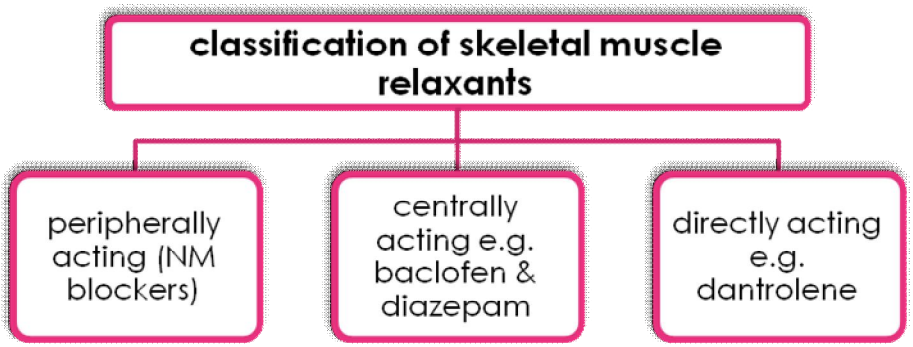
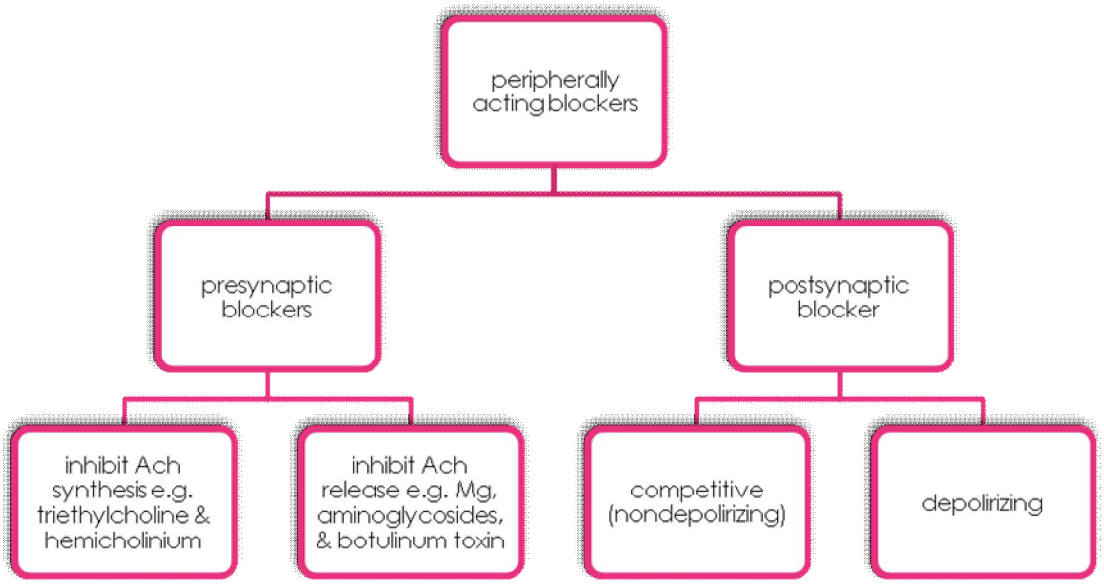
Skeletal muscle relaxants



Peripheral action NM blockers:



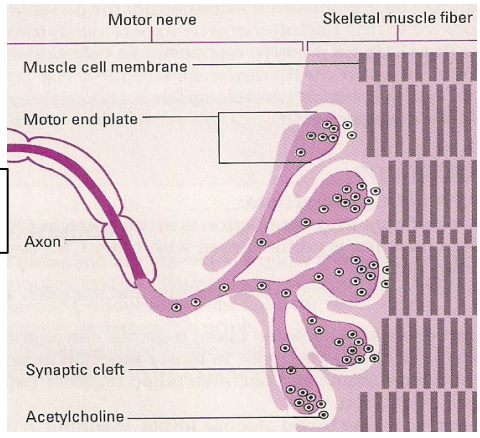
Postsynaptic NM blockers:

