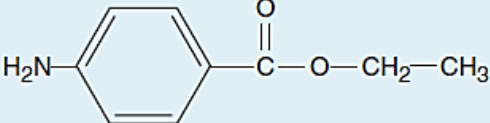
Ester-Based LA:

- ✓ Cocaine: 1860 (First LA)
- ✓ Benzocaine
- ✓ Procaine: 1905
- ✓ Chloroprocaine
- ✓ Tetracaine

Amide-Based LA:

- ✓ Lidocaine (Xylocaine): 1943
- ✓ Bupivacaine (Marcaine)
- ✓ Dibucaine (Cinchocaine)
- ✓ Levobupivacaine (Chirocaine)
- ✓ Mepivacaine
- ✓ Prilocaine
- ✓ Ropivacaine

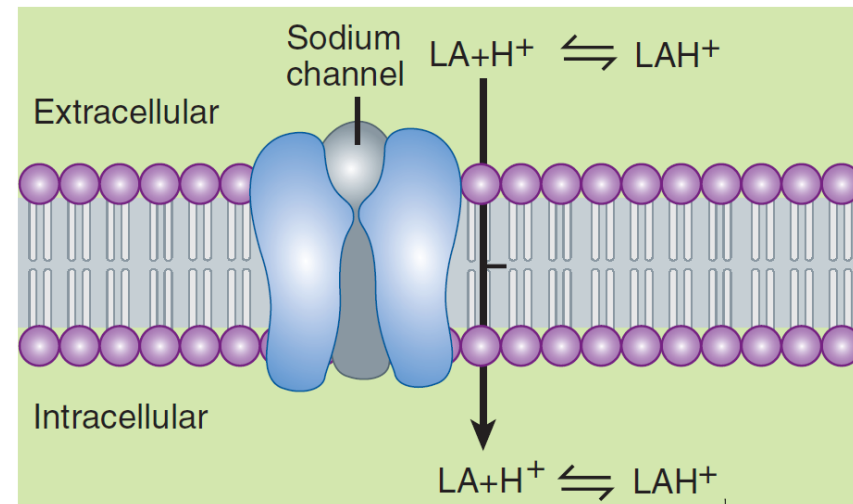
Chemical structure of LA

Structure	Structure
Esters Cocaine 	Amides Lidocaine (Xylocaine) 
Procaine (Novocain) 	Mepivacaine (Carbocaine, Isocaine) 
Tetracaine (Pontocaine) 	Bupivacaine (Marcaine), Levobupivacaine (Chirocaine) 
Benzocaine 	

Pharmacokinetics

Absorption

- Systemic absorption depends on
 - Dosage
 - Site of injection
 - Local tissue blood flow
 - Drug-tissue binding
 - Use of a vasoconstrictor
 - Physicochemical properties



Pharmacokinetics

Distribution

- Localized
 - Distribution at the site of the target organ
 - Distribution to CSF based on specific gravity and the patient's position
- Systemic
 - Distribution to the systemic circulation
 - Depends on concentration and speed of injection
 - The highly perfused organs (brain, liver, heart, kidney) face with high concentration

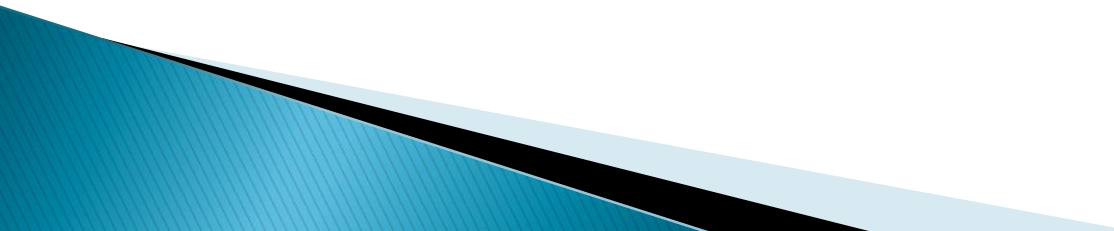
Pharmacokinetics

Metabolism and Excretion

- The local anesthetics are converted to water-soluble metabolites
 - Liver (amide type), P450 isozymes
 - Plasma (ester type), butyrylcholinesterase
- Ester types usually have a shorter duration of action
- Toxicity from amide types is more likely in patients with hepatic disease or low hepatic blood flow
- Inactive metabolite excretes in the urine
- Acidification of urine leads to more rapid elimination

