بســـم الله الرحمـــن الرحيـــم

Neuromuscular blockers: 1depolarizing drugs 2-non-depolarizing drugs

- All these blockers r given parenterally

1- depolarizing drugs: interrupt transmission at the skeletal neuromuscular junction by causing sustained depolarization of the motor end plate

- short duration

Mechanism of Action:

Phase I Block(depolarizing): succinycholine reacts with nicotinic receptors w b29eer 3na AP.

- produce a prolonged "flickering" of the ion conductance
- The depolarized membranes remain depolarized and unresponsive to subsequent impulses causing flaccid paralysis
- augmented by cholinesterse inhibitors

Phase II Block(desensitizing): with continued exposure, depolarization decreases and the membrane becomes repolarized and cannot be depolarized again because it is **desensitized**

- This phase is reversed by acetylcholinesterse inhibitors

- When ACH binds to its receptors in postsynaptic membrane → depolarization , b3deen be9eer propagation of AP.
- Ach is cleaved rapidly by Ach esterase . repolarization of end plate will occur and new AP and contraction can elicited by binding of another Ach to its receptors.

BUT: when succinylcholine bind to its receptors it won't degraded be Ach esterase →persistent depolarization of end plate→new AP and contraction **can't** be elicited .

- so**, here there is NO repolarization. Renewed opening of Na+ channel is IMPOSSIBLE**

- dibucaine numb. : a measure of ability of patient to metabolize succinylcholine .

2- non-depolarizing : Compete with acetylcholine at the nicotinic receptor sites at the NMJ.

ACTIONS NEUROMUSCULAR JUNCTION

1- **Skeletal Muscle Paralysis:**

Nondepolarizing Drugs:

a. effect is very rapid
b. Starts with small muscles, large muscles are more resistant to blockade and recover more rapidly
c. Diaphragm is last to be paralysed

Depolarizing Drugs:

a. starts by transient muscle fasiculations

b. Paralysis develops rapidly

c. Blockade lasts less than 10 minutes.

Difference	Depolarizers	Non-Depolarizers
Mechanism of Action	These reach the neuromuscular junction, block receptors and cause depolarization Persistently.	Also called stabilizers. These compete with receptors to cause them not to depolarize and action potential is stopped.
Effects	First paralyze large muscles (Abdominal & Limb) then Short muscles (Face, ear, nose) and respiratory muscles in the end.	First paralyze short muscles followed by larger ones and respiratory muscles in the end.
	Effect can not be antagonized.	Effect can be antagonized by reversible inhibitors.
	These directly lead to flaccid paralysis (no tone in muscles).	These stimulate action potential initially for a short while then flaccid paralysis is followed.

2- **Cardiovascular Effects:**

a- by autonomic or histamine receptors.

b- cause **hypotension**, which can be attenuated by antihistamines

3. **Hyperkalemia:** lead cardiac arrest

4. Increased Intraocular Pressure

5. Increased Intragastric Pressure

6. Muscle Pain

Drug Interactions of Neuromuscular Blockers

بتوقع انو الاسئلة رح تكون من بعد هاد الموضوع . انا بحكي بتوقع فممكن يكون توقعي خطأ . بس انا بحكي للي ملحوق ومش فاضي يقرأ كلشي ^_^

1- **Anesthetics :** Mostly with isoflurane.
increasing muscle blood flow.

- Adverse effect: *Malignant Hyperthermia*

2- **Antibiotics:**
Depress release of acetylcholine by blocking specific P-type calcium channels

- **Spasmolytic Drugs** : Diazepam, Baclofen, Tizanidine (Related to clonidine) , Gabapentin(antiepileptic)
  1- **Diazepam:** Acts at $GABA_A$ receptors , presynaptic inhibition , **Sedative.**
  2- **Baclofen:** Acts at $GABA_B$ receptors, resulting in hyperpolarization and presynaptic inhibition through reducing calcium influx**.**
- Can also reduce spasticity by inhibiting release of substance P in the spinal cord and excitatory transmitters. **cause drowsiness** . given intrathecally **. reduce craving** in alcoholics and in migraine

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Botulinum Toxin: Inhibits acetylcholine release , result in : diplopia (double vision), dysphagia (difficulty in swallowing.), dysarthia (difficult articulating), dyspnea (shortness of breath).

- Toxin is used for: opthalmic purposes, local muscle spasms, and in the cosmetic treatment of facial wrinkles around the eyes and mouth, as well as for generalized spastic disorders like cerebral palsy**.**

- **Directly Acting Drugs:**
  1- **Dantrolene**:Related to phenytoin, an antiepileptic.
  It interfere with the release of activator calcium by binding with the ryanodine receptor (RyR) channel of the sarcoplasmic reticulum.
- Cause : weakness, sedation, and hepatitis

Malignant Hyperthermia: Patients have a hereditary impairment of the sarcoplasmic reticulum to sequester calcium.

- The trigger can causes sudden and prolonged release of calcium, with massive contraction, lactic acidosis, and increased body temperature
- Treatment: **dantrolene** which reduce calcium release**.**