PHARMACOLOGY
TEAM 439

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MED439
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Editing file

Skeletal muscle relaxants

Lecture 1

OBJECTIVES:

-Identify classification of skeletal muscle relaxants
- Describe the pharmacokinetics and dynamics of neuromuscular relaxants
- Recognize the clinical applications for neuromuscular blockers
- Know the different types of spasmolytics
- Describe the pharmacokinetics and dynamics of spasmolytic drugs
- Recognize the clinical applications for spasmolytic drugs

We highly recommend that you study The physiology of muscle contraction and Neuromuscular transmission lectures before studying this lecture

Important

In male and female slides

Only in male slides

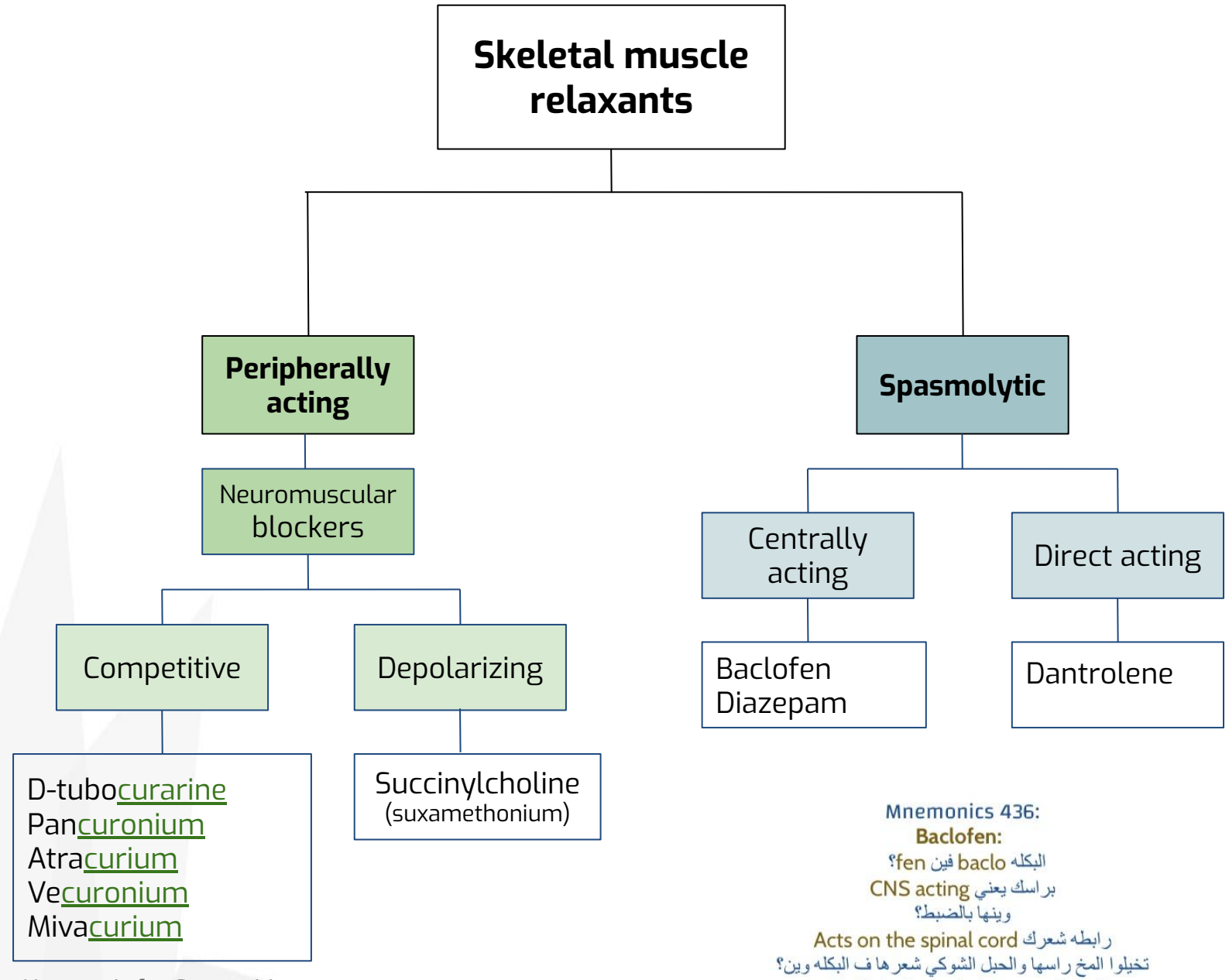
Only in female slides

Extra information

Skeletal muscle relaxants

