



Round : Anesthesia - Lecture 7.....

Group no : B 8.....

Done By : Layan Yaseen.....

Muscle relaxants

Done by:

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Definition

- a drug that reduces muscle contractility by blocking the transmission of nerve impulses or by decreasing the excitability of the motor end plate



Why do we need these Drugs?

- facilitate tracheal intubation.
- Provide complete muscle relaxation at lower anesthetic dose. Anesthetic drugs block sympathetic, sensory then lastly motor functions. But motor block requires higher doses, which increases the risks associated with it. But when we administer muscle relaxants, we get motor block without the need for high doses of anesthetics.
- allowing for more rapid recovery from anesthesia
- reducing postoperative respiratory depression. When using muscle relaxants, the last muscle to become paralyzed is the diaphragm, but it is the first to recover

Muscle Relaxants are classified as:

I) Peripherally acting

Target nicotinic receptors at the neuromuscular junction

A. Neuromuscular blocking agents:-

- 1) Depolarizing muscle relaxants.
- 2) Non-depolarizing muscle relaxants

B.) Directly acting: Dantrolene, Quinine

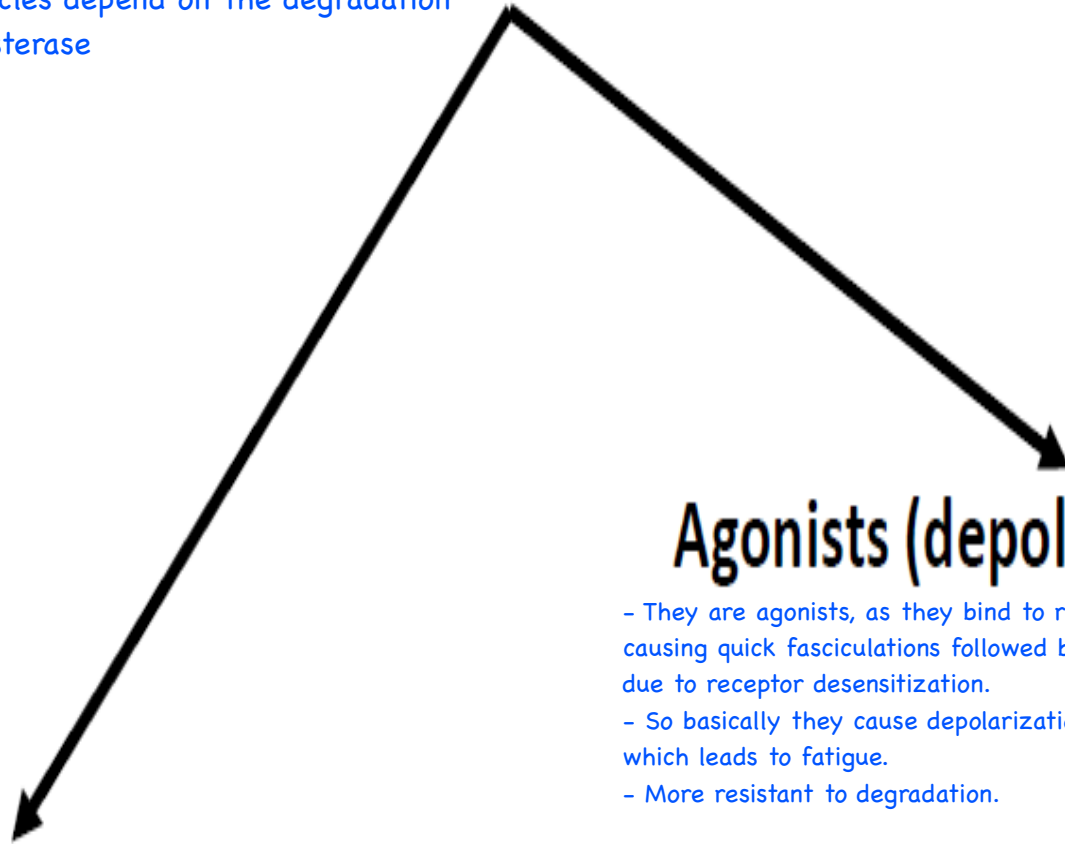
II) Centrally acting (spasmolytic) These decrease muscle rigidity by reducing muscles tone and involuntary movements.

- Chlorzoxazone, Chlormezanone, Diazepam, Baclofen, Tizanidine, Metaxalone.

Neuromuscular-blocking Agents

★ The most important step is the binding of ACH to the receptors

★ Relaxation of muscles depend on the degradation of ACH by choline esterase



Antagonists (nondepolarizing type)

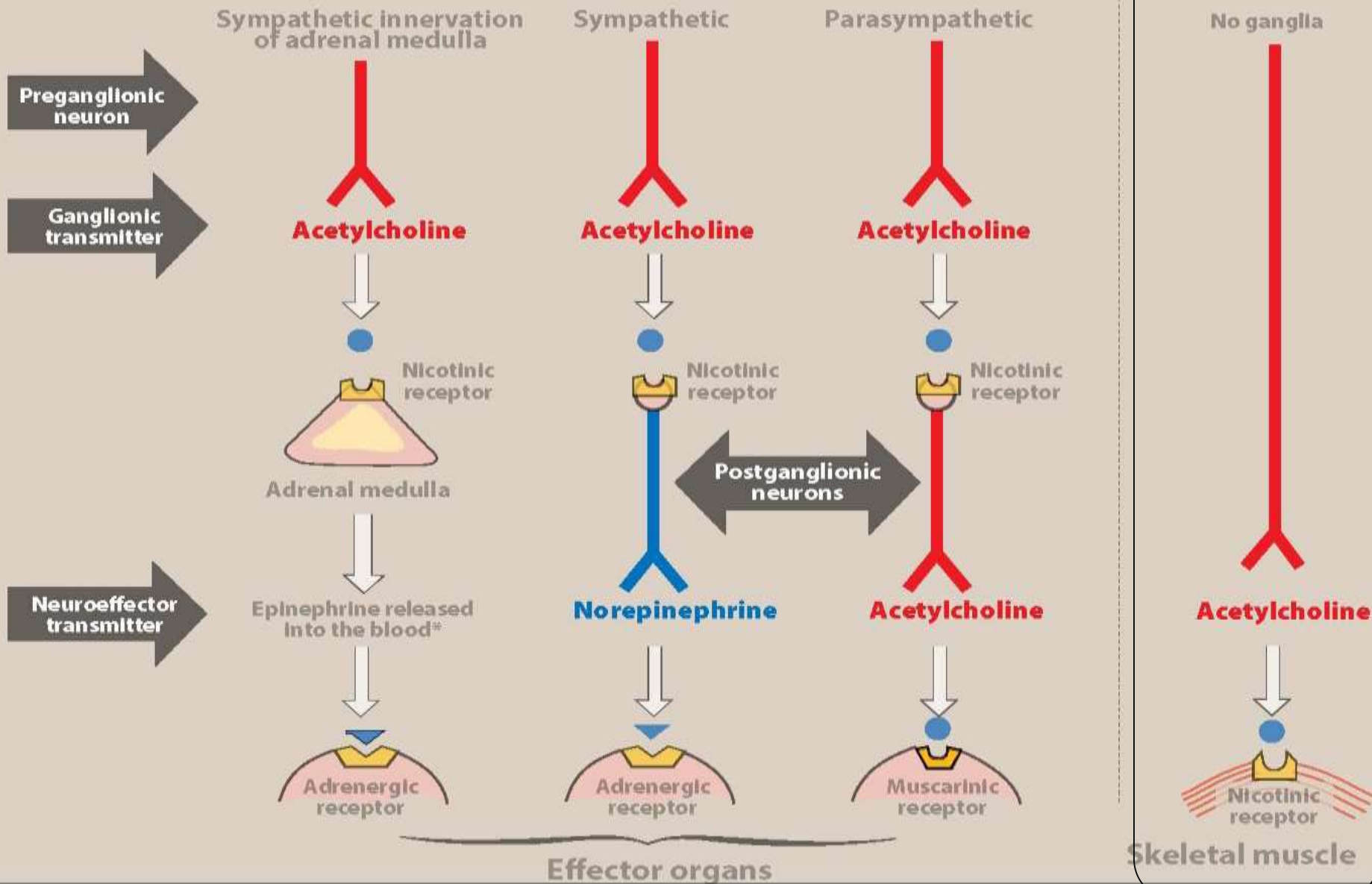
- Known as competitive neuromuscular agents since they compete with ACH to bind to the receptors, but they do not activate receptors at all. Instead prevent depolarization from occurring so called nondepolarizing agents.
- That's also why they are also said to be concentration dependent, you can overcome their effect by increasing the concentration of ACH at the NMJ.

