Topic: Introduction

Outcomes:

- List neuromuscular blocking drugs
- Describe mechanism of action and clinical uses of neuromuscular blocking drugs
Neuromuscular blocking drugs

- They block cholinergic transmission between motor nerve endings and the nicotinic receptors on the skeletal muscle.
- They act either as antagonists (non-depolarizing drug) or as agonists (depolarizing drug) at nicotinic receptors on motor endplate.
- They allow rapid recovery from anaesthesia and reduce postoperative respiratory depression.
- All drugs are given parenterally. They are highly polar drugs and do not cross the blood-brain barrier.

[Ref: 1, 5]
# Classification

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-depolarising (Competitive)</td>
<td>- Long acting: d-Tubocurarine, Pancuronium, Doxacurium, Pipecuronium</td>
</tr>
<tr>
<td></td>
<td>- Intermediate acting: Vecuronium, Atracurium, Cisatracurium, Rocuronium, Rapacuronium</td>
</tr>
<tr>
<td></td>
<td>- Short acting: Mivacurium</td>
</tr>
<tr>
<td>Depolarising</td>
<td>- Suxamethonium (Succinylcholine) Decamethonium</td>
</tr>
</tbody>
</table>

[Ref: 3]
Physiology of muscle contraction

- Impulse passes down a motor nerve to voluntary muscle
- Release of acetylcholine from the nerve endings into synaptic cleft
- ACh activates nicotinic receptors on the membrane of the motor endplate (a specialised area on the muscle fibre)
- Opening of sodium ion channels for momentary passage of ion
- Depolarisation of motor endplate and initiation of muscle contraction

[Ref: 2]
Mechanism of action: non-depolarising

- Competitive antagonists of acetylcholine
- Compete with acetylcholine and protect motor endplate from depolarisation by acetylcholine
- Thus inhibit muscular contraction and cause flaccid paralysis
- Small muscles of face and eye are paralysed first, followed by fingers, limbs, neck, and trunk muscles. Next, intercostal muscles and lastly, diaphragm
- Muscles recover in the reverse manner

[Ref: 1, 2]
Mechanism of action: depolarising

Suxamethonium acts like agonists to nicotinic receptor and depolarise the motor endplate like ACh

It persists at high concentrations in synaptic cleft (as metabolised by plasma butyrylcholinesterase) and constantly stimulate nicotinic receptor. ACh rapidly metabolised in synaptic cleft by acetylcholinesterase

Phase-I: opening of sodium channel associated with nicotinic receptors, which results in depolarisation of receptor. This leads to a transient twitching of the muscle (fasciculations)

Phase-II: continuous binding of depolarizing agent with nicotinic receptors causes resistance to depolarisation (receptor is desensitized to the effect of ACh) and flaccid paralysis. Afterwards continuous depolarisation gives way to gradual repolarisation as the sodium channel closes or blocked. During this phase, block is partially reversed by anticholinesterases

[Ref: 1-3]
Clinical uses

- Muscular relaxation during surgery, as adjuvants to general anaesthesia
- To assist mechanical ventilation in intensive care units
- During electroconvulsive therapy, to prevent injury from excessive muscular contraction
- Severe cases of tetanus and status epilepticus not controlled by other drugs
- Suxamethonium is applied for brief procedures (e.g. endotracheal intubation, laryngoscopy, bronchoscopy, esophagoscopy, reduction of fractures, dislocations, and to treat laryngospasm)

[Ref: 2, 3]
Adverse effects

- Hypotension: as tubocurarine causes (a) ganglion block and (b) histamine release from mast cells
- Bronchoconstriction: as tubocurarine causes histamine release from mast cells
- Tachycardia: pancuronium
- Postoperative muscle pain: suxamethonium
- Bradycardia: muscarinic agonist effect of suxamethonium
- Arrhythmia: suxamethonium increases potassium release from intracellular stores and causes hyperkalaemia
- Prolonged apnoea: suxamethonium is metabolised by pseudocholinesterase. Deficiency of this enzyme and electrolyte imbalance cause apnoea
- Raised intraocular pressure: nicotinic agonist effect of suxamethonium on extraocular muscles
- Malignant hyperthermia: suxamethonium causes intense muscle spasm and dramatic rise in body temperature, if mutation of the Ca$^{2+}$ release channel of the sarcoplasmic reticulum

[Ref: 1, 4]
Antagonist of competitive neuromuscular blocker

**Neostigmine:** anticholinesterase drugs, which allows accumulation of acetylcholine and reduces the effect of competitive neuromuscular blocker. It is mixed with glycopyrronium to prevent bradycardia caused by parasympathetic effects of neostigmine.

**Sugammadex:** low molecular weight sugar which can reverse neuromuscular block from rocuronium and vecuronium.

[Ref: 2]
Acknowledgement


Thanks for your valuable time. Regards.