MUSCULOSKELETAL SYSTEM

Subject : Pharmacology

Lec no : 6

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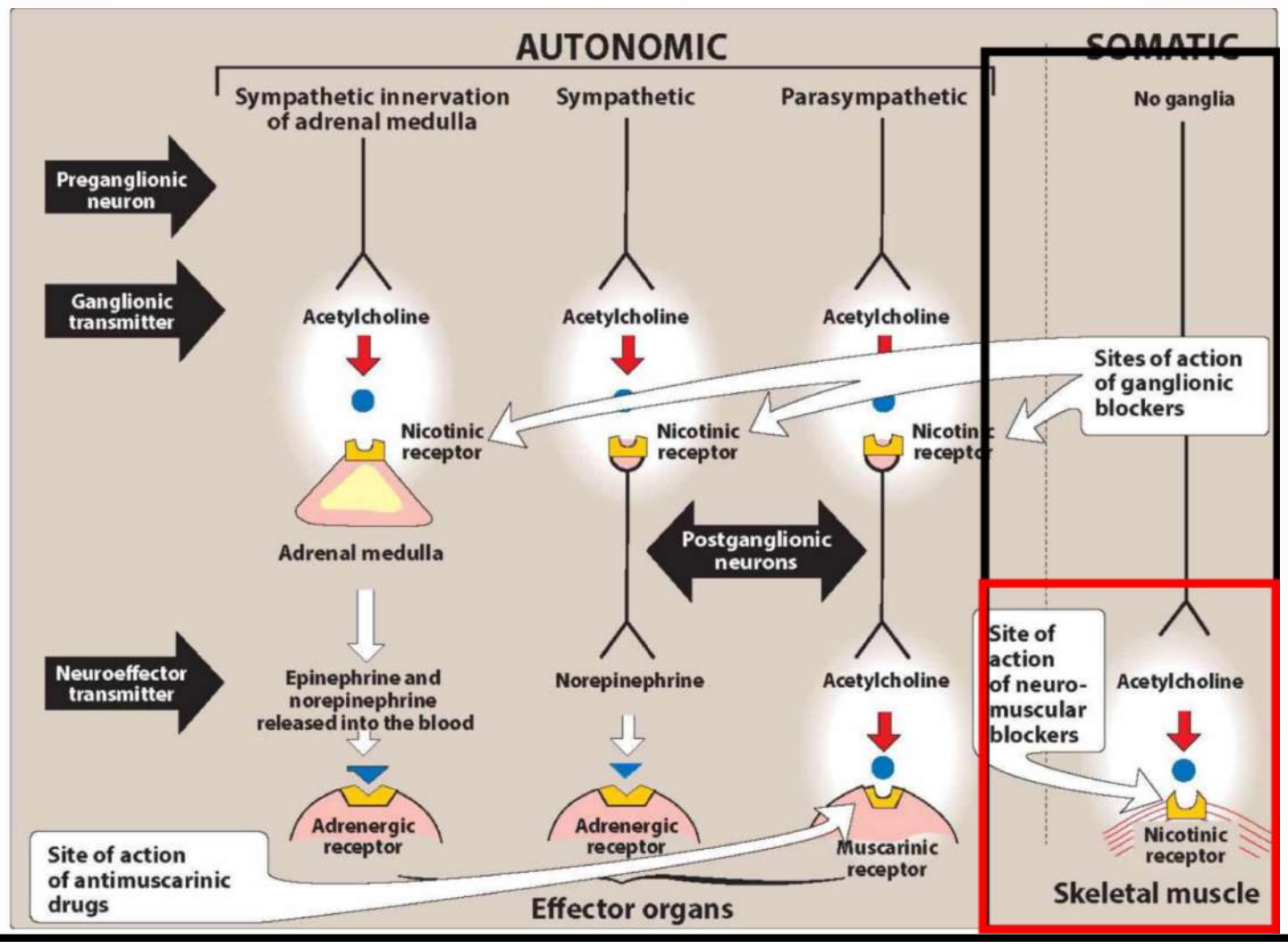
Musculoskeletal System

NEUROMUSCULAR-BLOCKING AGENTS (NMBs)



Cholinergic antagonist is a general term for agents that bind to cholinoceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists.

