بهذه المذكرة نكون قد انهينا جزء الكات الاول

نسأل الله وإياكم التوفيق والدرجات العالية في الدنيا والآخرة

اشكر الفارم بل تيم جزيل الشكر

ادعوا لهم بالتوفيق والنجاح

نأسف عن تأخير أي مذكرة

وتذكروا ما يبقي التيم على قيد الحياة هو انتم

نصائحكم أي غلط في المذكرة نرحب بالتنويه عليه

أي نقد نحن مستعدين بسماعه

ولكن ان يكون بناااااء

وليس فيه جرح للمشاعر

بالتوفيق للجميع

pharmpill team 426

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اللهم طهر قلبي من النفاق وعملي من الرياء ولساني من الكذب وعيني من الخيانة فأنت تعلم خائنة الأعين وما تخفي الصدور

اللهم اهدني لأحسن الأعمال والأخلاق ..

اخواني الطلاب .. اخواتي الطالبات دفعة 426

نحن فارم بل تيم قمنا بجمع مذكرات البنات مع الأولاد في هذه المذكرة

مع إضافة نوتات هذا العام

نسأل الله أن تنفعنا واياكم ... وتعود بالنفع لغيرنا

ان اصبنا فمن الله وان اخطانا فمنا ومن الشيطان

"اوجة شكر خالص الى الاخت دعاء البلوي دفعة 424 "

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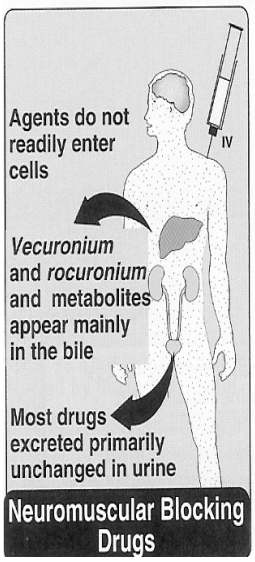
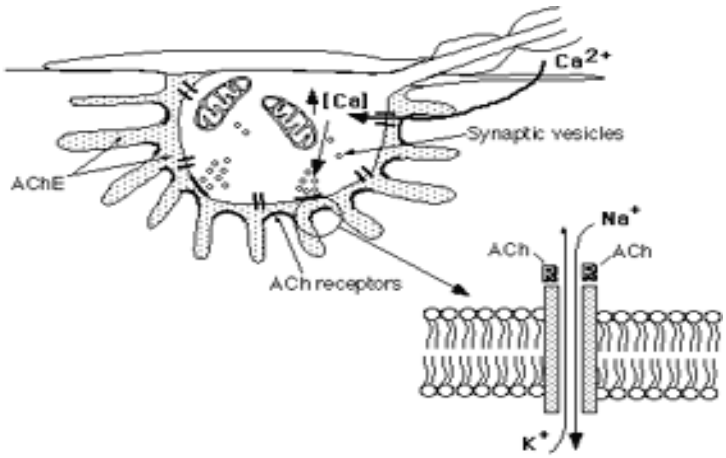
SKELETON MUSCLE RELAXANT

Classification:

- **Peripherally acting:** (neuromuscular blockers)
- **Centrally acting skeletal muscle relaxants:** (bactofen, diazepam)
- **Direct acting skeletal muscle relaxants:** (dantrolene)





Normal Neuromuscular Function :
it's (with arrival of an impulse at motor nerve terminal) influx of Ca++ , then release of Ach , then Ach diffuses across the synaptic cleft to nicotinic receptor located on motor end plate .
- blockade of end plate function is accomplished by two basic mechanism :

1- non-depolarizing drug :
it's pharmacological blockade of the physiologic agonist Ach , this mechanism called "antagonist neuromuscular blocking drugs".
- so , the drug is non-depolarizing agent because it inhibits the depolarizing agent (Ach) .
-these drugs prevent access of the neurotransmitter (Ach) to its receptor and prevent depolarization
-the prototype of nondepolarizing subgroup is tubocurarine .

