# LOCAL ANAESTHETICS

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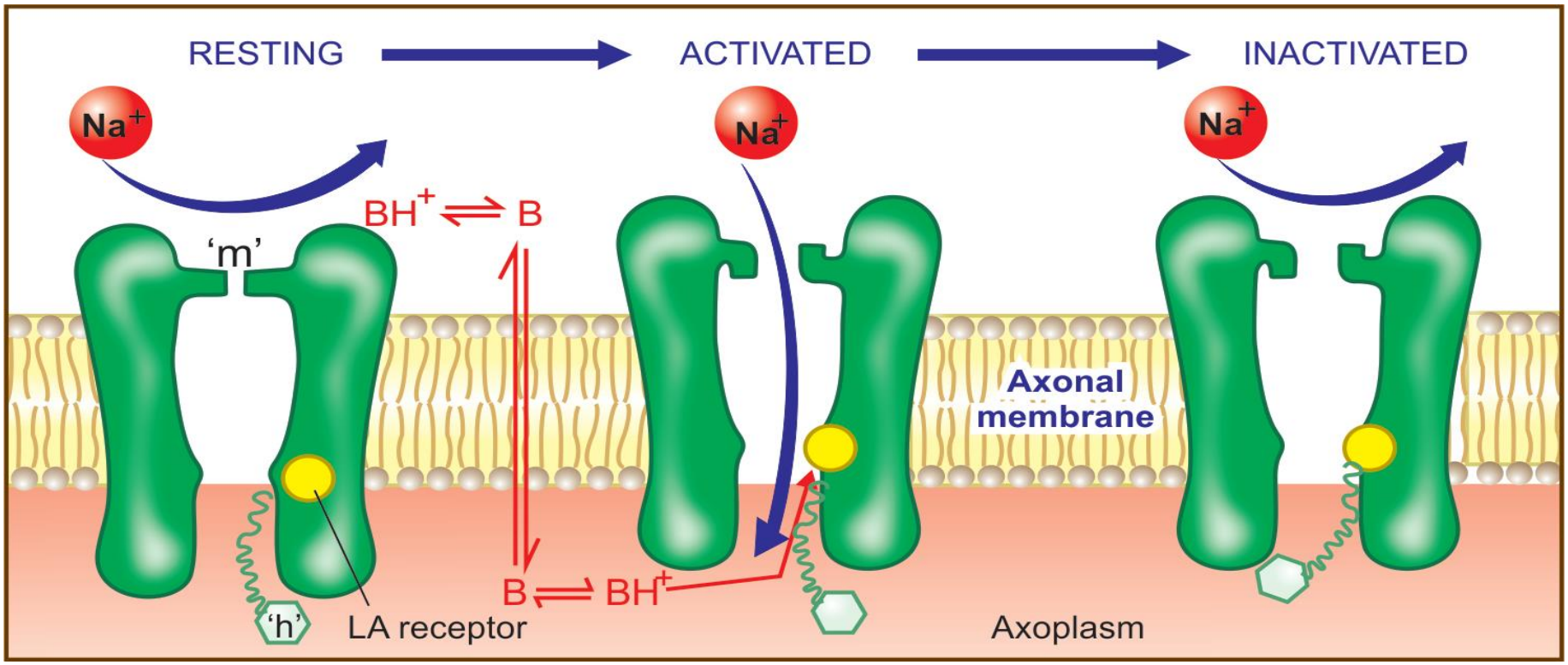
- Local anaesthetics (LAs) are drugs which upon topical application or local injection cause reversible loss of sensory perception, especially of pain, in a restricted area of the body.
- They block generation and conduction of nerve impulse at any part of the neurone with which they come in contact, without causing any structural damage.
- Thus, not only sensory but also motor impulses are interrupted when a LA is applied to a mixed nerve, resulting in muscular paralysis and loss of autonomic control as well.

