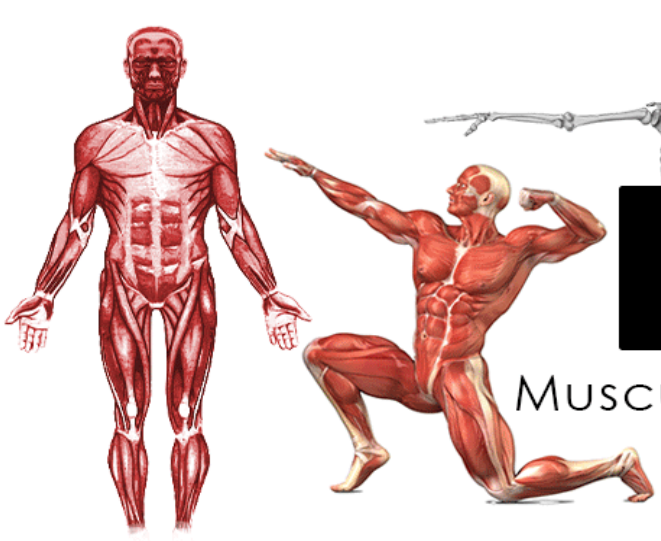
Online Lecture



MSS

Musculoskeletal System

Pharmacology

Doctor 2018 | Medicine | JU

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Introduction

A **muscle relaxant** is a drug that affects skeletal muscle function and decreases muscle tone. It can be used to alleviate the symptoms of muscle spasms and pain.

❖ There are different kinds of skeletal muscle relaxants:

- Neuromuscular Blockers
  - Nondepolarizing drugs
  - Depolarizing drugs
- Spasmolytics
- Directly Acting Drugs.

The arrows indicate the two main kinds.

Neuromuscular Blockers

Uses

- Neuromuscular blockers can be used in an array of conditions.
- Most importantly, they are used in surgical procedures and intensive care units (ICU).
- The purpose of muscle relaxants in these procedures is to ease the intubation process during anesthesia or in the ICU.
- Additionally, during surgical procedures, the effect of reduced muscle tone will make it easier to dissect through the muscles and perform the surgery.
- An additive value to their use is that neuromuscular blocking agents have significantly increased the safety of anesthesia because less anesthetic is required to produce muscle relaxation.

Chemistry

- The neuromuscular blocker's chemical structure consists of one or two quaternary nitrogens. Thus, they are poorly lipid soluble or highly polar compounds.
  - This means that these agents will not be absorbed through the GI system. Instead, they are given by injection (most likely IV) during the different procedures.
- It is a double acetylcholine molecule linked end to end and it may be concealed in a bulky semi-rigid ring system.

Pharmacokinetics

Remember that parenteral administration refers to any route of drug administration that does not involve drug absorption via the GI tract.

- Must be given parenterally by IV injection.
- **<u>Nondepolarizing Drugs</u>:**
  - Excreted in the kidneys or metabolized by the liver.
  - There are different kinds of these neuromuscular blockers. But we will be focusing mainly on the prototypes of these drugs while other chemical structures (or other drugs) will have different differences in their half-life or metabolism.
    - For example, **Mivacurium** is metabolized by cholinesterases. Therefore, this drug has a very short half-life.
    - **Atracurium** is spontaneously broken down by a reaction known as **Hofman Elimination**. This drug also has a short half-life compared to drugs metabolized by the liver.
- **<u>Depolarizing Drugs:</u>**
  - Have extremely short duration of action (5-10 minutes)
  - Metabolized by cholinesterases in the plasma and liver.
  - Only a small percentage of the drug reaches the neuromuscular junction (NMJ), where it diffuses away into the extracellular fluid.

Clarification from the textbook (not required, only added for the sake of understanding): Plasma cholinesterases have an enormous capacity to hydrolyze succinylcholine (a depolarizing drug), so only a small percentage of the original intravenous dose will ever reach the neuromuscular junction. In addition, because there is little if any plasma cholinesterase at the motor end plate, the blockade caused by the drug is only terminated by its diffusion away from the end plate.