2- depolarizing drugs :
- the excess amount of depolarizing agonist , namely Ach , can also block the transmission , and there is Ach agonist called "succinylcholine"
- if we use "succinylcholine" in high concentration we block the transmission , so it's called "depolarizing drugs" because we use the agonist of Ach (which is act like Ach ---> the depolarization) in excess amount .
-succinylcholine act in neuromuscular similar to Ach except that succinylcholine produce a longer effect at neurmuscular junction .
- However, because the block produced by these drugs cannot be controlled adequately, they are of no clinical value in this application.

Mechanism of Sk.muscle contraction

- **Initiation of impulse**
- **Release of acetylcholine**
- **Activation of nicotinic receptor at motor end plate**
- **Opening of ion channel, passage of Na+ , depolarization of end plate**
- **Muscle contraction.**
- **Neuromuscular blocking agents used in clinical practice interfere with this process.**
- **Drugs, can block neuromuscular transmission/ or muscle contraction by acting :**

1- Peripherally Acting: (it will produce its action peripherally)

A- Presynaptic neuromuscular blockers.

a. Inhibit Ach synthesis: triethylacholine, hemicholinium.
b. Inhibits Ach release: Mg^{+2}, aminoglycosides, botulinum toxin.

B- Postsynaptic neuromuscular blockers:

a. Competitive (non depolarizing) blockers.
b. Depolarizing blockers. (non-competitive)

Postsynaptic neuromuscular blockers:

1-Competitive neuromuscular blockers(Non depolarizing agents): - MCQ-

- d-Tubocurarine (Isoquinoline)
- Doxicurium ((Isoquinoline)
- Atracuronium (Isoquinoline)
- Pancuronium
- Mivacurium
- Gallamine

- Note : **Non depolarizing (majority):**
  Act by blocking acetylcholine receptors.
  * In some cases (in higher doses), act by blocking ion channels.

2-Depolarizing neuromuscular blockers:

- succinyl choline.(suxamethonium)
- Decamethonium

Note :

- depolarizing & non depolarizing drugs are structural analog of acetylcholine .
- They either act as antagonists (non depolarizing) **OR** agonist (depolarizing)

Uses of neuromuscular blockers:

- Control convulsions => electroshock therapy in psychotic patients.
- Relieve of tetanus and epileptic convulsions.
- Facilitate endoscopy.
- As adjuvant (helper) in general anesthesia to induce muscle relaxation.
- Orthopedic surgery.

to involve in this booklet, read these brief notes

Mechanism of Action :

a. Nondepolarizing Drugs :

in small doses :

-if nondepolarizing muscle relaxants are administered , they act predominantly at nicotinic receptor site by competing with Ach .

- the least potent of nondepolarizing agents have the fastest onset and shortest duration of action .

in large doses :

- nondepolarizing drugs enter the pore of the ion channel to cause a more intense motor blockade .
- this action further weakens neuromuscular transmission and diminishes the ability of acetylcholine inhibitors to antagonize the effect of nondepolarizing muscle relaxants .

b. Depolarizing Drugs :

1- Phase I block (depolarizing) :

- succinylcholine reacts with the nicotinic receptor to open the channel and cause prolong depolarization that produce flickering ion conductance , so the depolarized membrane remain depolarized and unresponsive to subsequent impulses (state of depolarizing block) .
- because excitation-concentration coupling requires end plate repolarizationand and repetitive firing to maintain muscle tension , a fluccid paralysis results .
- it is not reversed by cholinesterase inhibitors .

2- Phase II block (desensitizing) :

- with continued exposure to succinylcholine, the initial end plate depolarizing decreases and membrane becomes repolarized , despite this repolarization , the membrane cannot easily be depolarized again (it becomes desensitized) .
- regardless the mechanism , the channels behave as if they are in prolonged closed state .
- it's reversal by acetylcholinesterase .

Competitive neuromuscular blockers:

Mechanism of action:

- competitive antagonists: compete with Ach at the nicotinic receptors of neuromuscular junction.
- No depolarization of post junctional membrane.
- Cholinesterase inhibitors can reverse blockade.