They possess some chemical similarities to ACh

Neuromuscular-blocking Agents

- **Agonists (depolarizing type)**
- **Antagonists (nondepolarizing type)**

useful during surgery>> facilitate tracheal intubation and provide complete muscle relaxation at lower anesthetic doses>>rapid recovery from anesthesia and reducing postoperative respiratory depression

These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on the skeletal muscle. They possess some chemical similarities to ACh, and they act either as antagonists (nondepolarizing type) or as agonists (depolarizing type) at the receptors on the endplate of the NMJ.

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Musculoskeletal System

Nondepolarizing (Competitive) Blockers

حفظ اسماء الادوية

- Curare
- Used by native South American hunters "paralyzes prey"
- Significantly increased the safety of anesthesia, because less anesthetic is required to produce muscle relaxation.

NEUROMUSCULAR BLOCKERS
Cisatracurium NIMBEX
Mivacurium MIVACRON
Pancuronium GENERIC ONLY
Rocuronium GENERIC ONLY
Succinylcholine ANECTINE, QUELICIN
Vecuronium GENERIC ONLY

↳ **allowing patients to recover quickly and completely after surgery.**

***The first drug known to block the skeletal NMJ was curare, which native South American hunters.**

***The development of the drug tubocurarine followed, but it has been replaced by other agents with fewer adverse effects, such as cisatracurium, pancuronium, rocuronium, and vecuronium.**

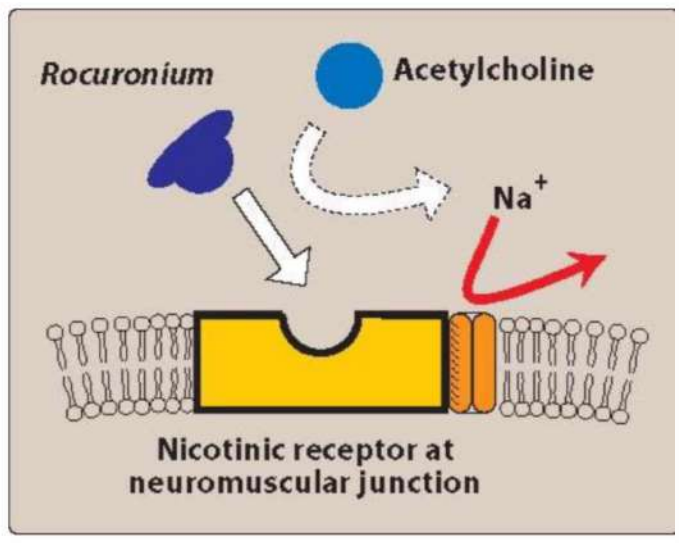
***Neuromuscular blockers should not be used to substitute for inadequate depth of anesthesia.**

Nondepolarizing (Competitive) Blockers

Mechanism of action

At low doses

- Competitively block Ach at nicotinic receptors (no stimulation)
- Prevent the depolarization of muscle cell membrane & inhibit muscular contraction
- How can you overcome/reverse this effect (pharmacologically)?



***They compete with ACh at the receptor without stimulating it.**

***Their competitive action can be overcome by administration of cholinesterase inhibitors, such as neostigmine and edrophonium.**

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Nondepolarizing (Competitive) Blockers

Mechanism of action

At low doses

- Using **cholinesterase inhibitors**, such as neostigmine and edrophonium >>> increase the concentration of ACh in the NMJ.
- This will shorten the duration of the neuromuscular blockade.
- muscle will respond to direct electrical stimulation from a peripheral nerve stimulator to varying degrees, allowing for monitoring of the extent of neuromuscular blockade

Nondepolarizing (Competitive) Blockers

Mechanism of action

At high doses

- block the ion channels of the motor endplate
- further weakening of neuromuscular transmission
- Would AChE inhibitors work in this case?
- With complete blockade, the muscle does not respond to direct electrical stimulation.

reducing the ability of cholinesterase inhibitors to reverse the actions of the nondepolarizing blockers.

