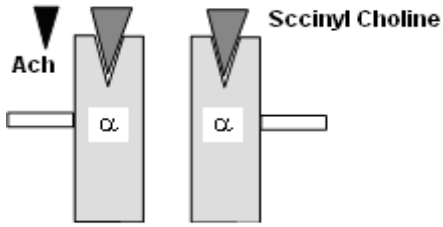
NEUROMUSCULAR BLOCKERS

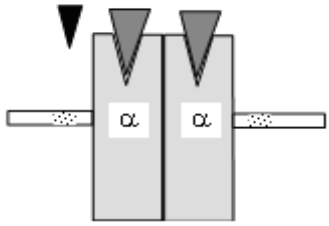
Neuromuscular blockers are drugs used to induce skeletal muscle paralysis by blocking the nicotinic Nm receptors at the motor end plate (MEP) of the skeletal muscles. There are 2 major subgroups: the **Depolarizing** *(non completive)* subgroup which contains only succinylcholine & the *non-depolarizing* (**Competitive**) or curare-like subgroup**.**

Neuromuscular blockers lead to flaccid skeletal muscle paralysis which involves all the skeletal muscles of the body, but usually the respiratory muscles are the last to be affected, and the first to recover. Initial fasciculations, may occur once before the start of paralysis, with the depolarizing subgroup.



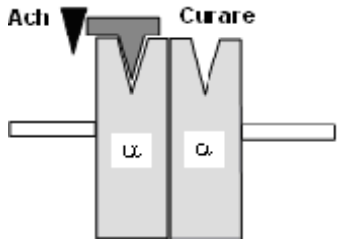
Phase I

Phase I (depolarizing phase): Succinylcholine induces persistent depolarization of the MEP since it is slowly hydrolysed by pseudocholine esterase enzyme.



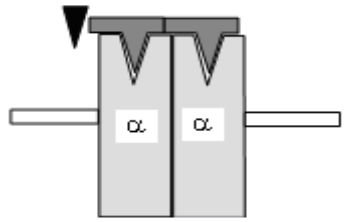
Phase II

Phase II (desensitization phase): On prolonged use, the MEP is repolarized BUT it becomes insensitive to ACh.



Small dose

Small dose → Competitive blockade of Nm receptors at MEP



Large dose

Large dose → Block presynaptic Nn receptors→↓ Ach release

Block ion channels of Nm receptors

Hydrolysis by plasma pseudocholine esterase enzyme e.g.

Succinyl choline → very short duration of action; < 10 minutes

Mivacurium → short duration of action; 10-20 minutes

Spontaneous non enzymatic hydrolysis e.g.

Atracurium, **Cisatracurium** → moderate duration of action; ⅓- ½ h

Gantacurium → very short duration of action

Hepatic elimination for steroid NMBs e.g.

Vecuronium, **Rocuronium** → moderate duration; ⅓- ½ h

Pancuronium, *Gallamine* → *more prolonged action*

Renal elimination e.g.

Tubocurraine → the longest duration of action ; > ¾ h

1) Endotracheal intubation:

Succinyl choline is of choice, however, there are alternatives.

2) To control convulsions

They are used if other antiepileptic drugs fail or during electroconvulsive therapy; **succinyl choline** is preferred since it is short acting.

3) During surgery:

They are used to facilitate muscle cutting or to prevent operative cough/ laryngospasm: competitive drugs are used since they are longer in their duration of action.

The choice depends on the patient

- In patients with **normal Kidney & Liver**: **Pancuronium** is of choice
- In patients with **hepatic or renal diseases** *atracurium* **or Cisatracurium** is preferred
- In patients with **CV diseases** Vecuronium and **Rocuronium** offer CV stability

4) To facilitate mechanical ventilation:

Competitive drugs are used by IV infusion.

The New agents are usually more potent with less adverse effects because they have: No ganglion blocking activity & No or minimal histamine-releasing effect

Tubocurarine

1) **Prolonged skeletal muscle paralysis** which can be controlled by neostigmine (preceded by atropine to prevent cardiac arrest). New methods can be used with individual drugs. Click to see Drug interaction.

2) **Allergy** e.g. bronchial asthma 2^{ry} to histamine release

3) **Hypotension** 2^{ry} to histamine release, ganglion Nn receptor blockade and muscle paralysis

Gallamine and pancuronium have atropine-like action → ↑ HR and ABP (so they are not used in cardiac patients)

Pharmacogenetic adverse effects

1) Succinylcholine apnoea

It is prolonged respiratory paralysis following succinylcholine. It is due to a genetic defect in the pseudocholine esterase enzyme (ChE) e.g. abnormal variant of ChE or acquired ChE deficiency e.g. 2^{ry} to liver disease

Control:

a) Prophylactic: give fresh frozen plasma or blood to supply the ChE enzyme

b) Keep the patient on artificial respiration; till succinylcholine diffuses away from the MEP.

c) *Neostigmine is controversial in patients with deficient ChE enzyme.*

2) Malignant hyperthermia

It is intense muscle spasm with marked rise of body temperature and acidosis (due to ↑ lactic acid production). It usually occurs with succinylcholine + halothane due to the presence of an abnormal sarcoplasmic reticulum (SR) calcium pumping mechanism.

Control:

It can be controlled by Dantrolene (to decrease Ca^{++} release from the SR) + Measures to lower the temperature and to correct acidosis

Effects 2^{ry} to persistent depolarization (& fasciculations):

1) **Muscle pain** due to unsynchronized muscle contractions

2) **Increase intraocular pressure** due to fasciculations of eye muscles

3) Increase intragastric pressure → **regurgitation** due to fasciculations of abdominal muscles

4) **Hyperkalemia** due to escape of K^+ from the open ion channel

Effects 2^{ry} to action on other receptor:

Parasympathomimetic effects e.g. **bradycardia, salivation**.

1. **What is the mechanism of action of curare?**
2. **What is the mechanism of action of succinylcholine?**
3. **Phase I action of succinylcholine is due to … … … … while phase II is due to … … … … … … … … … … …**
4. **Atracurium is eliminated mainly by … … … … … … while vecuronium is eliminated mainly by … … …**
5. **Succinylcholine is the shortest acting neuromuscular blockers (NMB) because … … … … … … … … … …**
6. **… … … & … … … are NMB preferred for endo-tracheal intubations because … … … … … …**
7. **Non depolarizing NMB are preferred to succinylcholine in … … … … … & … … … … … … …**
8. **Enumerate adverse effects of curare**
9. **Respiratory paralysis due to curare-like drugs can be reversed by a) … … … … … … b) … … … … … … and c) … … … … … … … … while due to succinylcholine is reversed by … … … … … …**
10. **How can neuromuscular blockers lead to hypotension?**
11. **NMB with atropine-like actions include … … … … … & … … … … … while those with cholinomimetic actions include … … … … … …**
12. **What are the adverse effects which occur secondary to persistent depolarization induced by succinylcholine**
13. **Discuss malignant hyperthermia**
14. **Discuss succinylcholine apnoea**