  - Some patients have a genetically abnormal variant of plasma cholinesterase.
    - Because of this, there will be variation in the plasma levels and half-lives of these drugs between individuals.
  - <u>Dibucaine Number</u>: A measure of the ability of a patient to metabolize succinylcholine (a depolarizing drug).

Table 27–1. Some properties of neuromuscular blocking drugs.

Drug	Elimination	Clearance (mL/kg/min)	Approximate Duration of Action (minutes)	Approximate Potency Relative to Tubocurarine
Isoquinoline derivatives				
Atracurium	Spontaneous[1]	6.6	20–35	1.5
Cisatracurium	Mostly spontaneous	5–6	25–44	1.5
Doxacurium	Kidney	2.7	> 35	6
Metocurine	Kidney (40%)	1.2	> 35	4
Mivacurium	Plasma ChE[2]	70–95	10–20	4
Tubocurarine	Kidney (40%)	2.3–2.4	> 35	1
Steroid derivatives				
Pancuronium	Kidney (80%)	1.7–1.8	> 35	6
Pipecuronium	Kidney (60%) and liver	2.5–3.0	> 35	6
Rocuronium	Liver (75–90%) and kidney	2.9	20–35	0.8
Vecuronium	Liver (75–90%) and kidney	3–5.3	20–35	6
Depolarizing agent				
Succinylcholine	Plasma ChE[2] (100%)	>100	< 8	0.4

[1]Nonenzymatic and enzymatic hydrolysis of ester bonds.
[2]Butyrylcholinesterase (pseudocholinesterase).

Notes on the Table:

- We can notice that most of these drugs are eliminated by the kidneys, while some are metabolized by plasma cholinesterases.
- There are differences in the half lives of these agents, which can be measured by the clearance. There are also differences in the duration of action and potency.
- These agents are compared to Tubocurarine, which is the prototype.

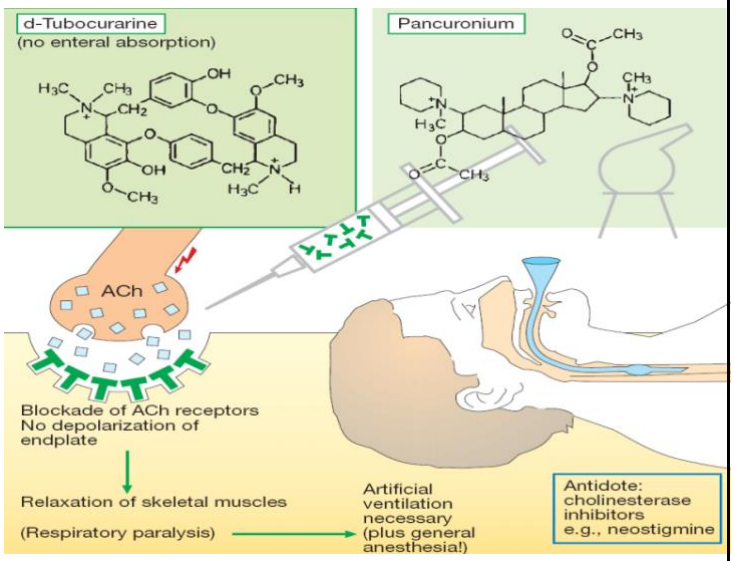
Mechanism of Action

Non-Depolarizing Drugs:

- They are competitive inhibitors of acetylcholine (ACh) at the nicotinic receptor sites at the NMJ. Thus, they prevent ACh from binding to its receptor and end plate potentials do not develop (no depolarization!). Therefore, muscle contraction is **not** stimulated.
- In high doses, the drug can enter the pore of the ion channel to cause a more intense blockade. In this case, even if the channel were to open, the drug blocks the flow of sodium ions through the ACh receptor, further preventing depolarization.