Agonists (depolarizing type)

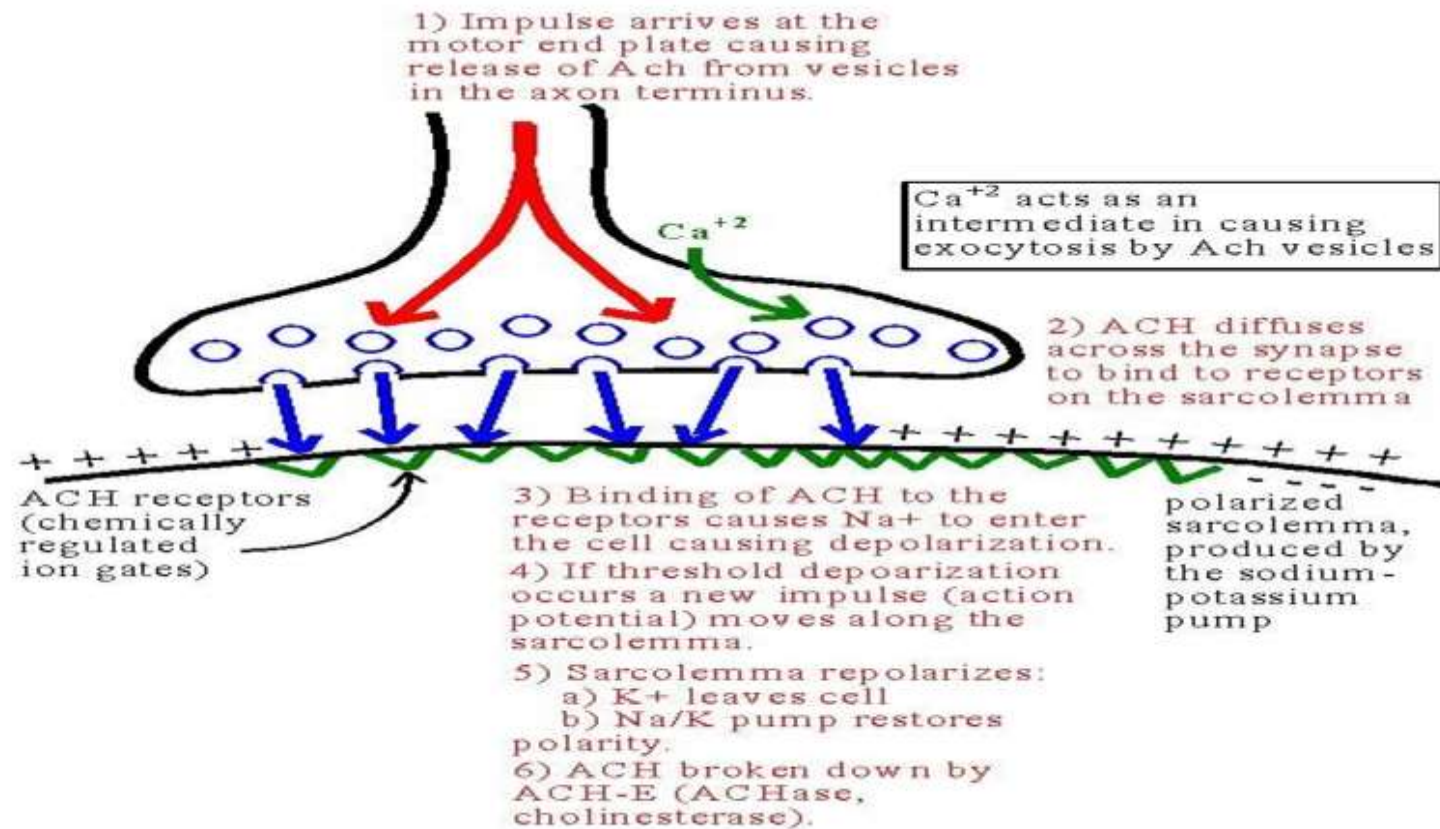
- They are agonists, as they bind to receptor and activate it, causing quick fasciculations followed by neuromuscular blockade due to receptor desensitization.
- So basically they cause depolarization without repolarization which leads to fatigue.
- More resistant to degradation.

