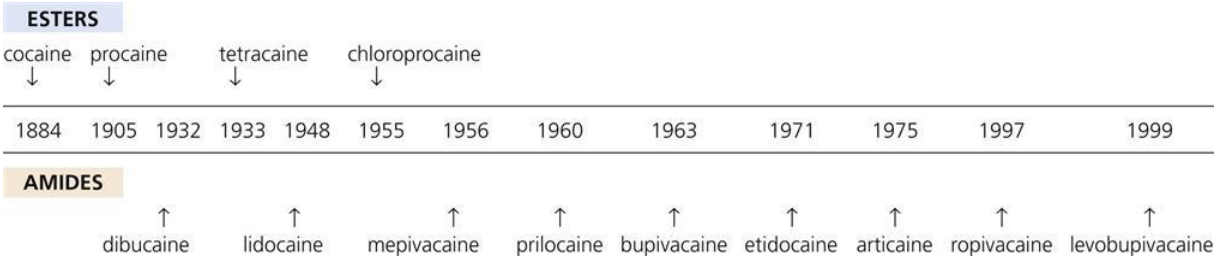
Local Anesthetics

Introduction and History

Cocaine is a naturally occurring compound indigenous to the Andes Mountains, West Indies, and Java. It was the first anesthetic to be discovered and is the only naturally occurring local anesthetic; all others are synthetically derived. Cocaine was introduced into Europe in the 1800s following its isolation from coca beans. Sigmund Freud, the noted Austrian psychoanalyst, used cocaine on his patients and became addicted through self-experimentation.
In the latter half of the 1800s, interest in the drug became widespread, and many of cocaine's pharmacologic actions and adverse effects were elucidated during this time. In the 1880s, Koller introduced cocaine to the field of ophthalmology, and Hall introduced it to dentistry



Overwiev

Local anesthetics (LAs) are drugs that block the sensation of pain in the region where they are administered. LAs act by reversibly blocking the sodium channels of nerve fibers, thereby inhibiting the conduction of nerve impulses. Nerve fibers which carry pain sensation have the smallest diameter and are the first to be blocked by LAs. Loss of motor function and sensation of touch and pressure follow, depending on the duration of action and dose of the LA used. LAs can be infiltrated into skin/subcutaneous tissues to achieve local anesthesia or into the epidural/subarachnoid space to achieve regional anesthesia (e.g., spinal anesthesia, epidural anesthesia, etc.). Some LAs (lidocaine, prilocaine, tetracaine) are effective on topical application and are used before minor invasive procedures (venipuncture, bladder

catheterization, endoscopy/laryngoscopy). LAs are divided into two groups based on their chemical structure. The amide group (lidocaine, prilocaine, mepivacaine, etc.) is safer and, hence, more commonly used in clinical practice. The ester group (procaine, tetracaine) has a higher risk of causing allergic reactions or systemic toxicity and is, therefore, reserved for patients with known allergies to drugs of the amide group. Overdose or inadvertent injection of an LA into a blood vessel can cause systemic toxicity, which mainly affects the CNS (tinnitus, seizures, etc.) and the CVS (bradycardia, arrhythmias, etc.).

Local anesthesia is used when:

- surgery is minor and does not require general or regional anesthesia
- the procedure can be done quickly and the patient does not need to stay overnight
- the operation does not need the muscles to be relaxed or for the patient to be unconscious

Examples include dental surgery, the removal of a verruca, a mole, or a cataract, and biopsies.

IDEAL PROPERTIES OF LOCAL ANAESTHETICS

1. Non-irritating to tissues and not causing any permanent damage
2. Low systemic toxicity
3. Effective whether injected into the tissue or applied locally to skin or mucous membranes
4. Rapid onset of anaesthesia and short duration of action