- They can also block prejunctional sodium channels to interfere with the mobilization of acetylcholine at the nerve ending.

As you can see in this picture, once these drugs are injected in the patient, they can compete with ACh for the binding sites on the nicotinic receptor, thus preventing ACh from binding and inducing contraction of the skeletal muscle. An example where we can see this effect is with the respiratory muscles. The inhibition of contraction will lead to the relaxation of the respiratory muscles, which can ease up the artificial ventilation necessary in general anesthesia processes.



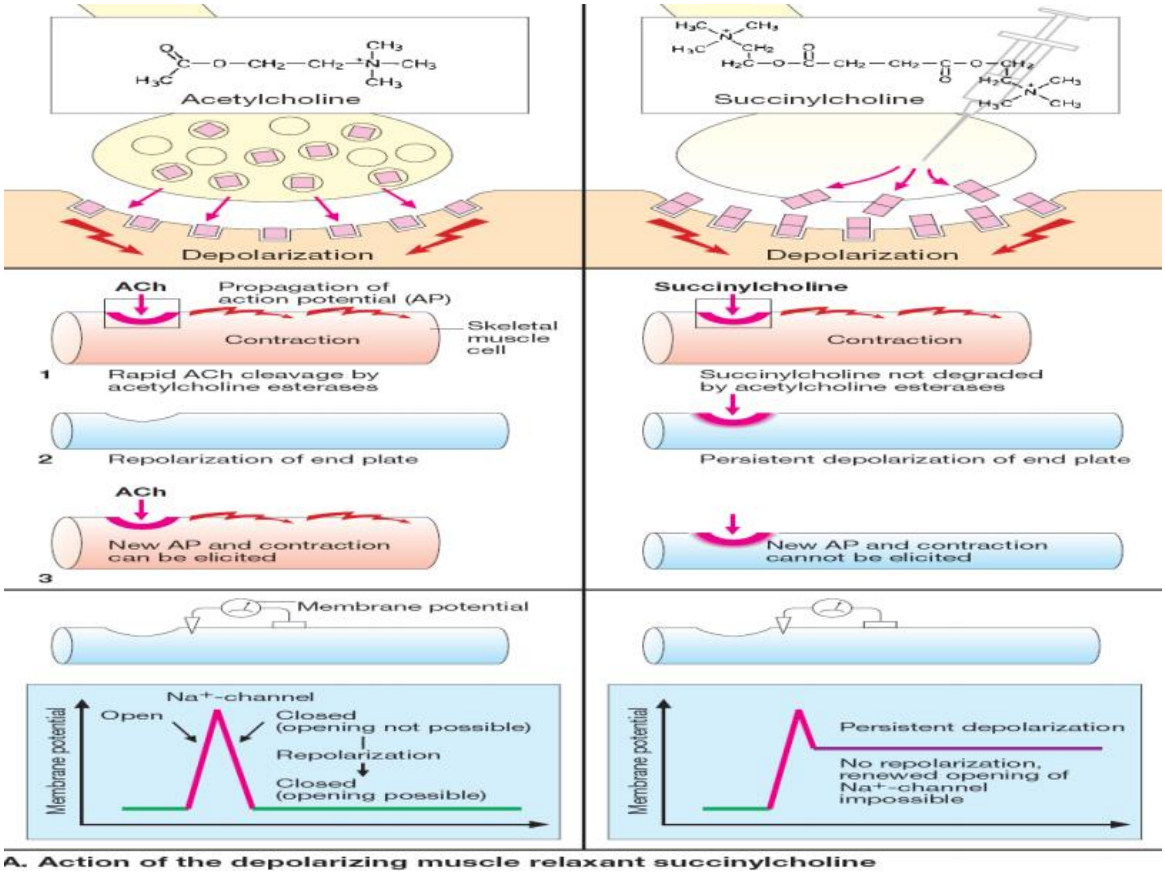
Succinylcholine has a very similar structure to acetylcholine. It's two ACh's are bound edge to edge

