

# Local Anaesthetics

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# What is local anaesthetics?

- Reversibly and effectively block impulse conduction along nerve axons and other excitable membranes that use sodium channels as the primary means of action potential generation

# History

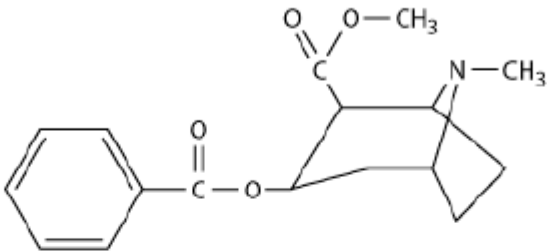
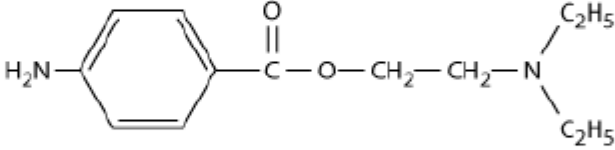
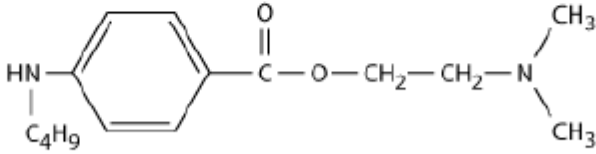
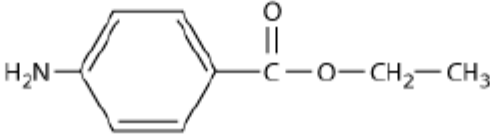
- First local anaesthetic introduced into medical practice, cocaine, was isolated by Niemann in 1860
- Procaine was synthesised by Einhorn in 1905 and became the dominant local anaesthetic for the next 50 years
- Lidocaine was synthesised in 1943 by Löfgren

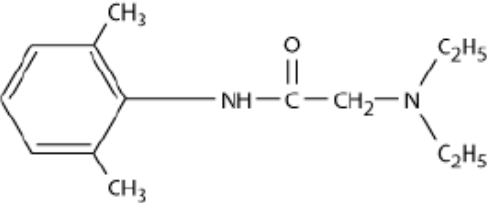
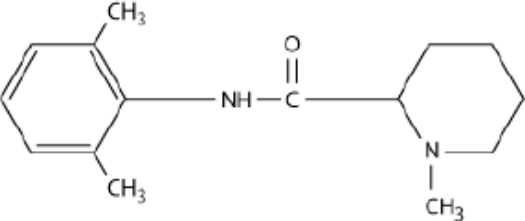
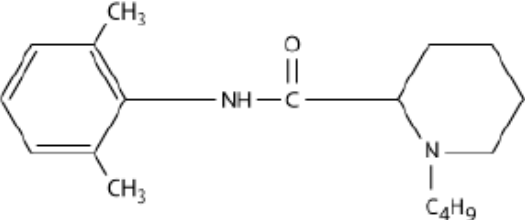
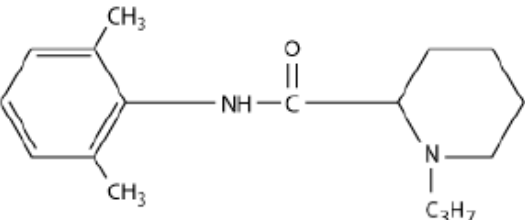
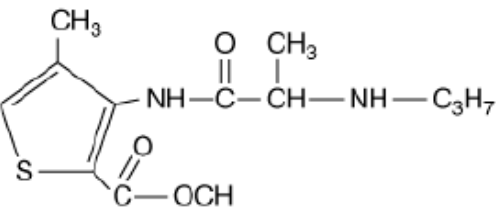
# Challenges

- It is difficult to reduce the toxicity of the local anaesthetics, because the common side effects represent extension of their therapeutic effects.
- A multivesicular liposomal formulation of bupivacaine (DepoBupivacaine), which is in the advanced stages of clinical development, can produce local anaesthetic effects lasting up to 72 hours

# Chemistry

- Consist of a lipophilic group (eg, and aromatic ring) connected by an intermediate chain via an ester or amid to an ionisable group
- Ester links are more prone to hydrolysis than amid links
  - esters usually have a shorter duration of action

	Structure	Potency (Procaine = 1)	Duration of Action
<b>Esters</b>			
Cocaine		2	Medium
Procaine (Novocain)		1	Short
Tetracaine (Pontocaine)		16	Long
Benzocaine		Surface	.