Pharmacokinetics

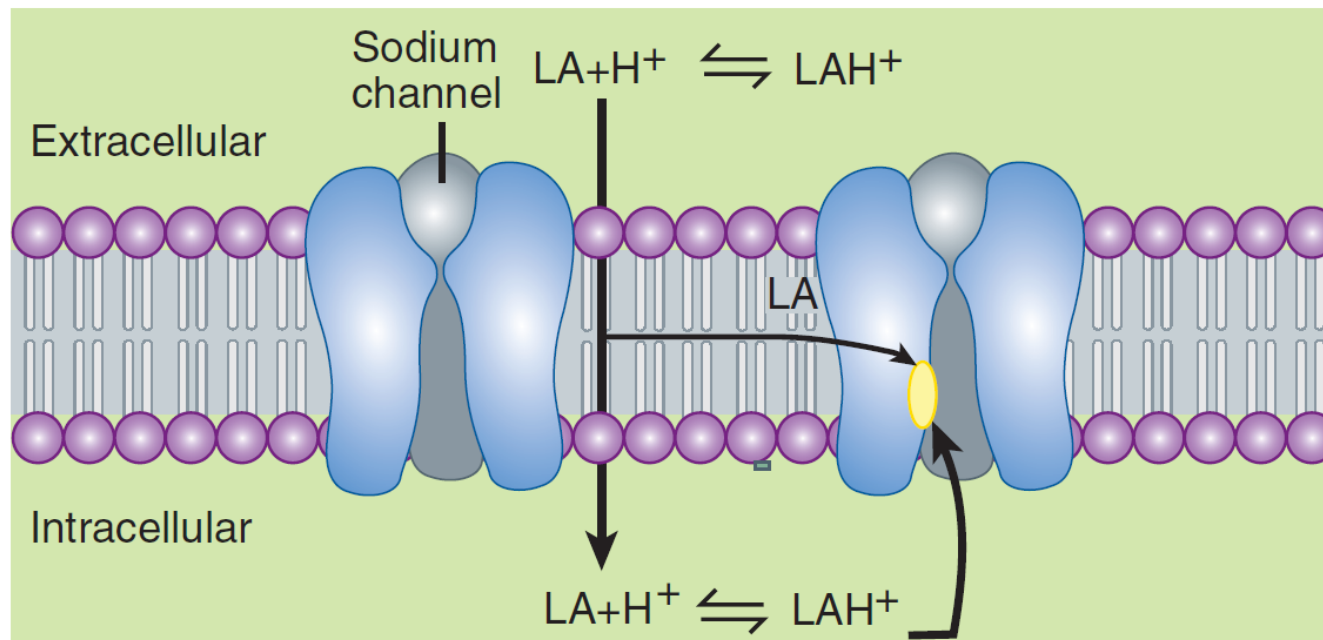
Duration of Action

- Short-Acting
 - Procaine, Chlorprocaine
 - Intermediate-Acting
 - Articaine, Lidocaine, Mepivacaine, Prilocaine
 - Long-Acting
 - Tetracaine, Bupivacaine
 - Levobupivacaine, Ropivacaine
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Pharmacodynamics

Mechanism of Action

- LAs block voltage-gated sodium channels
- LAs are weak bases, and their ionized form is active
- LAs are less effective in acidic tissues

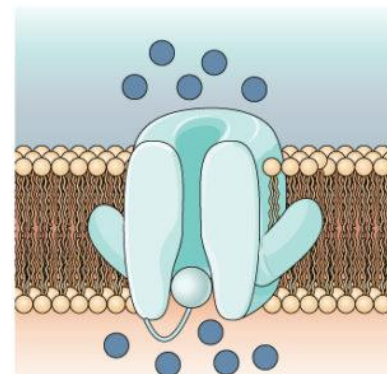
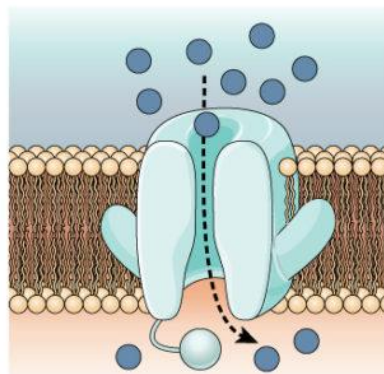
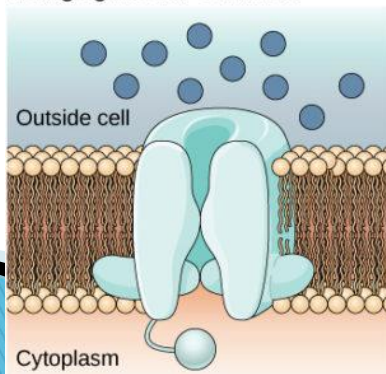