<u>Depolarizing Drugs:</u>

I. Phase I Block (*depolarizing*):
   - Succinylcholine reacts with nicotinic receptors to open the channel and <u>cause depolarization</u> of the motor end plate which will spread to adjacent membranes. Initially, this will cause contractions of muscle motor units.
   - It can then enter the channel to produce a prolonged "flickering" of the ion conductance.
   - The depolarized membranes <u>remain depolarized and unresponsive</u> to subsequent impulses (extra: This is because succinylcholine is not metabolized effectively at the synapse, so it will remain, cause a depolarizing blockade and not allow the muscle to respond to any new impulses). This causes flaccid paralysis which is augmented (increased and not reversed) by cholinesterase inhibitors.

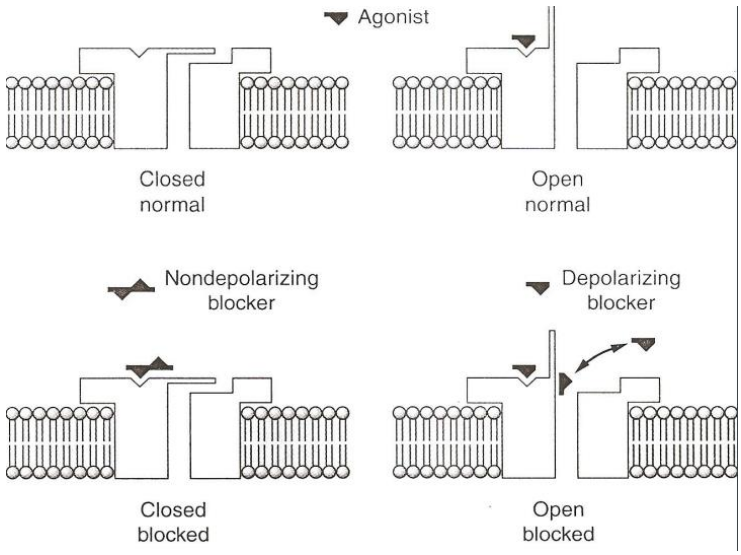
II. Phase II Block (*desensitizing*):
   - With continued exposure, depolarization decreases and the membrane becomes repolarized and cannot be depolarized again because it is desensitized. This may be due to blockade of the ion channel, which might be more important than the action of the agonist at the receptor, i.e. the channels behave as if they are in a prolonged closed state.
   - This phase is reversed by acetylcholinesterase inhibitors. This is because acetylcholine can bind and un-bind to the receptor more rapidly than

succinylcholine can. By increasing the concentration of ACh through acetylcholinesterase inhibitors, this helps ACh bind more, allowing repolarization of the end plate, and returns the receptor to its normal conformation faster.



A. Action of the depolarizing muscle relaxant succinylcholine

In this picture, we can see the differences between ACh and succinylcholine. Both of them cause initial depolarization of the muscle. The muscle stimulated by ACh will show relaxation after a period of time, which allows the muscle to repolarize and it can contract again. In the case of succinylcholine, there will be persistent depolarization with no repolarization, so renewed opening of the Na^+ channel becomes impossible.



	Rocuronium	Succinylcholine	
		Phase I	Phase II
Administration of tubocurarine	Additive	Antagonistic	Augmented[1]
Administration of succinylcholine	Antagonistic	Additive	Augmented[1]
Effect of neostigmine	Antagonistic	Augmented[1]	Antagonistic
Initial excitatory effect on skeletal muscle	None	Fasciculations	None
Response to a tetanic stimulus	Unsustained (fade)	Sustained[2] (no fade)	Unsustained (fade)
Posttetanic facilitation	Yes	No	Yes
Rate of recovery	30–60 min[3]	4–8 min	> 20 min[3]

1 It is not known whether this interaction is additive or synergistic (superadditive).
2 The amplitude is decreased, but the response is sustained.
3 The rate depends on the dose and on the completeness of neuromuscular blockade.