1) Competitive NM blockers (non-depolarizing)

- d- tubocurarine
- atracuri**um**
- Doxacurium
- Metocurine
- mevacurium
- gallamine
- Pancuronium
- Pipecuronium
- Rapacuronium
- Rocuronium
- vecuronium

Isoquinoline derivatives

steroid derivatives



2) Depolarizing blockers:

- Succinylcholine (suxamethonium)
- Decamethnoium

Uses of NM blockers:

1. Control convulsion →electroshock therapy in psychotic patients.
2. Relieve of tetanus and epileptic convulsions.
3. Facilitate endoscopy.
4. As adjuvant in general anesthesia to induce muscle relaxation (only when artificial respiration is available)
5. Orthopedic surgery.
6. control of ventilation (endotracheal intubation)

Competitive NM blockers:

Mechanism of action:

- Competitive antagonists: compete with Ach at the nicotinic receptors of NMJ.
- In higher dose they will block the ion channel.
- No depolarization of postjunctional membrane.
- Cholinesterase inhibitors can reverse blockade e.g. neostigmine
  - used to shorten the duration of blockage or overcome the over dosage
  - Cholenestrase inhibitors in high dose may cause depolarizing block because of more Ach at the junction.(toxicity)
  - In higher dose NM blockers will reduce the ability of the cholinesterase inhibitors to reverse the action
- Halogenated carbons, aminoglycosides, and Ca channel blocker synergize the effect of NM blockers

Pharmacokinetics:

- They are polar compounds (do not cross BBB and placenta).
- They have limited volume of distribution because they are highly ionized
- Inactive orally and taken parenterally.
- Metabolism depends upon kidney or liver except :
  - atracurium – mivacurium .
  - *atracurium undergoes spontaneous hydrolysis " automatic*

Pharmacological action:

a) used in skeletal muscle paralysis = flaccid paralysis.

- order of muscle to be paralyzed **:**

1. Small muscles, ptosis, difficulty in speech.
2. Muscles of limbs, neck and trunk.
3. Intercostal muscles and the diaphragm.

Recovery is in the reverse order

b) CVS :

1. Hypotension (because of histamine released)
2. ↑ heart rate.

- d-tubocurarine
- mivacurium
- atracurium
- gallamine
- pancuronium

Drug	Speed of onset	Duration of action	Main side -effects	Notes (additional)
Tubocurarine	Slow (5 min)	Long (1-2hrs)	Hypotension (ganglionic block plus histamine release) Broncohoconstriction	Plant alkaloid,rarely used. **Alcuronium** is semi - synthetic with similar properrties but few side effects
Gallamine	Slow	long	Tachycardia (muscarinic antagonist)	100% renal excretion, avoided in renal failure. Rarely used
Pancuronium	Intermediate (2-3 min)	long	Tachycrdia mild,no hypotension	Better side effect profile than tubocurarine.Widly used **Pipecuronium** is similar
Vecuronium	Intermediate	Intermediate (30-40 min)	Few side effects	Widely used.Occasionally causes prolong paralysis,probably due to active metabolite.**Rocuronium** is similar, with faster onset.
Atracurium	Intermediate	Intermediate (20-30 min)	Transient hypotension (histamine release)	Elimination by spontaneous non-enzymatic degradation in plasma. Degradation slowed by acidosis. Widely used.**Doxacurium** similar but stable in plasma, giving long duration of action.**Cisatracurium** isometric of atracurium,similar but with less release of histamine
Mivacurium	Fast (2 min)	Short (15 min)	Transient hypotensison (histamine release)	New,similar to **atracurium**,but rapidly inactivated by plasma cholinesetrase,longer acting in liver disease or in genetic ch-estrase defeciency.
Suxamethonium	Fast	Short (10 min)	Bradycardia(muscarinic agonist effect) Cardiac dysrhythmias(increased plasma k+ conc.avoid in burns and severe trauma.raised intraocular pressure,nicotinic agonist effect on extacellular	Act by depolarization, nicotinic effect, only drug of this type still in use. Paralysis preceded by transient muscle fasciculation. Short duration of action. used for brief procedures. **Rocuronium** has similar speed of onset and recovery with fewer unwanted effects.