<b>Amides</b>			
Lidocaine (Xylocaine)		4	Medium
Mepivacaine (Carbocaine, Isocaine)		2	Medium
Bupivacaine (Marcaine), Levobupivacaine (Chirocaine)		16	Long
Ropivacaine (Naropin)		16	Long
Articaine		nf <sup>2</sup>	Medium

# Chemistry

- Weak bases
- Made clinically as salts to increase solubility and stability
- In the body, they exist either as the unchanged base or as a cation
- The relative proportions of these two forms are governed by their  $pK_a$  and the pH of the body fluid (Henderson-Hasselbalch equation)

$$\log \frac{\text{Cationic form}}{\text{Unchange form}} = pK_a - pH$$



# Chemistry

- $pK_a$  of most local anaesthetics is in the range of 8.0-9.0
- Larger percentage in body fluid at physiologic pH will be the charged, cationic form
- The cationic form is the most active form at the receptor site
- The unchanged form is important for rapid penetration of biologic membranes and producing a clinical effect

# Pharmacokinetics

- The pharmacokinetics of the ester-based local anesthetics have not been extensively studied owing to their rapid breakdown in plasma (elimination half-life < 1 minute)
- Local anesthetics are usually administered by injection into dermis and soft tissues around nerves
  - Absorption and distribution are not as important in controlling the onset of effect as in determining the rate of offset of local analgesia and the likelihood of CNS and cardiac toxicity

# Absorption

- Systemic absorption is determined by:
  - Dosage
  - site of injection
  - drug-tissue binding
  - local tissue blood flow
  - use of vasoconstrictors (eg, epinephrine)
  - physicochemical properties of the drug
- For regional anesthesia, maximum blood levels of local anesthetic decrease according to the site of administration in the following order:
  - intercostal (highest) > caudal > epidural > brachial plexus > sciatic nerve (lowest).
- blood levels are lowered up to 30% when vasoconstrictors are added to local anesthetics

# Use of Vasoconstrictor

- In spinal anesthesia,
  - acting on  $\alpha_2$  adrenoceptors, which inhibit release of substance P (neurokinin-1) and reduce sensory neuron firing
  - Clonidine:  $\alpha_2$  agonist-antagonist
  - Dexmedetomidine: pure  $\alpha_2$  agonist
  - prolongs the local anesthetic effect by up to 50%.
- Vasoconstrictors are less effective in prolonging anesthetic action of the more lipid-soluble, long-acting drugs (eg, bupivacaine and ropivacaine),
  - because these molecules are highly tissue-bound