They are drugs used to induce skeletal muscle relaxation

They are classified according to the mechanism of their action :



Mnemonic for Competitive (non-depolarizing) NMB:

Very **P**ersonal **ATM**

Mnemonics 436:

Baclofen:

البكله baclo فين fen؟
براسك يعني CNS acting
وينها بالضبط؟
رابطه شعرك Acts on the spinal cord
تخيلوا المخ راسها والحبل الشوكي شعرها ف البكله وين؟
اكيد بالشعر يعني تشتغل على الحبل الشوكي

Diazepam:

نقسم اسم الدواء لقسمين:
١-Diaze تشبه كلمة dizzy و الدوخة تصير بالراس يعني CNS acting
٢-Zepam تشبه كلمة spasm و التشنج يصير بالعضلات
فلما نجمعهم مع بعض نتذكر ان هالدواء يشتغل على الجهاز العصبي المركزي ويعالج العضلات المتشنجة

- **Depolarizing** muscle relaxants act as **acetylcholine (ACh) receptor agonists**
- , **non-depolarizing** muscle relaxants function as **competitive antagonists**.

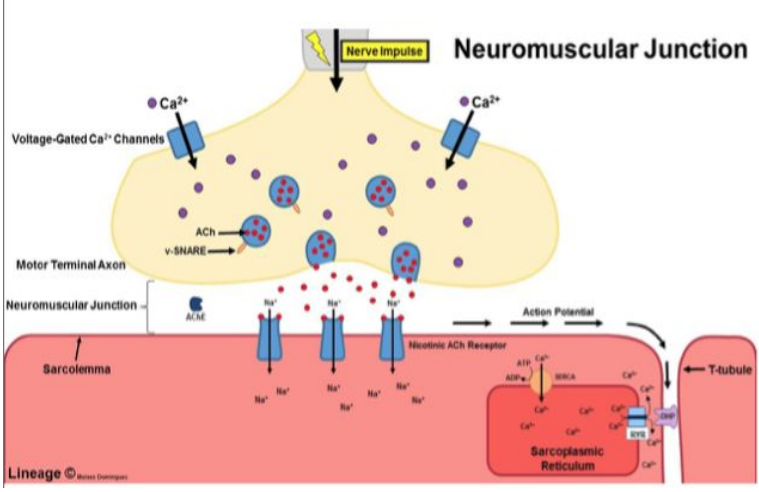
Peripheral acting SKM relaxants (Neuromuscular blockers)