CLASSIFICATION

Amide Type

Longer Acting: Bupivacaine, levo-Bupivacaine, Etidocaine, Ropivacaine, Dibucaine

Intermediate acting: Lidocaine (Xylocaine), Mepivacaine, Prilocaine

Ester Type

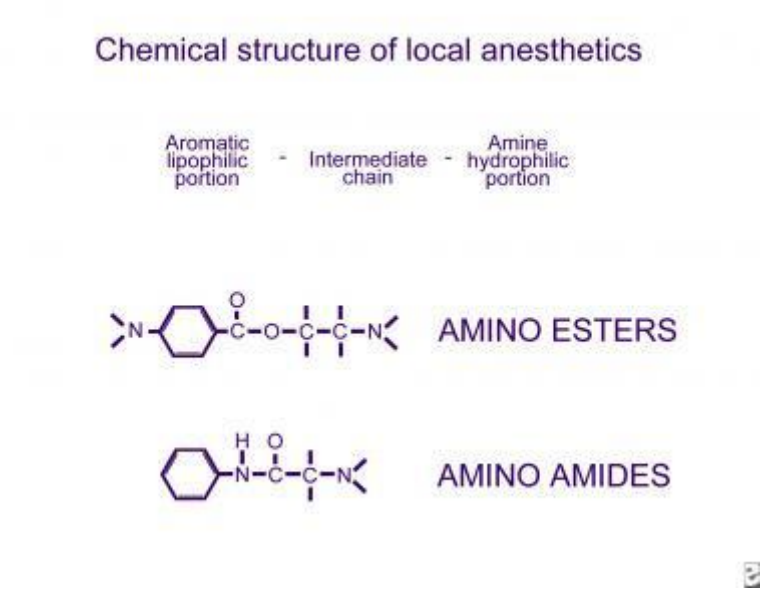
Longer Acting: Tetracaine (Amethocaine)

Intermediate Acting: Cocaine

Short Acting: Procaine, Chloroprocaine, Benzocaine, Betambenm Proparacaine

Miscellaneous: Pramoxine (Pramocaine), Dyclonine, Oxetacaine

Local anesthetics are formulated as hydrochloride salts with a pH less than 7, as the ionized molecule is more soluble and stable than the free base. Once injected, the local anesthetic solution is quickly buffered to the pH of the tissue.



Local Anesthetic molecules consist of an aromatic part & a basic amine side à both are linked with an ester or amide bond

These are weak bases à partly ionized with acids à unionized parts is lipophilic in nature and which helps the LA to penetrate into nerve membrane à after going inside the ionized part which is active at the receptor side

LAs à block the voltage gated Na+ channels during depolarisation à Na^+ permeability decreases à consequently nerve conduction is blocked

Blocking action of LA is favouored by depolarization & resting membrane is less sensitive to LA

Na+ channel has an Activation Gate (AG) on its extracellular site & Inactivation Gate (IG) on its intracellular site

Voltage – Gated Na+ channels exist in 3 functional states

Resting or Closed state à at the normal resting potential à AG is closed

Activated or Open state à favoured by brief depolarization à open AG to allow Na+ ions to follow in along concentration gradient

Inactivated or Blocked state à occlusion of channel by a floppy part of the intracellular region of the channel protein

Na+ ions flow ceases as soon as inactivation gate closes

LA receptor is located in the transmembrane pore of NA+ channel in its intracellular half

LA diffuses through the membrane in unionized lipophilic form à it then reionises & binds to the LA receptor à binding of LA to its receptor stabilizes the channel in the inactivated state à Inactivation gate closes & Na+ ion flow ceases à LAs prevent the initiation & propagation of the nerve impulse by reducing the passage of Na+ ions through voltage-gated Na+ channels