AUTONOMIC

SOMATIC

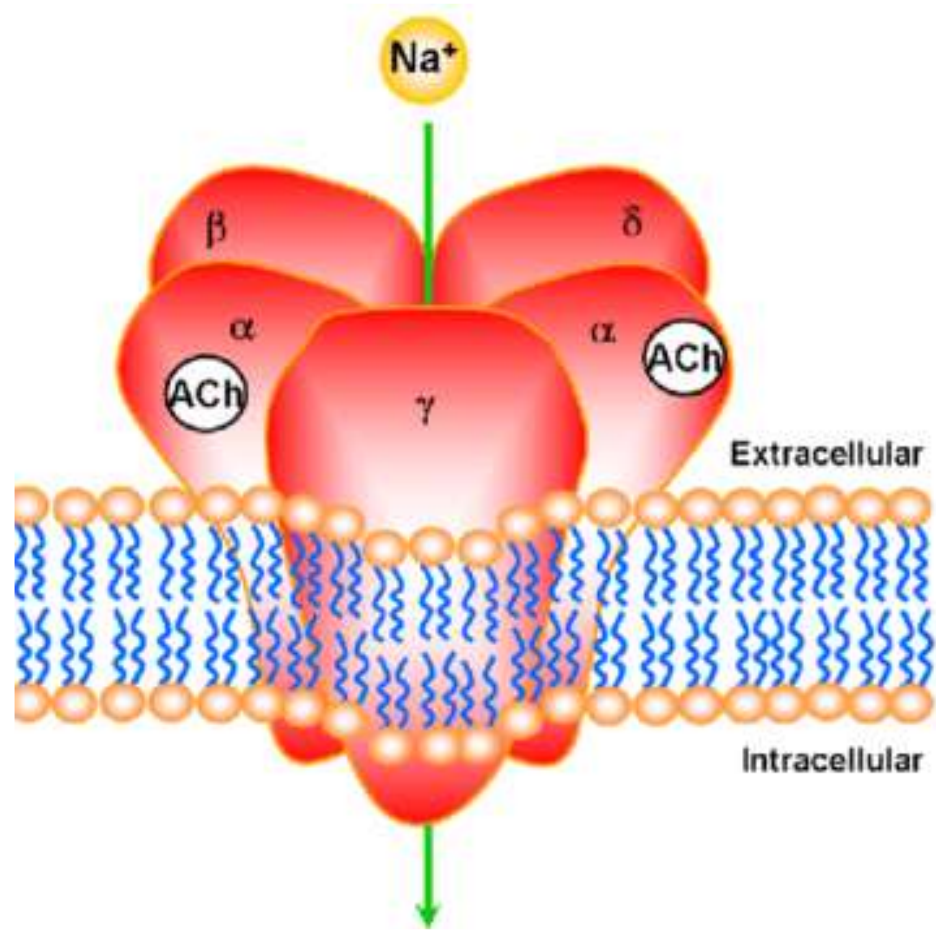


Physiology of neuromuscular junction



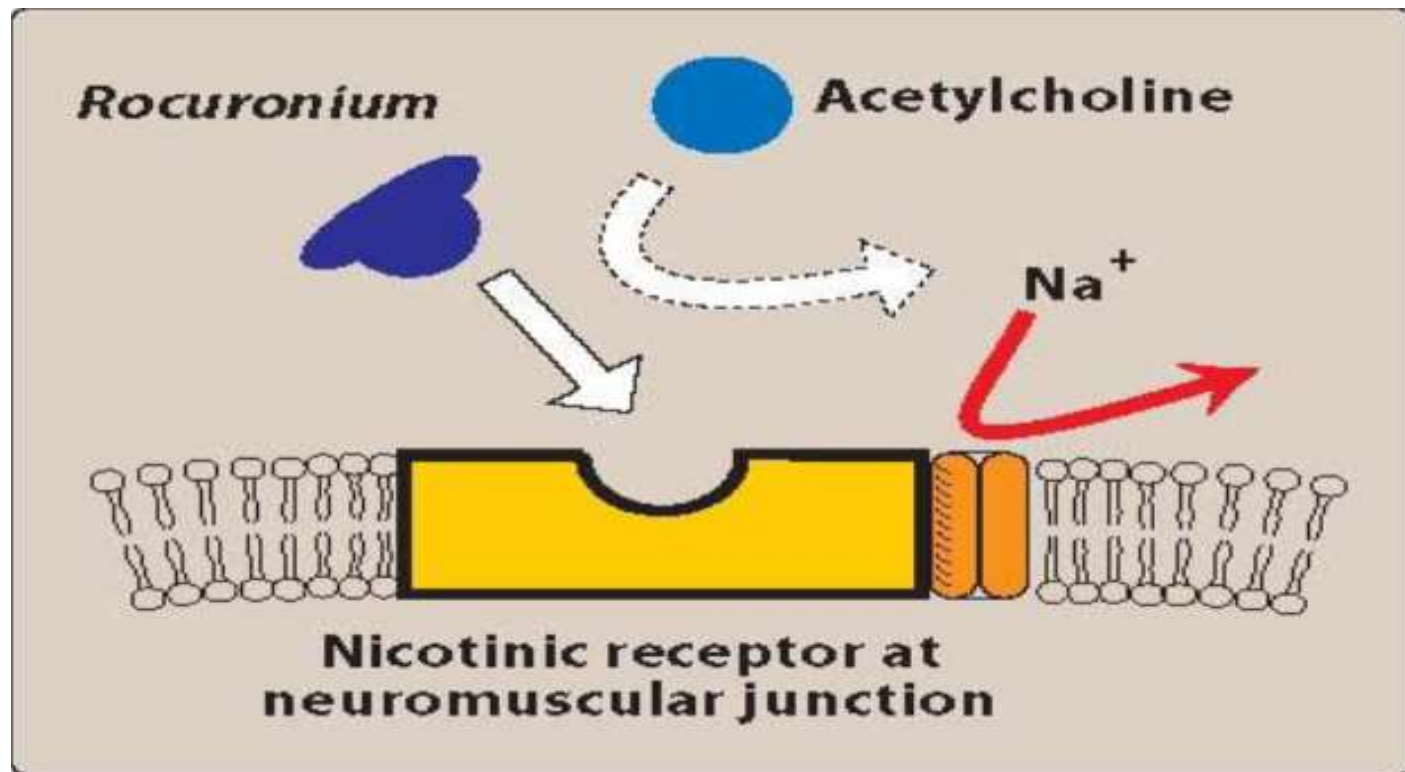
Nicotinic receptors

- we have muscle type & neuronal type
- it is ionotropic pentameric receptors
- it is activated by binding of ACh with 2 alpha chain, then the central pore will open to allow influx of Na^+ inside the myocyte and cause depolarization and muscle contraction



(1) Non depolarizing agents=competitive inhibitors

- firstly, let's start to talk about non-depolarizing agent



- **Mechanism of action :** ☆ They are water-soluble, hydrophilic so they are given IV.
☆ They can NOT reach the CNS as they can NOT cross BBB, thus no effect on the vasomotor center.
- They compete with Ach at nicotinic receptors preventing it from binding to nicotinic receptors and activating them, thereby preventing depolarization (pure antagonism)
- This action can be reversed by anticholine esterase (Physostigmine and neostigmine and edrophonium), which inhibit the enzyme that degrade Ach, so it increases the concentration of Ach and over comes the competing drug

