Topic: LOCAL ANAESTHETICS

By:

[Dr. Meenaxi M. Maste]

KLE College of Pharmacy, Belagavi

A constituent Unit of KLE Academy of Higher Education and Research

Nehru Nagar, Belagavi – 590 010, Karnataka, India

Phone: 0831-2471399 **Fax:** 0831-2472387 **Web:**http://www.klepharm.edu**E-mail:** principal@klepharm.edu

LOCAL ANAESTHETICS

INTRODUCTION

Local anaesthetics are medications used for the purpose of temporary and reversible elimination of painful feelings in specific areas of the body by blocking transmission of nerve fibre impulses. These drugs, unlike general anaesthetics, cause a loss of feeling in specific areas while keeping the patient conscious.

Local anaesthetics are used for pain relief, soreness, itching, and irritation associated with disturbance of the integrity of the skin and mucous membranes (cuts, bites, wounds, rashes, allergic conditions, fungal infections, skin sores, and cracking).

They are used during opthalmological procedures such as tonometry and gonioscopy, removal of foreign bodies, and minor surgical interventions. Local anaesthetics are widely used in surgery, gynaecology, and dentistry. In certain cases, local anaesthetics (lidocaine, procainamide) can be used as anti-arrhythmic drugs.

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

MECHANISM OF ACTION

A mechanism of local anaesthetic action in which they serve as sodium channel blockers has been proposed. According to this mechanism, the molecular targets of local anaesthetic action are the voltage-requiring sodium channels, which are present in all the neurons. The process of local anaesthesia by respective drugs can be represented in the following manner. In a resting condition, there is a specific rest potential between the axoplasm and the inner parts of the cell. This rest potential is maintained by relative concentration of sodium and potassium ions along the membrane of the nerve. During nerve stimulation, the membrane is depolarised and sodium channels in that area are opened, allowing sodium ions to rush into the cell. At the peak of depolarization, potassium channels are opened. The last ones leave the cell and the cell is

repolarised. This process lasts 1–2 msec, after which the nerve cell, having transmitted the necessary impulse, restores its ion gradient. It is believed that after introduction of local anaesthetic into the organism in the form of a water-soluble salt, equilibrium is established between the neutral and cationic forms of the used drug depending on the pKa of the drug and the pH of the interstitial fluid. It is also believed that only the uncharged (neutral) drug form can pass through – it passes through connective tissue surrounding the nerve fibre and through the phospholipid plasma membrane into the axoplasm. In the axoplasm, the base is once again ionised until it reaches an appropriate value determined by intracellular pH. It is suspected that these drugs selectively bind with the intracellular surface of sodium channels and block the entrance of sodium ions into the cell. This leads to stoppage of the depolarization process, which is necessary for the diffusion of action potentials, elevation of the threshold of electric nerve stimulation, and thus the elimination of pain. Since the binding process of anaesthetics to ion channels is reversible, the drug diffuses into the vascular system where it is metabolised, and nerve cell function is completely restored.

CLINICAL USES OF LOCAL ANAESTHETICS

Local anaesthesia is the loss of sensation in the body part without the loss of consciousness or the impairment of central control of vital functions, used for minor surgical procedures.

Local anaesthetics are categorised by the method of administration.

1. Topical anaesthesia: Anaesthesia of mucous membranes of the nose, throat, tracheobronchial tree, oesophagus, and genito-urinary tract can be produced by direct application of aqueous solutions of salts of many local anaesthetics or by suspension of the poorly soluble local anaesthetics. For prolonged duration of action, vasoconstriction can be achieved by the addition of a low concentration of a vasoconstrictor such as phenylephrine (0.005%): e.g., lignocaine (2–10%), cocaine (1–4%), and tetracaine (2%).

2. Infiltration anaesthesia: In this, local anaesthetics are injected directly into the tissue, which may be superficial tissue of the skin or deeper structures including intra-abdominal organs. The duration of infiltration anaesthesia can be doubled by the addition of epinephrine (5 μg/ml) to the

injection solution: e.g., lignocaine (0.5–1.0%), procaine (0.5– 1.0%), and bupivacaine (0.125–0.25%).

