CHAPTER 25

# Peripherally and centrally acting skeletal muscle relaxants

## Peripherally acting skeletal muscle relaxants

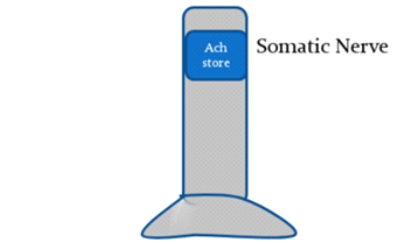
The drugs that relax the skeletal muscles by acting on neuromuscular junction (motor end plates) or by acting directly on skeletal muscle.

I. NEUROMUSCULAR BLOCKING AGENTS
II. DIRECTLY ACTING

I. NEUROMUSCULAR BLOCKING AGENTS
   1. Non depolarizing Blockers:
      i) Long acting: Pancuronium, Pipecuronium, Doxacurium
      ii) Intermediate acting: Vecuronium, Atracurium, Rocuronium
      iii) Short acting: Mivacurium
   2. Depolarizing Blockers:
      i) Succinylcholine

II. Directly acting
   i) Dantrolene sodium

**Mechanism of action** of Non depolarizing Blockers: (Fig.31A/31B)



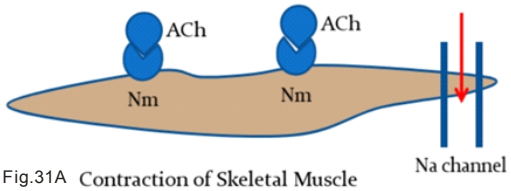




Fig.31A Contraction of Skeletal Muscle

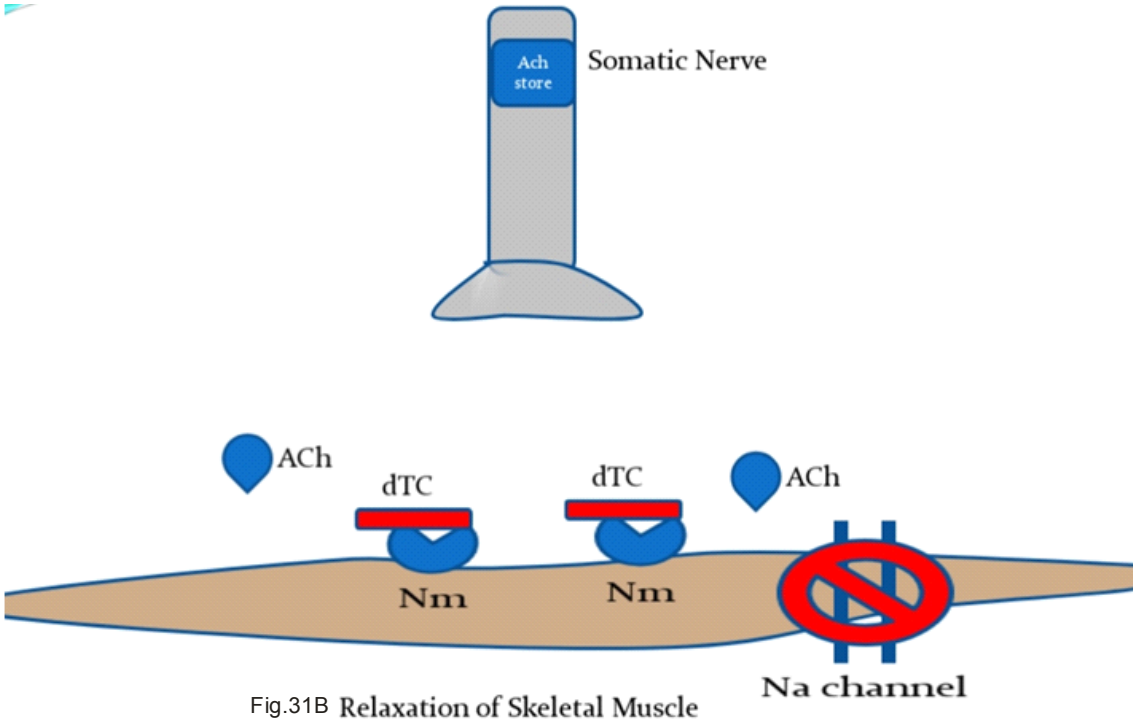



Fig.31B Relaxation of Skeletal Muscle

(Contraction)