No effect on cardiac or smooth muscles

- **Pharmacokinetics :**

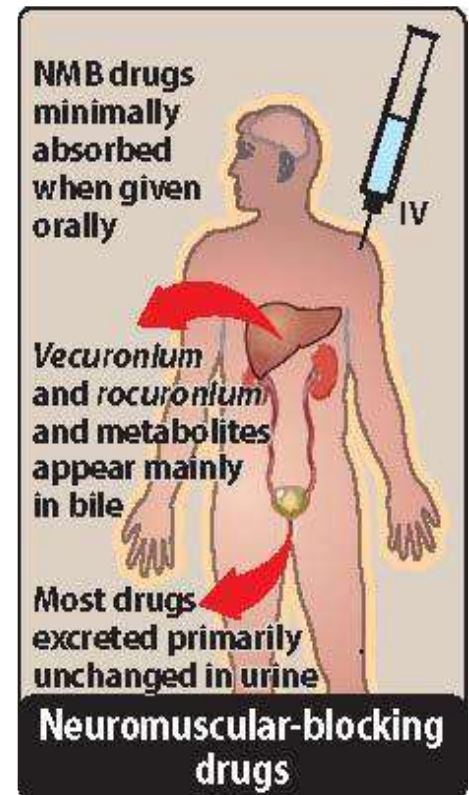
They are **polar** bulky drugs which containing **quaternary ammonium groups**(NH^+4) positively charged so they are **water soluble (hydrophilic)** and this means:-

1) they are not absorbed orally from stomach and you should give them IV(sometimes IM)

1) can't cross blood brain barrier or placenta

Doesn't provoke seizures, doesn't cause central apnea and doesn't have any effects on the ICP

- **metabolism :-**



- **drug interaction:-**

1-Halogenated hydrocarbon anesthetics--->e.g.**desflurane** ----> enhance the neuromuscular blockade Potentiation

2-Aminoglycoside or tetracycline antibiotics--->e.g,**gentamycin**---->inhibit ACh release from cholinergic neurons Potentiation

3-Calcium channel blockers(CCB)---->e.g,**verapamil**--->may increase the neuromuscular blockade Potentiation

4-**quinidine**(antiarrythemic drug)----->may increase the neuromuscular blockade Potentiation

5. Antagonization with choline esterase inhibitors.

- **Action of these drugs:-** ★ Higher number of NMJ indicates higher resistance to these agents which requires higher concentration of the drug to cause paralysis.

Inequal muscle sensitivity,so Small rapidly contracting muscles are more sensitive and paralyze first

face and eye--->**fingers, limbs, neck, and trunk muscles**

---->**intercostal muscles**---->**diaphragm** It has the highest resistance and the largest number of NMJ, so it is paralyzed last and recovered quick

Classification of non-depolarizing blockers

1)we can classify non-depolarizing blockers depending on it's chemical structure to:-

A-Isoquinoline(end with “curium” suffix)

B-Steroid (end with “ronium” suffix)

2)Or we can Classify of non-depolarizing blockers depending on it's duration of action to:-

A-short acting

B-intermediate acting

C-long acting

BROAD CLASSIFICATION

- These are broadly divided into steroidal compounds and benzylisoquinoline (BZIQ) compounds.

1-STEROIDAL COMPOUNDS: (vagolytic properties)

It includes PANCURONIUM, VECURONIUM, PIPECURONIUM, ROCURONIUM, RAPACURONIUM.

2-BZIQ (Benzylisoquinoline): (histamine release)

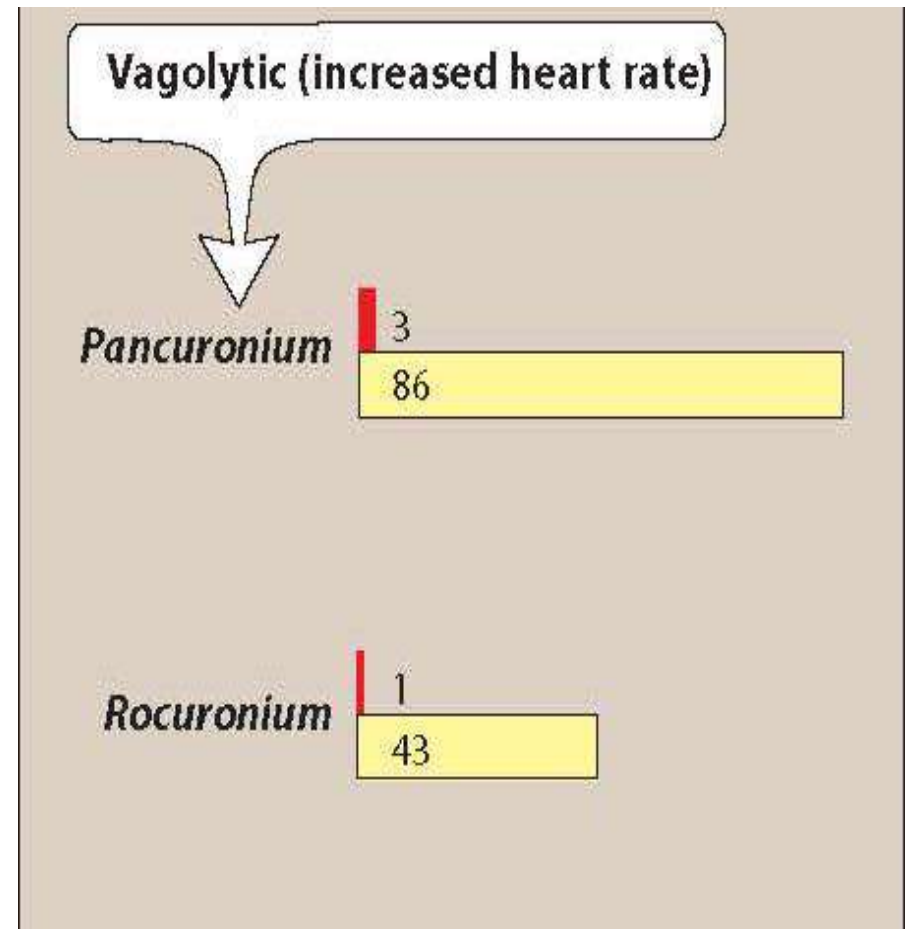
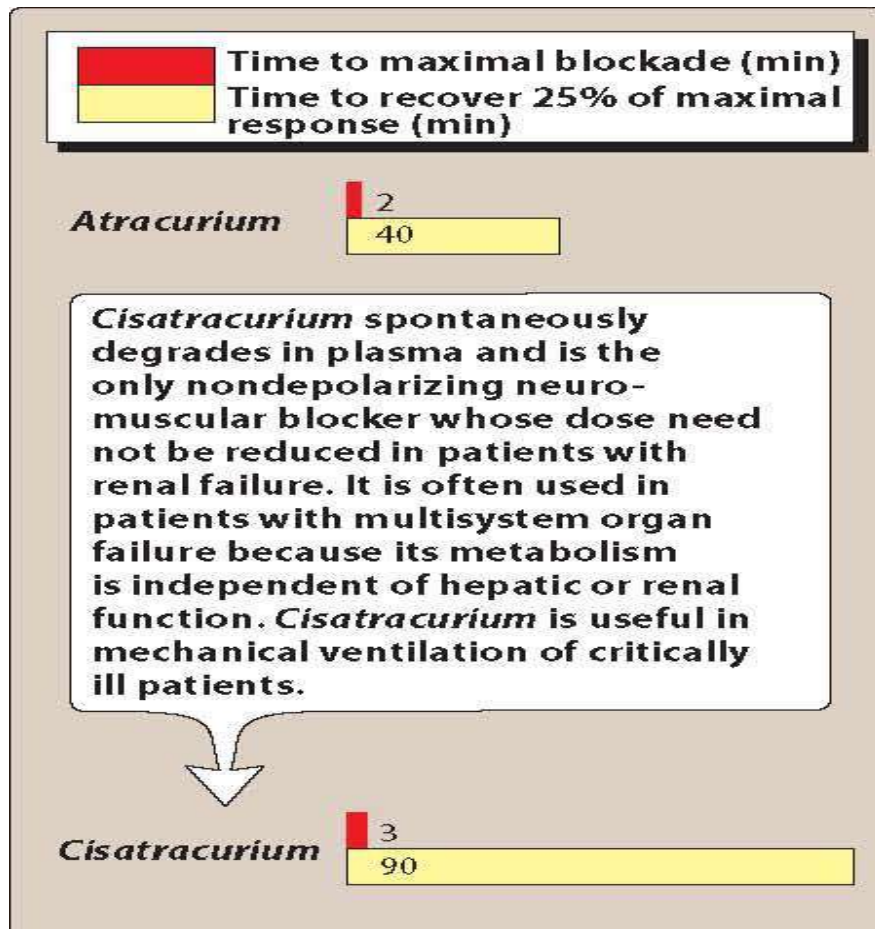
It includes d-Tubocurarine, Metocurine, Doxacurium, Atracurium, Mivacurium, Cisatracurium