Pharmacodynamics

Mechanism of Action

- LAs block voltage-gated sodium channels
 - State dependent block
 - Voltage & time dependent block
 - Use dependent block
- The refractory period increases
- The nerve conducts fewer action potentials

Voltage-gated Na⁺ Channels



Pharmacodynamics

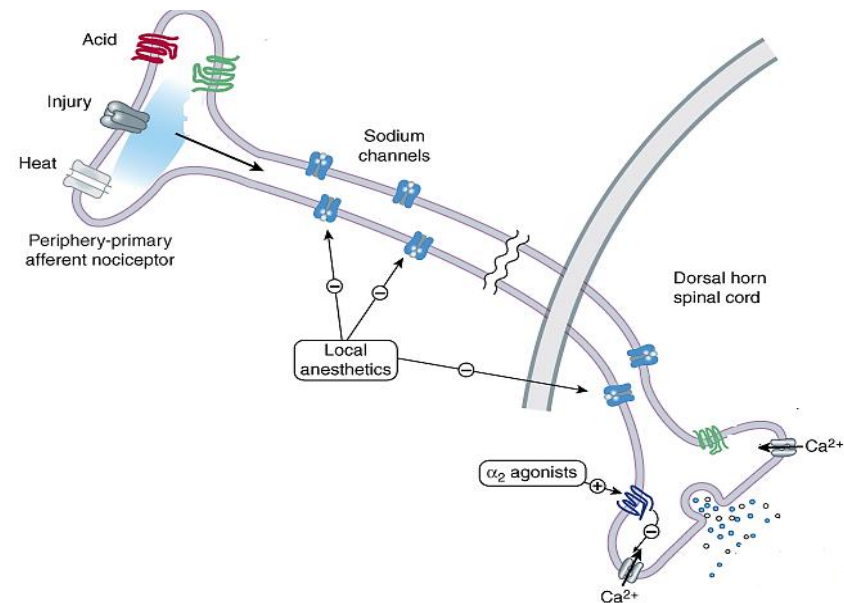
- Differential block of voltage-gated sodium channels
 - Temperature → pain → light touch → motor block

Fiber Type	Function	Diameter (μm)	Myelination	Sensitivity to Block
Type A				
Alpha	Proprioception, motor	12–20	Heavy	+
Beta	Touch, pressure	5–12	Heavy	++
Gamma	Muscle spindles	3–6	Heavy	++
Delta	Pain, temperature	2–5	Heavy	+++
Type B	Preganglionic autonomic	< 3	Light	++++
Type C				
Dorsal root	Pain	0.4–1.2	None	++++
Sympathetic	Postganglionic	0.3–1.3	None	++++

Pharmacodynamics

Mechanism of Action

- In Addition to voltage-gated sodium channels block
 - LAs inhibit action of substance P
 - LAs antagonize glutamate receptors (AMPA, NMDA)
 - LAs antagonize nicotinic acetylcholine receptors