# Distribution

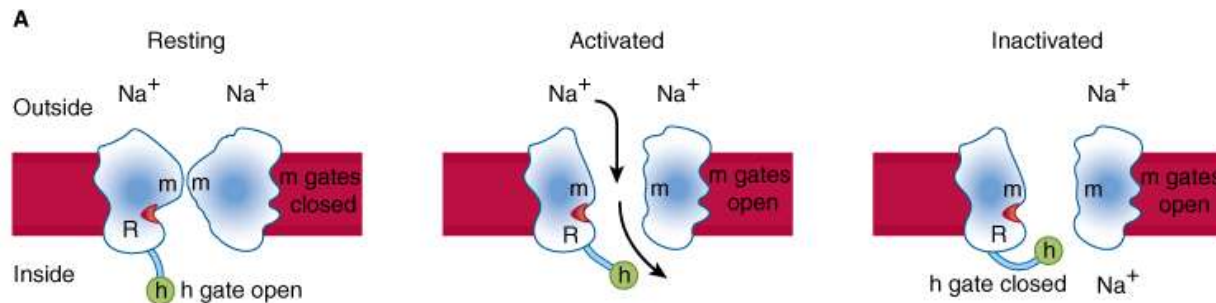
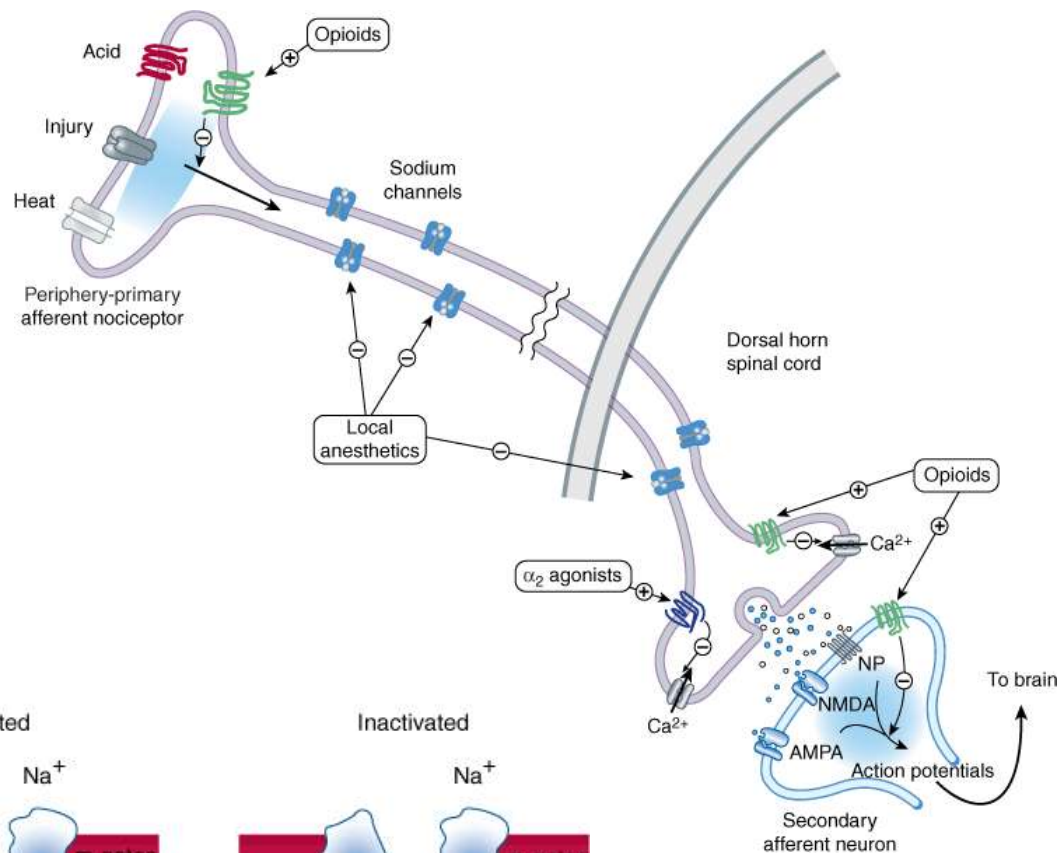
- The amide local anesthetics are widely distributed after intravenous bolus administration
  - highly perfused organs such as the brain, liver, kidney, and heart
- As a result of the extremely short plasma half-lives of the ester type agents, their tissue distribution has not been extensively studied.

# Metabolism and Excretion

- Ester-type local anesthetics are hydrolyzed very rapidly in the blood by circulating butyrylcholinesterase (pseudocholinesterase) to inactive metabolites
  - procaine and chlorprocaine have very short plasma half-lives (< 1 minute)
- The amide linkage of amide local anesthetics is hydrolyzed by liver microsomal cytochrome P450 isozymes.
  - prilocaine (fastest) > lidocaine > mepivacaine > ropivacaine > bupivacaine and levobupivacaine (slowest)
- Decreased hepatic elimination of local anesthetics would also be anticipated in patients with reduced hepatic blood flow. For example, the hepatic elimination of lidocaine in patients anesthetized with volatile anesthetics (which reduce liver blood flow) is slower than in patients anesthetized with intravenous (or balanced) anesthetic techniques.