Musculoskeletal System

Aspect	Low Doses	High Doses
Mechanism of Action	Competitively block ACh at nicotinic receptors without stimulation.	Block ion channels of the motor endplate, leading to further weakening of neuromuscular transmission
Depolarization Inhibition	Prevent depolarization of the muscle cell membrane, inhibiting muscular contraction.	Further reduces neuromuscular transmission, reducing the efficacy of cholinesterase inhibitors.
Overcoming Competitive Action	Cholinesterase inhibitors (e.g., neostigmine, edrophonium) can overcome competitive action by increasing ACh concentration.	Efficacy of cholinesterase inhibitors is diminished due to complete blockade of neuromuscular transmission.
Muscle Response to Electrical Stimulation	Muscle responds to direct electrical stimulation, allowing monitoring of neuromuscular blockade extent.	Muscle does not respond to direct electrical stimulation due to complete blockade.
Clinical Application (e.g., Anesthesia)	Used to shorten the duration of neuromuscular blockade.	High doses may lead to prolonged neuromuscular blockade, affecting anesthesia reversal
Overall Effect on Neuromuscular Function	Moderately inhibitory effect, reversible with cholinesterase inhibitors.	Pronounced inhibitory effect, less reversible with cholinesterase inhibitors, especially in complete blockade.

Nondepolarizing (Competitive) Blockers

Actions

- Inequal muscle sensitivity
- Small rapidly contracting more sensitive

face and eye → fingers, limbs, neck, and trunk muscles →intercostal muscles → diaphragm

(recovery in the reverse manner)

Not all muscles are equally sensitive to blockade by competitive agents. Small, rapidly contracting muscles of the face and eye are most susceptible and are paralyzed first, followed by the fingers, limbs, neck, and trunk muscles. Next, the intercostal muscles are affected and, lastly, the diaphragm. The muscles recover in the reverse manner.

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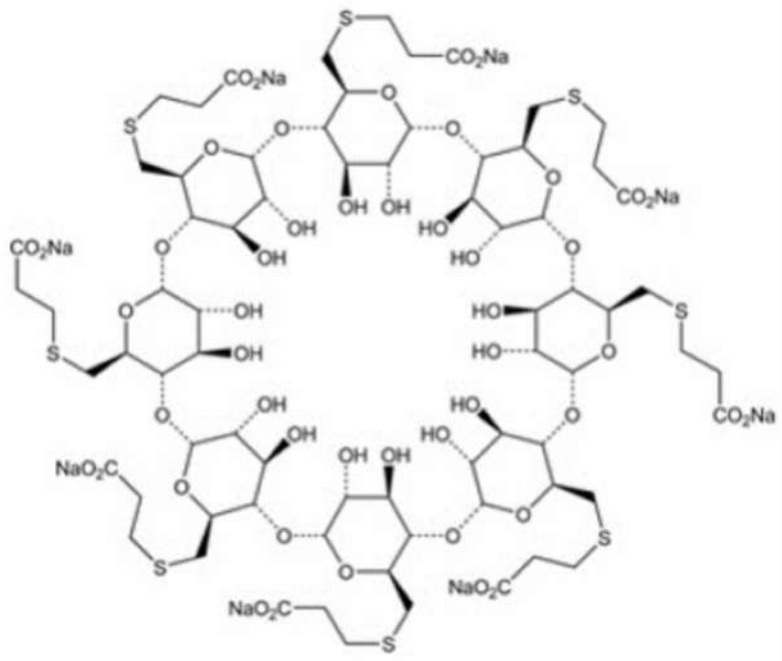
Sugammadex

- Selective relaxant-binding agent
- Terminates the action of both: rocuronium and vecuronium
- Wraps the NM blocker in 1:1 ratio
- Rapid reversal of neuromuscular blockade