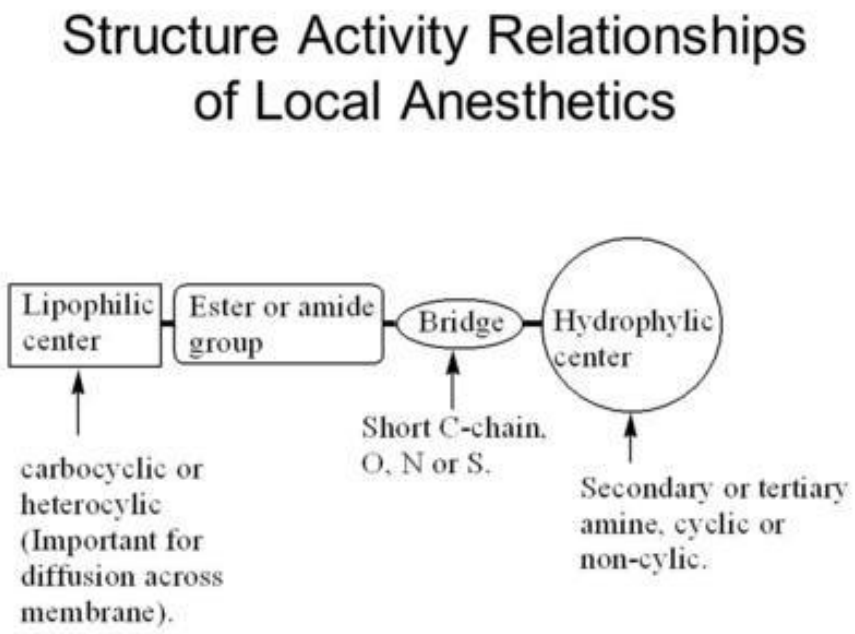
Effect of pH on LA action

LAs are basic in nature so à they are action is strong at alkaline pH & less at acidic pH à unionized form is needed for its diffusion through axon membrane

LAs are less effective in infected tissue, because in infected area the extracellular pH is acidic à LAs are poorly diffuses in infected tissue due to more ionization

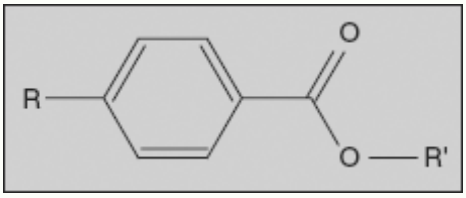
	Local anesthetics	Duration of action
Ester group	Procaine	Short
	Tetracaine	long
Amide type	Lidocaine	Intermediate
	Prilocaine	Intermediate
	Mepivacaine	Intermediate
	Bupivacaine	long
	Etidocaine	long
	Ropivacaine	long

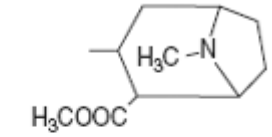
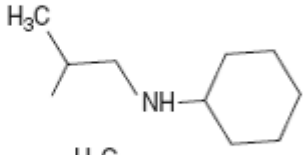
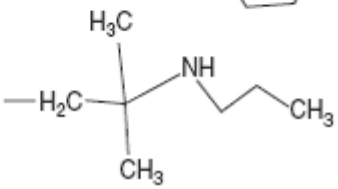
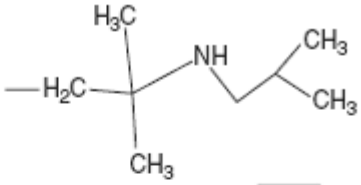
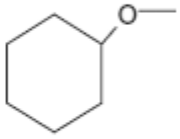
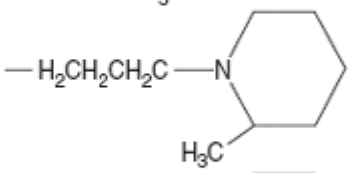
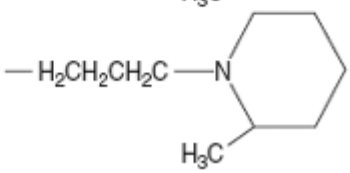
Ester LAs do not have an “i” in their names preceding “-caine.” Amide LAs have an "i" in their name preceding “-caine.”



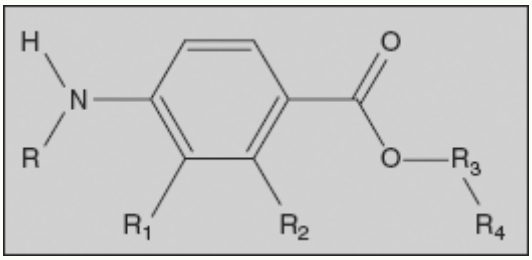
CLASSIFICATION OF LOCAL ANAESTHETICS

1. Benzoic acid derivatives



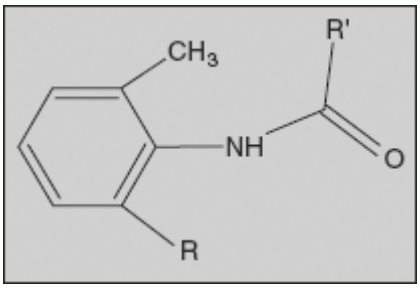
	R	R′
Cocaine	H	
Hexylcaine	H	
Meprylcaine	H	
Isobucaine	H	
Cyclomethycaine		
Piperocaine	H	