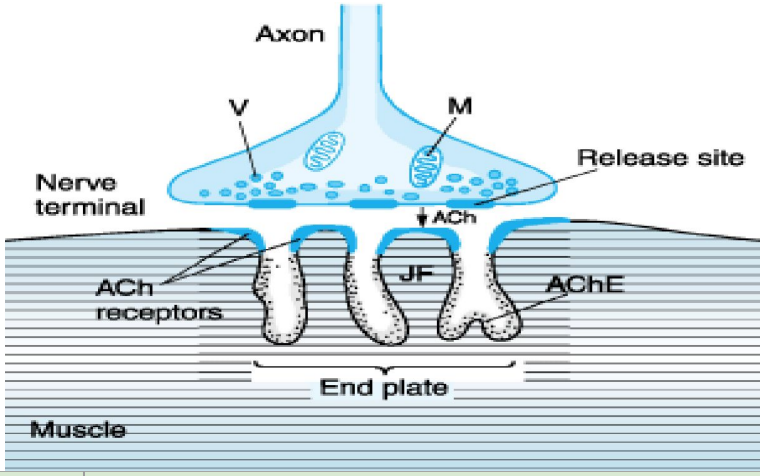
Neuromuscular blockers	Act by blocking neuromuscular junction or motor end plate leading to skeletal muscle relaxation			
According to mechanism of action **Competitive blocker (Non-Depolarizing)** (peripherally acting)	**Mechanism of action**	• Compete with Ach for the nicotinic receptors present in post junctional membrane of neuromuscular junction or motor end plate. • No depolarization of post junctional membrane (non depolarizing) .(Ach won't be able to activate the receptor so the Na will not influx and thats mean No depolarization) • Action can be reversed by increasing Ach concentration. • Cholinesterase inhibitors can reverse blockade (**Neostigmine**).		
	Drugs (details in the next slides)	**Long action**	**Intermediate acting**	**Short acting**
		-D-tubocurarine (prototype) -Pancuronium	-Atracurium -Vecuronium	-Mivacurium
	Pharmaco-kinetics	• Polar compounds • Taken parenterally(injection) and Inactive orally • Doesn't cross placenta (Can be used with pregnant) • Doesn't cross BBB (no central action) • Metabolism (excretion) depend on kidney or liver. EXCEPT: Mivacurium (degraded by **acetylcholinesterase enzyme**) Atracurium**(spontaneous degradation)** (only hydrolysis no need for enzyme activity)		
	Pharmaco-logical actions	• Skeletal muscle relaxation.(Small rapidly contracting muscles of face, eyes ,fingers ,neck ,trunk muscle ,intercostal muscles, diaphragm) • Recovery comes from REVERSE MANNER starting with diaphragm. Last is face and eyes. • They produce different effects on CVS • Some release histamine and produce hypotension • **d.Tubocurarine (severe release)most potent** **Atracurium(moderate release)less potent** • **Mivacurium (mild release)least potent** (not suitable for allergic patients) • Others produce tachycardia(Increase Heart rate) **(Pancuronium) (no histamine release)**		

Mechanism of action of Neuromuscular Blockers: (Extra explanation)

Normally in the neuromuscular junction, the acetylcholine will attach with the acetylcholine receptors (in skeletal muscle the receptors) are nicotinic receptors type 1 after that a lot of changes will happen so that the muscle contracts.
However, the Neuromuscular blockers will block the nicotinic receptors so acetylcholine cannot bind with the receptors, thus, preventing its action (muscle contraction) and if the muscle won't contract it'll relax

Pharma436





1- D-Tubocurarine

Duration	Contraindication (not good for)
1-2 h (long)	-
Metabolism and excretion	**Blocking target**
Eliminated by kidney 60% - liver 40%.	Blocks autonomic ganglia (Hypotension)
Side effects	**Potency**
Histamine releaser leading to: • Bronchospasm (constriction of bronchial smooth muscles). • Hypotension • Tachycardia	
Uses	**Notes**
Not used clinically due to adverse effects	Prototype skeletal muscle relaxant (**first muscle relaxant used clinically**)

2- Atracurium

Duration	Contraindication (not good for)
30 min (intermediate duration)	**Asthmatic patients**, because it causes bronchospasm due to histamine release. **(prevented by using Anti- histamine)**
Metabolism and excretion	**Blocking target**
• Eliminated by non enzymatic chemical degradation in plasma (spontaneous hydrolysis at body pH). No need of enzymatic activity.	No effect on muscarinic receptor nor (norepinephrine) ganglia
Side effects	**Potency**
1. Transient hypotension **(due to histamine release)** *Anti histamine pretreatment May prevent those side effect 2. Bronchospasm.	As potent as curare (1.5)
Uses	**Notes**
used in liver and kidney failure (**drug of choice**).	Mivacurium & Atracurium don't depend on the kidney or liver for metabolism