ACh stimulates the nicotinic receptors in the skeletal muscle ($N_M$ receptors) → opening of Na+ channel → Depolarization →↑ (stimulates) skeletal muscle → contracts skeletal muscle

Non depolarizing blockers ↓ (inhibit) the nicotinic receptors in the skeletal muscle competitively with ACh → ACh cannot occupy the receptors → No depolarization → No conduction of impulse →↓ (relaxation) of skeletal muscles

**Mechanism of action** of Depolarizing Blockers:

Drug → occupies the Nicotinic receptors ($N_M$) → depolarization like ACh, but persistent depolarization (no repolorization) → impulse cannot be transmitted → initial stimulation followed by relaxation of skeletal muscle.

**Mechanism of action** of directly acting drug:

Certain condition stimulates Ca++ release intracellularly → Ca++ →entry into skeletal muscles → violent contraction of skeletal muscles → hyperthermia. After Dantroline → ↓(inhibits) Ca++ entry into the skeletal muscles → no depolarization → relaxation of skeletal muscles → no violent contraction of skeletal muscle → temperature will come down.

## NON DEPOLARIZING AGENTS

**All the drugs are having similar Mechanism of action**

**All drugs are having similar Clinical uses**

They differ only in pharmacokinetic properties (according to the conditions, the drugs have to be selected)

- They are skeletal muscle relaxants.
- They are peripherally acting neuromuscular blockers.

**Mechanism of action :**(Ref above before)

**Pharmacological actions**

I. Action on skeletal muscle: Intravenous injection of non-depolarizing drugs rapidly produce muscle weakness followed by flaccid paralysis. Fast moving smaller muscles (fingers, extraocular) are affected first, paralysis spread hands, feet → arm, leg, neck, face → trunk→ intercostal muscles → finally diaphragm. Recovery occurs in the reverse sequence. Diaphragmatic contractions resume first.

II. On Histamine release → slight histamine release will cause slight fall in B.P.

III. On CVS → reduced venous return

IV. Autonomic ganglia ($N_N$). Some degree of ganglion blockade → Fall in BP

**Dose**:

Pancuronium - 0.05 – 0.1 mg/kg
Vecuronium - 0.05 – 0.1 mg/kg
Pipercurium - 0.05 – 0.1 mg/kg

**Clinical uses :**

1. The most important use of neuromuscular blockers is as adjuvant to general anaesthetic. Adequate skeletal muscle relaxation can be achieved in higher planes (less anaesthetic dose is required) to produce adequate skeletal muscle relaxation. In major surgery adequate skeletal muscle relaxation is needed, which cannot be achieved by general anaesthetics alone in therapeutic dose. Adequate skeletal muscle relaxation is useful for the surgeon and the patients (small incision is sufficient, so small wound → less infection → healing will be quick, less painful). Also reduce the reflex muscle contraction in the region undergoing surgery.

2. To assist maintenance of controlled ventilation during anaesthesia
3. They are useful in major surgery, intubation, endoscopies and orthopaedic manipulations
4. For assisted ventilation in critically ill patients in .I.C.U (need ventilator support.) This can be facilitated by continuous IV infusion of neuromuscular blockers
5. To protect the patients from convulsion during eletroconvulsive therapy.
6. In severe cases of tetanus and status epilepticus.

**Adverse effects**

-respiratory paralysis. prolonged apnoea are the most common problem ( antidote Neostigmine is given to reverse the action very quickly), histamine release –fall in BP.