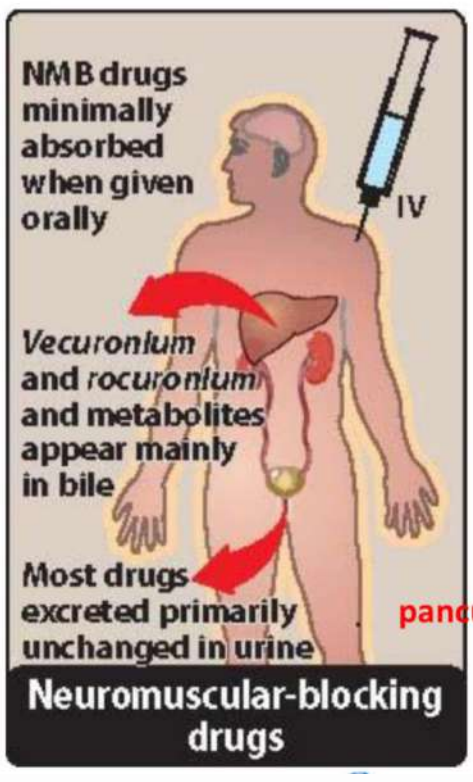
Sugammadex

السلايد عليها سؤال الدكتور ركز عليها

Nondepolarizing (Competitive) Blockers

Pharmacokinetics:

- Given IV (sometimes IM)
- Possess two or more quaternary amines in their bulky ring structure preventing absorption from the gut.
- Very poor membrane penetration; Do not enter cells or cross the BBB
- **Pancuronium** is excreted unchanged in **urine**.
- **Cisatracurium** metabolized to laudanosine, which is further metabolized and **renally** excreted.
- **Vecuronium and Rocuronium** are deacetylated in the **liver and excreted unchanged in bile.**
- **Mivacurium is eliminated by plasma cholinesterase**.



*They are not effective orally.

*The amino steroid drugs vecuronium and rocuronium are deacetylated in the liver, and their clearance may be prolonged in patients with hepatic disease.

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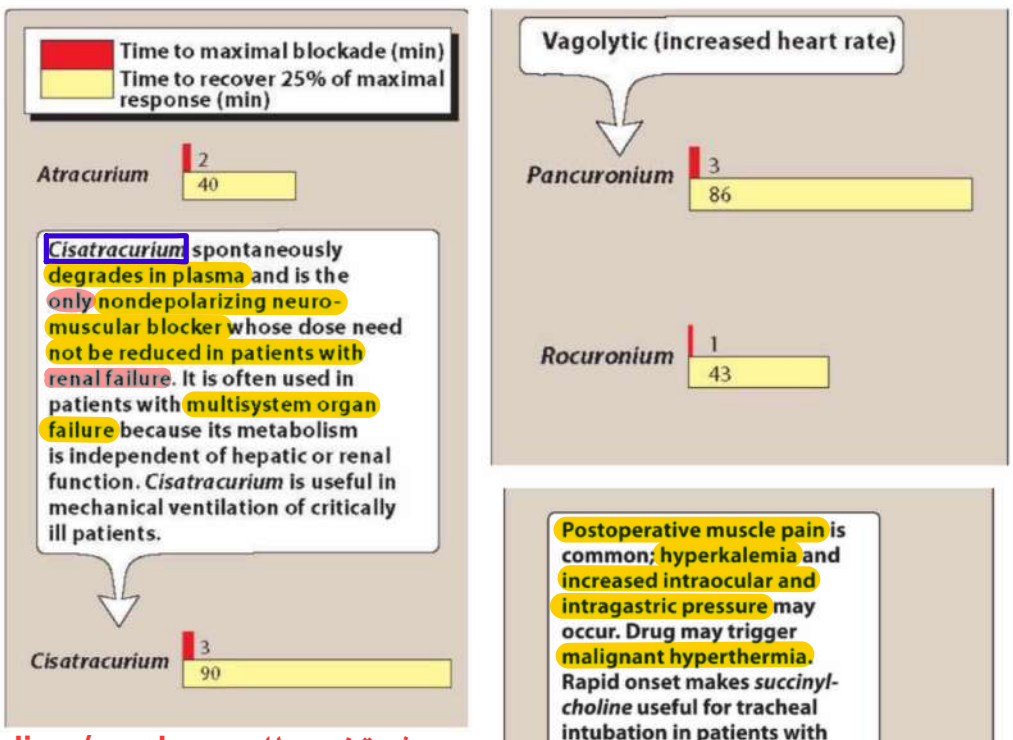
Musculoskeletal System

الرسمة مهمة و الارقام مو حفظ
بس ضروري تعرفوا الترتيب

Onset, Duration of Action and Adverse Effects of Neuromuscular-blocking Drugs.



