Muscle Relaxants

Lecture no.3

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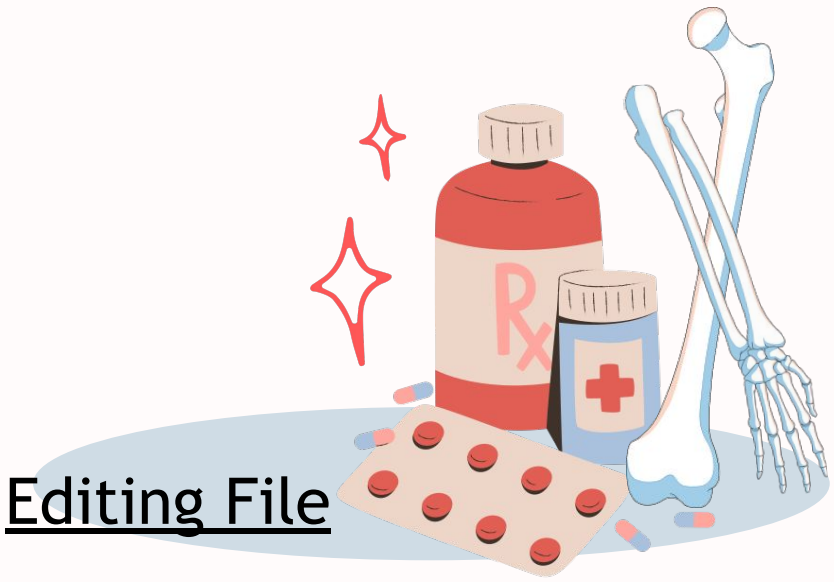

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Objectives

- Identify classification of skeletal muscle relaxants.
- Describe the pharmacokinetics and dynamics of neuromuscular relaxants.
- Recognize the clinical applications for neuromuscular blockers.
- Know the different types of spasmolytics.
- Describe the pharmacokinetics and dynamics of spasmolytic drugs.
- Recognize the clinical applications for spasmolytic drugs.

Skeletal muscle relaxants (SKM relaxants) :

- Are drugs used to induce skeletal muscle relaxation.
- Drugs that can act peripherally at the neuromuscular junction/fiber itself or centrally in the cerebrospinal axis to reduce muscle tone and/or cause paralysis. (classified according to site of action).

SKM Relaxants

Peripherally acting (Acts on neuromuscular junction)

- **Competitive**
- **Depolarizing**

Spasmolytic

Centrally acting (Acts on CNS) :

