MSS

PHARMACOLOGY

 # 1

WRITER:
Tasneem Alremawi

CORRECTOR:
محمد العتوم

DOCTOR:
Alia Shatanawi

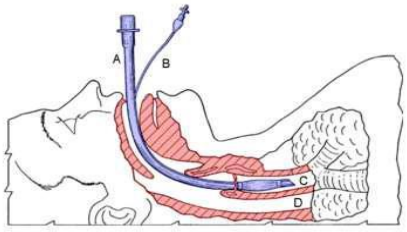
PERIPHERALLY ACTING SKELETAL MUSCLE RELAXANTS

Slides will be in this color.
Doctors notes will to be in this color.

We are going to talk about drugs that work peripherally on nicotinic receptors on muscles and cause muscle relaxation.

PERIPHERALLY SKELETAL MUSCLE RELAXATION USES:

In conjugation with General Anesthetics. These drugs don't make the patient unconscious, but rather help the general anesthetics doing their job, the purpose of using these drugs (skeletal muscle relaxants) is to keep muscles relaxed not tense during operations.
They are used to:



- **Facilitate intubation of the trachea.** Relaxing the tracheal muscles eases up entering the tubes to the trachea for ventilation or suctioning.
- **Facilitate mechanical ventilation.**
- **Optimize surgical working conditions.** In operations if we want to dissect through a muscle it's going to be easier if it was relaxed.

HISTORY OF SKELETAL MUSCLE RELAXANTS:

Curare was the first skeletal muscle relaxant discovered by ancient tribes in America who used it to hunt animals, they would dip the arrow in this poison and use a bamboo tube to shoot out the arrow targeting animals and it cause muscle relaxation and paralysis.

Curare is a common name for various plant extract alkaloid arrow poisons originating from Central and South America.

Source: is a plant called **Chondrodendrone tomentosum** (it's ok the doctor also had a hard time reading it) **and Strychnos toxifera.**

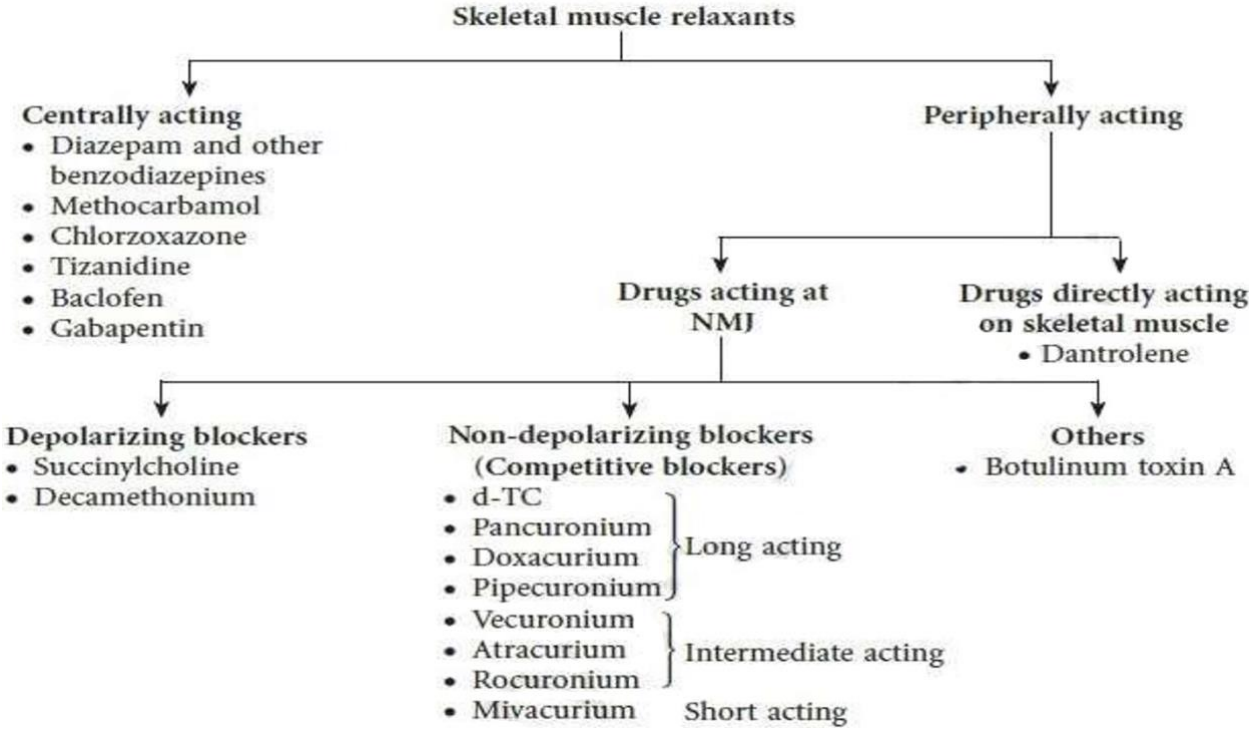
Tubocurarine (the used drug) **name because of packing in "hollow bamboo tubes". Tubo:** for the tube that was used.

