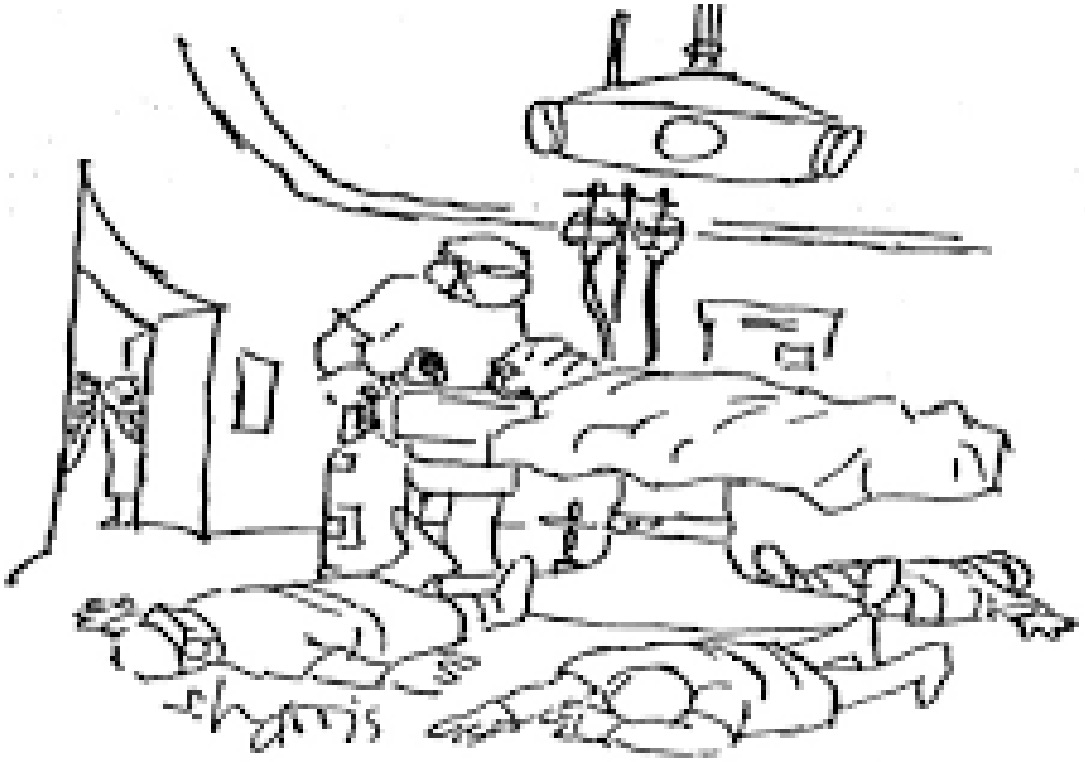
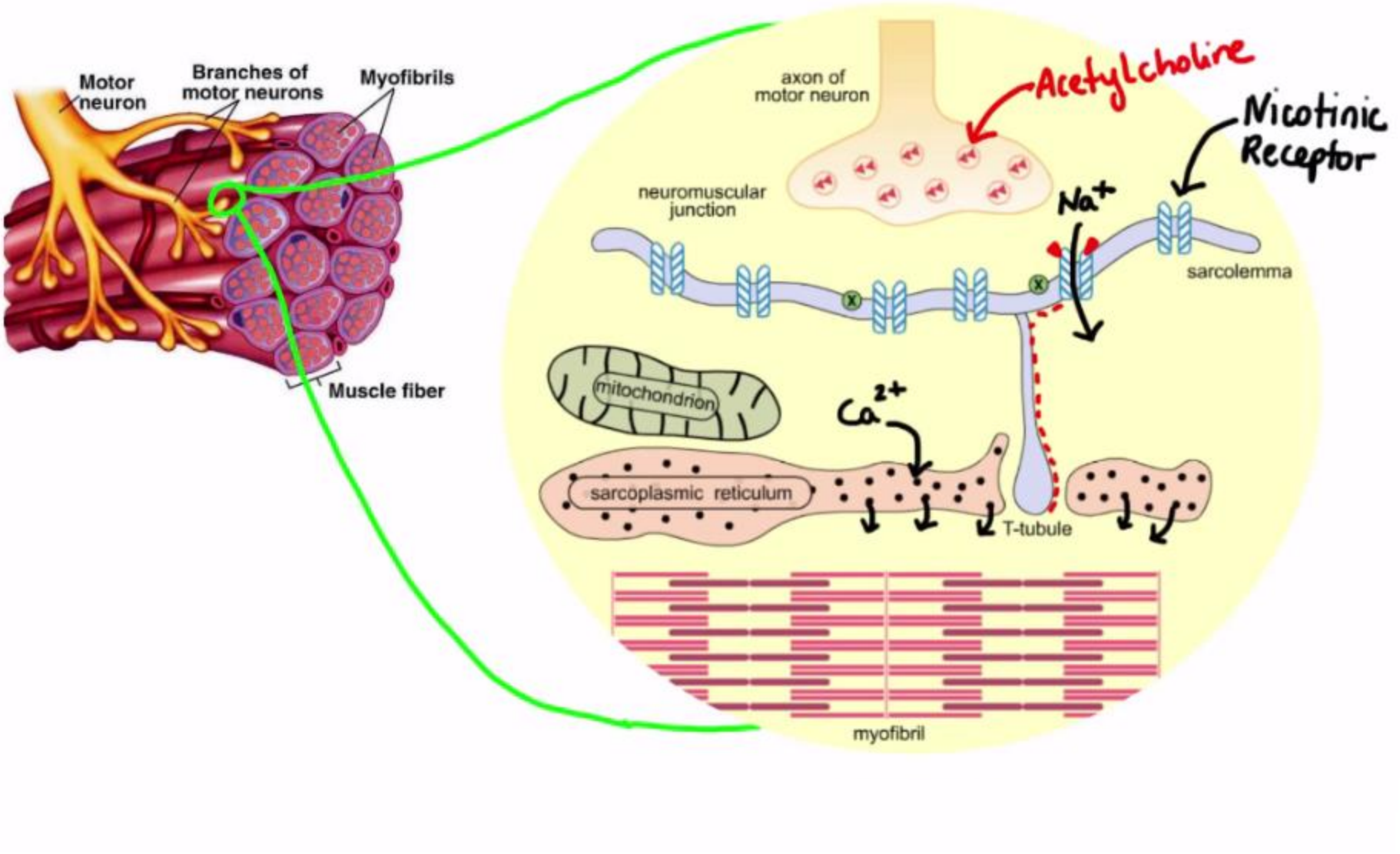
Neuromuscular Blocking agents