More details :

a) At low doses:

- These drugs combine with nicotinic receptors and prevent acetylcholine binding.
- Thus prevent depolarization at end-plate.
- Hence inhibit muscle contraction, relaxation of skeletal muscle occurs.
- Their action can be overcome by increasing conc. Of acetylcholine in the synaptic gap (a way to increase the Ach is by giving the patient cholinesterase inhibitors)
- e.g.: Neostigmine ,physostigmine ,edrophonium (choline estrase inhibitor)

b)At high doses

- These drugs block ion channels of the end plate.
- Leads to further weakening of the transmission and reduces the ability of Ach-esterase inhibitors to reverse the action.

ACTIONS

- All the muscles are not equally sensitive to blockade.
- Small and rapidly contracting muscles are paralyzed first.
- Respiratory muscles are last to be affected and first to recover.

Pharmacokinetics:

- they are polar compounds.
- Inactive orally and taken I.V or I.M .
- Cross blood brain barrier poorly (they are poorly lipid soluble)
- Not cross placenta and CNS.
- Metabolism depends upon kidney or liver . (except) atracurium, mivacurium (they have short duration of action because they degraded by cholinesterase)

- Some are not metabolized in liver, their action is terminated by redistribution, excreted slowly and excreted in urine unchanged (tubocurarine, mivacurium, metocurine).
- They have limited volume of distribution as they are highly ionized.
- Some (vecuronium, rocuronium) are acetylated in liver.(there clearance can be prolonged in hepatic impairment)
- Can also be excreted unchanged in bile.
- Atracurium is degraded spontaneously in plasma by ester hydrolysis ,it releases histamine and is metabolized to laudanosine(which can provoke seizures)
- non depolarizers are excreted via kidney ,have long half life and duration of action than those which are excreted by liver.

Pharmacokinetics of Neuromuscular Blocking Drugs :

- All of neuromuscular blocking drugs are highly polar , so they cannot given orally because they will not absorbed , therefore, they always administered intravenously or intramuscularly .

a. Non-depolarizing drugs :

- the rate of disappearance from blood characterized by a rapid initial distribution phase followed by a slower elimination phase .
- the route of elimination is strongly correlates with duration of action of non depolarizing relaxants , e.g drugs that excreted by the kidney have longer half-life leading to longer duration of action and result in longer elimination , however, the drugs eliminated by the liver have somewhat shorter half-life and duration of action
- (vecuronium and rocuronium) is intermediate-acting steroid muscle relaxants , it's commonly used clincally than the long acting drugs .
- Atracurium is isoquinoline nondepolarizing muscle relaxants ,

it's inactivated primarily by spontaneous breakdown and to lesser extent by hepatic mechanism .
the main product of breakdown Atracurium is laudanosin , however , laudanosin is very slowly metabolized by the liver and has long elimination half-life .
laudanosin readily cross blood-brain barrier (BBB) ,therefore, high concentration laudanosin in the blood may cause seizures .

b. Depolarizing drugs :

- the extremely short duration of action of succinylcholine is due to its rapid hydrolysis by plasma cholinesterase , therefore , only small fraction of original intravenous dose reaches the neuromuscular junction
- there is no or little amount plasma cholinesterase at end motor plate .

Pharmacological actions:

- **Skeletal muscle paralysis (could be due to prolonged relaxation) = flaccid paralysis.**
  1- small muscles, ptosis, difficulty in speech.
  2- Muscles of limb, neck and trunk.
  3- Intracostal muscles and diaphragm. → cause respiratory failure
  4- Recovery in reverse order.
- **CVS:**
  1- hypotension (due to histamine release): caused by d-tubocurarine, atracurium.
  2- Increased heart rate: gallamine, pancurium.

Drug interactions :

- cholinestrase inhibitors such as neostigmine, pyridostimine and edrophonium reduces or overcome their activity. But if the relaxants were given in high doses and their effects reached the ion channels, Choline esterase inhibitors may not be that effective.
- halogenated hydrocarbons (general ansthetics),aminoglycosides ,calcium channel blockers synergize their effect.

d-Tubocurarine (curare):

this is the parent drug like the atropine

- More potent than gallamine.
- Long duration of action (1-2 hours).
- Eliminated by kidney 60% - liver 40%.
- Histamine releaser:
  - ✓ Bronchospasm. (skeletal muscle relaxant
  - ✓ Hypotension.
- Blocks autonomic ganglia (hypotension).