Classification of non-depolarizing blockers depend on chemical structure

	Drug	Eliminated by	Duration of action (minuets)
1) Isoquinoline	Tubocurarine	Kidney 40%	>35
	Atracurium	<u>Spontaneous</u>	20-35
	Mivacurium	Plasma cholinesterase	10-20
2) Steroid	Vecuronium	Liver(75-90%) , kidney	20-35
	tocuronium	Liver(75-90%) , kidney	20-35
	Pipecuronium	Liver , kidney 60%	>35

- classification of non-depolarizing NMB depend on duration of action □ □

there is the variable onset/duration of action of different members of this class



1-short acting

(effect between 10-20min)

Mivacurium → Plasma cholinesterase degrades it

2-Intermediate acting

(effect between 20-35min)

- Atracurium + Cisatracurium → Hoffman elimination

- Vecuronium
- Rocuronium } Liver metabolism

3-Long acting (effect >35min)

Pancuronium + Pipecuronium → Rely on renal elimination

*Atracurium is inactivated by spontaneous breakdown into

laudanosine which crosses BBB and may cause seizures,  In patients with liver failure

however cisatracurium is also degraded spontaneously but does not produce laudanosine and has no centrally adverse effects 

Under normal PH of the blood and normal temperature

1-Mivacurium

☆ It has the shortest duration between nondepolarizing but does NOT have the most rapid onset of action. The most rapid is rocuronium.

- **Dose:-70-250 mg/kg**

Reduce dose if given with general anesthetics that potentiate its activity (eg, isoflurane)

- **Onset:-2-4 min**
- **Duration:-10-20 min = short acting**
- **Metabolism:-metabolise by plasma**

cholinesterase Not used in patients with liver impairment because the enzyme that metabolize it is synthesized by the liver.

- **Excretion:-in urine and bile**

side effect:-

- 1-histamine release(skin flushing, hypotension, tachycardia...etc)
- 2-hypersensitivity reaction
- 3-acute myopathy

2 .Atracurium Indication &Doses

- Dose:-0.4-0.5 mg/kg

Reduce dose if given with general anesthetics that potentiate its activity (eg, isoflurane)

- Onset:-2-2.5 min; may be slightly delayed in patients with renal failure
- Duration:-20-35 min = intermediate acting
- Metabolism:-metabolise to laudanosine by non-enzymatic cleavage (spontaneous degradation, Hoffman elimination) independent of hepatic/renal function → so it is ideal for patient with hepatic and renal insufficiency
- Excretion:-principally in urine & also in feces via biliary elimination

Adverse effects:

Two important adverse effects (major)

CNS problems and seizures due to laudanosine

Allergic reaction due to histamine release

1. Skin flush (due to histamine release and VD)
2. Erythema (due to histamine release and VD)
3. Pruritus
4. Urticaria (BUT NOT malignant hyperthermia)
5. Wheals
6. Wheezing
7. Increased bronchial secretions
8. Bronchospasm
9. Cyanosis
10. Changes in heart rate(hypotension and tachycardia , but transient)
11. Cardiac arrest
12. seizures(by laudanosine)

skin

RS

CVS

CNS

3. **Cisatracurium**:(a cis-isomer of *atracurium*)

★Drug of choice for a patient with liver impairment

- **DOSE:-** Initial intubating doses: 0.15-0.2 mg/kg IV
- **Uses:-**
 - Adjunct to general anesthesia to induce muscle relaxation for endotracheal intubation, mechanical ventilation
 - Cisatracurium** is an **IDEAL** agent for patients with renal or hepatic insufficiency requiring muscle relaxation .

- **Onset:** 2.4-2.6 min (mean for 0.15-0.2 mg/kg adult dose)

but in Hepatic impairment: onset time is faster (~1 min) and recovery is slower (~1 min)

- **Duration:** 55-65 min
- **Metabolism:** forms inactive metabolites; It undergoes hydrolysis in the plasma by a nonenzymatic process referred to as Hoffman elimination(Much less laudanosine is produced compared to atracurium , so NO CNS adverse effects→ it is better), and by an ester hydrolysis reaction.
- **Excretion:** urine 95%
So Maximum blockage time about 1 min slower in renally impaired pts.

4. Vecuronium : Dosing Forms & Strengths

- **Dose:-** we give initial 0.08-0.1 mg/kg over 60 sec (or 0.04-0.06 mg/kg after succinylcholine- assisted intubation and anesthesia
- **Uses:-** Adjunct to general anesthesia-induce muscle relaxation for endotracheal intubation, mechanical ventilation
- **Onset:-** 3-5 min
- **Duration:-** 20-35 min (intermediate action)

- **Metabolism:-**it is metabolized in liver,then the metabolite will eliminate in the bile and kidney
- **CAUTION:** hepatobiliary obstruction, or renal dysfunction will significantly prolong duration of action of Vecuronium

elimination half time is increased 24-56% in the setting of renal failure, duration is longer and more variable.