بنستخدمه للي معه liver/renal او failure multiorgan failure

*Many of the drugs are not metabolized, and their actions are terminated by redistribution. Cisatracurium is degraded spontaneously in plasma and by ester hydrolysis. [Note: Atracurium has been replaced by its isomer, cisatracurium. Atracurium releases histamine and is metabolized to laudanosine, which can provoke seizures. Cisatracurium, which has the same pharmacokinetic properties as atracurium, is less likely to have these effects.]

*The choice of an agent depends on the desired onset and duration of the muscle relaxation. The onset, duration of action.

*Adverse effects: In general, these agents are safe with minimal side effects.

Why are neuromuscular-blocking agents typically administered intravenously or intramuscularly and not orally?
A. They are rapidly metabolized in the digestive system.
B. They contain quaternary amines that hinder gut absorption.
C. They cause histamine release when taken orally.
D. They are too large to be absorbed by the digestive tract.
Answer : D

Why is cisatracurium preferred over atracurium in clinical use?
A. Cisatracurium has a faster onset of action.
B. Atracurium is metabolized to laudanosine, which can provoke seizures.
C. Cisatracurium releases histamine, minimizing allergic reactions.
D. Atracurium has a longer duration of action.
Answer : B

Why are amino steroid drugs like vecuronium and rocuronium deacetylated in the liver?
A. To increase their absorption rate.
B. To enhance their duration of action.
C. To facilitate excretion in urine.
D. To minimize adverse effects.
Answer : C
Certainly! Here's a tricky multiple-choice question (MCQ) based on the provided information:

What sets cisatracurium apart from other nondepolarizing neuromuscular blockers?
A. Its rapid metabolism in patients with renal failure.
B. The need for a reduced dose in patients with renal failure.
C. Independence from hepatic or renal function in its metabolism.
D. Limited usefulness in critically ill patients undergoing mechanical ventilation.
Answer : C

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Nondepolarizing (Competitive) Blockers

Drug interactions

1. Cholinesterase inhibitors: e.g., neostigmine → overcome the action of nondepolarizing NM blockers. Remember low vs high dose.
2. Halogenated hydrocarbon anesthetics: e.g., desflurane → enhance the neuromuscular blockade
3. Aminoglycoside antibiotics: e.g., gentamycin and tobramycin → inhibit ACh release from cholinergic neurons → enhance NM blockade.
4. Calcium channel blockers: may increase the neuromuscular blockade

From The book :

a. Cholinesterase inhibitors: Drugs such as neostigmine, physostigmine, pyridostigmine, and edrophonium can overcome the action of nondepolarizing neuromuscular blockers.
However, with increased dosage, cholinesterase inhibitors can cause a depolarizing block as a result of elevated ACh concentrations at the endplate membrane. If the neuromuscular blocker has entered the ion channel, cholinesterase inhibitors are not as effective in overcoming blockade.

b. Halogenated hydrocarbon anesthetics: Drugs such as desflurane act to enhance neuromuscular blockade by exerting a stabilizing action at the NMJ. These agents sensitize the NMJ to the effects of neuromuscular blockers.

c. Aminoglycoside antibiotics: Drugs such as gentamicin and tobramycin inhibit ACh release from cholinergic nerves by competing with calcium ions. They synergize with pancuronium and other competitive blockers, enhancing the blockade.

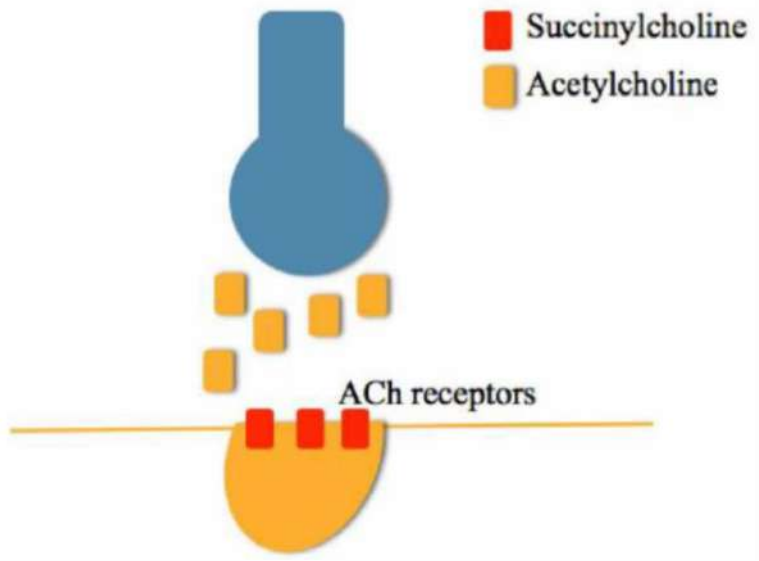
Musculoskeletal System

Depolarizing Blockers

- Work like ACh → persistently depolarize the membrane of the muscle fiber
- So how are they different? more resistant to degradation by acetylcholinesterase (AChE)