# CLASSIFICATION

- ***Injectable anaesthetic***
  - *Low potency, short duration*
    - Procaine
    - Chloroprocaine
  - *Intermediate potency and duration*
    - Lidocaine (Lignocaine)
    - Prilocaine
  - *High potency, long duration*
    - Tetracaine (Amethocaine)
    - Bupivacaine
    - Ropivacaine
    - Dibucaine (Cinchocaine)
- ***Surface anaesthetic***
  - *Soluble*
    - Cocaine
    - Lidocaine
    - Tetracaine
    - Benoxinate
  - *Insoluble*
    - *Benzocaine
    - *Butylaminobenzoate (butamben)
    - *Oxethazaine

# MECHANISM OF ACTION:




- The Na+ channel has an activation gate (make or 'm' gate) near its extracellular mouth and an inactivation gate ( halt or 'h' gate) at the intracellular mouth.
- In the resting state the activation gate is closed. Threshold depolarization of the membrane opens the activation gate allowing Na+ ions to flow in along the concentration gradient.
- Within a few msec, the inactivation gate closes and ion flow ceases.
- The channel recovers to the resting state in a time-dependent manner.

- The LAs block nerve conduction by decreasing the entry of Na+ ions during upstroke of action potential (AP).
- As the concentration of the LA is increased, the rate of rise of AP and maximum depolarization decreases causing slowing of conduction.
- Finally, local depolarization fails to reach the threshold potential and conduction block ensues.
- At physiological pH, the LA molecule is partly ionized.
- The equilibrium between the unionized base form (B) and the ionized cationic form (BH+) depends on the pKa of the LA.
- Potency of a LA generally corresponds to the lipid solubility of its base form (B).

# *LOCAL ACTIONS OF LOCAL ANAESTEHTICS*

- The clinically used local anaesthetics have no/minimal local irritant action.
- They block sensory nerve endings, nerve trunks, neuromuscular junction, ganglionic synapse and receptor which function through sodium channels.
- Reduces release of acetylcholine from nerve endings.
- Applied to the tongue, bitter taste is lost first followed by sweet and sour, and salty taste at last.
- Location of the fibre within a nerve trunk determines the latency, duration and often the depth of local anaesthesia.
- Nerve sheaths restrict diffusion of the local anaesthetic into the nerve trunk.
- They easily enter the axon at the nodes of Ranvier.
- The Local anaesthetics often fails to afford adequate pain control in inflamed tissues (due to increased blood flow).

Addition of a vasoconstrictor, e.g. Adrenaline to local anesthetic causes effects like;

- Prolongs duration of action of local anaesthetics by decreasing their rate of removal from the local site into the circulation.
- Enhances the intensity of nerve block.
- Reduces systemic toxicity of local anaesthetics.
- Provides a more bloodless field for surgery.
- Increases the chances of subsequent local tissue edema and necrosis as well as delays wound healing.
- May raise BP and promote arrhythmia.

## SYSTEMIC ACTIONS OF LOCAL ANAESTHETICS

**On CNS:**

- All local anaesthetics are capable of producing a sequence of stimulation followed by depression.
- *Cocaine is* a powerful CNS stimulant causing in sequence;
- euphoria—excitement—mental confusion— restlessness—tremor and twitching of muscles— convulsions—unconsciousness—respiratory depression—death, in a dose-dependent manner.
- *Procaine and other synthetic local anaesthetics are much* less potent.

- At safe clinical doses, they produce little apparent CNS effects.
- Higher dose or accidental i.v. injection produces CNS stimulation followed by depression.
- The early neurological symptoms of overdose with *lidocaine and other clinically used local anaesthetics* are—numbness, abnormal sensation in the tongue, dizziness, blurred vision, tinnitus followed by drowsiness, dysphoria and lethargy.
- Still higher doses produce excitation, restlessness, agitation, muscle twitching, seizures and finally unconsciousness.
- The basic action of all local anaesthetics is neuronal inhibition; the apparent stimulation seen initially is due to inhibition of inhibitory neurones.
- At high doses, all neurones are inhibited and flattening of waves in the EEG is seen.

## On C.V.S:

- ***Heart:***
- *Local anaesthetics are cardiac depressants.*
- At high doses or on inadvertent i.v. injection, they decrease automaticity, excitability, contractility, conductivity and prolong effective refractory period (ERP).
- They have a quinidine like anti-arrhythmic action.
- *Procaine is not used* as anti-arrhythmic because of short duration of action and propensity to produce CNS effects.
- QT interval is prolonged and local anaesthetics can themselves induce cardiac arrhythmias.
- *Bupivacaine is relatively more cardiotoxic and* has produced ventricular tachycardia or fibrillation.
- *Lidocaine has little effect on contractility* and conductivity.

