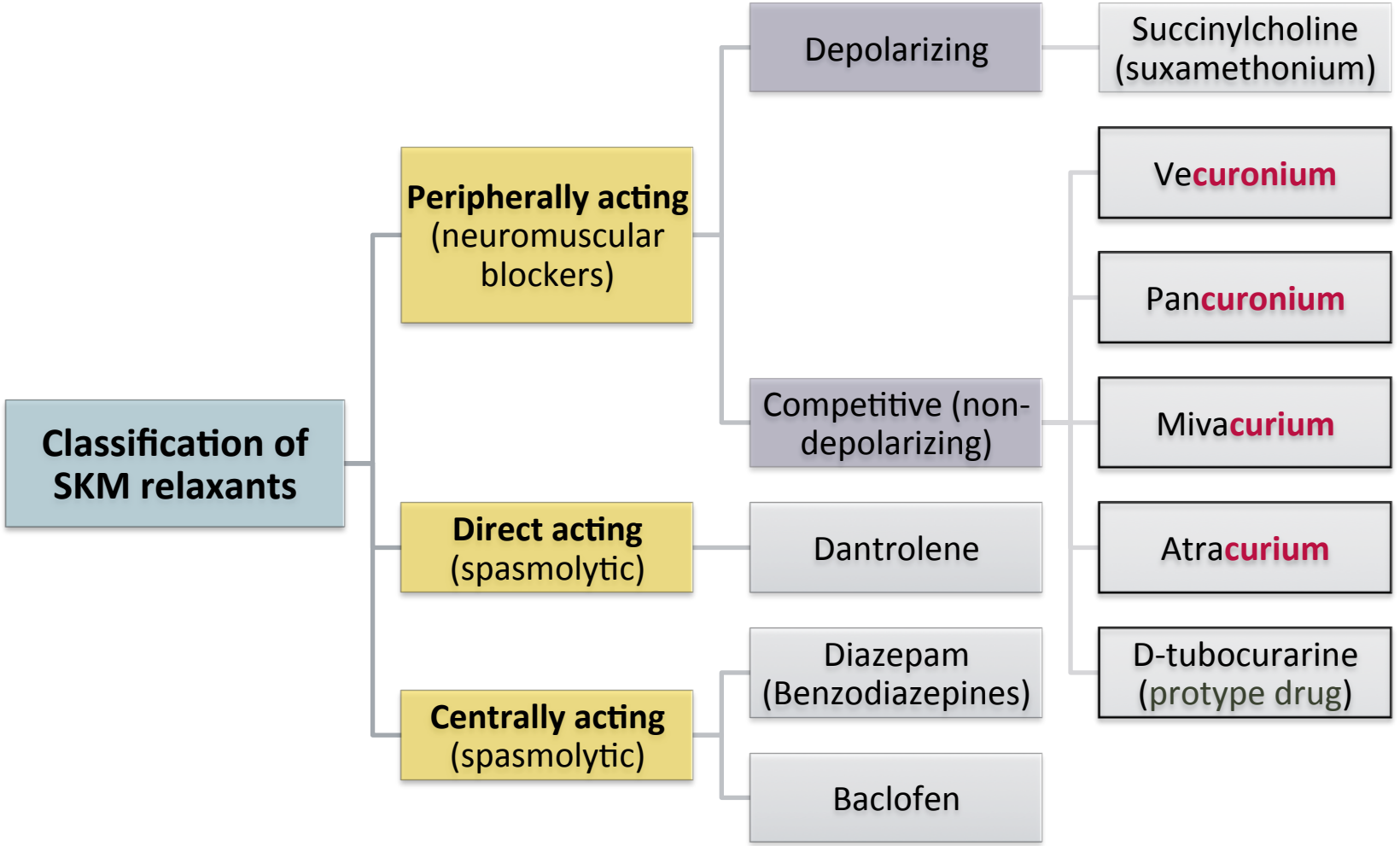
Lecture 1

Skeletal muscle relaxants

Objectives:

1. Identify classification of skeletal muscle relaxants.
2. Describe the pharmacokinetics and dynamics of neuromuscular relaxants
3. Recognize the clinical applications for neuromuscular blockers
4. Know the different types of spasmolytic
5. Describe the pharmacokinetics and dynamics of spasmolytic drugs
6. Recognize the clinical applications for spasmolytic drugs

- Additional Notes
- Important
- Explanation –Extra-



- **Neuromuscular Blockers** acts by blocking neuromuscular junction or motor end plate.
- **Centrally acing** means acting on the CNS to inhibit muscle contraction.
- **Protype Drug** means the first drug was invented in its group.
- Drugs excreted by the kidney has **longer** duration of action than drugs excreted be the liver.
- Releasing Histamine drugs are **Contraindicated** for patients with Asthma because they cause bronchospasm.