NOTE:-Vecuronium is considered a long-acting agent in infants, due to their immature livers.

Adverse effects :

- 1-Skeletal muscle weakness or paralysis
- 2-Respiratory insufficiency or apnea
- 3-Hypersensitivity reactions associated with histamine release
e.g.,(bronchospasm, flushing, erythema,acute urticaria,
hypotension, tachycardia)
- 4-Less histamine release than **pancuronium** or **atracurium** so Less cardiovascular effects(less effect on HR & MAP) & It is a popular agent because it does *not* produce any undesirable cardiovascular side effects even when administered rapidly in large doses , so it is used in *coronary artery surgery*.
- 5-Little effect on intraocular/intracranial pressure

5-Rocuronium

Rapid
Onset

It has the most rapid onset of action between all nondepolarizing drugs

- **Dose:**-0.6-1 mg/kg

Reduce dose if given with general anesthetics that potentiate its activity (eg, isoflurane)

- **Onset:**-rapid onset 60-90 sec
- **Duration:**-30-40min = **intermediate acting**
- **Metabolism:**-metabolized by liver mainly (with no active metabolite)
- **Excretion:**-in kidney

***So prolonged effect have been observed in patients with hepatic or renal impairment**

side effect:-minimal CVS side effect with mild histamine release

antidote:-is **Sugammadex**

- **6-Pancuronium**

★ Contraindicated in patients with renal impairments

- **Dose:-0.08-0.12 mg/kg**

Reduce dose if given with general anesthetics that potentiate its activity (eg, isoflurane)

- **Onset:-3-5min**
- **Duration:-60-90 min = long acting**
- **Metabolism:-metabolized by liver mainly (with no active metabolite)**
- **Excretion:-in kidney**

***So prolonged effect have been observed in patients with hepatic or renal impairment**

side effect:-slight increase in HR and blood pressure

For competitive antagonist

- **Contraindications**

1-Hypersensitivity to the agent

2-Lack of ventilatory support(because it is cause respiratory muscle paralysis)

3-neuromuscular disease(such as duchenne disease)

- **Cautions**

1-Severe anaphylactic reactions to neuromuscular blocking agents have been reported; these reactions have, in some cases, been life threatening and fatal; because of the potential severity of these reactions, the necessary precautions, such as the immediate availability of appropriate emergency treatment, should be taken

2-Do not administer before unconsciousness

3-May cause a profound effect in those with myasthenia gravis or the myasthenic syndrome so reduce the dose

4-May require higher doses in burns(because the pharmacokinetics and pharmacodynamic of drugs is significantly altered in the burn)

Reversal action of competitive NMB

- 1-by cholinesterase inhibitor drug:-

Muscle relaxation produced by **nondepolarizing** neuromuscular agents may be "reversed" by **anticholinesterase agents** such as **edrophonium** and **neostigmine**. These agents prevent the breakdown of acetylcholine in the NMJ $\rightarrow \uparrow \text{ACh} \rightarrow$ the increased concentration of acetylcholine at the NMJ competes with the muscle relaxant which allowing the receptor once again to become responsive to acetylcholine

•But the increased concentrations of acetylcholine also stimulate the muscarinic cholinergic receptors (present in all the body except in muscles+neurons), resulting in bradycardia, salivation, and increased bowel peristalsis.

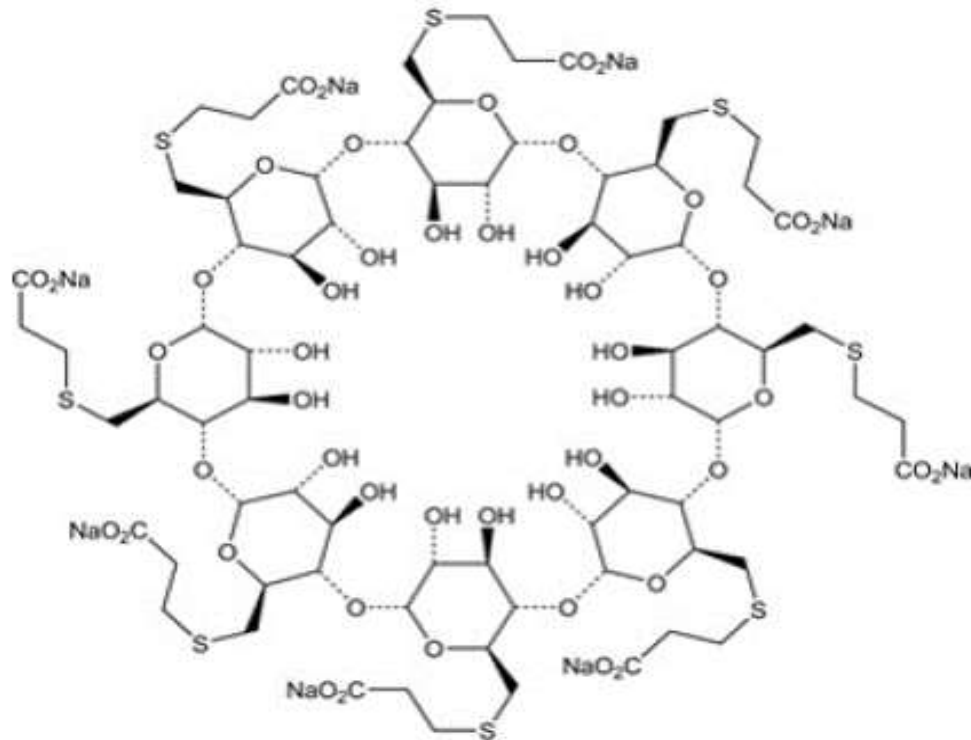
So to prevent cholinergic crisis which happens by AChE inhibitor, we should give Anticholinergic agents such as atropine and glycopyrrolate prior to reversal, to block these unwanted muscarinic effects.

So we give cholinesterase inhibitors with atropine in order to get rid of the parasympathetic adverse effect associated with such drugs like neostigmine

Common combinations of anticholinergic and anticholinesterase agents used to reverse a neuromuscular block are atropine 0.01 mg/kg with edrophonium 0.5 - 1.0 mg/kg, or glycopyrrolate (anticholinergic) with neostigmine 0.05- 0.07 mg/kg intravenously.