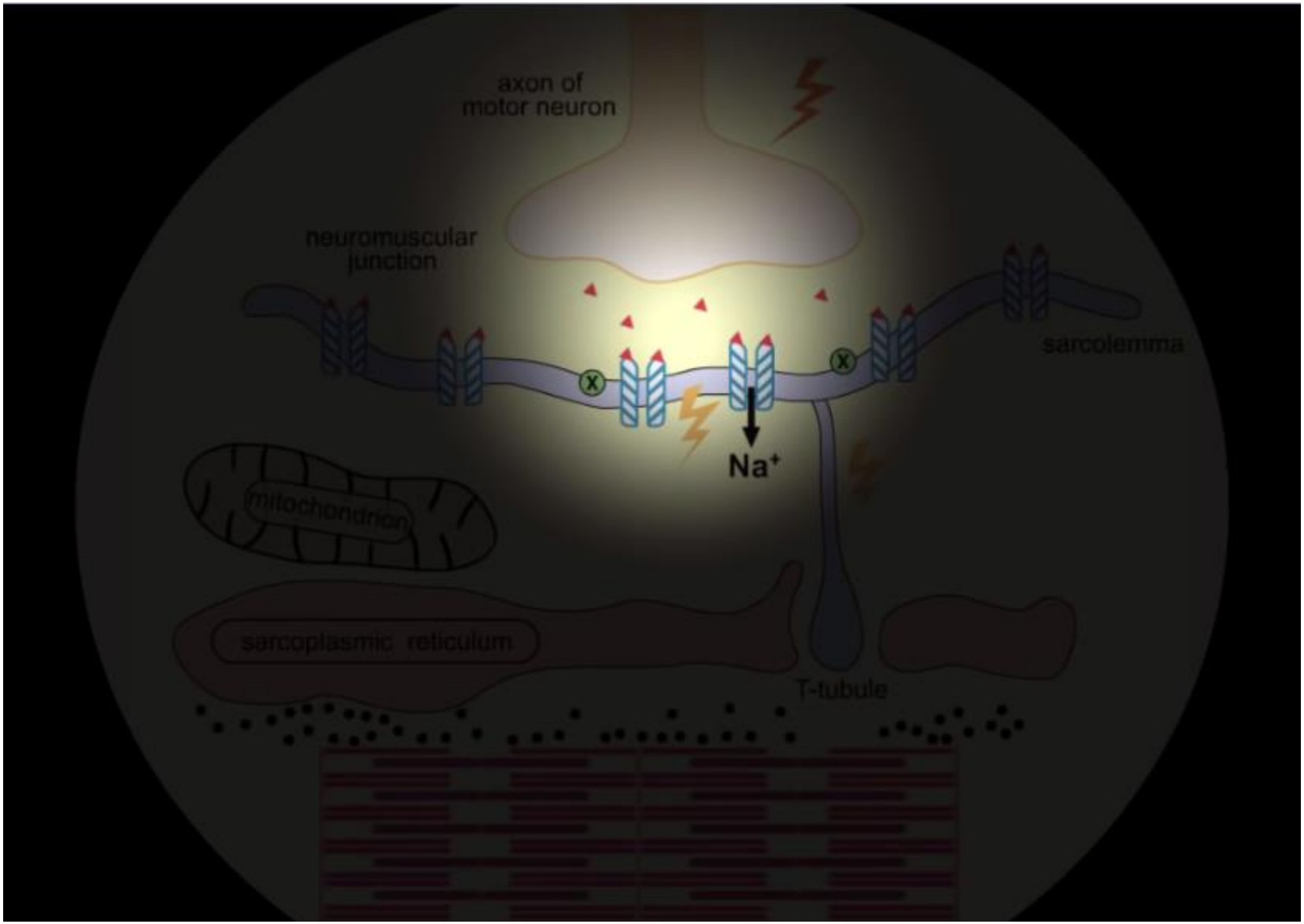


Griffith and Johnson first described the use of **curare** to facilitate muscle relaxation in a healthy man undergoing an appendectomy in 1942.

Neuromuscular Blockers

Block cholinergic trans. b/w Nerve endings and Nm Rc in skeletal m.


Motor neuron
Branches of motor neurons
Myofibrils
Muscle fiber
axon of motor neuron
Acetylcholine
Nicotinic Receptor
neuromuscular junction
Na+
sarcolemma
mitochondrion
Ca2+
sarcoplasmic reticulum
T-tubule
myofibril


axon of
motor neuron
neuromuscular
junction
sarcolemma
Na+
mitochondrion
sarcoplasmic reticulum
T-tubule

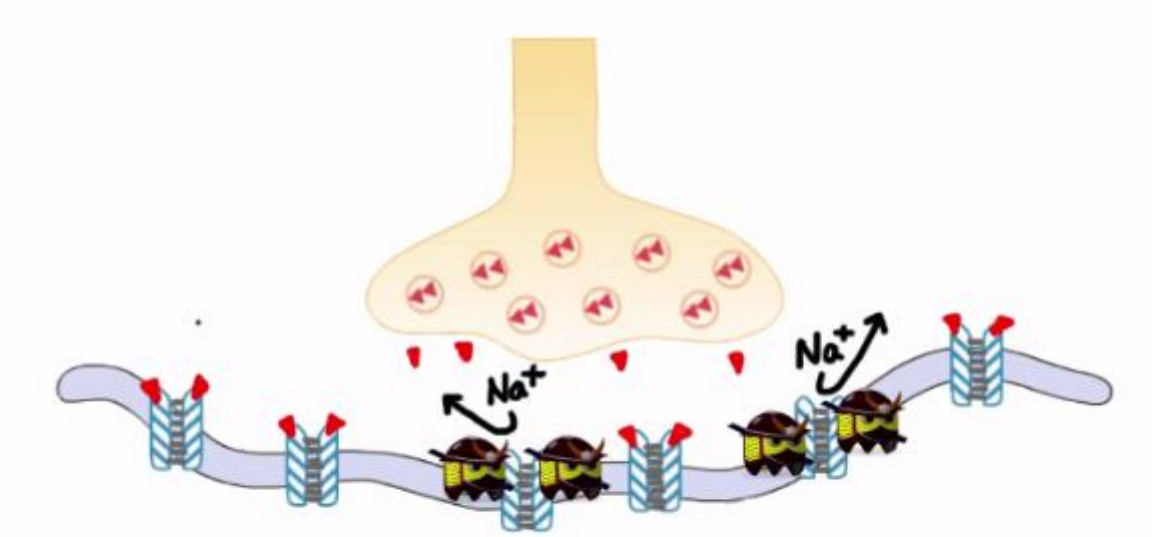
Two types of NMB drugs

1) Depolarizing agents

succinylcholine

two Ach molecules joined thru the acetate methyl gp >> more resistance to degradation by **Acetylcholinestrase.**