3- Mivacurium

Duration	Contraindication (not good for)
15 min (The shortest)	Longer duration in patient with **liver disease** or genetic **cholinesterase deficiency** Or **malnutrition**.
Metabolism and excretion	**Blocking target**
• Fast onset of action • Metabolized by pseudo cholinesterases.	-
Side effects	**Potency**
Transient hypotension (due to histamine release). Less than D-Tubocurarine	-
Uses	**Notes**
Used with liver or kidney failure patients (Mivacurium & Atracurium don't depend on the kidney or liver for metabolism. Remember?)	• Mivacuriuam induced prolonged muscle paralysis • can be reversed by acetycholinesterase inhibitors such as endrophonium, • acetycholinesterase inhibitors increase the Ach level in NMJ and displace Mivacuriam from nicotinic receptors in NMJ. • Chemically related to atracurium

4- Pancuronium

Duration	Contraindication (not good for)
1-2 Hours (long duration)	patient with coronary diseases.
Metabolism and excretion	**Blocking target**
• metabolized in **liver** • excretion by the kidney(80 %). • Long duration of action **(metabolic products have some NM blocking activities).**	-
Side effects	**Potency**
1. Hypertension 2. Tachycardia 3. Increase norepinephrine release from adrenergic nerve endings 4. Antimuscarinic action (block parasympathetic action). 5. Blocks muscarinic receptor in SA node 6. angina (Chest pain) 7. (the adverse effects are caused by the high potency)	More potent than curare (6 times)
Uses	**Notes**
	You can remember the drug by the word **PAiN** since it causes chest pain Antimuscarinic action → Parasympathetic block action → increased sympathetic activity → Increased Heart rate → Chest pain and heart complications in cardiac patients

5- Vecuronium

Duration	Contraindication (not good for)
4o min (Intermediate duration)	**Liver failure patients** since its metabolised by the liver and excreted in the bile
Metabolism and excretion	**Blocking target**
• Metabolized mainly by **liver**. • Excretion mainly in **bile.** **Advantages:** • **No** histamine release • **No** tachycardia	-
Side effects	**Potency**
• No ganglion block. • No antimuscarinic action.	More potent than tubocurarine (6 times).
Uses	**Notes**
• Good for patients with renal failure because its excreted by the bile • Good for Cardiac patients because it has no antimuscarinic effect (no release of norepinephrine therefore no tachycardia)	No Anti-muscarinic action → Normal Parasympathetic activity → Normal sympathetic activity → Normal heart rate → no Cardiac complications

	D-Tubocurarine	Atracurium	Mivacurium	Pancuronium	Vecuronium
Drug	Prototype skeletal muscle relaxant (first muscle relaxant used clinically)	Chemically related			
Duration	1-2 h (long)	30 min (intermediate duration)	15 min (The shortest)	1-2 h (long)	40 min (Intermediate duration)
Metabolism and excretion	Eliminated by kidney 60% - liver 40%.	Eliminated by non enzymatic chemical degradation in plasma (spontaneous hydrolysis at body pH).	-Fast onset of action -Metabolized by pseudo cholinesterases.	-metabolized in **liver** -excretion is **renal** (80 %). -Long duration of action (metabolic products have some NM blocking activities).	-Metabolized mainly by **liver**. -Excretion mainly in **bile**. **Advantages:** -**No** histamine release -**no** tachycardia
Side effects	Histamine releaser leading to: -Bronchospasm (constriction of bronchial smooth muscles). -Hypotension -Tachycardia	-Liberate histamine causing Transient hypotension (due to histamine release) -bronchospasm.	Transient hypotension (due to histamine release).	1-Hypertension 2-Tachycardia 3- Increase norepinephrine release from adrenergic nerve Endings 4-Antimuscarinic action (block parasympathetic action). 5-Blocks muscarinic receptor in SA node	-No ganglion block. -No antimuscarinic action.
Uses	**Not used clinically**	used in liver and kidney failure (**drug of choice).**	Liver and kidney failure	-	Renal failure and cardiac patients
Contraindication	Renal failure	Asthmatic patients, because it causes bronchospasm due to histamine release.(prevented by using Anti-histamine)	Longer duration in patients with liver disease or genetic cholinesterase deficiency Or malnutrition	patient with coronary diseases.	Patients with liver failure
Blocking target	Blocks autonomic ganglia (Hypotension)	No effect on muscarinic receptor nor ganglia	-	-	-
potency	-	As potent as curare (1.5)	-	More potent than curare (6 times).	