But what happens when these hunters eat their prey, does the poison affect them?
Actually it doesn't, because of its structure that contains a bulk of highly polar quaternary ammonium group that prevents its absorption from the GIT (it doesn't enter the circulation).
And for that reason when giving these drugs to patients we give them IV infusion or injection .

CLASSIFICATION:

We have two kind of skeletal muscles relaxants: **centrally** and **peripherally acting drugs.**

Centrally acting drugs aren't required for now, we are going to talk about them in the CNS system إن شاء الله.
A brief overview on the centrally acting drugs (that isn't included in the exam and you can comfortably skip what is written in this color). Diazepam [valium] is the prototype for benzodiazepines that are sedative muscle relaxant drugs used in minor procedures when we want to calm patients down without complete anesthesia.



We have two types of peripherally acting skeletal muscle relaxants:

1. **Drugs directly acting on skeletal muscles**. (explained further in the next lec) They work on muscle contraction mechanisms (that we took in the physiology part of this system), for example some drugs modulate the conc. of Ca++ (the most important ion in muscle contraction).

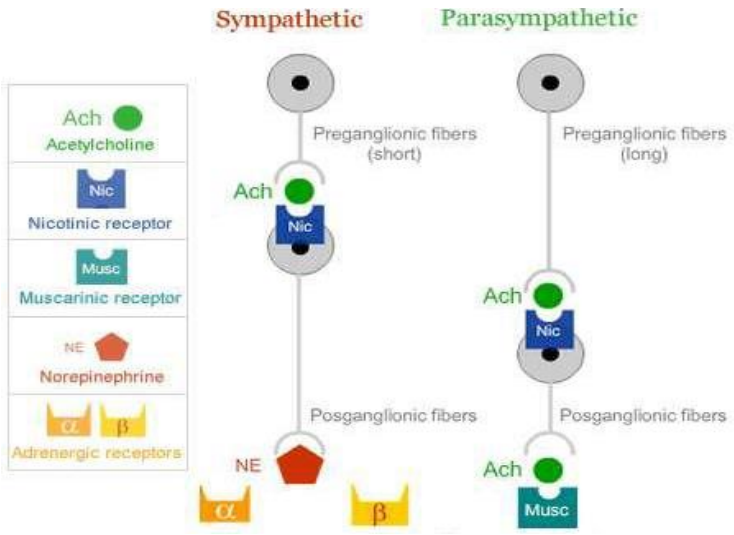
2. Drugs acting at neuromuscular junction (NMJ) are divided into:

-Depolarizing blockers: Succinylcholine (the only depolarizing drug that is used clinically) and **Decamethonium** (used for research only).