Succinylcholine



Phase I

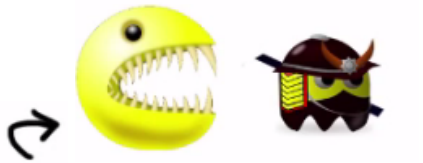
prolonged depolarization (fasciculation)

Phase II

repolarization (flaccid paralysis) .

Succinylcholine

- used in **tracheal intubation** in 1.0-1.5 mg /kg produces profound block within 60s and recover after 10 min



Plasma pseudocholinestrase

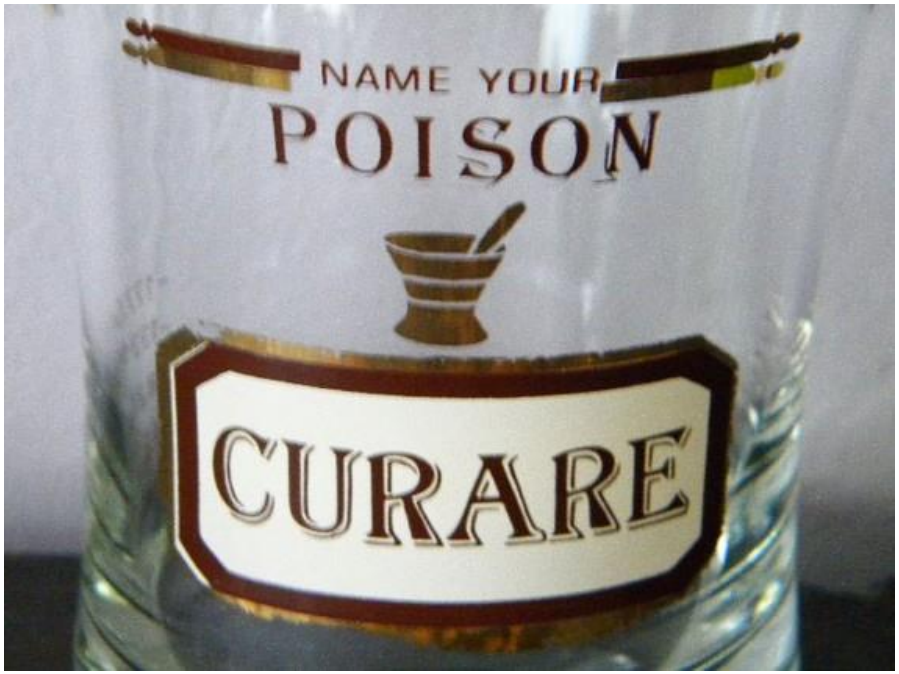
Succinylcholine side effects

Side effect	Mechanism
Bradycardia	Stimulation of muscarinic receptors in the sino-atrial node
Muscle pain	Due to initial fasciculations and occurs in unusual sites, such as the diaphragm, intercostal muscles
Increased serum potassium	from swollen or damaged muscle cells
Malignant hyperthermia	cc by sever muscle contraction and high body temp
Increased intra-ocular pressure	increases in choroidal blood volume, extra-ocular muscle tone and aqueous humour outflow resistance

- Patient with deficiency of the **pseudocholinestrase** → prolonged paralysis

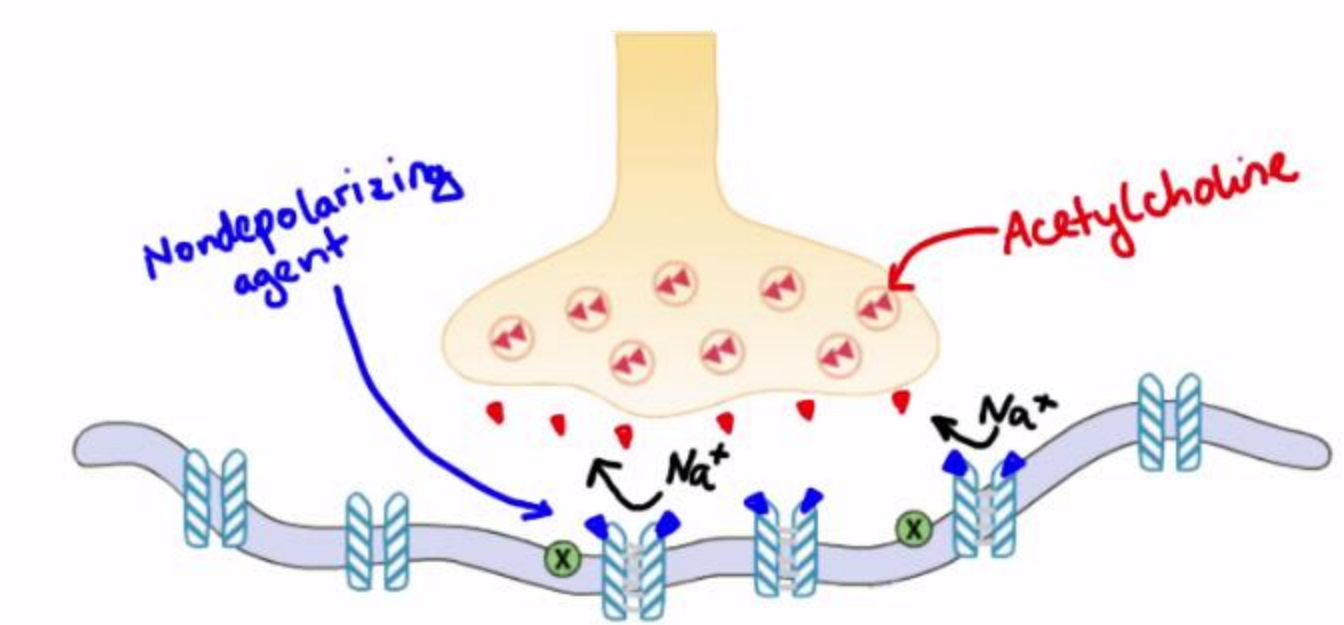
Prolonged apnea

2) Non Depolarizing agents



Non Depolarizing agents

antagonize the action of ACh in a competitive manner at the postsynaptic nicotinic receptor