-Baclofen -Diazepam

Direct acting
(Directly acting on muscle fibers)
- Dantrolene

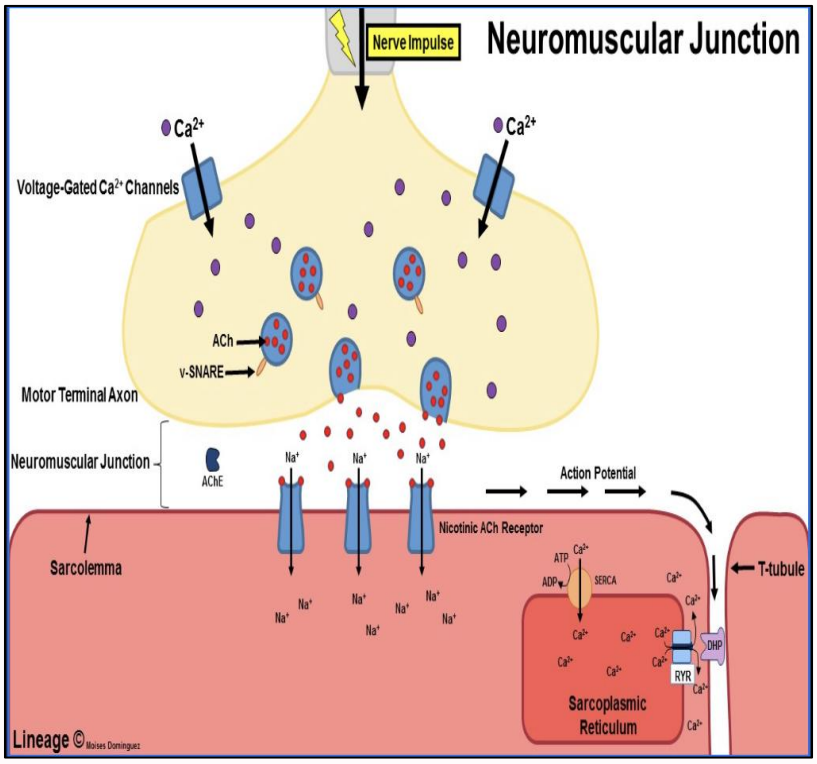
Indications of muscle relaxants

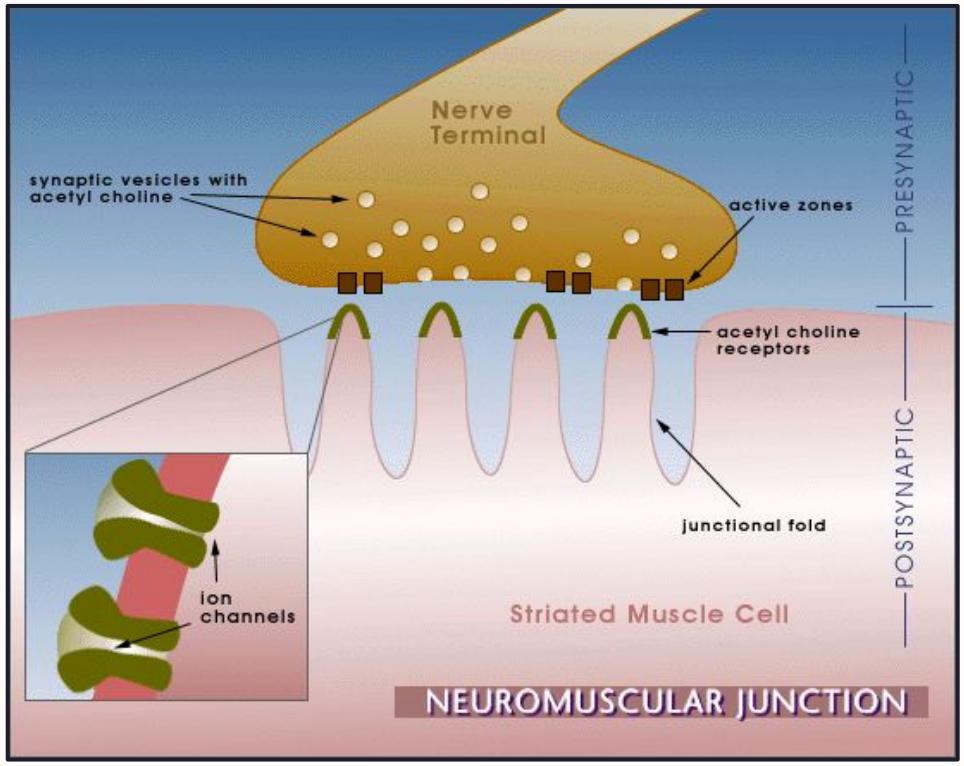
Males' Slides:

➔ These agents are used primarily in conjunction with **general anesthetics to provide muscle relaxation** for **surgery.**

➔ While **centrally acting muscle relaxants** are used mainly for **painful muscle spasms and spastics neurological conditions.**

Neuromuscular Junction





Mechanism of action of neuromuscular blockers (extra explanation). Normally in the neuromuscular junction, the acetylcholine will attach with the acetylcholine receptors (in skeletal muscle the receptors) are nicotinic receptors type 1 after that a lot of changes will happen so that the muscle contracts. However, the Neuromuscular blockers will block the nicotinic receptors so acetylcholine cannot bind with the receptors, thus, preventing its action (muscle contraction) and if the muscle won't contract it'll relax.