NEUROMUSCULAR BLOCKERS

Succinylcholine ANECTINE, QUELICIN



***They can more persistently depolarize the muscle fibers.**
***Succinylcholine is the only depolarizing muscle relaxant in use today.**

Depolarizing Blockers

Mechanism of action

- Succinylcholine attaches to the nicotinic receptor and acts like ACh to depolarize the junction
- Succinylcholine persists at high concentrations in the synaptic cleft
- Produces sustained depolarization of the muscle cell
- How is it degraded then?

hydrolysis by plasma pseudocholinesterase

Unlike ACh, which is instantly destroyed by AChE, the depolarizing agent persists at high concentrations in the synaptic cleft, remaining attached to the receptor for a relatively longer time and providing constant stimulation of the receptor.
[Note: The duration of action of succinylcholine is dependent on diffusion from the motor endplate and hydrolysis by plasma pseudocholinesterase. Genetic variants in which plasma pseudocholinesterase levels are low or absent lead to prolonged neuromuscular paralysis.]

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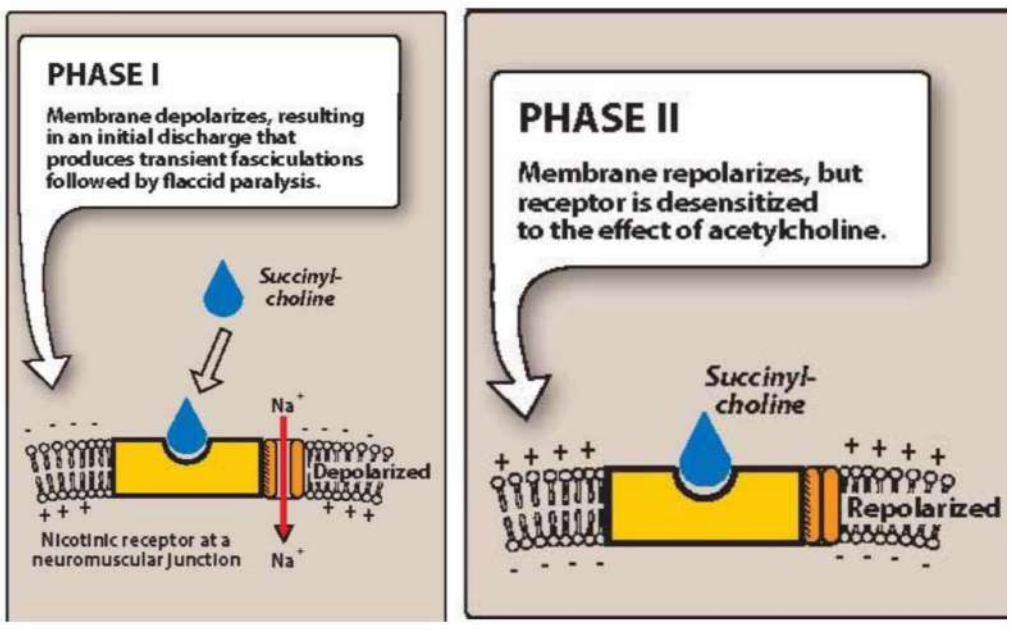
Depolarizing Blockers

Mechanism of action

- **Phase I:** opening of nicotinic receptor-associated Na+ channel → depolarization of the receptor → a transient twitching of the muscle (fasciculations).
- **Phase II:** continuous binding leads to receptor desensitization → flaccid paralysis



With time, continuous depolarization gives way to gradual repolarization as the sodium channel closes or is blocked. This causes a resistance to depolarization (Phase II) and flaccid paralysis.