Non Depolarizing agents

used in **tracheal intubation & facilitate muscle relaxation in general surgery** to use lower dose of anesthesia

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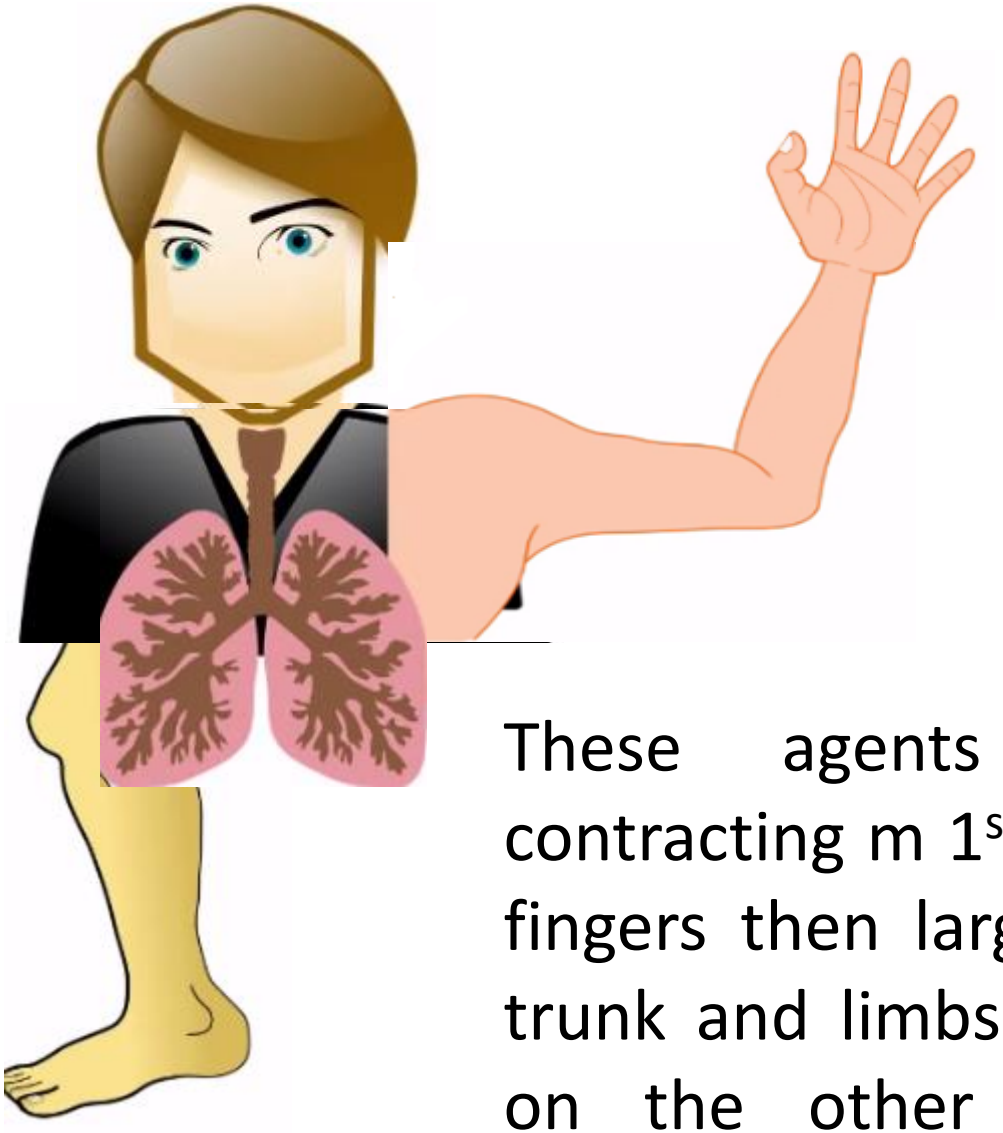


These agents paralyse fast contracting m 1st like eyes> face> fingers then larger m like neck , trunk and limbs lastly diaphragm on the other hand these m recover on the reverse manner

Drugs	Remarks
Tubocurarine	long onset of action and a prolonged duration of effect causes marked histamine release and thus hypotension
Atracurium	intermediate duration of action (40 min) ; histamine relaese → flushing ; ↓ BP ; bronchocostriction Metaboilsed to laudanosine a toxic substance has **epileptogenic** properties so replaced by isomer Cisatracurium

Drugs	Remarks
Pancuronium	Long duration of action (90 min) has sympathomimetic properties. It causes an increase in heart rate, blood pressure and cardiac output.
Vecuronium	duration of action of about (30 min) Metabolized by liver so the action may be prolonged in Pt. with hepatic dysfunction

Reversal of neuromuscular blockade

1- **RECURARIZATION**

After surgery >> spont. Resp. (neostigmine)>> after 2 hr (no neostigmine) >> if Ptn has deficiency of esterase > (resp. problem) due to recuraruization .

Antidote : give more neostigmine

2. **SCOLIN APNEA**

After surgery > before neostigmine , no spon resp. (long) (ptn has defeciency of **pseudocholinestrase**)

Antidote

- Controlled ventilation is required until spontaneous recovery occurs.
- blood transfusion