Competitive (non-depolarizing)

Drug	D-Tubocurarine	Atracurium used in liver failure & kidney failure (*drug of choice*).	Mivacurium	Pancuronium	Vecuronium
Duration	Long duration of action (1 - 2 h)	Has intermediate duration of action (30 min).	Has the shortest duration of action (15 min) of all competitive neuromuscular blockers.	Long duration of action.	Intermediate duration of action
Side effects	Histamine releaser leading to: Bronchospasm (constriction of bronchial smooth muscles). Hypotension Tachycardia	Histamine release (Transient hypotension) - Should be avoided in asthmatic patients-, reflex tachycardia, and cutaneous flush	Transient hypotension (due to histamine release). Longer duration in patient with liver disease or genetic cholinesterase deficiency or malnutrition.	Hypertension, tachycardia, ↑ NE release from adrenergic nerve endings., and Antimuscarinic action (block parasympathetic action). Avoid in patient with coronary diseases	Has few side effects. -No histamine release. -No tachycardia.
Metabolized by	Liver and kidney	spontaneous hydrolysis at body pH (7.35)	pseudo-cholinesterase.	Excreted by the kidney -80 % -	Metabolized mainly by liver and excreted in bile.
Mechanism of action	Compete with Ach for the nicotinic receptors present in postjunctional membrane of neuromuscular junction or motor end plate. No depolarization of postjunctional membrane				

Peripheral acting

Peripheral acting

Depolarizing	
Drug	**Succinylcholine (suxamethonium)**
Duration	Short duration of action (5-10 min)
Side effects	Hyperkalemia (Cardiac arrest), CVS arrhythmia. , Increase IOP (**I**ntraocular **p**ressure **c**ontraindicated) -due to contraction of extra-ocular muscle- not used in case of glaucoma , Liver disease or CVS Diseases , Can produce **malignant hyperthermia**, Half life is prolonged in Neonates and Elderly and in the case of Pseudo-cholinesterase deficiency, May cause **succinylcholine apnea** due to deficiency of pseudo-cholinesterase deficiency due to (liver disease or malnutrition or genetic cholinesterase deficiency).
Metabolized by	Pseudo-cholinesterase in plasma
Mechanism of action	combine with nicotinic receptors in post-junctional membrane of neuromuscular junction → initial depolarization of motor end plate → muscle twitching → persistent depolarization → SKM relaxation

- **Succinylcholine apnea** is a respiratory disorder occurs due to to the relaxant of the diaphragm and intercostal muscles - they are skeletal muscles - due Muscle Relaxant Drugs.
- **Malignant Hyperthermia** is an inherited condition caused by drugs (e.g. **Succinylcholine**). This drug in these patient cause the inability to bind calcium by **Sarcoplasmic Reticulum** → ↑ Ca release , intensive muscular contraction (spasm, hyperthermia).

Peripheral acting

Pharmacokinetics of competitive NM blockers:

-They are **polar compounds**
-Inactive orally & taken parentrally
-Do not cross BBB (no central action)
- Do not cross placenta
-Metabolism depend upon kidney or liver

Except

Mivacurium (degraded by acetyl cholinesterase)
Atracurium (spontaneous degradation in blood)

Pharmacological actions of competitive NMBs:

-Skeletal muscle relaxation.
-They produce different effects on CVS
-Some release histamine and produce hypotension:
d-Tubocurarine
Atracurium
Mivacurium
-Others produce tachycardia (↑ H.R):
Pancuronium

Uses of neuromuscular blockers:

-control convulsion → electroshock therapy in psychotic patients.
-Relieve of tetanus and epileptic convulsion.
-As adjuvant in general anesthesia to induce muscle relaxation
-Facilitate endotracheal intubation
-Orthopedic surgery.

Drugs and diseases that modify effects of neuromuscular blockers:

-Diseases such as myasthenia gravis can modify the response to muscle relaxants.
-Drugs as aminoglycosides (e.g. streptomycin), magnesium sulphate, general anesthetics can potentiate or enhance the effect of neuromuscular blockers.

Spasmolytic

Drug	Baclofen	Diazepam (Benzodiazepines)	Dantrolene
Mechanism of action	GABA agonist act on spinal cord (**Centrally acting**)	Facilitate GABA action on CNS (**Centrally acting**)	-Orally, IV, (t ½ = 8 - 9 h) -interferes with the release of calcium from its stores in SM (sarcoplasmic reticulum) -inhibits **execration-contraction coupling** in the muscle fiber (**Direct action**)
Uses of spasmolytic	-Reduce muscle spam in spastic state produced by neurological disorders as : ★ Spinal cord injury ★ Cerebral stroke ★ Cerebral palsy		-Malignant hyperthermia. -Reduce muscle spam in spastic state produced by neurological disorders as : ★ Spinal cord injury ★ Cerebral stroke ★ Cerebral palsy

- **Execration-contraction coupling** is the interaction between Actin & Myosin filaments.