Depolarizing Blockers

Actions:

- Brief muscle fasciculations (causes muscle soreness) can be prevented with small dose of nondepolarizing neuromuscular blocker prior to succinylcholine
- The respiratory muscles are paralyzed last
- Redistribution to plasma is necessary for metabolism (therapeutic benefits last only for a few minutes).
- useful when rapid endotracheal intubation is required.
- It is also used during electroconvulsive shock treatment.

during the induction of anesthesia (a rapid action is essential if aspiration of gastric contents is to be avoided during intubation

As with the competitive blockers, the respiratory muscles are paralyzed last. Succinylcholine initially produces brief muscle fasciculations that cause muscle soreness. This may be prevented by administering a small dose of nondepolarizing neuromuscular blocker prior to succinylcholine.
Normally, the duration of action of succinylcholine is extremely short, due to rapid hydrolysis by plasma pseudocholinesterase.
However, succinylcholine that gets to the NMJ is not metabolized by AChE, allowing the agent to bind to nicotinic receptors, and redistribution to plasma is necessary for metabolism (therapeutic benefits last only for a few minutes)

Depolarizing Blockers

Pharmacokinetics

- IV
- Short duration of action (onset ~ 30 seconds).

Adverse effects

A. Malignant hyperthermia

-rare, life-threatening condition

-caused by excessive skeletal muscle aerobic metabolism

-circulatory collapse and death

-**antidote**: dantrolene

Its brief duration of action results from redistribution and rapid hydrolysis by plasma pseudocholinesterase. Therefore, it is sometimes given by continuous infusion to maintain a longer duration of effect.

Depolarizing Blockers

Adverse effects

B. Apnea

deficiency in plasma cholinesterase **OR** atypical form of the enzyme can lead to prolonged apnea due to paralysis of the diaphragm **OR** electrolyte imbalances (rapid release of potassium).

The rapid release of potassium may also contribute to prolonged apnea in patients with electrolyte imbalances who receive this drug. In patients with electrolyte imbalances who are also receiving digoxin or diuretics (such as heart failure patients) succinylcholine should be used cautiously or not at all.

C. Hyperkalemia

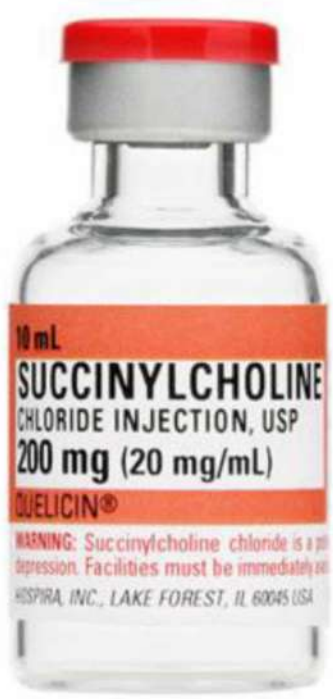
-Succinylcholine increases potassium release from intracellular stores

This may be particularly dangerous in burn patients and patients with massive tissue damage in which potassium has been rapidly lost from within cells.

Therapeutic Uses of Neuromuscular Blockers

Main Therapeutic Use: Adjunct to General Anesthesia

- Muscle relaxation: orthopedic, abdominal surgeries
- Facilitation of intubation, mechanical ventilation
- Succinylcholine during electroconvulsive therapy



Quiz Time...

5.2 Sarin is a nerve gas that is an organophosphate cholinesterase inhibitor. Which of the following could be used as an antidote to sarin poisoning?

A. Pilocarpine.
B. Carbachol.
C. Atropine.
D. Physostigmine.
E. Nicotine.

Correct answer = C. Sarin is an organophosphate cholinesterase inhibitor. It causes an increase in ACh levels in tissues that leads to cholinergic crisis by the activation of muscarinic as well as nicotinic receptors. Most of the symptoms of cholinergic crisis are mediated by muscarinic receptors and, therefore, the muscarinic antagonist atropine is used as an antidote for sarin poisoning. Cholinergic agonists such as pilocarpine, carbachol, physostigmine (indirect agonists), and nicotine will worsen the symptoms of sarin poisoning.

5.3 Atropine is one of the ingredients in the antidiarrheal combination diphenoxylate/atropine available in the United States. Which of the following effects is produced by atropine that contributes to its antidiarrheal effect?