-Non-depolarizing blockers (competitive blockers), all can be used clinically: **d-TC** (d-tubocurarine) is the prototype and first discovered drug then its structure was changed a bit every time giving a new drug with different pharmacokinetic and pharmacodynamic properties, producing **long acting, Intermediate acting and short acting blockers** (explained later in this lec).

-others (botulinum toxin).

ACETYLCHOLINE:



Acetylcholine is a major neurohumoral transmitter at autonomic, somatic and central nervous system:

1.All preganglionic sites at the ganglia **(Both Parasympathetic and sympathetic)** on nicotinic receptors.

Nicotine can activate both sympathetic and parasympathetic systems, and the affect is determined by the dominant tone in the tissue, even if it was innervated by the two.

For example; blood vessels are only innervated by the sympathetic system and have parasympathetic receptors without direct endogenous intervention, when nicotine comes around it will bind to both receptors but the effect that is seen is from the sympathetic receptors (α1) which is vasoconstriction, that's why smoking (continues nicotine ingestion) leads to persistent constrictions of blood vessels which is going to underly different

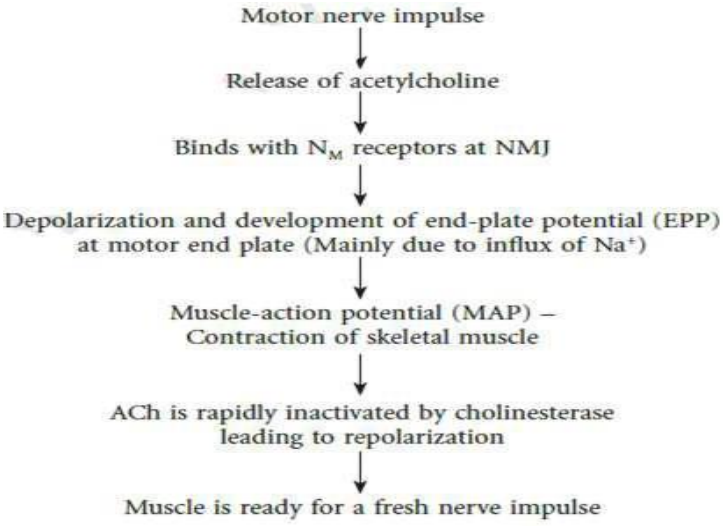
diseases like vascular dysfunction of heme and inability to vasodilate, which is a precursor for multiple cardiovascular diseases including: hypertension, atherosclerosis,arteriosclerosis and stiffness of blood vessels. Which can lead to different heart problems, in addition to all the lung problems it cause.

In post ganglionic fibers of the sympathetic system Ach causes the release of norepinephrine to its adrenal receptors (alpha and beta), and in the parasympathetic system Ach is released from the post ganglionic fibers to its muscarinic receptors.

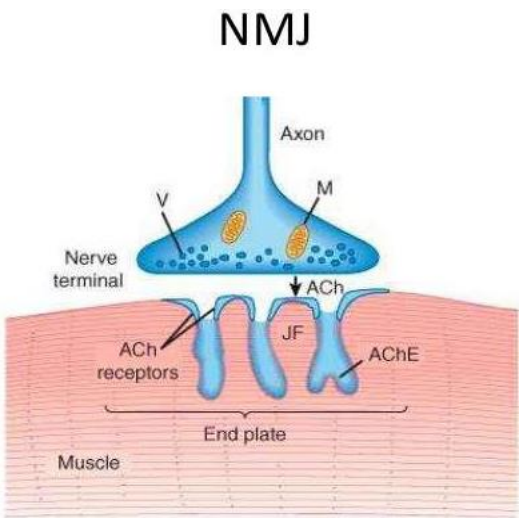
Parasympathetic Stimulation → Acetylcholine (ACh) release at neuroeffector junction (post ganglionic)→ biological effects.