Thanks to Team441

Skeletal Muscle Reactants -MOA

Males' Slides:

- Normal:Ach+Nm receptor → Na channel opening → Na ion transportation → depolarization → muscle contraction

- Site of action of both competitive and depolarizing blockers is the end plate of skeletal muscle fibres specifically Nm receptors.

Peripheral acting SKM relaxants (Neuromuscular blockers):

Act by blocking NM junction or motor end plate leading to skeletal muscle relaxation. NMB drugs interfere with transmission at the NM end plate & lack CNS activity.

These are competitive antagonists meaning they compete with the other drugs on the receptor binding site to inhibit its action unlike noncompetitive antagonists which go and bind to the allosteric site.

Competitive ("non depolarizing blockers")

E.g.
- Atracurium
- Mivacurium
- Pancuronium
- d-tubocurarine (prototype)
- Vecuronium
- Rocuronium

Depolarizing blockers

E.g.
- Succinylcholine

(it is an agonist and all agonists bind to receptors)

Competitive Blockers (non-depolarizing) Peripherally Acting :

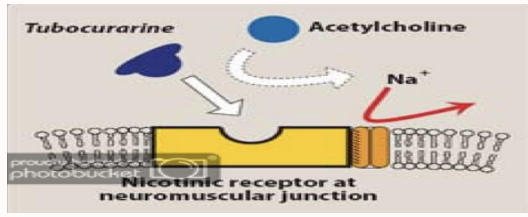
Mechanism of action:

❖ Are competitive antagonists for Ach at the nicotinic receptors present in post junctional membrane of neuromuscular junction or motor end plate. But have no intrinsic activity → Block Nm receptor binding from Ach → prevent depolarization → prevent contraction → muscle relaxation.

❖ No depolarization of post junctional membrane (non depolarizing).

❖ Action can be reversed or overcome by increasing cholinesterase inhibitors (neostigmine) which increase Ach concentration at motor end plate.

-Acetylcholinesterase (AchE) breaks down or hydrolyzes Ach, so AchE inhibitors will increase Ach concentration."443 note"



Drugs

Long acting:

-D-tubocurarine (prototype).
First muscle relaxant used clinically
-Pancuronium

Intermediate acting:

-Atracurium
-Vecuronium
-Rocuronium

Short acting:

-Mivacurium

443 note:

'If the drug ended with curium or curonium it means that it is a SKM relaxant acting peripherally and mainly competitive'

Pharmacokinetics

❖ They are polar compounds.
➢ Inactive orally & taken parenterally.
➢ Do not cross BBB (no central action).
➢ Do not cross placenta. (can be used for pregnant women)
❖ Metabolism depend upon kidney or liver.

EXCEPT:
❖Mivacurium (degraded by acetylcholinesterase).
❖Atracurium (spontaneous degradation in blood).

Pharmacological action

❖Skeletal muscle relaxation (Small rapidly contracting muscles of face, eyes ,fingers ,neck ,trunk muscle ,intercostal muscles,diaphragm).
❖Recovery comes from REVERSE MANNER starting with diaphragm, last is face and eyes.
❖They produce different effects on CVS (cardiovascular system).
❖Some release histamine and produce hypotension.
➢d-Tubocurarine (severe release of histamine) "the most one"
➢Atracurium
➢Mivacurium
❖Others produce tachycardia (Increase Heart rate)
➢Pancuronium

1- D-Tubocurarine (curare)

Duration	1-2 Hours (long duration) (443 note: if the excretion is mainly in the Kidney (high percentage) , this means long duration of action. All of them have relatively short half life)
Metabolism and excretion	Eliminated by kidney 60% - liver 40%
Side effects	**Histamine releaser leading to:** 1.Bronchospasm (constriction of bronchial smooth muscles) 2.Hypotension (Blocks autonomic ganglia) 3.Tachycardia
Uses	Not used clinically due to adverse effects.(side effects)
Notes	More safer derivatives are now available to be used in clinical settings.