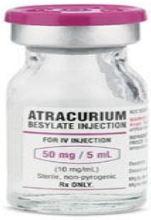
Gallamine (flaxedil):

- less potent than curare (1/5)
- Metabolized mainly by kidney 100% → contraindicated in renal failure cases.
- Long duration of action.
- Causes tachycardia due to :
  1. Atropine like action.
  2. Release of norepinephrine from adrenergic nerve endings.

D – tubocurarine:

- More potent than gallamine.
- Has a long duration of action (1-2 h).
- Eliminated by kidney 60% - by liver 40%.
- Causes histamine release → act on mast cells → causes its rupture and then release of Histamine.
- Action of histamine:
    1. Bronchospasm
    2. Hypotension
- Blocks all autonomic ganglia (hypotension).

Atracurium:



- Almost as potent as curare (1.5).
- Has an intermediate duration of action (30 min).
- Eliminated by non enzymatic chemical degradation in plasma (spontaneous hydrolysis at body pH).
- Used in liver failure and kidney failure (drug of choice).
- Liberates histamine → (cause transient hypotension).
- No effect on muscarinic receptors or ganglia.

Mivacurium:

- Chemically related to atracurium.
- Metabolized by pseudocholinestrase.
- Fast onset of action.
- Short duration of action (15mins)
- Transient hypotension (histamine releaser)
- Longer duration of action in patients with:
    - Liver disease.
    - Genetic cholinesterase deficiency.
    - Malnutrition.
    - Organophosphorous compound toxicity.
    - Renal failure (they have decreased level of cholinesterase).

Duration of action when metabolized by:

- *Liver → short*
- *Enzymes → shorter*
- *Kidney → long*

Pancuroium:

- More potent than curare (6 times).
- Excreted by the kidney (80%)
- Long duration of action.
- Tachycardia:
    - Antimuscarinic action.
    - Increases NE release at adrenergic nerve endings.

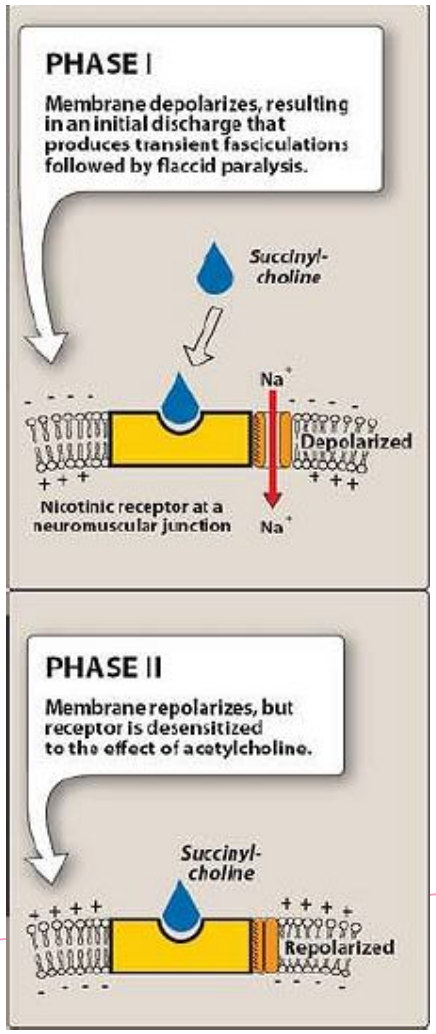
Drug	Elimination	Approximate potency relative to Tubocurarine
Atracurium	Spontaneous	1.5
Doxacurium	Kidney	6
Mivacurium	Plasma cholinesterase	4
Metocurine	Kidney 40%	4
Tubocurarine	Kidney 40%	1
Panacurium	Kidney 80%	6
Rocuronium	Liver 70-80%,kidney	0.8
vecuronium	Liver 75-90%,kidney	6
pipecuronium	Kidney ,liver	6
Rapacuronium	liver	0.4

Vecuronium:

- More potent than tubocurarine.
- Metabolized mainly by the liver.
- Short duration of action.
- No histamine release.
- No ganglion block.
- No antimuscarinic action.