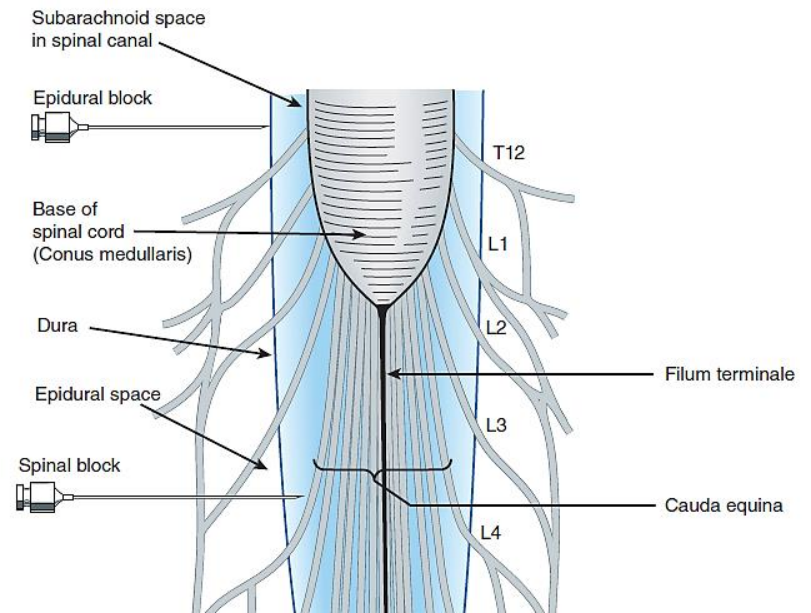
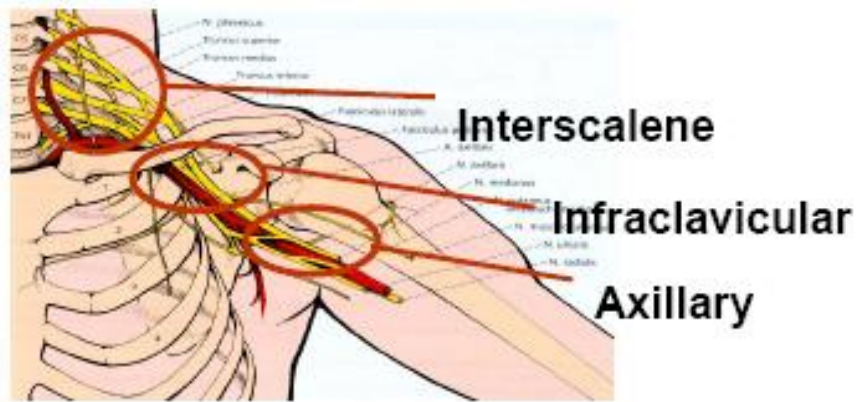
Clinical indication

- Acute pain and painful procedures
 - Bandage exchange
 - Biopsy
 - Colonoscopy
 - Laryngoscopy
 - Dental procedures
 - Incision of soft tissue
 - drainage of abscesses
- Chronic pain
- Antiarrhythmic



Anesthesia techniques

- **Topical** application (dermal, nasal, mucosal)
- **Infiltration** (injection to target margin)
- **Nerve block** (injection to vicinity of major nerve trunks)
- **Epidural & spinal** anesthesia (injection into the epidural or subarachnoid spaces)



Toxicity

Localized toxicity

- Direct Neurotoxicity leading to Neuropathy
- At High doses (when used for spinal anesthesia)
- Chloroprocaine & Lidocaine are More neurotoxic than other LAs
- Spinal neurotoxicity does not result from excessive sodium channel blockade

Toxicity

Systemic toxicity

➤ *CNS* :

- Sleepiness, Light-headedness
- Visual and auditory disturbances, Restlessness
- Convulsion
 - Premedication with diazepam or midazolam
 - General anesthetics: Thiopental, Propofol
 - Succinylcholine

Toxicity

Systemic toxicity

➤ *Cardiovascular :*

- Decrease of pace maker activity
- Decrease of myocardial contractility (except cocaine)
- Direct arteriolar dilation (hypotension)
- Bupivacaine is more cardio-toxic than others (Vascular collapse)
- Levobupivacaine has lower CV toxicity
- Lidocaine with epinephrine has more risk of cardiac arrhythmia

Toxicity

Systemic toxicity

➤ *Hematologic effects :*

- Large doses of prilocaine → toxic metabolite
 - o-toluidine (an oxidizing agent)
 - Hemoglobin → methemoglobin
- Prilocaine administration should be stopped
- Treatment with methylene blue or ascorbic acid

Toxicity

Systemic toxicity

➤ *Allergic Reactions :*

- Ester-based drugs (benzocaine, tetracaine)
- Metabolized to PABA derivatives
- These metabolites are the reason of allergic reactions
- Amides are not metabolized to PABA, and allergic reactions to them are extremely rare

**ANY
QUESTIONS?**