Gallamine (Flaxedil):

- The least potent (less potent than curare 1/5)
- Metabolized mainly by kidney 100% # Renal failure.
- Long duration of action.
- Tachycardia due to:
  - ✓ Block muscarinic receptor .
  - ✓ Atropine like action. (block muscarinic receptor)
  - ✓ Release of noradrenaline from adrenergic nerve endings.

Atracurium: -MCQ-

- As potent as curare (1.5).
- Has intermediate duration of action (30 min).
- Eliminated by non enzymatic chemical degradation in plasma (spontaneous hydrolysis at body PH).
- Used in liver failure and kidney failure (drug of choice).
- Liberate histamine => transient hypotension.
- No effect on muscarinic receptors nor ganglia.

Mivacurium

- Chemically related to atracurium.
- Metabolized by pseudocholinesterase.
- Fast onset of action.
- Short duration of action (15min).
- Transient hypotension (histamine release).
- Longer duration in patient with liver disease or genetic cholinesterase deficiency.

◙ **note** : that the liver is the factory for the enzymes . any disease in the liver will not produce enzyme. this drug will not metabolized and its duration will be long

Pancuronium: -MCQ-

- More potent than curare (6 times).
- Excreted by the kidney (80%).
- Long duration of action.
- Tachycardia:
  - ✓ Antimuscarinic action.
  - ✓ Increase norepinephrine release from adrenergic nerve endings.

Vecuronium

- More potent than tubocurarine (6 times).
- Metabolized by liver mainly.
- Intermediate duration of action.
- Has few side effects.
  - ✓ No histamine release.
  - ✓ No ganglionic block.
  - ✓ No antinuscarinic action.

- **Unwanted effects of non-depolarizing skeletal muscle relaxants.**
- **Fall in arterial pressure** chiefly a result to ganglionic block , may also be due to histamine release which may give rise to bronchospasm (especially with tubocurarine ,mivacurium ,and atracurium). Histamin also causes periphral vasodilation with subsequent hypotension.

- Gallamine and pancuronium block, muscarinic receptors also, particularly in heart which may results in to tachycardia

Keep in mind that Tachycarida may reflexly result from vasodilation and its subsequent severe decrease in the blood pressure.

- Drug Interaction between non-depolarizing muscle relaxants and choline esterase inhibitors
-
- choline estrase inhibitors such as neostigmine, pyridostimine and edrophonium reduces or overcome their activity. But if the relaxants were given in high doses and their effects reached the ion channels, Choline esterase inhibitors may not be that effective.
- halogenated hydrocarbons (general ansthetics),aminoglycosides ,calcium channel blockers synergize their effect.

Depolarizing neuromuscular blockers:

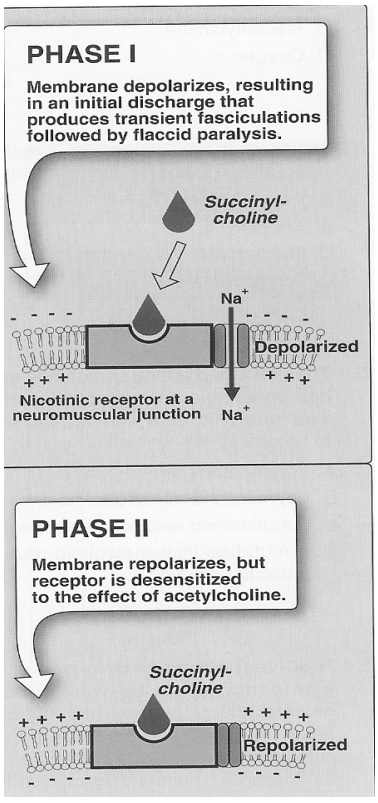
Mechanism of action:

Phase I (depolarizing):

- Combine with nicotinic receptors => depolarization of motor end plate => muscle fasciculations => persistent depolarization => paralysis.
- Is augmented not reversed by anticholinesterases (e.g neostigmine) , But may be reversed by Ach. Receptor blockers (e.g. Atropine)

Phase II (desensitization block) :

- Continuous exposure to succinylcholine => depolarization decreases and the membrane become repolarized, but the membrane cannot be depolarized by Ach as long as succinylcholine is present => desensitization of the membrane.