Depolarizing (Peripherally acting)	Mechanism of action	**Phase I**: combine with nicotinic receptor in post-junctional membrane of neuromuscular junction ⟶ **initial** depolarization of motor end plate ⟶ muscle twitching **Phase II: Persistent** depolarization ⟶ **Skeletal muscle relaxation** paralysis (Phase II clinically resembles non-depolarizing muscle relaxants)
	pharmaco kinetics	• Fast onset of action (1 min.). • Short duration of action (5-10 min.). • Metabolized by pseudo-cholinesterase in plasma • Half life is prolonged in: • Neonates (Low enzymes) • Elderly (Liver function declined due to aging) • Pseudo-cholinesterase deficiency (liver disease or malnutrition or genetic cholinesterase deficiency).
	Contraind-i cations	*Glaucoma (high eye pressure) *Patient with cardiac disease
	Pharmacolo gical action	• **Skeletal muscles**: twitching ⟶ relaxation (Usually used before surgery). • Fasciculation. ⟶ Spastic paralysis • **Hyperkalemia** (due to muscle contraction):Cardiac arrest. • **CVS**: ↑ arrhythmia (heart beats with an irregular or abnormal rhythm) • **Eye**: intraocular pressure (due to contraction of extra-ocular muscle). • **GIT**: intragastric pressure regurgitation of gastric content to esophagus.
	drugs	**Succinylcholine (suxamethonium)**
	Side effects	• Hyperkalemia (elevated levels of potassium in the blood serum) • CVS arrhythmia • ↑ Intraocular pressure contraindicated in: • glaucoma • Can produce malignant hyperthermia (severe muscle contraction) • May cause succinylcholine apnea due to deficiency of pseudo-cholinesterase by liver disease, Malnutrition. • Organophosphorus poisoning (acetylcholinesterase inhibition).(will increase the Ach in the body)

Mechanism of Depolarizing Blockers: (Extra explanation) Pharma437

They fool Ach receptors in the muscular end point by attaching to them and stimulating the same effect as the Ach(acetylcholine) so they initiate the contractions of muscles fasciculation (twitching) by opening the Na+ sodium voltage channels. in the beginning. but after the sodium inside the muscle is used. the depolarizing blocker will still be attached to the Ach receptors. which will prevent repolarization. This called **hyperpolarization** so no more contractions will occur. e.g of depolarization NMB is: ***succinylcholine*** **They are agonist drugs**

Malignant hyperthermia

Is a rare **bizarre** inherited condition of having body temperature greatly above normal

Is an example of Idiosyncrasy

occurs upon administration of drugs as (Sensitive to some drugs):

- general anesthesia e.g. **halothane**
- neuromuscular blockers e.g. **succinylcholine**

Mechanism of the disease:

Inability to bind calcium by sarcoplasmic reticulum in some patients due to **genetic defect.**

↑ Ca release, muscular rigidity(spasm) , metabolic acidosis, tachycardia, hyperpyrexia.(hyperthermia)

Treatment by : Dantrolene

Uses of neuromuscular blockers

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

Drugs and diseases that modify effects of neuromuscular blockers

Diseases:

Myasthenia gravis and Parkinson increase the response to muscle relaxants (modify the response to muscle relaxants).

Drugs:

as aminoglycosides (e.g. streptomycin),magnesium sulphate(may antagonize the effect of muscle relaxants), general anesthetics can potentiate or enhance the effect of neuromuscular blockers.