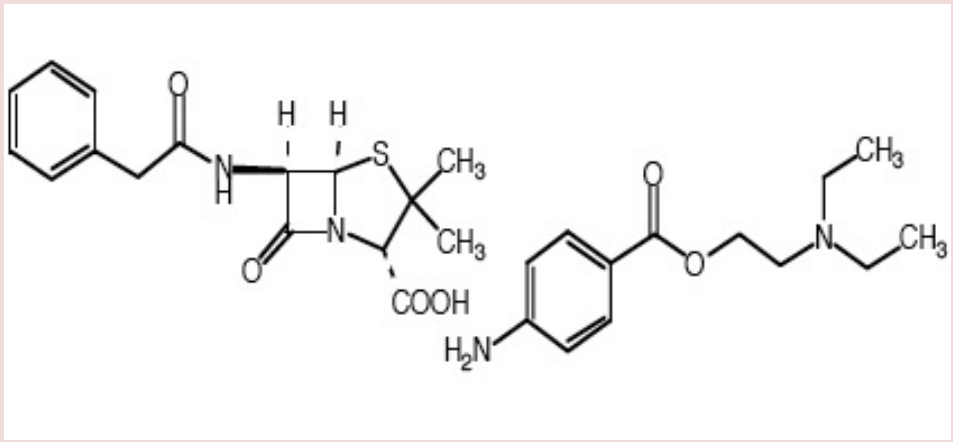

Break

Local Anesthetics

• The first local anaesthetic was **Cocaine** (**leaves of E. Coca**) that was introduced into clinical practice by **Koller** in 1884 as an ophthalmic anaesthetic. Cocaine has powerful central stimulating side effects and induces dependence

• The first synthetic local anaesthetic was **Procaine** which introduced in 1905. It produce adverse effects like **local irritation and tissue damage in addition to systemic toxicity.** At present, it is only used as an amide (procainamide) for cardiac arrhythmias and in procaine penicillin for slow release of penicillin.

***E.* Coca**



procaine penicillin

Local Anesthetics

produce a transient and reversible loss of sensation in a restricted region of the body without loss of consciousness.

Common Uses of Local Anesthetics

Excision

Dermatology

Dentistry

Spinal Anesthesia

Local anesthetic mechanism of action

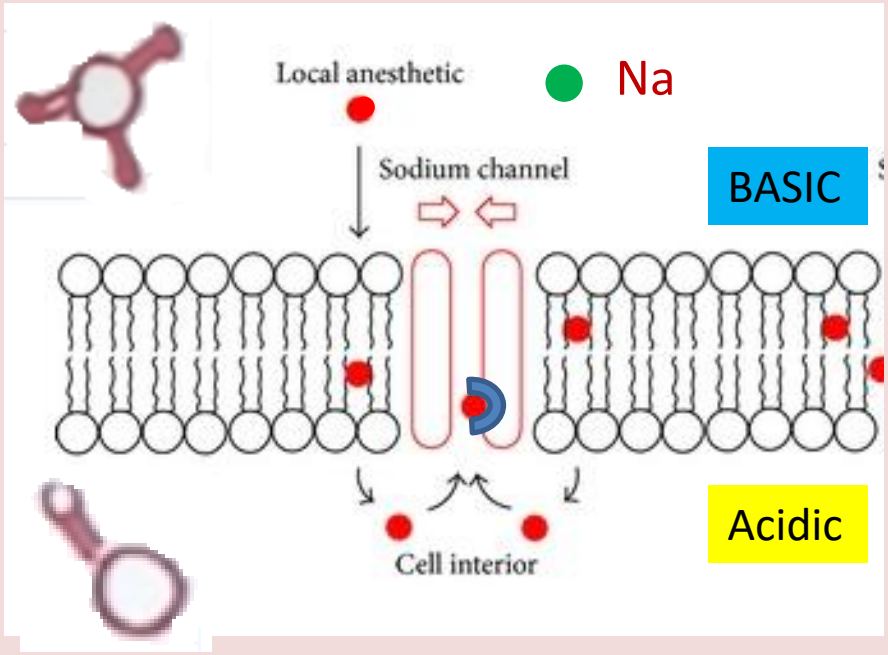
Un-Ionized form = can penetrate cell membrane (effective)

LA Weak base (pka 8-9)

Unionized can penetrate cell membrane

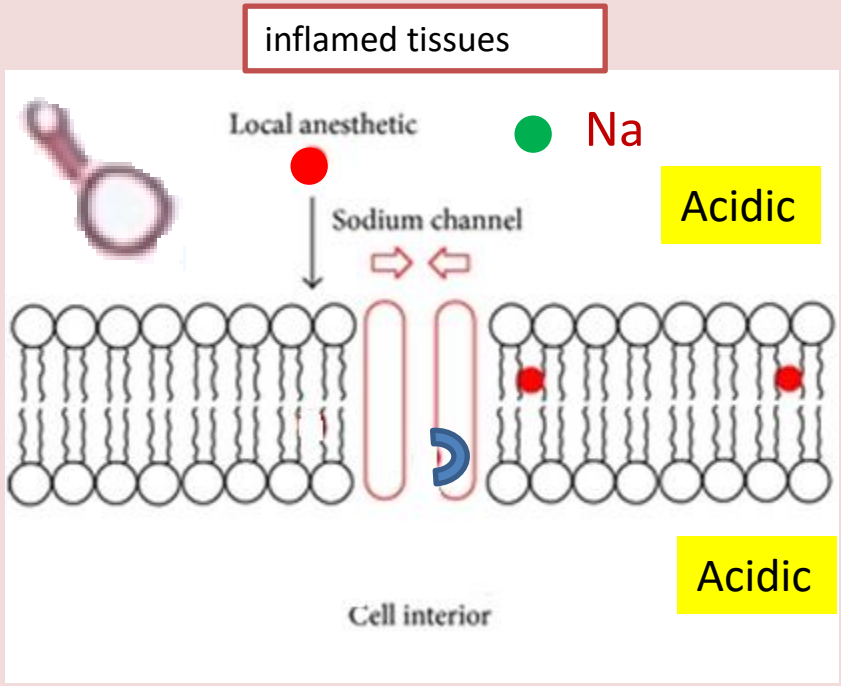
Weak base

ionized form in acidic media



Local anaesthetic in inflamed tissues

Reduced pH ,as in inflamed tissues, increases the prevalence of the **ionized form**, which reduces diffusion into nerves and thereby reduces local anaesthetic effectiveness.



Local Anesthetics
Chemistry and Toxicity

- **Esters**

Procaine, Cocaine, Benzocaine, Tetracaine

are metabolized by **plasma and tissue esterases**

- (Slow & Rapid metabolizers **Genetic poly morphism**)
- short acting & may cause allergic reaction
- **antagonize** the action of **sulfonamides** due to degradation of PABA.