# Pharmacodynamics

- The primary mechanism of action of local anesthetics is **blockade of voltage-gated sodium channels**
  - bind to receptors near the intracellular end of the sodium channel and block the channel in a time- and voltage-dependent fashion
- When progressively increasing concentrations of a local anesthetic are applied to a nerve fiber:
  - threshold for excitation increases
  - impulse conduction slows
  - the rate of rise of the action potential declines
  - the action potential amplitude decreases
  - finally, the ability to generate an action potential is completely abolished





# Pharmacodynamics

- If the sodium current is blocked over a critical length of the nerve, propagation across the blocked area is no longer possible.
  - In myelinated nerves, the critical length is two to three nodes of Ranvier.
- Channels in the rested state, which predominate at more negative membrane potentials, have a much lower affinity for local anesthetics than activated (open state) and inactivated channels, which predominate at more positive membrane potentials (see Figure 26–2).
- Elevated extracellular calcium partially antagonizes the action of local anesthetics owing to the calcium-induced increase in the surface potential on the membrane (which favors the low-affinity rested state).
- Increases in extracellular potassium depolarize the membrane potential and favor the inactivated state, enhancing the effect of local anesthetics.

- Lidocaine, procaine, and mepivacaine are more water-soluble than tetracaine, bupivacaine, and ropivacaine. The latter agents are more potent and have longer durations of local anesthetic action.

# Size of nerve fibres

Fiber Type	Function	Diameter (m)	Myelination	Conduction Velocity (m/s)	Sensitivity to Block
<b>Type A</b>					
Alpha	Proprioception, motor	12–20	Heavy	70–120	+
Beta	Touch, pressure	5–12	Heavy	30–70	++
Gamma	Muscle spindles	3–6	Heavy	15–30	++
Delta	Pain, temperature	2–5	Heavy	5–25	+++
<b>Type B</b>					
	Preganglionic autonomic	< 3	Light	3–15	++++
<b>Type C</b>					
Dorsal root	Pain	0.4–1.2	None	0.5–2.3	++++
Sympathetic	Postganglionic	0.3–1.3	None	0.7–2.3	++++

- Myelinated nerves tend to become blocked before unmyelinated nerves of the same diameter.
  - For this reason, the preganglionic B fibers are blocked before the smaller unmyelinated C fibers involved in pain transmission.
- Type A delta and C fibers are smaller-diameter fibers that participate in high-frequency pain transmission.
  - Therefore, these fibers are blocked earlier and with lower concentrations of local anesthetics than are the large A alpha fibers
- In large nerve trunks, fibers located circumferentially are the first to be exposed to the local anesthetic when it is administered into the tissue surrounding the nerve.
  - In the extremities, proximal sensory fibers are located in the outer portion of the nerve trunk, whereas the distal sensory innervation is located in the central core of the nerve.

# Clinical pharmacology

- Local anesthetics can provide highly effective analgesia in well-defined regions of the body.
- The usual routes of administration include:
  - topical application (eg, nasal mucosa, wound [incision site] margins)
  - injection in the vicinity of peripheral nerve endings (perineural infiltration) and major nerve trunks (blocks),
  - injection into the epidural or subarachnoid spaces surrounding the spinal cord (Figure 26–4).
  - Intravenous regional anesthesia (so-called Bier block) is used for short surgical procedures (< 60 minutes) involving the upper and/or lower extremities.

# Clinical pharmacology

- The onset of local anesthesia can be accelerated by the addition of sodium bicarbonate (1–2 mL) to the local anesthetic solution.
  - This maximizes the amount of drug in the more lipid-soluble (unionized) form.
- Repeated injections of local anesthetics can result in loss of effectiveness (ie, tachyphylaxis) due to extracellular acidosis.
  - Tachyphylaxis to local anesthetics is common in areas with a limited buffer capacity (eg, the cerebrospinal fluid).