In this table, we can see a comparison between a typical nondepolarizing muscle relaxant (rocuronium) and a depolarizing muscle relaxant (succinylcholine). They are typically compared to tubocurarine.

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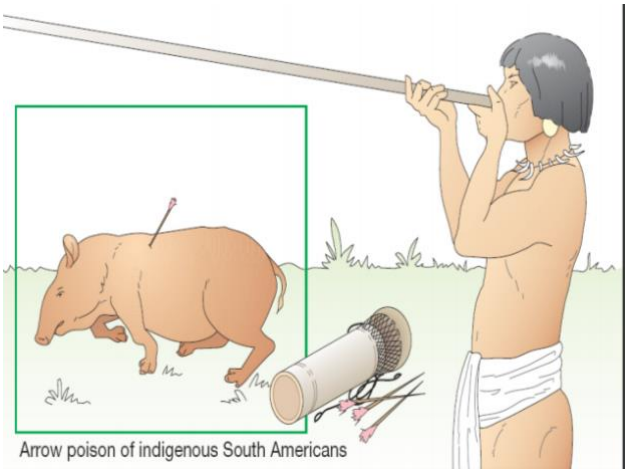
Skeletal Muscle Paralysis

Nondepolarizing Drugs

- Onset of effect is very rapid.
- Motor weakness followed by flaccidity.
- Starts with small muscles, large muscles are more resistant to blockade and recover more rapidly. Diaphragm is last to be paralyzed.
- Effects lasts for 45-60 minutes.

This is one of the earliest uses of tubocurarine, which was used by native hunters as a poison for hunting animals. Since, as mentioned, the drug doesn't get absorbed by the GI tract, it would not harm the individual after they ingested the poisoned meat in the animal when they consumed it. The clinical use of this drug, however, did not start until the early 1940s.


Arrow poison of indigenous South Americans

Depolarizing Drugs:

- Action starts by transient muscle fasciculations over the chest and abdomen within 30 seconds. (a fasciculation, or muscle twitch, is a small, local, involuntary muscle contraction and relaxation).

- Paralysis develops rapidly (within 90 seconds) in the arm, neck, and leg muscles followed by the respiratory muscles.
- Blockade lasts less than 10 minutes. (remember their quick metabolism)

Side Effects of Neuromuscular Blockers

A. Cardiovascular Effects

- Mediated by autonomic effects or histamine receptors (or histamine release).
- Both sympathetic and parasympathetic ganglia and muscarinic receptors in the heart can be stimulated by these agents.
- Usually cause hypotension, which can be attenuated (reduced) by antihistamines.

B. Hyperkalemia

- Especially in patients with burns, nerve damage, neuromuscular disease, head injury, and other trauma.
- This can result in cardiac arrest.

C. Increased Intraocular Pressure

- Due to tonic contraction of myofibrils or transient dilation of ocular choroidal blood vessels.

D. Increased Intragastric Pressure

- In obese, heavily muscled, diabetics, and traumatic patients. Fasciculations of succinylcholine can increase intragastric pressure and therefore cause regurgitation and aspiration of gastric contents.

Regurgitation is when the contents of the stomach are brought up into the esophagus. Aspiration is the inhalation of those contents into the lungs.

E. Muscle Pain

- Due to unsynchronized contractions of adjacent muscle fibers just before the onset of paralysis.

Drug Interactions of Neuromuscular Blockers

A. Anesthetics

- Remember that neuromuscular blockers are used in general anesthesia procedures.
- This unwanted drug interaction is important, especially with halogenated anesthetics such as isoflurane (most), and least with nitrous oxide.
- May be due to a central action and increased muscle blood flow.
- This interaction is unwanted because it can cause Malignant Hyperthermia. For example, when halothane, an anesthetic, is administered with succinylcholine, occasionally, malignant hypothermia occurs. It is associated with muscle rigidity and pyrexia (fever). This happens especially in genetically susceptible individuals. One

important treatment for this condition is administration of a directly acting muscle relaxant called Dantrolene. Dantrolene blocks the release of Ca^{2+} from the sarcoplasmic reticulum, reducing heat production and relaxing the muscle tone.