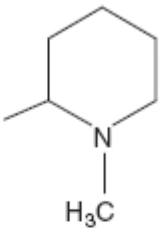
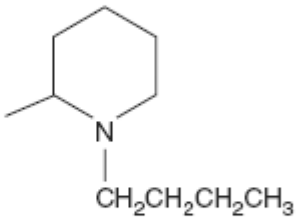
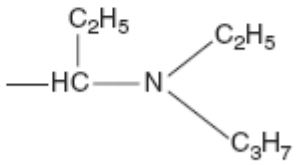
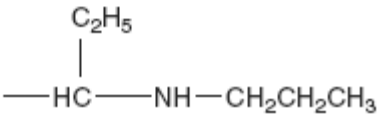
2. *p*-Aminobenzoic acid derivatives



	R	R_1	R_2	R_3	R_4
Benzocaine	H	H	H	$—CH_2CH_3$	—
Butamben	H	H	H	$—(CH_2)_3CH_3$	—
Procaine	H	H	H	$—CH_2CH_2—$	$—N(C_2H_5)_2$
Chloroprocaine	H	H	Cl	$—CH_2CH_2—$	$—N(C_2H_5)_2$
Tetracaine	Butyl	H	H	$—CH_2CH_2—$	$—N(C_2H_5)_2$
Butacaine	H	H	H	$—CH_2CH_2—$	$—N(C_4H_{9(n)})_2$
Benoxinate	H	H	butoxy	$—CH_2CH_2—$	$—N(C_2H_5)_2$
Propoxycaine	H	H	propyloxy	$—CH_2CH_2—$	$—N(C_2H_5)_2$

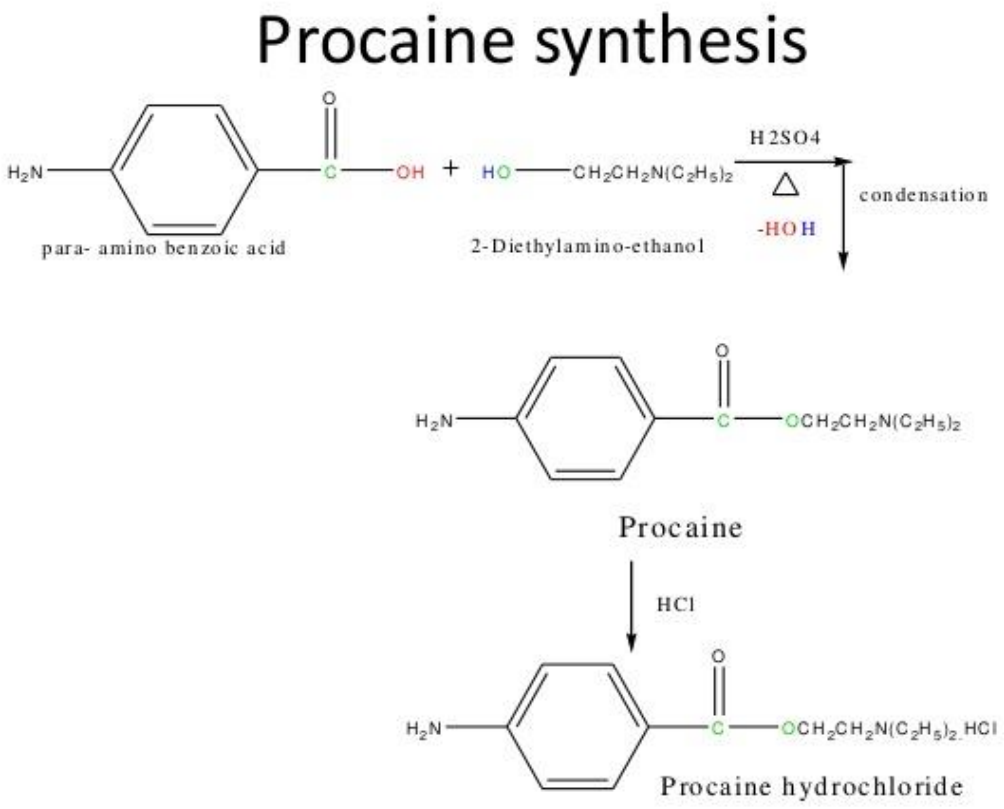
3. Anilides



	R	R′
Lignocaine	CH_3	$—CH_2N(C_2H_5)_2$
Mepivacaine	CH_3	
Bupivacaine	CH_3	
Etidocaine	CH_3	
Prilocaine	H	