Depolarizing NM blockers:

Mechanism of action:



1. Phase 1(depolarization):

Combine with nicotinic receptors→ depolarization of motor end plate → muscle fasciculation→ persistent depolarization→ paralysis.

P.S. Phase 1 blockers are augmented, not reversed by anticholinestrase.

2. Phase 2 (desensitization block):

Continued exposure to succinylcholine →depolarization decreases and the membrane becomes repolarized, but the membrane cannot be depolarized by ACH as long as succinylcholine is present (because the membrane is desensitized)

- Reversed by anticholinestrases.

Pharmacokinetics:

- Short onset of action (1min).
- Short duration of action (5-10 mins).
- Destroyed by pseudocholinestrase.
- Given parentrally (continued infusion)

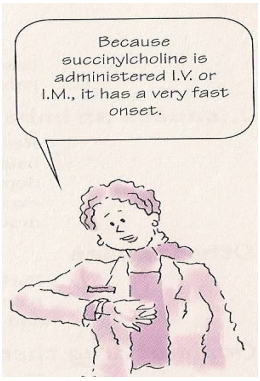
Succinylcholine (suxamethonium):

Pharmacological actions:

- Skeletal muscle fasciculation →spastic paralysis.
- Hyperkalemia→cardiac arrest.
- Eye→increases intraocular pressure due to contraction of extraocular muscle (contraindicated with glaucoma).
- GIT→ increases intragastric pressure→ regurgitation of gastric contents to esophagus, and emesis and aspiration of gastric content
- CVS: arrhythmia.
- Stimulate autonomic ganglion.
- Low dose → -ve ionotropic and chronotropic
- High dose → +ve ionotropic and chronotropic

Side effects:

- Hyperkalemia.
- CVS arrhythmia (bradycardia,extrasystol, and cardiac arrest) because the drug acts on ganglionic and muscarinic receptors.
- Increases intraocular pressure (glaucoma).
- Malignant hyperthermia.
- Succinylcholine apnea due to:
  - Liver disease (neonates and elderly)
  - Malnutrition
  - Organophosphorous compounds-toxicity
  - Genetic disease



Spasmolytics:

1. Baclofen: centrally acting(GABA agonist, spinal cord)
   - Act through $GABA_B$ receptors.
   - It causes hyper polarization by increased K+ conductance reducing calcium influx and reduces excitatory transmitter in brain as well as spinal cord
   - It also reduces pain by inhibitory substance P. in spinal cord
   - It is less sedative
   - It is rapidly and completely absorbed orally
   - It has a half life of 3- 4 hours
   - It may increases seizures in epileptics
   - It is also useful to prevent migraine.
2. Diazepam (benzodiazepines): centrally acting (facilitate $GABA_A$ action on spinal cord and CNS).
3. Dantrolene: has a direct action on skeletal muscles.

Uses of spasmolytics: Release muscle spasm in:

- Spinal cord injury
- Stroke
- Cerebral palsy.

Dantrolene:

Mechanism of action:

1. It interferes with the release of calcium from its stores in skeletal muscle (Sarcoplasmic Reticulum)
2. It inhibits the excitation-contraction coupling in muscle fibers.

Uses:

- Malignant hyperthermia
- Spastic states
- Half-life= 8-9 hours when given orally or intravenously.

Malignant hyperthermia:

- Inability of calcium binding to sacroplasmic reticulum in some patients due to genetic defects.
- Sensitive to some drugs:
  - ✓ General anesthetics e.g. halothane.
  - ✓ Elicited by succinylcholine
  - ✓ NM blockers: succinylcholine.

Increased calcium release, intense muscle spasm, rise in temperature.