B. Antibiotics

- Certain antibiotics can interact with neuromuscular blockers.
- They depress/decrease release of acetylcholine due to blockade of specific P-type of calcium channels.
- Additionally, aminoglycoside antibiotics, such as gentamicin or tobramycin, can inhibit the acetylcholine release from cholinergic nerves by competing with calcium ions. This synergizes with tubocurarine (and other competitive blockers), enhancing the action of the blockers.

C. Local Anesthetics and Anti-Arrhythmic Drugs

D. Other Neuromuscular Blockers

We also have to be careful about the use of neuromuscular agents with c and .

Spasmolytic Drugs

They are drugs used in conditions of spasticity.

Diazepam

- Acts at $GABA_A$ receptors in the CNS.
- Its action in reducing spasticity is at least partially mediated in the spinal cord as it is somewhat effective in patients with cord transection.

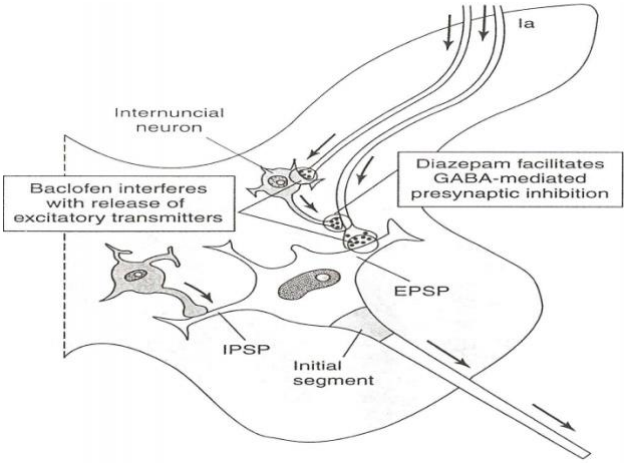
Extra: cord transection refers to a tear within the spinal cord, which can cause spasticity.

- Benzodiazepines (such as diazepam) facilitate the action of GABA in the central nervous system.
- Sedative (side effect). Additionally, there is a tendency for tolerance and dependency associated with these agents.
- Although diazepam can be used in patients with muscle spasm of almost any origin (including local muscle trauma), it also produces sedation at the doses required to reduce muscle tone. The patient should be informed of possible sedation when using these agents.
- Other benzodiazepines, such as midazolam, has been used as a spasmolytic agent, but the clinical experience with them is very limited.

Baclofen

- Mainly 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.
- Less sedative than benzodiazepines but can cause drowsiness.
- Can be given intrathecally (injection of drug into the spinal canal).
- Can reduce cravings in alcoholics and migraines.



This picture shows us the sites of action of the two previously discussed drugs in the CNS (spinal cord).

Tizanidine

- Related to clonidine.
- Used to treat muscle spasticity especially due to spinal cord injury or multiple sclerosis.
- Alpha 2 agonist
- BP lowering??? Clonidine is used as an antihypertensive agent, though the effect of Tizanidine as a blood pressure reducer is much less effective than that of clonidine by a factor of (1/10) or (1/15)
- Side effects: dizziness, weakness, depression, hallucinations (related to CNS).
- Dry mouth is another side effect. Some patients experience constipation, while others experience diarrhea.

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Gabapentin

- An antiepileptic glycine.

Directly Acting Drugs

Dantrolene

- Related to phenytoin, an antiepileptic.
- Interferes with excitation-contraction coupling in the muscle fibers by interfering with the release of activator calcium by binding with the ryanodine receptor (RyR) channel of the sarcoplasmic reticulum.
- Can cause weakness, sedation, and hepatitis.