Sympathetic stimulation → Noradrenaline (NA) at neuroeffector junction → biological effects.

2.Skeletal Muscles.



Physiology of skeletal muscle contraction



Neuromuscular junction

Skeletal muscles nicotinic receptors (ligand gated ion channels) that Ach can bind to in case of action potential, causing the influx of Na+ into the cell and activation of Ca++ channels and its entry leading to depolarization and formation of motor end plate potential and contraction of the muscle, then Ach is rapidly inactivated by acetylcholinesterases leading to repolarization and the muscle is ready for anther round of activation.

3.CNS: Cortex Basal ganglia, spinal cord and others.

PERIPHERALLY ACTING NEUROMUSCULAR BLOCKERS:

•Depolarizing Blockers:

–Mimic the action of acetylcholine (ACh).

–Agonists (bind to the receptor and activate it).

–Succinylcholine (SCh) is the only drug used clinically.

•Non-Depolarizing blockers:

–Interferes with the action of Ach.

–Competitive Blockers (Antagonist) (compete with the endogenous ligand at the same binding site, its binding doesn't cause any intrinsic activity and the effect is seen from the prevention of the Ach binding and causing relaxation (no contraction=relaxation).

–Further divided into short, intermediate and long acting non-depolarizing drugs.

DEPOLARIZING BLOCKERS – SUCCINYLCHOLINE:

•Succinylcholine have affinity and sub-maximal (not to the same degree as Ach, less activity) **intrinsic activity** (it's going to activate the receptor and cause contraction) **at Nm** (neuromuscular)**receptor.**

•It acts on sodium channels, open them and causes initial twitching and fasciculation(small fast repetitive muscle contractions).

•It does not dissociate rapidly from the receptors resulting in prolonged depolarisation and inactivation of Na+ channels (longer duration).

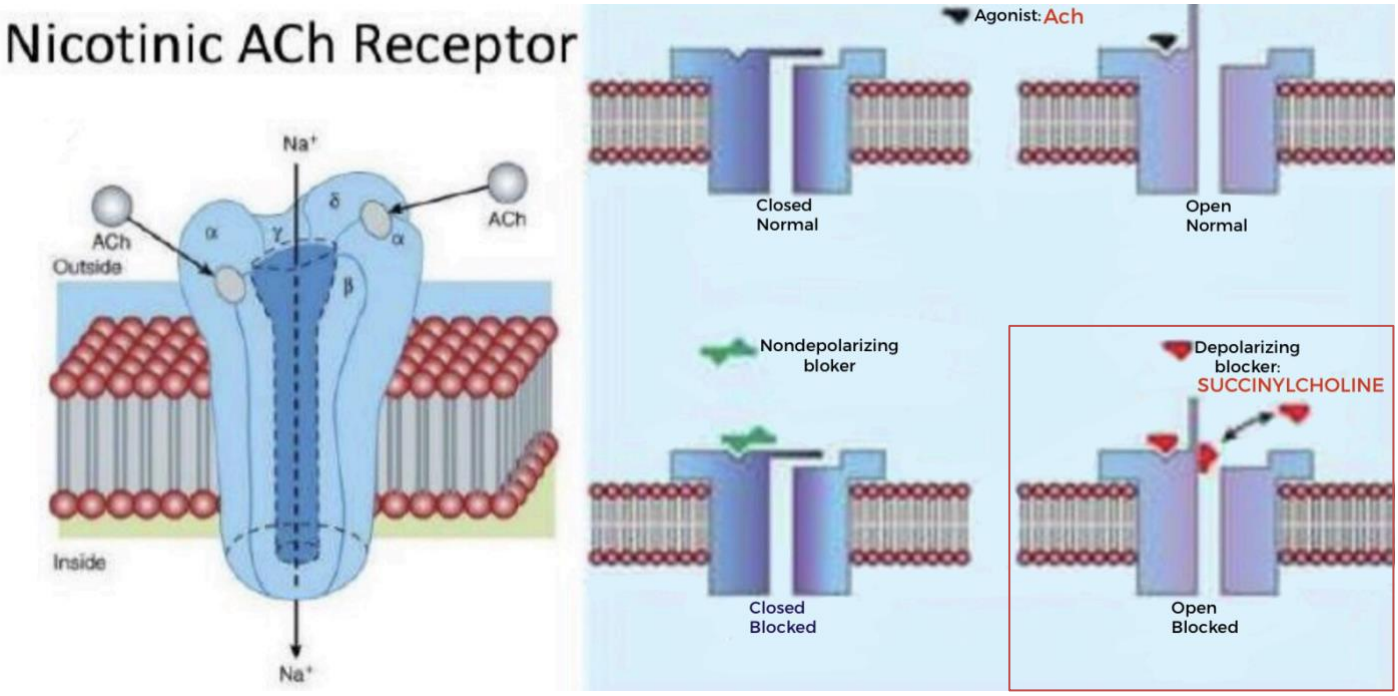
•It doesn't bind in the same pattern as Ach.