- **Amides**

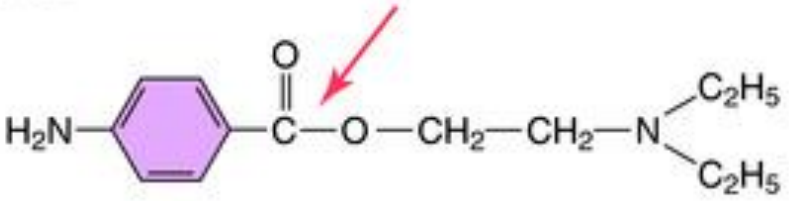
Lidocaine , Bupivacaine, Mepivacaine

are metabolized by **liver amidases** so (**Liver state is very important)**

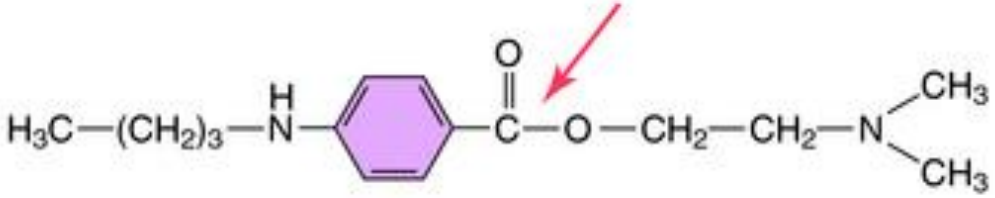
- long acting & less allergic reaction

Local Anesthetics

Esters

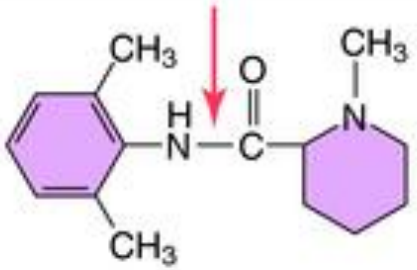


Procaine

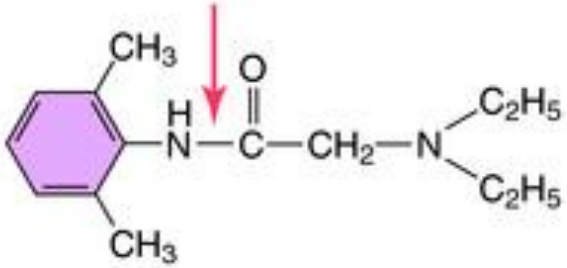


Tetracaine

Amides



Mepivacaine



Lidocaine

Local Anesthetics

- **Absorption**
  - **Co administration with α_1 agonists (Adrenaline);**
    - Decrease LA diffusion into the systemic circulation >> decrease toxicity
    - Prolong LA effects.

Local Anesthetics

- **Side effects ;**
- **Neurotoxicity:** **All LAs** if absorbed in systemic circulation can cause CNS toxicity manifests as excitation (**seizure**) followed by depression. Initial excitation is due to inhibition of inhibitory neurons.

- **Cardiotoxicty:** The primary site of action is the myocardium, decreases in electrical excitability, conduction rate, and force of contraction.

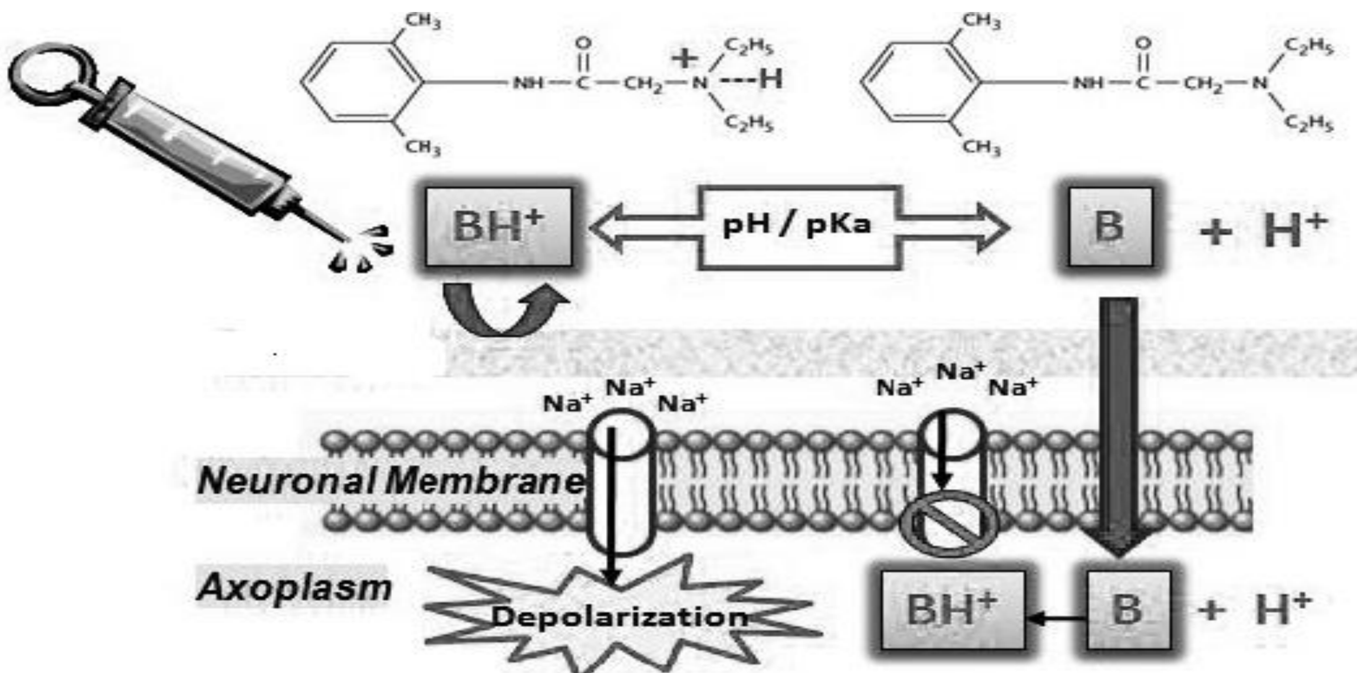
  All LAs decrease BP except cocaine (increases).