- Dantrolene can be used as an antidote for patients exhibiting malignant hyperthermia, which is induced by the combination of succinylcholine with anesthetic agents such as halothane. There is a genetic mutation related to this side effect, and the genetic mutation is related to the ryanodine receptor.

Malignant Hyperthermia

- Rare heritable disorder triggered by a variety of stimuli, including general anesthetics and neuromuscular blockers.
- Patients have a hereditary impairment of the sarcoplasmic reticulum to sequester calcium.
- The trigger can cause sudden and prolonged release of calcium, with massive contraction, leading to lactic acidosis and increased body temperature.
- Treatment is by cooling, correcting acidosis, and dantrolene to reduce calcium release.

Botulinum Toxin

- Produced by Botulinum bacteria.
- Also used as a muscle relaxant or, mainly, for muscle paralysis.
- Inhibits acetylcholine release.
- Food poisoning caused by this bacteria can result, within 12-36 hours, in diplopia (double vision), dysphagia (swallowing difficulties), dysarthria (slurred or slow speech), and dyspnea (shortness of breath).
- The toxin is use therapeutically for ophthalmic 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.

Additional Information (Last 5 Minutes of the Video)

Muscle Relaxant Intoxication

Now, we need to try to identify the different antidotes for muscle relaxant intoxication.

- Nondepolarizing agents are competitive inhibitors of ACh, preventing its binding to nicotinic receptors at the skeletal muscle endplate.
- If we want to reverse the effect of these agents, we need to use a drug that will increase the concentration of ACh at the skeletal muscle endplate, this will cause

ACh to be able to compete better and bind to more nicotinic receptors, reversing the action of the drug and causing muscle contraction.

- The drugs we can use for this are the reversible acetylcholinesterase inhibitors such as neostigmine, pyridostigmine, or edrophonium. By blocking acetylcholinesterase, this leads to a higher concentration of ACh at the site of action.

Nondepolarizing Drugs

- There are different agents that belong to the nondepolarizing drugs such as tubocurarine (prototype), mivacurium, and atracurium. They have the same mechanism of action, but they differ in their side effects, onset of action, and duration of action.
- For example, tubocurarine, mivacurium, pancuronium, metocurine, and doxacurium are excreted in the urine unchanged. While, atracurium is spontaneously degraded in the plasma by ester hydrolysis.
- Additionally, we have two drugs that get metabolized by the liver such as Rocuronium and Vecuronium, so the half-life of these drugs can be prolonged in individuals with hepatic problems or disease. These agents are mainly secreted unchanged in the bile.
- Some of them have effects on lowering blood pressure. For example, atracurium has an effect on histamine release leading to dilation of blood vessels and lowering of blood pressure.
- One special effect of Atracurium is that it is metabolized to laudanosine, which can provoke seizures. On the other hand, cisatracurium, which has the same pharmacokinetic properties as atracurium, is less likely to cause this side effect.
- It's very important to differentiate between the pharmacokinetic properties of these agents to decide on which agent to use in each particular case for each patient.
- Depending on the condition of the patient, we choose which chemical entity of this group of agents is best to administer.

Depolarizing Agents

- Regarding depolarizing agents, we focused on succinylcholine and represented them by succinylcholine's actions.
- Depolarizing agents' therapeutic uses are limited by the short duration of action of these agents. They might be useful only when rapid endotracheal intubation is required because of their rapid onset of action. But due to their short duration of

action we have to keep supplementing the patient with these agents and monitoring their effect.

- Hyperthermia is mainly associated with succinylcholine. However, certain patients have the side effect of apnea (cessation of breathing), especially in patients who have a genetic deficiency in plasma cholinesterases. This can lead to delayed or prolonged apnea due to paralysis of the diaphragm. We need to be careful when administering these drugs to patients with this genetic deficiency.