(Phase 1) Succinylcholine binds to Ach binding site **and binds to the inner side of the channel** (look at the picture in the next page for better understanding), causing the channel to remain open for **longer periods of time** (longer than if it was Ach).

(Phase 2) This leads to continuous stimulation and sustained contraction, and because it didn't go back to repolarization it won't be able to generate new action potentials even if Ach binds after succinylcholine dissociate. These continues contractions make the muscle **desensitized** and tired unable to contract anymore so it goes into a state of "**flaccid paralysis**".

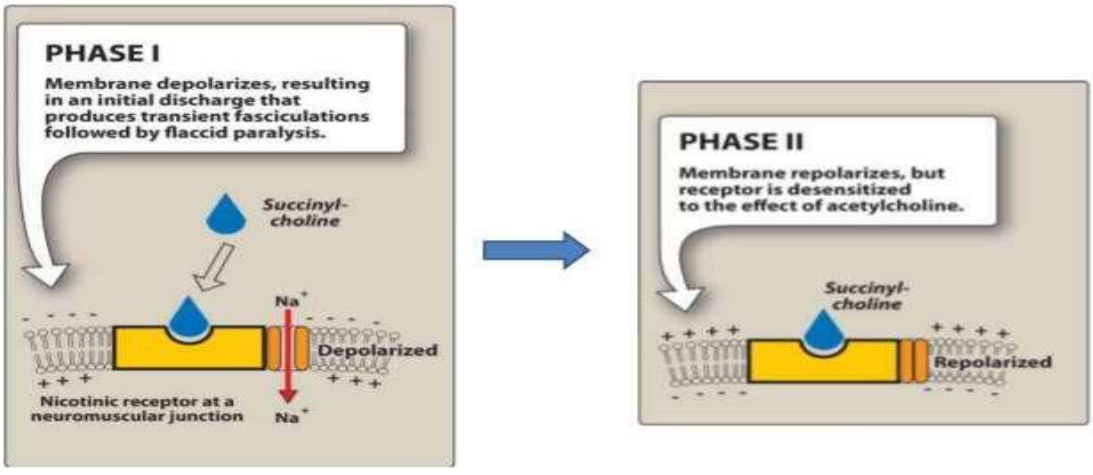
∴ Succinylcholine gives lower response for longer duration of action than Ach.