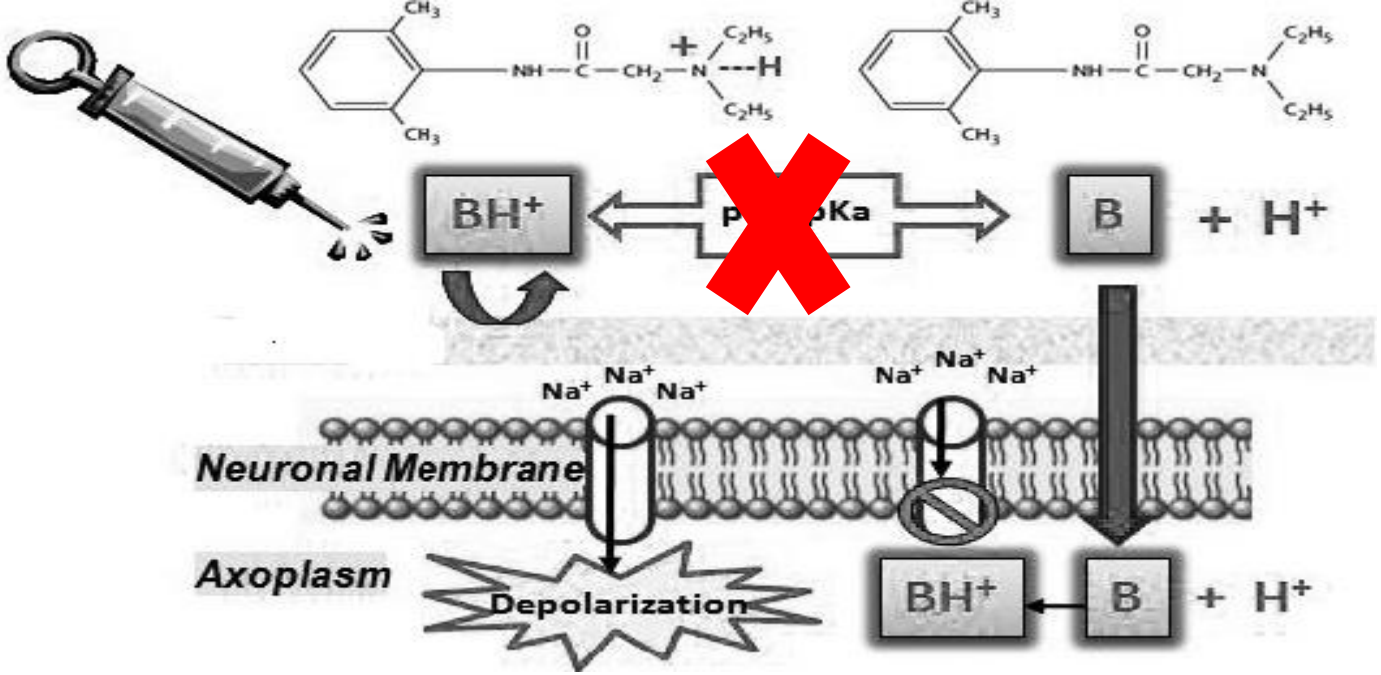
Local Anesthetics

Tachyphylaxis

* Local anaesthetics are weak bases and marketed as hydrochloride salts (pH 4 to 6) for reasons of solubility and stability.

* After injection, the salts are buffered in the tissue to physiological pH, thereby providing sufficient free base for diffusion through axonal membranes.





However, repeated injections deplete the local available buffer. The ensuing acidosis **increases the extracellular cationic** form, which diffuses poorly into axons.

Call tachyphylaxis, especially in areas of limited buffer reserve, such as the cerebrospinal fluid. Therefore, an agent with a long duration of action like bupivacaine is preferred in this condition to **avoid repeating the dose**.

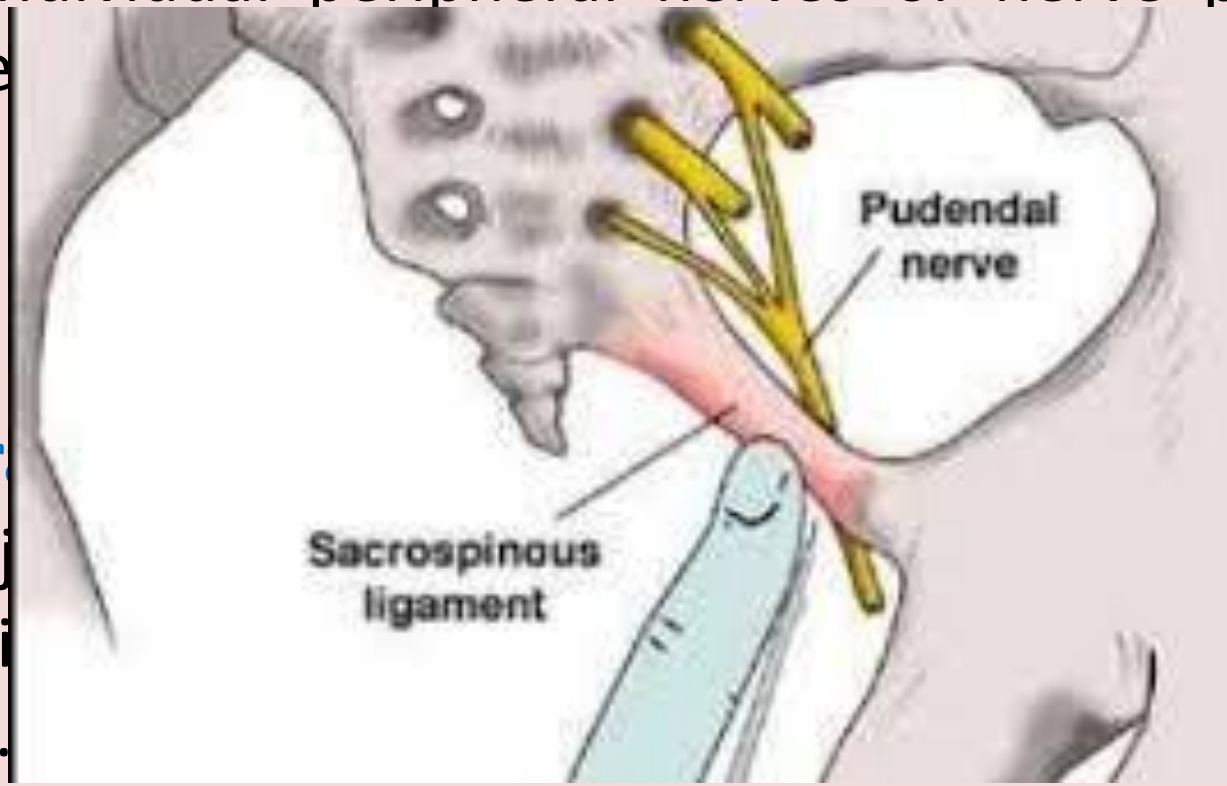
Local anesthetic administration

- **Topical** [**Lignocaine** is the commonly used agent for topical anesthesia of mucous membranes].