## DEPOLARIZING AGENT (SUCCINYLCHOLINE)

- It is a depolarizing skeletal muscle relaxant

**Mechanism of action :**Ref above before

**Pharmacological actions**

I. Action on skeletal muscle: It produces initial fasciculation and twitching followed by skeletal muscle relaxation. Other actions on skeletal muscle are similar to that of non – depolarizing agents. It produces excellent intubating conditions, viz. relaxed jaw, vocal cord apart, and immobile with no diaphragmatic movement is obtained within 2 min.

II. No Histamine release

III. Autonomic ganglia → slight stimulation of sympathetic ganglia → rise in BP

**Clinical uses :**

1. It is employed for brief procedures like endotracheal intubation, laryngoscopy, bronchoscopy, esophagoscopy, reduction of fractures, dislocation and to treat laryngospasm.

**Adverse effects:** ↑ (rise in) BP, tachycardia, hyperkaelemia (common in burns, uraemia and arrhythmia), Prolonged apnoea in patients with atypical pseudocholinesterase, soreness of muscle (due to fasciculation).

## DANTROLINE

**Mechanism of action** : (ref: before)

**Clinical uses :**

1. In malignant hyperthermia due to general anaesthetic like Halothane

2. Reduce the spasticity in the upper motor neurone disorders like hemiplegis, paraplegia and multiple sclerosis. It reduces the voluntary muscle power also. (Hence centrally acting skeletal muscle relaxants are useful in the above mentioned conditions, since they do not affect the voluntary muscle power)

**Adverse effects**: muscular weakness, sedation, troublesome diarrhoea.

Advantages of newer neuromuscular blockers over the older ones:

1. No cardiac or vascular side effects
2. No/minimum Histamine release
3. Rapid and short acting – easy reversal

## CENTRALLY ACTING SKELETAL MUSCLE RELAXANTS:

They are also called as spasmolytic of skeletal muscle.

### DRUGS:

Mephenesin group: Mephenesin, Chlorzoxazone

Diazepam

Baclofen

Tizanidine

Gabapentine

### Mechanism of action :

They ↓ (Inhibit) the internuncial neurones in the spinal cord → ↓ (inhibit) the stretch reflex → ↓ (reduce) skeletal muscle spasticity → ↓ (inhibit) pain due to spasticity

They selectively depress spinal and supraspinal polysynaptic reflexes involving in the regulation of muscle tone without affecting the voluntary muscle power.

Diazepam : ↑ (Facilitate) the action of GABA in the synapses of the brain → ↓ (inhibition) of stretch reflux → acts at the level of supraspinal site.

### Clinical uses :

1. In upper motor neurone disorders- hemiplegia, paraplegia, multiple sclerosis or any hypertonia of spinal cord injury
2. In acute muscle spasm; Over stretching muscle, sprain, tearing of ligament and tendons, dislocations, fibrositis, bursitis, which cause painful spasm of muscles
3. Anxiety with muscle spasm (Diazepam)
4. Tetanus (IV Diazepam)
5. Orthopaedic manipulations: Under the influence of Diazepam, it is very easy for reduction.


These drugs produce reversible loss of sensory perceptions, especially pain at the local site of administration of local anaesthetics.

## CLASSIFICATION

### *Injectable anaesthetic*

*Low potency, short duration*

Procaine

Chloroprocaine

*Intermediate potency and duration*

Lidocaine (Lignocaine)

Prilocaine

*High Potency, long duration*

Tetracaine (Amethocaine)