# Clinical pharmacology

- Pregnancy appears to increase susceptibility to local anesthetic toxicity.
  - Cardiac arrest leading to death following the epidural administration of 0.75% bupivacaine to women in labor resulted in temporary withdrawal of the high concentration of this widely used long-acting local anesthetic
- Since local anesthetics have membrane-stabilizing effects, both parenteral (eg, intravenous lidocaine) and oral (eg, mexiletine, tocainide) formulations of local anesthetics have been used to treat patients with neuropathic pain syndromes because these syndromes are thought to involve uncontrolled, rapid, sensory fiber firing

# Toxicity

- The two major forms of local anesthetic toxicity are:
  1. systemic effects following absorption of the local anesthetic from their site of administration
  2. direct neurotoxicity from the local effects of anaesthetics when high concentrations are administered in close proximity to the spinal cord and other major nerve trunks



# CNS toxicity

- All local anesthetics have the ability to produce
  - Sleepiness
  - light-headedness
  - visual and auditory disturbances
  - Restlessness
- Symptoms of local anesthetic toxicity are:
  - circumoral and tongue numbness
  - metallic taste
  - nystagmus and muscular twitching
  - tonic-clonic convulsions
  - generalized CNS depression

# Neurotoxicity

- Chloroprocaine and lidocaine appear to be more neurotoxic than other local anesthetics when used for spinal anesthesia
- Although the precise mechanism of this neurotoxic action has not been established, both interference with axonal transport and disruption of calcium homeostasis have been implicated.
  - Spinal neurotoxicity does not result from excessive sodium channel blockade.

# Cardiovascular system

- Local anesthetics block cardiac sodium channels and depress abnormal cardiac pacemaker activity, excitability, and conduction.
- At extremely high concentrations, local anesthetics can also block calcium channels.
- local anesthetics also depress myocardial contractility and produce direct arteriolar dilation, leading to systemic hypotension.

# Cardiovascular system

- Cocaine blocks norepinephrine reuptake
  - Vasoconstriction (local ischaemia)
  - Hypertension
  - cardiac arrhythmias
- Bupivacaine:
  - more cardiotoxic than other long-acting local anesthetics
  - ECG: a slow idioventricular rhythm with broad QRS complexes and eventually electromechanical dissociation.
  - Resuscitation from bupivacaine cardiovascular toxicity is extremely difficult
  - Recent studies suggest that propofol can be useful in resuscitating patients acutely exposed to toxic levels of bupivacaine.

# Haematologic effect

- The administration of large doses ( $> 10$  mg/kg) of prilocaine during regional anesthesia may lead to accumulation of the metabolite *o*-toluidine, an oxidizing agent capable of converting hemoglobin to methemoglobin
- The treatment of methemoglobinemia involves the intravenous administration of a reducing agent (eg, methylene blue or ascorbic acid), which rapidly converts methemoglobin to hemoglobin.

**Thank you**

# CNS toxicity

- If seizures do occur, it is important to prevent hypoxemia and acidosis. Although administration of oxygen does not prevent seizure activity, hyperoxemia may be beneficial after onset of seizures. Hypercapnia and acidosis may lower the seizure threshold, and so hyperventilation is recommended during treatment of seizures. In addition, hyperventilation increases blood pH, which in turn lowers extracellular potassium. This action hyperpolarizes the transmembrane potential of axons, which favors the resting (or low-affinity) state of the sodium channels, resulting in decreased local anesthetic toxicity.

- . The muscular manifestations of a seizure can be blocked using a short-acting neuromuscular relaxant drug (eg, succinylcholine, 0.25–0.5 mg/kg IV). It should be emphasized that succinylcholine does not alter the CNS manifestations of local anesthetic-induced seizure activity. Rapid tracheal intubation can prevent pulmonary aspiration of gastric contents and facilitate hyperventilation.