2-Atracurium

Duration	30 min (intermediate duration)
Metabolism and excretion	Eliminated by non enzymatic chemical degradation in plasma (spontaneous hydrolysis at body pH) no enzymes involved يفكك نفسه
Side effects	Transient hypotension (due to histamine release), bronchospasm.
Uses ★	**Used in liver failure and kidney failure (drug of choice)**
Contraindication **(not good for)**	Asthmatic patients because it releases histamine leading to bronchospasm
Potency	As potent as curare (1.5)
Notes	Anti-histamine pretreatment may prevent these side effects. No effect on muscarinic receptor nor ganglia

3-Mivacurium

Duration	15 min (The shortest duration) of all competitive neuromuscular blockers.
Metabolism and excretion ★	❖Fast onset of action ❖Metabolized by pseudo-cholinesterase. Dr's note: Enzyme present in plasma excretion that breaks down any ester (442).
Side effects	Transient hypotension (due to histamine release).
Uses	Used with liver or kidney failure patients. (Mivacurium & Atracurium don't depend on the kidney or liver for metabolism. Remember?)
Contraindication (not good for)	Longer duration in patient with liver disease (enzymes come from the liver, so liver diseases will prevent forming the enzyme that metabolize this drug) or genetic cholinesterase deficiency or malnutrition (lead to protein deficiency which is important to form enzymes)
Notes	**•Chemically related to atracurium** Mivacurium induced prolonged muscle paralysis. Can be reversed by acetylcholinesterase inhibitors such as edrophonium acetylcholinesterase inhibitors increase the Ach level in NMJ and displace Mivacurium from nicotinic receptors in NMJ. " team 43 "

4-Pancuronium

Duration	Long duration of action(1-2 hours) (metabolic products have some NM blocking activities)
Metabolism and excretion	Metabolized in liver and excreted by the kidney (80%) (renal)
Side Effects	❖Hypertension, tachycardia. ❖Increase norepinephrine release from adrenergic nerve endings. ❖Antimuscarinic action (block parasympathetic action, atropine-like action) ❖Blocks muscarinic receptor in SA sinoatrial node.
Contraindication (not good for)	Patient with coronary diseases or kidney diseases since 80% of excretion occurs there
Potency	More potent than curare (6 times)

5-Vecuronium

Duration	Intermediate duration (40 min)
Metabolism and excretion	Metabolized mainly by liver & Excreted mainly in bile.
Advantages	❖No histamine release. ❖No tachycardia. ❖No atropine like actions. (No antimuscarinic action) ❖No ganglion block.
Uses	Good for patients with renal failure because its excreted by the bile good for cardiac patients because it has no antimuscarinic effect (no release of norepinephrine therefore no tachycardia) **Team439**
Contraindication (not good for)	Liver failure patients since its metabolised by the liver and excreted in the bile " 443 note"
Notes	More potent than tubocurarine (6 times).

6-Rocuronium *FEMALE SLIDES ONLY*

Duration	Intermediate duration
Metabolism and excretion	Biliary excretion.
Advantages	❖No histamine release. ❖No tachycardia. ❖No vagal blockade =atropine like actions

Depolarizing Peripherally Acting NMBs

Mechanism of action:

❖Combine with nicotinic receptor in post-junctional membrane of neuromuscular junction→ **initial** depolarization of motor end plate → muscle twitching→ Persistent depolarization(the depolarized membranes remain depolarized & unresponsive to subsequent impulses (i.e, a state of depolarizing blockade) —> **Skeletal muscle relaxation**