Bupivacaine

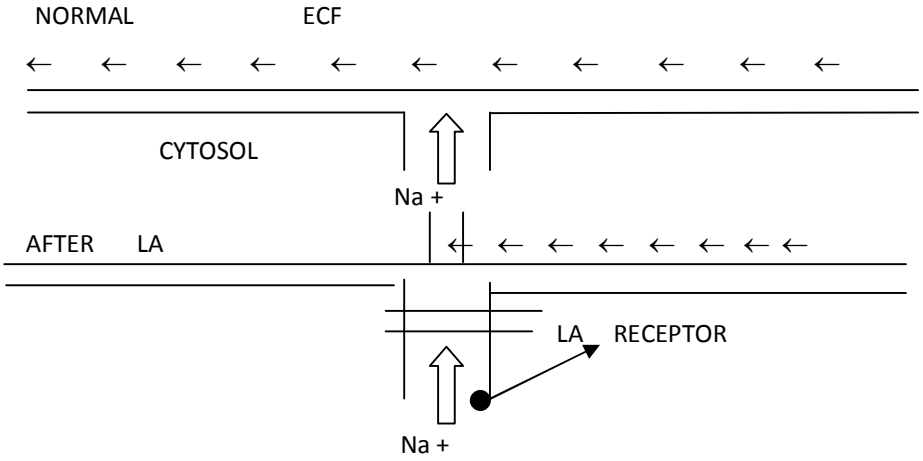
Ropivacaine

Dibucaine (Cinchocaine)

### *Surface anaesthetic*

| Soluble | Insoluble |
|---|---|
| Cocaine | Benzocaine |
| Lidocaine | Butylaminobenzoate |
| Tetracaine | (Butamben) |
| Benoxinate | Oxethazaine |

**Mechanism of action : (Fig.32)**




LA – Local Anaesthetic

**Fig.32 Conduction of pain impulse through sensory nerves and site of action of LA**

Normally if any impulse comes across nerve → Na+ enters through voltage gated Na+ channel → generates and conducts nerve impulse → pain is felt.

After local anaesthetic → LA binds with LA receptor present near the intracellular end of the voltage gated Na+ channel → ↓ ( blocks) them → ↓ (prevents) the entry of Na+ through voltage gated Na+ channel → ↓ ( blocks) both the generation and conduction of impulses → anaesthesia is produced in the proximal areas of the block

Local actions:

1. Block the sensory and motor nerves
2. Smaller sensory nerves are anaesthetized first
3. LAs fail to provide adequate pain relief in inflammed areas
4. Normally Adrenaline is combined with local anaesthetics : The advantages are i) Prolong the duration of action of LAs. ii) reduces the systemic toxicity iii)reduces the bleeding in the field of surgery and iv) enhances the intensity of anaesthesia

Systemic actions: if LAs are absorbed i)vasodilatation and fall in BP ii) CNS stimulation followed by CNS depression. iii) inhibit the heart- (bradycardia)

**Clinical uses :** LIGNOCAINE

1. As surface anaesthesia: local application on skin and mucous membrane: to relieve pain in corneal ulcer, corneal surgery, tonometry, stomatitis, sore throat, endoscopies, endotracheal intubation, ulcer, burns, itching, dermatoses etc.,
2. As infiltration anaesthesia: LAs are injected subcutaneously in and around the area to be anaesthetised, for I.V. cannulation, skin surgery, for catheterization, in fissure and painful piles, proctoscopy

3. As nerve block anaesthesia: injection of LAs near the nerve trunk. (lingual nerve block in tooth extraction)
4. As spinal and epidural anaesthesia: LAs are injected into subarachnoid space/epidural space: Useful for operation on the lower limbs, pelvis, lower abdomen, prostatectomy, hydrocele operation, caesarean section
5. As antiarrhythmic: ( ref : antiarrhythmic drugs )

**Dose** of Lignocaine – 1-2%

**Adverse effects**: I.V. injection of LAs in arrhythmia, they produce fall in BP, bradycardia, CNS stimulation followed by CNS depression

Delay wound healing

Adrenaline is combined with Lignocaine in surface, infiltration and nerve block anaesthesia (not in arrhythmias).

Contraindication of Lignocaine + Adrenaline preparation: in hypertenstion and ischaemic heart diseases.