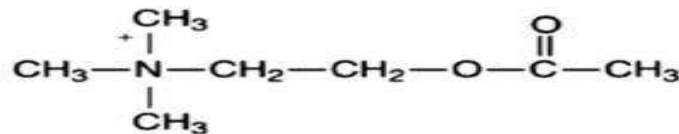
2-by Sugammadex:-It is Selective relaxant binding agent which terminates the action of both **rocuronium** and **vecuronium** by wraps the NM blocker in 1:1 ratio which lead to rapid reversal of neuromuscular blockade

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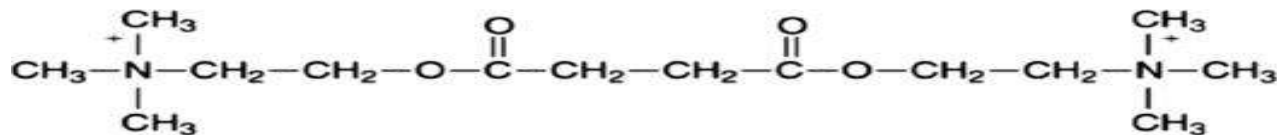


2-Depolarizing agent(SUXAMETHONIUM)

- Simply they are **agonist for a little then persistant antagonist** , so they result in initial fasciculation (mild muscle contraction) then flaccid paralysis .
- **Succinylcholine (suxamethonium) :-**It is formed by **combination of 2 molecules of Ach** which work like ACh and lead to depolarize the membrane of the muscle fiber



Acetylcholine



Succinylcholine

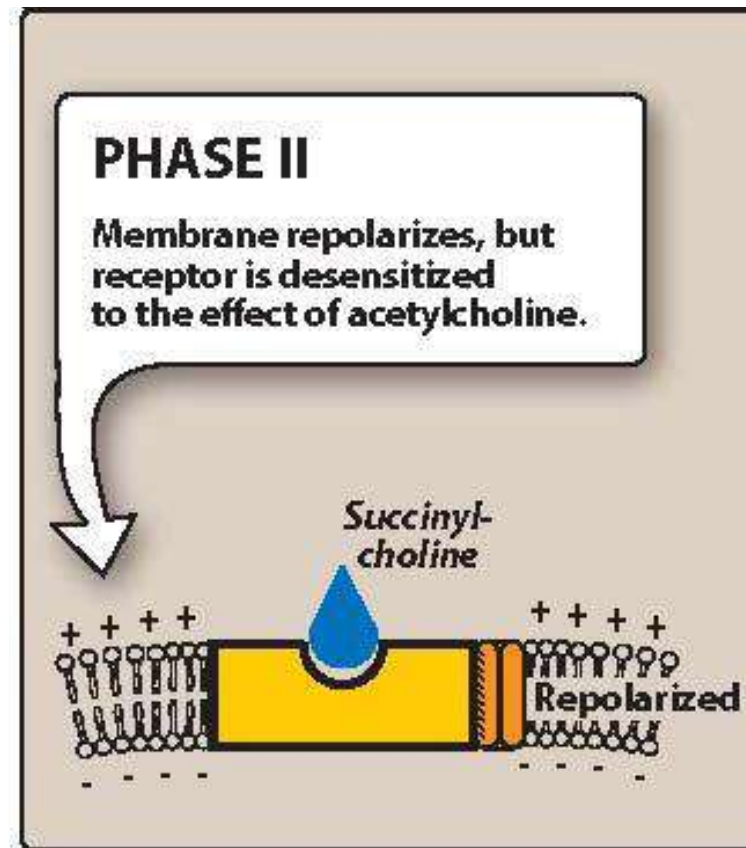
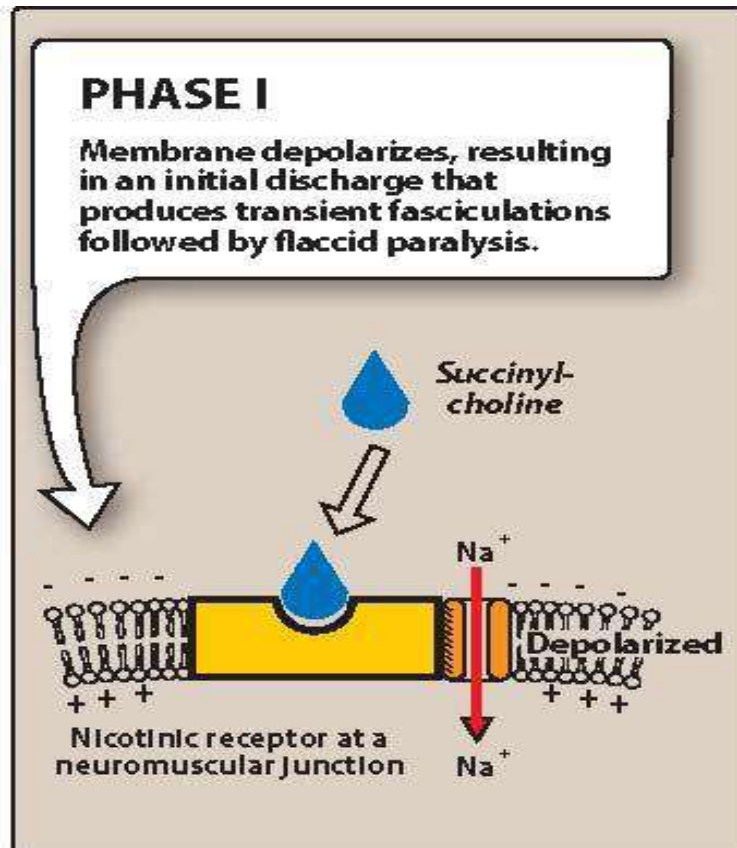
- Mechanism of action :

Phase I (depolarization) : it stimulates NMJ the same way as Ach but action lasts longer → contraction of motor units → succinylcholine is not effectively metabolized at the synapse so the membrane remains depolarized and unresponsive for further stimuli → prolonged depolarization → flaccid paralysis

Phase II (desensitization) : with continued exposure to succinylcholine the membrane becomes repolarized but can not be depolarized again (it becomes desensitized) the mechanism is unknown but the channels may become closed for a prolonged period similar to competitive agents

*this effect is not reversed (but augmented) by anticholine esterase

Anticholinesterase will lead to $\uparrow$ persistent depolarization = $\uparrow$ duration of blocking



Succinylcholine (suxamethonium)

★ It is the fastest muscle relaxant because it is similar to choline (basically it is two molecules of choline) So binds to the receptors faster than non-depolarizing agents.

- **Pharmacokinetics**

Quaternary ammonium compound (lipophobic)

similar to non depolarizing agents **not absorbed orally** and can **not cross BBB**

- **Metabolism:-**

Metabolized by plasma choline esterase (Bu chE, Pseudo chE, false chE) after it diffuses away from the end plate

★ Rapid onset, short duration of action

- **Duration of action:-5-10 minutes(very short)**

Succinylcholine apnea:-is the case of some patients which have genetically abnormal variant of plasma choline esterase with defective elimination of succinylcholine (they have little Bu chE (Butyrylcholinesterase) , so the succinylcholine won't be broken and its action will be prolonged , so prolonged paralysis leading to apnea prolonged apnea

In this condition, we are more worried about the development of malignant hyperthermia not the RS symptoms.