✸Summary

Drug	Duration	Side effects	Notes
Tubocurarine	Long 1-2 h	Hypotension	# Renal failure
Pancuronium	Long 1-2 h	Tachycardia	# Renal failure
Atracurium	Short 30 min.	Transient hypotension Histamine release	Spontaneous degradation Used in liver and kidney failure
Vecuronium	Short 40 min.	Few side effects	# Liver failure
Mivacurium	Short 15 min.	Similar to atracurium	Metabolized by pseudocholinesterase # Choline esterase deficiency
Succinyl choline	Short 10 min.	Hyperkalemia Arrhythmia Increase IOP	# CVS Diseases # Glaucoma # Liver disease

MCQs

1. Which is an example for direct acting skeletal muscle relaxants?
A) Diazepam
B) Benzodiazepines
C) Dantrolene
D) Baclofen

2. Which undergoes spontaneous degradation in blood?
A) Atracurium
B) Micavurium
C) Pancuronium
D) Vecuronium

3. Which produces tachycardia?
A) Mivacurium
B) Atracurium
C) Pancuronium
D) d-Tubocurarine

4. Which is not used clinically?
A) Vecuronium
B) Atracurium
C) Pancuronium
D) d-Tubocurarine

5. Which has least side effects?
A) Vecuronium
B) Atracurium
C) Mivacurium
D) d-Tubocurarine

6. One of the uses of Spasmolytics?
A) Orthopedic surgery
B) Electroshock therapy
C) Cerebral stroke
D) Epileptic convulsion

Answers:
1- C
2- A
3- C
4- D
5- A
6- C

Good luck!

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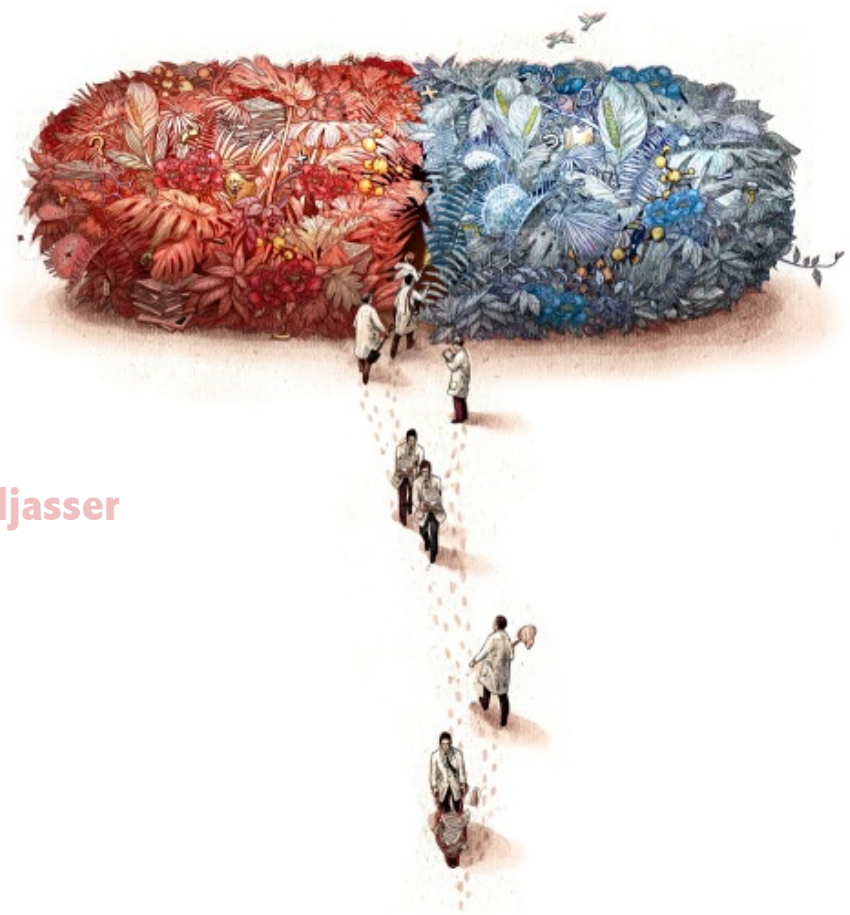

For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology434@gmail.com