❖ Not reversed by cholinesterase inhibitors

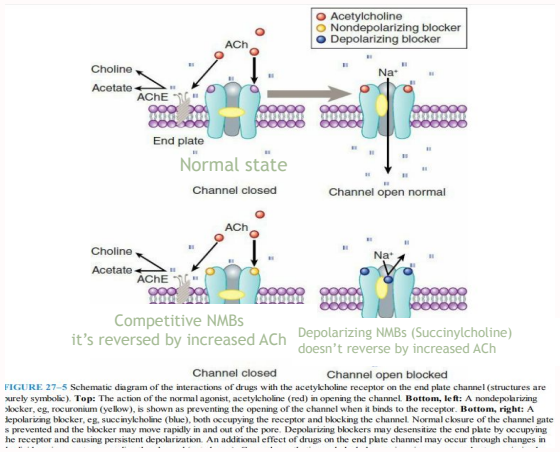


FIGURE 27–5 Schematic diagram of the interactions of drugs with the acetylcholine receptor on the end plate channel (structures are purely symbolic). **Top:** The action of the normal agonist, acetylcholine (red) in opening the channel. **Bottom, left:** A nondepolarizing blocker, eg, rocuronium (yellow), is shown as preventing the opening of the channel when it binds to the receptor. **Bottom, right:** A depolarizing blocker, eg, succinylcholine (blue), both occupying the receptor and blocking the channel. Normal closure of the channel gate is prevented and the blocker may move rapidly in and out of the pore. Depolarizing blockers may desensitize the end plate by occupying the receptor and causing persistent depolarization. An additional effect of drugs on the end plate channel may occur through changes in

Drugs

Succinylcholine (suxamethonium)

Pharmacokinetics
(only in females' slides)

❖Fast onset of action (1 min)
❖Short duration of action (5-10 min.).
❖Metabolized by pseudocholinesterase in plasma.
❖Half life is prolonged in:
➢Neonates (Low enzymes)
➢Elderly (Liver function declined due to aging)
➢Pseudocholinesterase deficiency (liver disease or malnutrition or genetic cholinesterase deficiency).

Pharmacological action ★

- Skeletal muscles: initial twitching → relaxation
- Hyperkalemia (due to muscle contraction): Cardiac arrest.
- CVS: arrhythmia
- Eye: increase intraocular pressure (due to contraction of extraocular muscle).
- Apnea : Prolonged apnea & paralysis can occur in case of pseudocholinesterase or plasma cholinesterase deficiency

Contraindication
(not good for)

- Glaucoma (high eye pressure)
- Patient with cardiac diseases

Side effects ★

- Hyperkalemia (elevated levels of potassium in the blood serum)
- CVS arrhythmia
- increased Intraocular pressure contraindicated in glaucoma
- Can produce malignant hyperthermia (severe muscle contraction)
- May cause succinylcholine apnea* due to deficiency of pseudo-cholinesterase.

*Prolonged apnea and paralysis can occur with succinylcholine and mivacurium in case of plasma cholinesterase deficiency.

Summary of Neuromuscular Blockers

Drug	Duration	Side effects	Notes
Tubocurarine	Long (1-2h)	-Hypotension	-Renal failure
Pancuronium	Long (1-2h)	-Tachycardia	
Atracurium	Short (30min)	-Transient Hypotension -Histamine release	-Spontaneous degradation -Used in liver and kidney failure
Vecuronium	Short (40min)	-Few side effects	-Liver failure
Mivacurium	Short (15min)	-Similar to Atracurium	-Metabolized by pseudocholinesterase -Cholinesterase deficiency
Succinylcholine	Short (10min)	-Hyperkalemia -Arrhythmia -Increase IOP	-CVS diseases -Glaucoma -Liver disease

Uses of Neuromuscular Blockers

01 control convulsion (تشنجات) for electroshock therapy in psychotic patients.

02 Relieve of **tetanus** and **epileptic** (الصرع) convulsion.

03 As adjuvant in general anesthesia to induce muscle relaxation.

04 Facilitate endotracheal intubation.

05 Orthopedic surgery.

Drugs and diseases that modify the effects of NMBs

FEMALE SLIDES ONLY

Diseases:

Myasthenia gravis is a disease which already cause muscle relaxation, in turn it causes an increase in response to muscle relaxants.

Drugs:

Drugs as aminoglycosides (e.g.streptomycin),magnesium sulphate and general anesthetics can potentiate or enhance the effect of neuromuscular blockers.