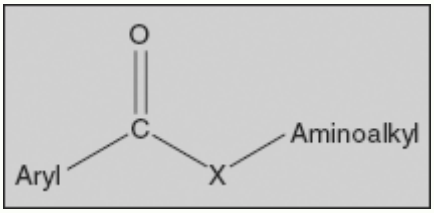
4. Miscellaneous: Phenacaine, Diperodon, Dimethisoquin, Pramoxine, Dyclonine, Dibucaine

5. Newer drugs: Ropivacaine, Levobupivacaine



Structure-activity relationships (SAR) of benzoic acid derivatives

The benzoic acid derivatives are represented as follows:



Aryl group

- The clinically useful local anaesthetics of this series possess an aryl radical attached directly to the carbonyl group.
- Substitution of aryl group with substituents that increase the electron density of the carbonyl oxygen enhances activity.
- Favourable substituents in aryl ring include (electron-donating groups) alkoxy (propoxycaine), amino (procaine), and alkylamino (tetracaine) groups in the *para* or *ortho* positions. This homologous series increases partition coefficients with

increasing number of methylene group (-CH_2-). Local anaesthetics activity peaked with the C4-, C5-, or C6-homologous: e.g., tetracaine, cyclomethycaine.

- Aryl aliphatic radicals that contain a methylene group between the aryl radical and the carbonyl group result in compounds that have not found clinical use.

Bridge X

- The bridge X may be carbon, oxygen, nitrogen, or sulphur.
- In an isosteric procaine series, anaesthetic potency decreased in the following order: sulphur, oxygen, carbon, nitrogen.
- These modifications also affect duration of action and toxicity. In general, amides (X=N) are more resistant to metabolic hydrolysis than esters (X=O). Thioesters (X=S) may cause dermatitis.
- In procaine-like analogues, branching (especially at the alpha carbon) will increase duration of action. This effect is not seen in the lidocaine series.
- Increasing the chain length will increase potency but will also increase toxicity.

Aminoalkyl group

- The aminoalkyl group is not necessary for local anaesthetic activity, but it is used to form water-soluble salts (HCl salts).
- Tertiary amines result in more useful agents. The secondary amines appear to be of longer activity, but they are more irritating; primary amines are not very active and cause irritation.
- The tertiary amino group may be diethylamino, piperidine, or pyrrolidino, leading to the products that exhibit essentially the same degree of activity.
- The more hydrophilic morpholino group usually leads to diminished potency.
- Some analogues have no amino group at all, such as benzocaine. They are active but have poor water solubility.

Epidural and Spinal Anesthesia

Epidural and spinal blocks are types of anesthesia in which a local anesthetic is injected near the spinal cord and nerve roots. It blocks pain from an entire region of the body, such as the belly, the hips, the legs, or the pelvis. Epidural and spinal anesthesia are used mainly for surgery of the lower belly and the legs. Epidural anesthesia is often used in childbirth. But it can also be used to help control pain after major surgery to the belly or chest.

Epidural anesthesia involves the insertion of a hollow needle and a small, flexible catheter into the space between the spinal column and outer membrane of the spinal cord (epidural space) in the middle or lower back. The area where the needle will be inserted is numbed with a local anesthetic. Then the needle is inserted and removed after the catheter has passed through it. The catheter remains in place. The anesthetic medicine is injected into the catheter to numb the body above and below the point of injection as needed. The catheter is secured on the back so it can be used again if more medicine is needed.

Spinal anesthesia is done in a similar way. But the anesthetic medicine is injected using a much smaller needle, directly into the cerebrospinal fluidthat surrounds the spinal cord. The area where the needle will be inserted is first numbed with a local anesthetic. Then the needle is guided into the spinal canal, and the anesthetic is injected. This is usually done without the use of a catheter. Spinal anesthesia numbs the body below and sometimes above the site of the injection. The person may not be able to move his or her legs until the anesthetic wears off.