3. Field block anaesthesia: It is produced by subcutaneous injection of a local anaesthetics solution in such a manner as to anaesthetise the region distal to the injection. The advantage of field block anaesthesia is that less drug can be used to provide a greater area of anaesthesia than when infiltration anaesthesia is used: e.g., lignocaine (0.5–1.0%), procaine (0.5–1.0%), and bupivacaine (0.125–0.25%).

4. Nerve block anaesthesia: This involves injection of a solution of local anaesthetics into or about individual peripheral nerves or nerve plexus: e.g., lignocaine (1.0–1.5%), mepivacaine (up to 7mg/kg of 1.0–2.0%), and bupivacaine (2–3 mg/kg of 0.25–0.375%). Addition of 5 μg/ml epinephrine prolongs duration.

5. Intravenous regional anaesthesia: This technique relies on using the vasculature to bring the local anaesthetics solution to the nerve trunks and endings. It is used most often for the forearm and hand, but can also be adapted for

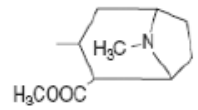
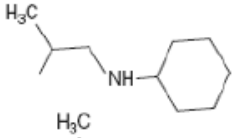
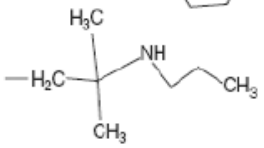
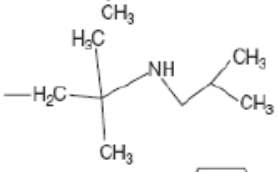
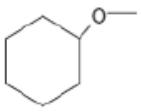
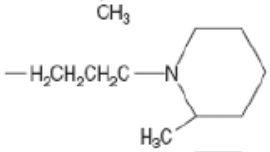
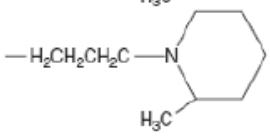
the foot and distal leg: e.g., lignocaine (0.5%) and procaine (0.5%).

6. Spinal anaesthesia: It follows the injection of local anaesthetics into the cerebrospinal fluid in the lumbar space: e.g., lignocaine, tetracaine, and bupivacaine.

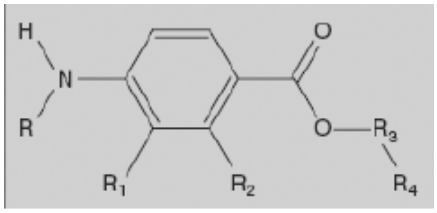
7. Epidural anaesthesia: In this, local anaesthetics is injected into epidural space – the space bounded by the ligamentum flavum posteriorly, the spina periosteum laterally, and the dura anteriorly: e.g., bupivacaine (0.5–0.75%), etidocaine (1.0–1.5%), lignocaine (2%), and chloroprocaine (2–3%).

CLASSIFICATION OF LOCAL ANAESTHETICS

1. Benzoic acid derivatives

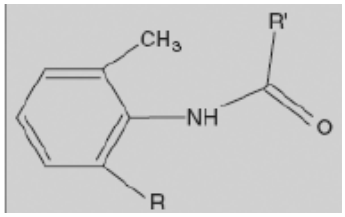
	R	R′
Cocaine	H	
Hexylcaine	H	
Meprylcaine	H	
Isobucaine	H	
Cyclomethycaine		
Piperocaine	H	

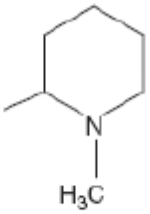
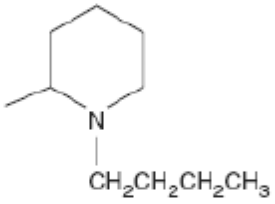
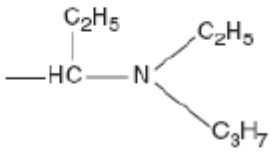
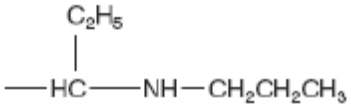
2. *p*-Aminobenzoic acid derivatives