Cholinesterase inhibitors may enhance the effect of depolarizing relaxants but decrease the effect of nondepolarizing relaxants

Spasmolytic	They reduce muscle spasm in septic states	
	Baclofen	**Centrally** acting GABA agonist - acts on spinal cord (centrally acting drugs are usually used for sport injuries)
	Diazepam (Benzodiazepines)	**Centrally** acting Facilitate GABA action on CNS (centrally acting drugs are usually used for sport injuries)
	Dantrolene	**Direct** action on skeletal muscles. Used in treatment of malignant hyperthermia
		Mechanism of action • Acts directly on skeletal muscles • It interferes with the release of calcium from its stores in skeletal muscles (sarcoplasmic reticulum). • It inhibits excitation-contraction coupling in the muscle fiber. • Calcium is released from the sarcoplasmic reticulum via a calcium channel, called the ryanodine receptor (RyR) channel and dantrolene blocks the opening of these channels • Orally, IV, ($t_{1/2}$ = 8 - 9 h). • **Used in the treatment of**: **Spastic states** **Malignant hyperthermia**

GABA: γ-Aminobutyric acid is the chief inhibitory neurotransmitter in the mammalian CNS. It plays the principal role in reducing neuronal excitability throughout the nervous system, thus reducing contraction.

Uses of spasmolytic

They **reduce muscle spasm** in spastic states produced by neurological disorders as:

- Spinal cord injury
- Cerebral stroke
- Cerebral palsy

MCQ

MQ team made some Questions for you to solve!! **Check them out here**

1- Which of the following drug should not be considered if a patient has asthma?			
A- Vecuronium	**B-** Atracurium	**C-** Suxamethonium	**D-** Pancuronium

2- What is the best choice of drug to give to a patient with liver disease?			
A- Diazepam	**B-** Atracurium	**C-** Tubocurarine	**D-** D-Tubocurarine

3- Which of the following drug should not be considered for a patient with CVS problems ?			
A- Atracurium	**B-** Vecuronium	**C-** Pancuronium	-

4- Which of the following is an example of depolarizing blockers?			
A- Pancuronium	**B-** Suxamethonium	**C-** Vecuronium	-

5- Where does the metabolism of Atracurium occur?			
A- Blood	**B-** Liver	**C-** Kidney	-

6- Which of the following has a long duration of action?			
A- Mivacurium	**B-** Vecuronium	**C-** Tubocurarine	-

7- Which of the following acts on the CNS ?			
A- Atracurium	**B-** Dantrolene	**C-** Baclofen	**D-** Suxamethonium

8- Which of the following NM blockers hydrolyze at body pH?			
A- Pancuronium	**B-** Atracurium	**C-** Vecuronium	**D-** Suxamethonium

ANSWERS

1	2	3	4	5	6	7	8
B	B	C	B	A	C	C	B

SAQ

1) Define Skeletal muscle relaxants

2) What is the mechanism if action of peripheral acting drugs?

3-4 A patient was being prepared for surgery and got administered suxamethonium. The patient started developing high fever and the anesthesiologist is suspecting malignant hyperthermia

3) What is the possible cause of this condition?

4) What is the suitable treatment?

5) What is the pharmacodynamic effect of suxamethonium in the eyes

6) What is the main mechanism of action of spasmolytic?

7) Why doesn't the use of muscle relaxants during cesarean surgery has not effect on uterus?

ANSWERS

A1) ~~drugs used to induce skeletal muscle relaxation~~

A2) ~~They act by blocking neuromuscular junction or motor end plate leading to skeletal muscle relaxation~~

A3) ~~Administration of drugs such as (general anesthesia e.g halothane) (neuromuscular blockers e.g succinylcholine)~~

A4) ~~Dantrolene~~

A5) ~~increase intraocular pressure~~

A6) ~~Reduce muscle spasm in spastic states~~

A7) ~~Because it doesn't affect the smooth muscles.~~

GOOD LUCK!

REPEAT AFTER ME:
"My current situation is not my final destination."

Team leaders

طرفة الشريدي
حمود القاضب

Girls team members

منيرة السدحان
لينا المزيد
سديم الحازمي
نورة المسعد
وسام ال حويس
رانيا المطيري
الجوهرة البنيان
شادن العبيد
سديم آل زايد
روان باقادر
ميس العجمي
نورة السالم
نوف السبيعي
ندى بابللي
دانه نائب الحرم

Boys team members

بسام الاسمري
ماجد العسكر
باسل فقيها
عبدالرحمن الدويش
حمد الموسى
راكان الدوهان
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