Pharmacokinetics:

- Short onset of action (1 min).
- Short duration of action (5-10 min).
- Destroyed by pseudocholinesterase.
- Taken intravenously.
- Due to rapid inactivation by plasma cholinestrase, it should be given by continued infusion.

Succinylcholine (Suxmethonium) :

- **SuccinylCholine = Ach. + Ach.**

- It acts like acetylcholine but diffuse slowly to the end plate and remain there for long enough that the depolarization causes loss of electrical excitability
- It stimulate ganglion sympathetic and para sympathetic both.
- It causes paralysis without appreciable ganglion-blocking-activity.
- In other words, these drugs paralyze the muscles by hyperstimulating them to continuously depolarize then not being able to repolarize in order to contract again which will cause the muscles to be relaxed ultimately.

- Produces a transient twitching of skeletal muscle before causing block

- It causes maintained depolarization at the end plate, which leads to a loss of electrical excitability.
- It has shorter duration of action.

- In low dose it produces negative ionotropic and chronotropic effect

- In high dose it produces positive ionotropic and chronotropic effect.

- It should be noted that If cholinestrase is inhibited ,it is possible for circulating acetylcholine to reach a level sufficient to cause depolarization block.

Pharmacological actions:

- **Skeletal muscle:** fasciculation => spastic paralysis.

Side effects:

- Hyperkalemia in patients with trauma or burns
- Bradycardia (-ve chornotropic effect) preventable by atropine.
- CVS arrhythmia (extrasystole and cardiac arrest) may be partially caused by the abnormally high blood K+ level which had been released in response to the sustained depolarization.
- Increases intraocular pressure ==glaucoma.
- increase intragastric pressure which may lead to emsesis and aspiration of gastric content.
- Malignant hyperthermia. (type B)

It is a rare inherited (idiosyncratic) condition probably caused by a mutation of Ca++ release channel of sarcoplasmic reticulum,which results in muscle spasm and dramatic rise in body temprature in response to the administration of suxamethonium.

- Succinylcholine apnea (respiratory failure due to prolonged paralysis (relaxation) of the intercostals muscle):- due to any factor which reduce the activity of plasma cholinesterase:-

  - ✓ Malnutrition (there is no protein from the diet so there will be no enzymes because enzymes manufactured by proteins).
  - ✓ Organophosphorus compounds poisoning.
  - ✓ genetic variants as abnormal cholinesterase, or its severe deficiency.
  - ✓ anti -cholinesterase drugs (neostigmine or pyridostigmine)
  - ✓ neonates (their enzymes required for clearance and excretion of Suxamethonium may be less active)
  - ✓ liver disease (it directly causes decrease in the level of choline esterase which causes delayed inactivation of suamethonium action)
  - ✓

Decamethonium is another example for depolarizing muscle relaxants.

Centrally acting skeletal muscle relaxant:

Spasmolytic:

►spasmolytic can be direct or centrally
►spasticity is characterized by an increase in tonic stretch reflexes and flexor muscles spasms together with muscle weakness .

Baclofen:

BACLOFEN
exerts its spasolytic activity at GABA b receptors .
- activation of these receptors in the brain by BACLOFEN results in heperpolarization by increase K+ conductance .
- hyperpolarization causes presynaptic inhibition by reducing Ca++ influx and reduce excitatory transmitter in both brain and spinal cord .
- it's reduce the pain in patient with spaticity by inhibition the release of substance P in the spinal cord .
- it doesn't reduce overall muscle strength as much as dantrolene .
- adverse effect :
  * drowsiness
  * the patient become tolerent with chronic administeration

- Centrally acting (GABA agonist –spinal cord).
- It causes hyper polarization by increased K+ conductance reducing calcium influx and reduces excitatory transmitter in brain as well as spinal cord
- also reduces pain by inhibitory substance P. in spinal cord
- it is less sedative
- It is rapidly and completely absorbed orally
- it has a half life of 3- 4 hours
- It may increases seizures in epileptics
- it is also useful to prevent migraine.

Diazepam (benzodiazepines):

- Centrally acting (facilitate GABA action on spinal cord and CNS).

Dantrolene:

- Direct action on skeletal muscles.