	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



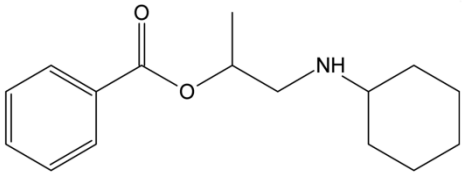
	R	R′
Lignocaine	CH_3	$—CH_2N(C_2H_5)_2$
Mepivacaine	CH_3	
Bupivacaine	CH_3	
Etidocaine	CH_3	
Prilocaine	H	

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

5. Newer drugs: Ropivacaine, Levobupivacaine

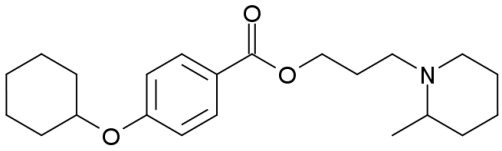
STRUCTURES, SYNTHESIS, AND STRUCTURE-ACTIVITY RELATIONSHIP (SAR) OF BENZOIC ACID DERIVATIVES

1. **Hexylcaine Hydrochloride** 1-(Cyclohexylamino)-2-propanol benzoate



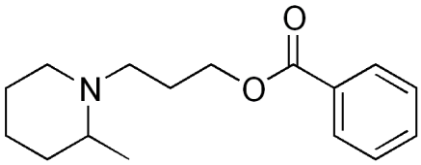
It acts by inhibiting sodium channel conduction. Overdose can lead to headache, tinnitus, numbness and tingling around the mouth and tongue, convulsions, inability to breathe, and decreased heart function. Hexylcaine has been discontinued in the US market.

2. Cyclomethycaine Sulphate 3-(2-Methylpiperidino)propyl-*p*-(cyclohexyloxy) benzoate sulphate



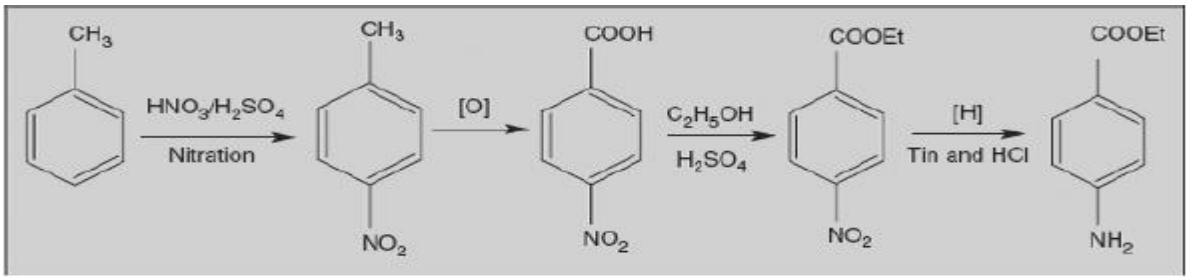
USES: It is used as an local anaesthetic

3. Piperocaine 3-(2-Methylpiperidino)propyl benzoate



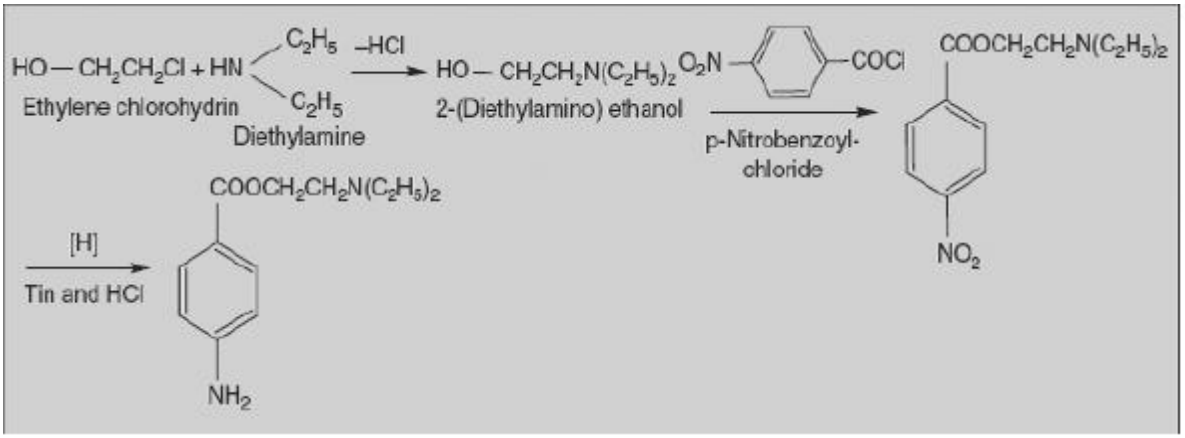
USES: Piperocaine is a local anesthetic drug developed in the 1920s and used as its hydrochloride salt for infiltration and nerve blocks.