MECHANISM OF ACTION: SUCCINYLCHOLINE



Succinylcholine acts on the Nicotinic receptors of the muscles, stimulate them and ultimately cause their relaxation (in the second phase).
This process occur in two phases:

- **Phase I: During Phase I (depolarizing phase), they cause muscular fasciculations while they are depolarizing the muscle fibers** (acts like Ach).
- **Phase II: After sufficient depolarization has occurred, phase II (desensitized phase) sets and the muscle is no longer responsive to Ach released by the nerve endings, a state of "flaccid paralysis" or relaxation.**



SUCCINYLCHOLINE:

Advantages:

- **Most commonly used for Tracheal intubation** (because it's a short procedure that doesn't require general anesthesia).
- **Rapid onset (1-2 min).**
- **Good intubation conditions – relax jaw, separated vocal chords with immobility, no diaphragmatic movements.**
- **Short duration of action (5-10 minutes)** after that we will have recovery, this means that if we want the muscles to be paralyzed for longer than 10 min we would have to keep infusing the patient with this drug to keep performing its effect.
- **Dose 1-1.5mg/kg** (according to the wight of the patient).
- **Used as continuous infusion occasionally.**

You need to differentiate between these two:
The onset of action: Is when we start to see the effect of the drug.
The duration of action: For how long does this effect stay in the body.

Disadvantages:

- **Cardiovascular: unpredictable BP, heart rate** (can increase or decrease) **and** induce **arrhythmias.**
- **Fasciculation** (fast twitching that can be painful).
- **Muscle pain.**
- **Increased intraocular pressure.**
- **Increased intracranial pressure.**
- **Hyperkelemia: k+ efflux from muscles, life threatening in Cardiac Heart Failure, patient with diuretics etc.**

People with heart failure or history of arrhythmias require extra attention when given succinylcholine, because one of the disadvantages of succinylcholine is causing hyperkelemia (high K+ levels), and as we know K+, Na+ and Ca++ levels govern the contraction of the heart, especially K+ levels because it modulates the action and resting membrane potentials and any change in the potassium level can lead to a problem and disruption

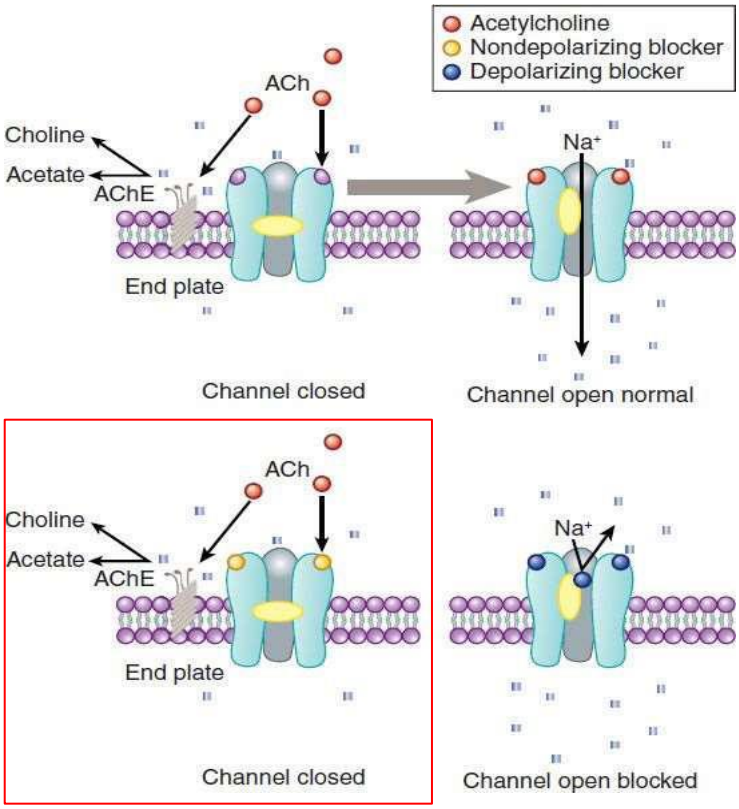
of the resting membrane potential and threshold especially in susceptible patients with heart problems.

NON-DEPOLARISING DRUGS:

•Competitive Blockers have no intrinsic activity, they bind only on the binding sites of Ach (don't bind on the inner site too like the depolarizing drugs).