Spasmolytic Drugs

(They **reduce muscle spasm** in spastic states)

Muscle Relaxant	Baclofen	Diazepam (Benzodiazepines)	Dantrolene
Action	Centrally acting		Directly Acting
Acts on	GABA agonist - acts on spinal cord	Facilitate GABA action on CNS	**Direct action** on skeletal muscles. **Mechanism of action:** • Acts directly on skeletal muscles. • It inhibit excitation-contraction coupling in the muscle fiber by binding to ryanodine receptor 1. • Ryanodine receptor mediate the release of calcium from sarcoplasmic reticulum, an essential step in muscle contraction.
Clinical uses	They reduce muscle spasm and stiffness caused by neurological disorders as: • Spinal cord injury • Cerebral stroke • Cerebral palsy • **Multiple sclerosis**		All on the left + • Orally, IV, (t 1/2 = 8 - 9 h) • Used in the treatment of: 1.Spastic states **2.Malignant hyperthermia**

Malignant Hyperthermia

only in females' slides

It's a rare inherited condition that occurs due to inability to bind calcium by sarcoplasmic reticulum in some patients to genetic defect, and also it is an example of idiosyncrasy*.

Sensitive to some drugs such as:
- General anesthesia e.g. halothane
- NMBs e.g. succinylcholine

*Abnormal unexpected side effects such as anaphylaxis from penicillin

Causes ↑ Ca release, muscular rigidity, metabolic acidosis, tachycardia and hyperpyrexia (high body temperature >41.5C)

MCQs

Q1.Which of the following drugs should not be considered if a patient has asthma?			
a) Vecuronium	b) Atracurium	c) Suxamethonium	d) Pancuronium

Q2.What is the best choice of drug to give to a patient with liver or kidney failure ?			
a) Diazepam	b) Atracurium	c) Tubocurarine	d) D-Tubocurarine

Q3.Which of the following drugs should not be considered for a patient with CVS problems ?			
a) Atracurium	b)Vecuronium	c) Pancuronium	d) Rocuronium

Q4.Where does the metabolism of Atracurium occur?			
a) Blood	b) Liver	c) Kidney	d) Bile

Q5.Which of the following acts on the CNS ?			
a)Atracurium	b)Dantrolene	c)Diazepam	d)Suxamethonium

Answers:

1)B
2)B
3)C
4)A
5)C

MCQs

Q6. Which of the following NM blockers gets hydrolyzed at body pH?			
a) Pancuronium	b) Atracurium	c) Vecuronium	d) Suxamethonium

Q7. Which of the following has no histamine release?			
a) Vecuronium	b) Atracurium	c) Mivacurium	d) Curare

Q8. Which of the following drugs block the parasympathetic action & muscarinic receptor?			
a) Pancuronium	b)Atracurium	c) Vecuronium	d) D-Tubocurarine

Q9. Which of the following drugs is metabolized by pseudocholinesterase?			
a) Vecuronium	b) Atracurium	c) Mivacurium	d) Pancuronium

Q10. Which drug is most likely to cause hyperkalemia ?			
a)Baclofen	b)Dantrolene	c)Pancuronium	d)Succinylcholine

Answers:
6)B
7)A
8)A
9)C
10)D

SAQs

1 **Define skeletal muscle relaxants?**

drugs used to induce skeletal muscle relaxation

2 **What is the mechanism of action of peripheral acting drugs?**

They act by blocking neuromuscular junction or motor end plate leading to skeletal muscle relaxation

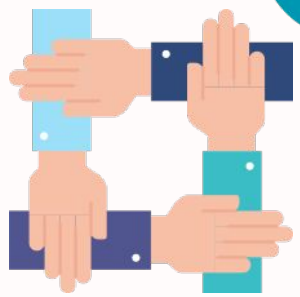
3 **Why avoid use of pancuronium for patients with coronary diseases ?**

- Hypertension, tachycardia.
- Increase norepinephrine release from adrenergic nerve endings.
- Antimuscarinic action (block parasympathetic action, atropine-like action).

4 **If a patient comes with an overdose of a competitive muscle relaxant, how can you treat the patient?**

by neostigmine

Team Leaders:



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