Quiz

1. **Which of the following is correct regarding the neuromuscular blockers (NMBs)?**

A. Nondepolarizing NMBs are administered orally.
B. Cholinesterase inhibitors reduce the effects of nondepolarizing NMBs.
C. Nondepolarizing NMBs affect diaphragm muscles first.
D. Effects of depolarizing neuromuscular blockers can be reversed using cholinesterase inhibitors.

2. **Which of the following is correct regarding drug interactions with nondepolarizing neuromuscular blockers (NMBs)?**

A. Desflurane reduces the effects of nondepolarizing NMBs.
B. Cholinesterase inhibitors increase the effects of nondepolarizing NMBs.
C. Aminoglycosides increase the effects of nondepolarizing NMBs.
D. Calcium channel blockers reduce the effects of nondepolarizing NMBs.

3. **A patient was administered a neuromuscular blocker (NMB) prior to a surgical procedure to produce skeletal muscle paralysis. This NMB drug caused initial skeletal muscle fasciculations before the onset of paralysis. The effect of this drug could not be reversed with neostigmine. Which of the following neuromuscular blockers was most likely administered to this patient?**

A. Cisatracurium.
B. Succinylcholine.
C. Diazepam.
D. Tubocurarine

4. **This intermediate-acting isoquinoline-type intermediate acting nondepolarizing drug exhibits Hofman elimination (spontaneous breakdown).**
   A. Pancuronium
   B. Atracurium
   C. Vecuronium

5. **Botulinum toxin, which may be used to manage ocular blepharospasm as well as control other muscle spasms, blocks neuromuscular transmission mainly through inhibition of acetylcholine release.**
   A. True
   B. False

6. **Which of the following statements is false?**
   A. Phase I blockade could be potentiated by edrophonium
   B. Benzodiazepines (such as diazepam) facilitate the action of GABA in the central nervous system
   C. Nondepolarizing agents tend to have a longer duration of action than depolarizing agents
   D. The combination of dantrolene with succinylcholine can possibly cause malignant hypothermia

7. **Succinylcholine, an example of a depolarizing neuromuscular blocker, exhibits longer duration compared to acetylcholine mainly due to which one(s) of the following?**
   A. Tighter binding to the acetylcholine receptor
   B. Resistance to inactivation by acetylcholinesterase

Answers

1. B

Nondepolarizing NMBs such as cisatracurium and vecuronium are highly polar compounds and are poorly absorbed from the GI tract. Therefore, they are administered parenterally, not orally. Nondepolarizing NMBs are competitive antagonists at nicotinic receptors. Therefore, increasing the levels of ACh at the neuromuscular junction reduces the effects of these agents. Cholinesterase inhibitors increase the levels of ACh at the neuromuscular junction and reduce the effects of nondepolarizing NMBs, but may enhance (not reverse) the effects of depolarizing NMBs. Nondepolarizing NMBs first affect rapidly contracting muscles seen in the face and eyes and affect the diaphragm muscles last.

2. C (Explanations for A+D not included, but kept for your information)

Halogenated hydrocarbon anesthetics such as desflurane enhance the effects of nondepolarizing NMBs by exerting a stabilization effect at the neuromuscular junction (NMJ). Acetylcholinesterase inhibitors increase the levels of ACh at the NMJ and reduce the effects of nondepolarizing NMBs. Aminoglycoside antibiotics increase the effects of nondepolarizing NMBs by reducing the release of ACh from the cholinergic neurons. Calcium channel blockers increase the effects of nondepolarizing NMBs, possibly by affecting ion transport at the NMJ.

3. B

Depolarizing NMBs cause muscle fasciculations before causing paralysis, and their effects cannot be reversed using cholinesterase inhibitors such as neostigmine. Nondepolarizing NMBs do not cause muscle fasciculations, and their effects can be reversed using cholinesterase inhibitors. Therefore, the NMB used in this patient is succinylcholine, which is a depolarizing NMB. Cisatracurium and tubocurarine are nondepolarizing NMBs, and diazepam does not cause paralysis of skeletal muscles.

4. B
5. A
6. D
7. B