•They only bind and affect closed channels, they aren't going to affect **open** channels.

As you can see in this picture 👉 The non depolarizing drugs work as blockers and block the binding of Ach when channels are closed.



•These are of 3 types based on their activity:

–Long Acting : d-TC, Pancuronium, Pipecuronium, Gallamine (Kidney Excretion).

The place of metabolism and excretion of a drug controls its half life, if a drug is metabolized in the liver then excreted by the kidney it would take a long time, so it have long duration of action (long acting).

–Intermediate Acting : Vecuronium, Rocuronium, **Atracuronium (eliminated by liver).

If we have a drug that has an intermediate and is metabolized and excreted by the liver, it doesn't have to go to the kidney, so it would take some time (intermediate acting).

–Short Acting : Mivacuronium, Ropcacuronium. (inactivated by plasma cholinesterase).

These drugs get deactivated or metabolized very quickly in the plasma by the cholinesterases , so their half life is going to be too short (short acting).

-Succinylcholine (which is a depolarizing drug that doesn't belong to any of these three groups) is also metabolized by acetylcholinesterases and its why it have a short half life (5-10 min).

**ATRACURIUM:

-Is a non-depolarizing intermediate acting peripheral muscle relaxant.

–Rapid recovery.

–Safe in hepatic & renal impairment.

–Spontaneous inactivation to laudanosine (seizures).

-It is destructed by a fast spontaneous reaction called **Hoffman elimination** (it's a hydrolysis reaction that includes water and can happen anywhere in the body), this reaction produces a toxic product **laudanosine** if it gets acclimated in our body, it can cross the BBB and reach the brain where it can cause **seizures** because this metabolite is stimulatory for the brain.

EFFECTS OF NON-DEPOLARIZING BLOCKERS:

The effect of the non depolarizing blockers differ depending on the dose.

•**Low Doses:**

–Competitive antagonists of Ach can be overcomed (their action can be reversed) by increasing the concentration of Ach, by using cholinesterases (acetylcholinesterases) inhibitors (ex. Neostigmine and physostigmine).

–Action can be reversed by ACh esterase inhibitors.

•**Large Doses:**

–Ion Channel is blocked (even if higher amounts of Ach are available it's not going to be overcoming this blockage).

–More weakness of neuromuscular transmission.

–Action could not be reversed by ACh esterase inhibitors.

Clinical case:

If I have a patient in the surgery and for some reason I need to stop the action of the non-depolarizing muscle relaxants, how do I overcome their toxicity? Or if I want a patient to recover very quickly from the effect of non-depolarizing muscle relaxants and the paralysis what do I do?

-Give the patient neostigmine or physostigmine.

•**Other actions:**

–Can block pre-junctional Na+ channels and interfere with mobilization of ACh at nerve endings.

TEST BANK:

• All are true about depolarizing agents except:

A. they get metabolized by pseudocholinesterase in the plasma and liver, and only a small percentage reaches the neural muscular junction where they diffuse away to the extracellular fluid.

B. Genetic variants in which plasma pseudocholinesterase levels are low or absent lead to prolonged neuromuscular paralysis.

C. long duration of action.

D. it has 2 phases of action, the second one only can be reversed by acetylcholinesterase inhibitors.

• Choose the false sentence about non-depolarizing Drugs:

A. Onset of effect is very rapid.
B. Motor weakness followed by flaccidity.
C. Starts with small muscles, large muscles are more resistant to blockade and recover more rapidly. Diaphragm is last to be paralyzed.
D. Effects lasts for 10 minutes.

• Choose the false sentence about the action of neuromuscular blockers:

A. Skeletal Muscle Paralysis.
B. hypotension Mediated by autonomic or histamine receptors.
C. Hyperkalemia.
D. Increased Intraocular Pressure and increased Intragastric Pressure.
E. there is no muscle pain.

V2

In page 9 open channels not closed.