Uses of spasmolytic:

Reduce muscle spasm in:

- ✓ spinal cord injury.
- ✓ Stroke.
- ✓ Cerebral palsy.

Dantrolene: -MCQ- (لم يخلو اختبار من هذا الدواء)

- **DANTROLENE** reduces skeletal muscle strength by interfering with excitation-contraction coupling in the muscle fiber .
- DANTROLENE interfers with the release of activator Ca++ through this sarcoplasmic reticulum calcium channel .
- only about one-third of an oral dose of dantrolene is absorbed .
- the elimination half-life of drug id about 8 hours .
- adverse effects :
  - * generalized muscle weakness .
  - * sedation .
  - * occasionally hepatitis .
- it's used in treatment of malignant hyperthermia .

Mechanism of action:

1- it interferes with the release of calcium from its stores in skeletal muscles (sarcoplasmic reticulum).
2- Inhibits excitation-contraction coupling in the muscle fiber.

Uses:

1- Spastic states.
2- I.V., orally, $T_{1/2}$ =8-9 hrs.

This drug is one of the fewest that can be administered orally as well as intravenously. Oral absorption is only one third.

3- It is very useful in the treatment of malignant hyperthermia (type B) caused by depolarizing relaxants.

0 It is not useful in surgery because it is not selective .It causes generalized muscle **contraction**, hence weakness.

Approximate potency relative to Tubocurarine	Elimination	Drug
1.5	spontaneous	Atracurium
6	Kidney	Doxacurium
4	Plasma cholinestrase	Mivacurium
4	Kidney 40%	Metocurine
1	Kidney 40%	Tubocurarine
6	Kidney 80%	Panacurium
0.8	Liver 70-80%,kidney	Rocuronium
6	Liver 75-90%,kidney	Vecuronium
6	Kidney ,liver	Pipecuronium
0.4	liver	Rapacuronium

Drug	Speed of onset	Duration of action	Main side -effects	Notes (additional)
Tubocurarine	Slow (5 min)	Long (1-2hrs)	Hypotension (ganglionic block plus histamine release) Broncohoconstriction	Plant alkaloid,rarely used. **Alcuronium** is semi - synthetic with similar properrties but few side effects
Gallamine	Slow	long	Tachycardia (muscarinic antagonist)	100% renal excretion, avoided in renal failure. Rarely used
Pancuronium	Intermediate (2-3 min)	long	Tachycrdia mild,no hypotension	Better side effect profile than tubocurarine.Widly used **Pipecuronium** is similar
Vecuronium	Intermediate	Intermediate (30-40 min)	Few side effects	Widely used.Occasionally causes prolong paralysis,probably due to active metabolite.**Rocuronium** is similar, with faster onset.
Atracurium	Intermediate	Intermediate (20-30 min)	Transient hypotension (histamine release)	Elimination by spontaneous non-enzymatic degradation in plasma. Degradation slowed by acidosis. Widely used.**Doxacurium** similar but stable in plasma, giving long duration of action.**Cisatracurium** isometric of atracurium,similar but with less release of histamine
Mivacurium	Fast (2 min)	Short (15 min)	Transient hypotensison (histamine release)	New,similar to **atracurium**,but rapidly inactivated by plasma cholinesetrase,longer acting in liver disease or in genetic ch-estrase defeciency.
Suxamethonium	Fast	Short (10 min)	Bradycardia(muscarinic agonist effect) Cardiac dysrhythmias(increased plasma k+ conc.avoid in burns and severe trauma.raised intraocular pressure,nicotinic agonist effect on extacellular	Act by depolarization, nicotinic effect, only drug of this type still in use. Paralysis preceded by transient muscle fasciculation. Short duration of action. used for brief procedures. **Rocuronium** has similar speed of onset and recovery with fewer unwanted effects.

- To make it easier to memorize the table, you should know the followings:-
- 1- A drug with slow onset will have long duration of action.
- 2- A drug with intermediate onset will usually have intermediate duration.
- 3- A drug with fast onset will have slow duration.
- 4- Drugs that are used clinically should generally be intermediate to fast in onset with the fewest possible side effects.
- 5- side effects range from mere release of little histamin and upto severe hypotension (tubocurarine)and tachycardia (gallamine).