  [**Oxethazaine** (mucaine) can be used to provide symptomatic relief in gastritis (it remains unionized in the acidic pH of stomach]

- **Infiltration** [injected s.c. in the area of operation site for blocking the sensory nerve endings used in minor surgeries like excisions, suturing. **Adrenaline** can be added to the LA to prolong its duration of action and to prevent systemic side effects].

- **Nerve block** [Injection of local anesthetic into or about individual peripheral nerves or nerve plexuses produce ngerous , skills,



- **Epidur ative pain** ; inj space ; li high skill . e.g. ine, often with 2 µg/mL of fentanyl added, frequently are used to provide analgesia during labor

- **Intravenous regional Block (Bier's Block)** indicated for any procedure on the **arm below the elbow or leg below the knee that will be completed within 40-60 minutes.** An intravenous cannula is inserted in a distal vein in the limb scheduled for surgery. The tourniquet is then applied to the upper arm or thigh.
- The drug of choice for IVRA is **prilocaine**

- **Spinal nerve block** [injection of local anesthetic into the CSF in the lumbar space.]

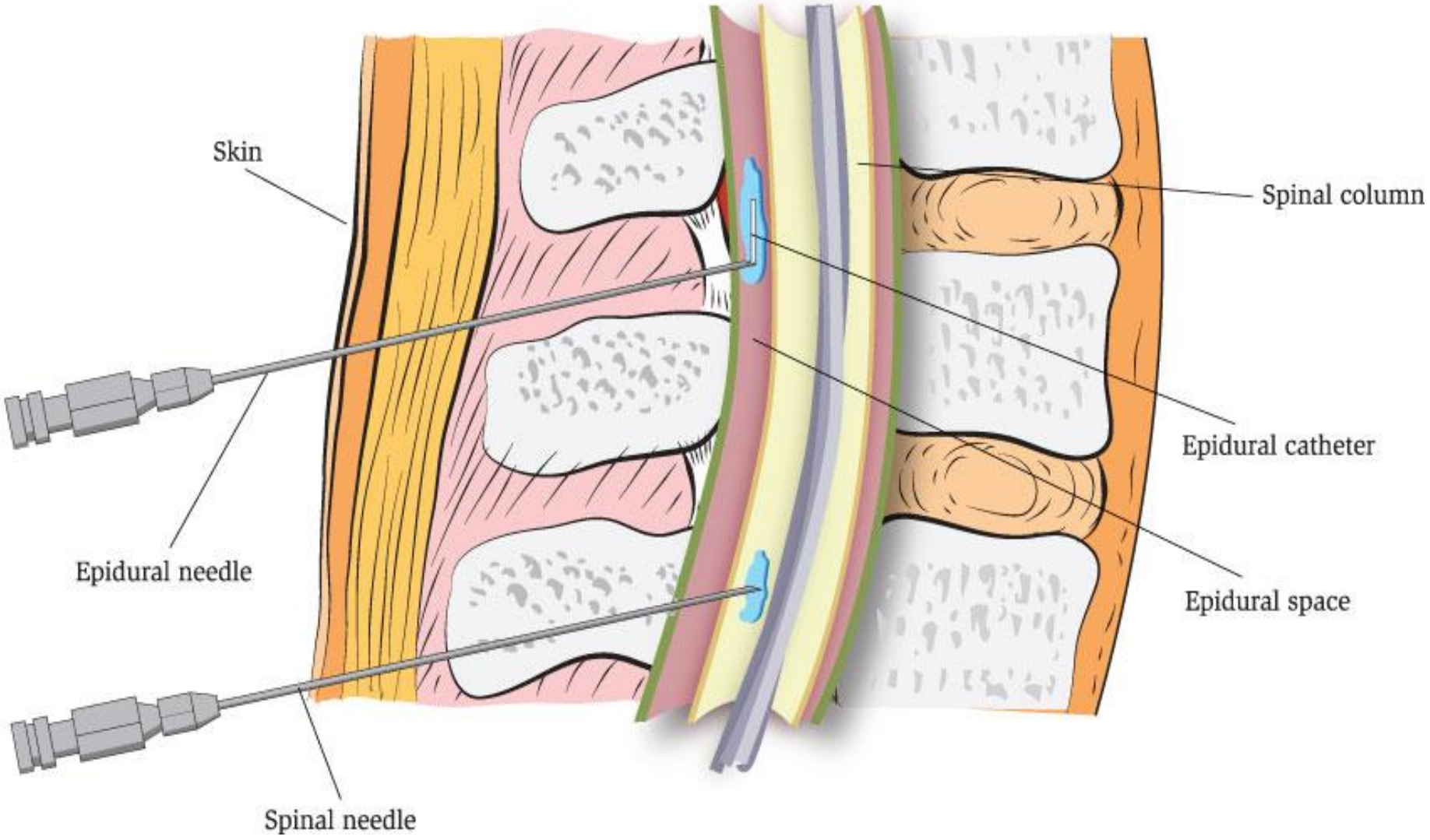
Drugs used for Spinal Anaesthesia

- Lignocaine – 5% in 7.5% dextrose
- Bupivacaine – 0.5% in 8% dextrose

Indications

- Orthopaedic surgery of lower limbs and pelvis.
- Surgery of lower abdomen (all pelvic and perineal surgeries, hernia, hydrocele, appendix)
- Gynaecological and obstestrics surgeries (hysterectomy, cervical surgeries, tubectomy, tuboplasty, caesarean section).

s/e : headache (CSF leakage), hypotension


Skin
Spinal column
Epidural catheter
Epidural needle
Epidural space
Spinal needle

Special remarks

- **All LAs are vasodilators except cocaine** (act as sympathomimetic due to inhibition of nor-adrenaline reuptake) which is a vasoconstrictor.
- **Chlorprocaine** is the **shortest acting** local anaesthetic and is **contra-indicated in spinal anaesthesia** (It may cause paraplegia due to the presence of sodium metabisulphite as preservative, which is neurotoxic).
- **Lignocaine** is the most commonly used LA and is the drug of choice for ventricular tachycardia.