## On C.V.S:

- ***Blood vessels:***
- Local anaesthetics tend to produce fall in BP. This is primarily due to sympathetic blockade.
- Bupivacaine is more vasodilatory than lidocaine, while prilocaine is the least vasodilatory.
- Toxic doses of local anaesthetics produce cardiovascular collapse.
- *Cocaine has* sympathomimetic property; causes local vasoconstriction, marked rise in BP and tachycardia.

## PHARMACOKINETICS

- Because local anaesthetics act near their site of administration, pharmacokinetic characteristics are not important determinants of their efficacy, but markedly influence their systemic effects and toxicity.

- Soluble surface anaesthetics (lidocaine, tetracaine) are rapidly absorbed from mucous membranes and abraded areas, but absorption from intact skin is minimal.
- Procaine does not significantly penetrate mucous membranes.
- Rate of absorption depends on the blood flow to the area of application or injection
- The absorbed local anaesthetic being lipophilic is widely distributed; rapidly enters highly perfused brain, heart, liver, and kidney, followed by muscle and other viscera.
- Procaine is negligibly bound to plasma proteins, but amide LAs are bound to plasma α1 acid glycoprotein.
- Local anaesthetics are rapidly but temporarily bound to tissues, especially nerves, at the site of injection.

- Ester-linked anaesthetics (procaine, etc.) are rapidly hydrolysed by plasma pseudocholinesterase and the remaining by esterases in the liver.
- Amide-linked anaesthetics (lidocaine, etc.) are degraded only in the liver microsomes by dealkylation and hydrolysis.
- Metabolism of lidocaine is hepatic blood-flow dependent.
- After oral ingestion both procaine and lidocaine have high first pass metabolism in the liver.
- Thus, they are not active orally for anti-arrhythmic purposes.

## ADVERSE EFFECTS

- Systemic toxicity on rapid i.v. Injection.
- Toxicity after topical application or regional injection is influenced by the relative rates of absorption and metabolism.
- Those rapidly absorbed but slowly metabolized are more toxic.

### Hypersensitivity reactions:

- Rashes, angioedema, dermatitis, contact sensitization and asthma.
- These are more common with ester-linked agents, but rare with lidocaine or its congeners.
- Cross reactivity is frequent among ester compounds, but not with amide-linked LAs.
- Often methylparaben added as preservative in certain local anaesthetic solutions is responsible for the allergic reaction.

## PRECAUTIONS AND INTERACTIONS

- Before injecting the local anaesthetic, aspirate lightly to avoid intravascular injection.
- Inject the LA slowly and take care not to exceed the maximum safe dose, especially in children.
- Propranolol (probably other β blockers also) may reduce metabolism of lidocaine and other amide anaesthetics by reducing hepatic blood flow.
- Vasoconstrictor (adrenaline) containing local anaesthetic should be avoided for patients with ischaemic heart disease, cardiac arrhythmia, thyrotoxicosis, uncontrolled hypertension, and those receiving β blockers (rise in BP can occur) or tricyclic antidepressants (uptake blockade & potentiation of Adr).

## INJECTABLE ANAESTHETIC – LOW POTENCY & SHORT DURATION

### Procaine:

- It is the first synthetic local anaesthetic introduced in 1905.
- Its popularity declined after the introduction of lidocaine, and it is not used now.
- It is not a surface anaesthetic.
- Procaine forms poorly soluble salt with benzyl penicillin.
- *Procaine penicillin injected i.m. acts for 24 hours due to* slow absorption from the site of injection.

# INJECTABLE ANAESTHETIC – INTERMEDIATE POTENCY & DURATION

## Lidocaine (Lignocaine):

- Introduced in 1948, it is currently the most widely used local anaesthetic.
- It is good both for surface application and injection and is available in a variety of forms.
- Injected around a nerve it blocks conduction within 3 min (procaine may take 15 min).
- Anaesthesia is more intense and longer lasting.
- Vasodilatation occurs in the injected area.
- It is used for surface application, infiltration, nerve block, epidural, spinal and intravenous regional block anaesthesia.
- Cross sensitivity with ester LAs is not seen.
- Early central effects of lidocaine are depressant, i.e. drowsiness, mental clouding, dysphoria, altered taste and tinnitus.
- Overdose causes muscle twitching, convulsions, cardiac arrhythmias, fall in BP, coma and respiratory arrest like other LAs.
- Lidocaine is a popular antiarrhythmic.