4. Benzocaine Ethyl-*p*-aminobenzoate



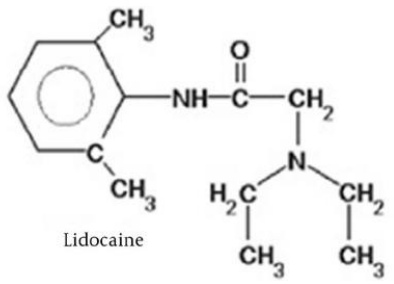
Toluene on nitration with nitrating mixture affords 4-nitro toluene, which on oxidation followed by esterification yields ethyl ester derivative. Nitro group is reduced with tin and HCl affords benzocaine. The mechanism of benzocaine action differs slightly from that mentioned above. It presumably acts by diffusing across the phospholipid membrane and then stretching it out. This deforms the sodium channels, which in turn—and in a unique manner—lowers sodium conduction.

5. Procaine 2-(Diethylamino)ethyl-*p*-aminobenzoate



Ethylene on reaction with hypochlorous acid yields ethylene chlorohydrin, which on reaction with diethylamine affords 2- (diethylamino) ethanol. Benzoylation of alcohol followed by reduction affords procaine.

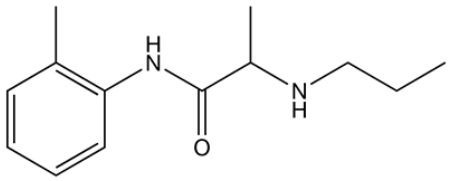
6. Lidocaine



Lidocaine

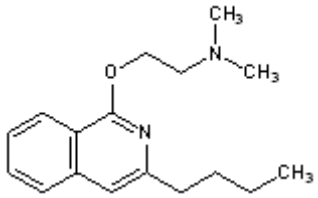
Lidocaine is a local **anesthetic** (**numbing** medication). It works by blocking nerve signals in your body. Lidocaine topical (for use on the skin) is used to reduce pain or discomfort caused by skin irritations such as sunburn, insect bites, poison ivy, poison oak, poison sumac, and minor cuts, scratches, or burns.

7. Prilocaine



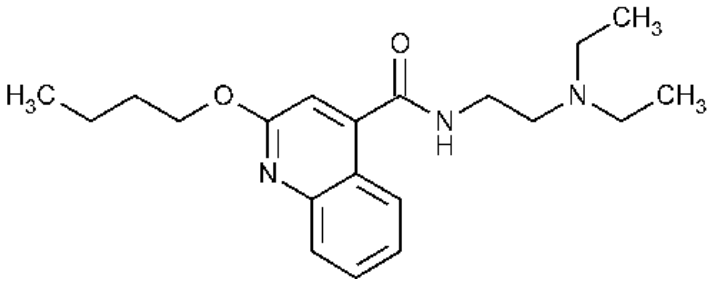
It is used on normal, unbroken skin or on the outer genital area to prevent pain before certain procedures such as inserting a needle, skin grafts, or skin laser surgery. It works by temporarily numbing the skin and surrounding area.

8. Dimethisoquin



Dimethisoquin (BAN and USAN) is a topical anesthetic used as an antipruritic.

9. Dibucaine



Dibucaine topical (for the skin) is an antiseptic, or numbing medicine. Dibucaine topical is used to treat pain and itching cause by minor burns, insect bites, hemorrhoids, sunburn, or other minor skin irritations.