A. Increase in gastrointestinal motility.
B. Reduction in gastrointestinal motility.
C. Increase in salivation.
D. Increase in acid secretion.

Correct answer = B. Muscarinic agonists produce an increase in gastrointestinal motility, salivation, and acid secretion. Atropine is a muscarinic antagonist and therefore causes a reduction in gastrointestinal motility that contributes to its antidiarrheal effect.

5.4 A patient with chronic obstructive pulmonary disease (COPD) was prescribed a β_2 agonist for the relief of bronchospasm. However, the patient did not respond to this treatment. Which of the following drugs or classes of drugs would you suggest for this patient as the next option?

A. β_1 Agonist.
B. Muscarinic agonist.
C. Physostigmine.
D. Ipratropium.
E. Phentolamine.

Correct answer = D. Major receptors present in the bronchial tissues are muscarinic and adrenergic-β_2 receptors. Muscarinic activation causes bronchoconstriction, and β_2 receptor activation causes bronchodilation. Therefore, direct or indirect (physostigmine) muscarinic agonists will worsen bronchospasm. Ipratropium is a muscarinic antagonist that can relax bronchial smooth muscles and relieve bronchospasm in patients who are not responsive to β_2 agonists. α_1 and β_1 receptors are not commonly present in bronchial tissues and, therefore, β_1 agonists or α antagonists (phentolamine) do not have any significant effects on bronchospasm.

5.5 Which of the following drugs would be the most effective anti–motion sickness drug for a person planning to go on a cruise?

A. Atropine.
B. Tropicamide.
C. Scopolamine.
D. Darifenacin.
E. Tiotropium.

Correct answer = C. All muscarinic antagonists (anticholinergic drugs) listed above are theoretically useful as anti–motion sickness drugs; however, scopolamine is the most effective in preventing motion sickness in practice. Tropicamide mostly has ophthalmic uses, and tiotropium is used for respiratory disorders (COPD). Darifenacin is used for overactive bladder.

5.6 Which of the following is correct regarding ganglion-blocking drugs?

A. Blockade of sympathetic ganglia could result in reduced blood pressure.
B. Blockade of parasympathetic ganglia could result in reduced heart rate.
C. Nicotine is a nondepolarizing ganglion blocker.
D. Atropine is a nondepolarizing ganglion blocker.

Correct answer = A. Selective blockade (in theory) of the sympathetic ganglion causes reduction in norepinephrine release and therefore reduction in heart rate and blood pressure. Selective blockade (in theory) of the parasympathetic ganglion causes reduction in ACh release and therefore an increase in heart rate. Receptors at both sympathetic and parasympathetic ganglia are of the nicotinic type. Nicotine is an agonist at nicotinic receptors and produces a depolarizing block in the ganglia. Atropine is a muscarinic antagonist and has no effect on the nicotinic receptors found in the ganglia.

Quiz Time...

5.7 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.

Correct answer = 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.

5.8 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.

Correct answer = C. 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.

5.9 A patient was administered a neuromuscular blocker (NMB) prior to a surgical procedure to produce skeletal muscle paralysis. This NMB drug affected small, rapidly contracting muscles of the face and eyes first and diaphragm muscles last. The effect of this drug was easily reversed with neostigmine. Which of the following neuromuscular blockers was most likely administered to this patient?

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

Correct answer = A. There are two types of NMBs: depolarizing and nondepolarizing NMBs. Depolarizing NMBs are agonists at the nicotinic receptors, whereas nondepolarizing NMBs are antagonists at the nicotinic receptors. Both types of NMBs affect the rapidly contracting muscles (face, eye, etc.) first and diaphragm muscles last. However, cholinesterase inhibitors such as neostigmine increase ACh levels in the NMJ and reverse the effects of nondepolarizing NMBs, but not those of depolarizing NMBs. Therefore, the NMB administered to this patient is most probably rocuronium, which is a nondepolarizing NMB. Tubocurarine is also a nondepolarizing NMB, but it is not used in practice. Succinylcholine is a depolarizing NMB, and diazepam is a benzodiazepine that does not cause paralysis of skeletal muscles.

5.10 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.

Correct answer = 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.