**DOSE:** 2% jelly, 2% viscous, 5% ointment, 1% and 2% injection

# INJECTABLE ANAESTHETIC – HIGH POTENCY & LONG DURATION

## Tetracaine (Amethocaine):

- A highly lipid soluble PABA ester, more potent and more toxic due to slow hydrolysis by plasma pseudocholinesterase.
- It is both surface and conduction block anaesthetic.
- Its use is restricted to topical application to the eye, nose, throat, tracheobronchial tree and rarely for spinal or caudal anaesthesia of long duration.
- Though it is slow acting, absorption from tracheobronchial spray is very fast and blood concentrations approach those attained after i.v. injection.

**DOSE:** ANETHANE powder for solution, 1% ointment.

# INJECTABLE ANAESTHETIC – HIGH POTENCY & LONG DURATION

## Bupivacaine:

- A potent and long-acting amide linked local anaesthetic: used for infiltration, nerve block, epidural and spinal anaesthesia of long duration.
- 0.25–0.5% solution injected epidurally produces analgesia without significant motor blockade.
- As a result, it has become very popular in obstetrics (mother can actively cooperate in vaginal delivery) and for postoperative pain relief by continuous epidural infusion.
- It has high lipid solubility; distributes more in tissues than in blood after spinal/epidural injection.
- It is less likely to reach the foetus (when used during labour) to produce neonatal depression.
- Bupivacaine is more prone to prolong QT interval and induce ventricular tachycardia or cardiac depression—should not be used for intravenous regional analgesia.
- Epidural anaesthesia with 0.75% bupivacaine during labour has caused few fatalities due to cardiac arrest; use of this concentration is contraindicated.
- MARCAIN 0.5%, 1% (spinal anaesthesia).

# SURFACE ANAESTHETIC – SOLUBLE

## Cocaine:

- It is a natural alkaloid from leaves of *Erythroxylon coca, a south American plant growing on the* Andes.
- Cocaine is a good surface anaesthetic and is rapidly absorbed from buccal mucous membrane.
- It was first used for ocular anaesthesia in 1884.
- Cocaine should never be injected.
- It is a protoplasmic poison and causes tissue necrosis.
- Cocaine produces prominent CNS stimulation with marked effect on mood and behaviour.
- It induces a sense of wellbeing, delays fatigue and increases power of endurance.
- In susceptible individuals it produces a state referred to as ‘high’ leading to strong psychological but little physical dependence.
- Cocaine is unique among drugs of abuse in not producing significant tolerance on repeated use; sometimes reverse tolerance is seen (behavioural effects are experienced at lower doses).
- Cocaine also stimulates vagal centre→bradycardia; vasomotor centre→rise in BP; vomiting centre→nausea and vomiting; temperature regulating centre→pyrexia.

# SURFACE ANAESTHETIC – SOLUBLE

## Cocaine:

- In the periphery, it blocks uptake of NA and Adr into adrenergic nerve endings, *resulting in higher* concentration of the transmitter around the receptors.
- It produces sympathomimetic effect.
- Local vasoconstriction, tachycardia, rise in BP and mydriasis are the manifestations of its sympathomimetic action.
- The only indication for cocaine is in ocular anaesthesia.
- However, it causes constriction of conjunctival vessels, clouding and rarely sloughing of cornea.

## Benoxinate:

- It is a good surface anaesthetic for the eye; has little irritancy.
- A 0.4% solution rapidly produces corneal anaesthesia sufficient for tonometry without causing mydriasis or corneal damage.
- BENDZON 0.4% eye drops.

# SURFACE ANAESTHETIC – INSOLUBLE

## Benzocaine and Butamben:

- Because of very low aqueous solubility, these local anaesthetics are not significantly absorbed from mucous membranes or abraded skin.
- They produce long-lasting anaesthesia without systemic toxicity.
- They are used as lozenges for stomatitis, sore throat; as dusting powder/ointment on wounds/ulcerated surfaces and as suppository for anorectal lesions.
- Both are PABA derivative—can antagonize sulfonamides locally.
- Butamben – 1% ointment with framycetin and hydrocortisone acetate: for piles.
- PROCTOQUINOL 5% ointment of benzocaine.