Supportive treatment

-Treatment of this case is done by **controlled ventilation** and give the patient **fresh frozen plasma** which contain a correct form of Plasma cholineesterase

Therapeutic treatment, could also give genetic recombinant enzyme

-diagnosis of this case is done by take blood samples to confirm the diagnosis and identify the enzyme genotype by Dibucane number test

☆ Patients with no plasma cholinesterase, if they were given succinylcholine it will result to paralysis, most importantly to the diaphragm as the drug can not be cleared and keeps shifting between blood and tissues.

Heterozygous mutation: duration of action will extend to 30 mins.

Homozygous mutation: the duration of action will extend to 8 hours.

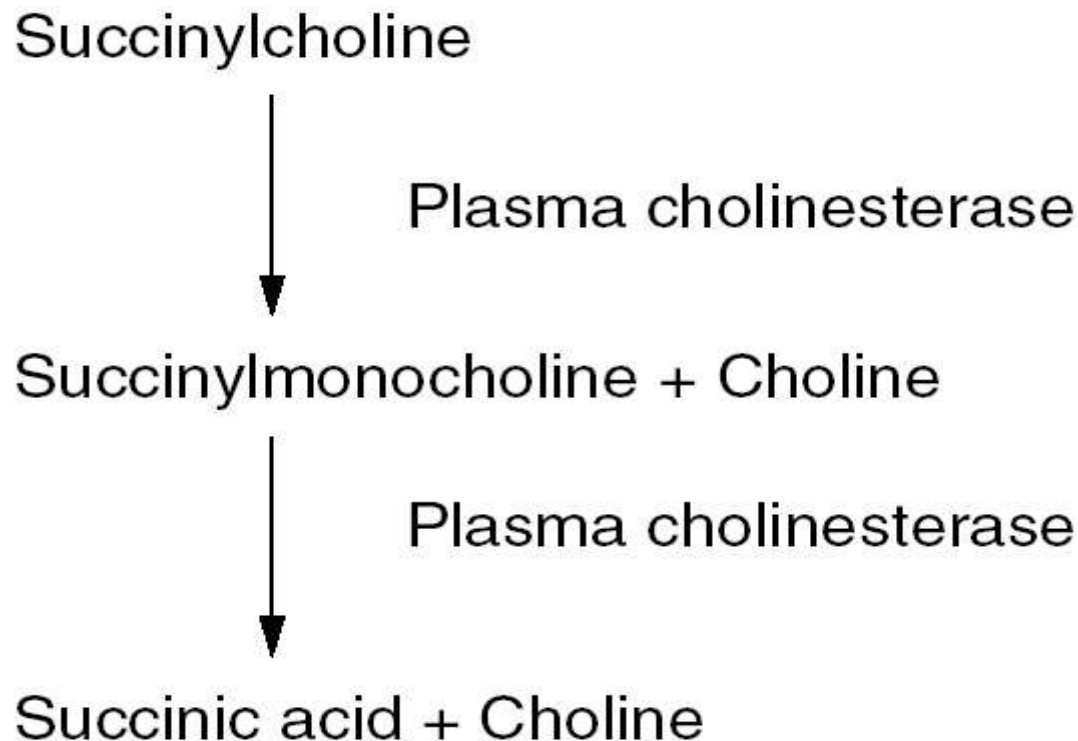
Dibucaine number	Plasma cholinesterase	Neuromuscular recovery	Incidence
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≥ 70	Normal	Normal	—
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35–65	Heterozygous atypical	Minimal increase	1/480
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≤ 30	Homozygous atypical	Prolonged by hours	1/3200
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- Onset: **IV: 30-60 sec**; IM: 2-3 min
- Duration: **IV 2-10 min**; IM 10-30 min
- Metabolism: rapid, by plasma pseudocholinesterase to weakly active metabolite
- Metabolites: succinylmonocholine & choline
- Excretion: urine



- **Pharmacological actions:-**
- After IV administration --->transient muscle fasciculation especially over the chest and abdomen then complete paralysis develop at arm, leg, neck, are affected first followed by facial and pharyngeal muscles finally rapidly by diaphragm
- Succinylcholine **stimulates autonomic ganglia and cardiac muscarinic receptors** and slightly stimulates **histamine release**

• Uses

- 1) Surgical relaxation
- 2) Control of ventilation to prevent resistance to ventilators
- 3) Decrease musculoskeletal manifestations of seizures, epilepsy, toxin induced seizures
- 4) Succinylcholine use during electroconvulsive therapy
- 5) Rapid sequence intubation

Rapid Sequence Intubation

Prepare equipment (IV, ECG, oximeter, BVM, suction, ETT)



C-Spine Immobilization p.r.n.



Preoxygenate with 100% O₂



Give Sedative:

- Midazolam 0.1–0.3 mg/kg IV or
- Thiopental 1–3 mg/kg IV or
- Ketamine 1–2 mg/kg IV or
- Etomidate 0.3 mg/kg IV or
- Diazepam 0.2 mg/kg IV (max. 20 mg)



If Pt. <2 y.o., **give Atropine 0.02 mg/kg IV** (blocks reflex bradycardia)



Give Succinylcholine 1–1.5 mg/kg IV, or: Rocuronium 0.6–1.2 mg/kg IV, or: Vecuronium 0.1 mg/kg IV



Intubate (apply cricoid pressure p.r.n.)



Inflate Cuff;

Verify Tube Placement:

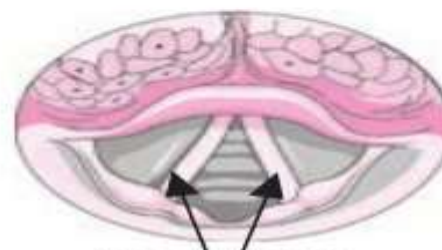
- Check Chest Expansion
- Check Lung Sounds
- Fogging of tube
- Apply CO₂ Detector
- Secure with ETT holder & C-collar



*Place Pt. in sniff position:
hyperventilate w/O₂*



*Lift tongue leftward &
visualize vocal cords*



Vocal cords



*Insert ETT; inflate cuff;
check breath sounds*

Adverse effects

1-Cardiovascular: Produces muscarinic effects as acetylcholine, therefore causes bradycardia (but when given high doses causes tachycardia because of stimulation of nicotinic receptors at sympathetic ganglions)

Direct stimulation of muscarinic receptors of the heart.

2-Hyperkalemia: Occurs due to excessive muscle fasciculations and muscle degradation. Ventricular fibrillation can occur due to hyperkalemia

Using this drug increases potassium concentration by 0.5 eq/L. It's not of that much important except in four risky groups:

3-CNS: Increases intracranial tension (due to contraction of neck vessels)

- 
1. Patients with renal failure.
 2. Patients taking digoxin or spironolactone. (Relative)
 3. Unexplained in pediatric patients.
 4. Massive tissue damage (sepsis, burn, trauma..)

4-Eye: Increases intraocular pressure.

5-GIT: Increases intra-gastric pressure , salivation, peristalsis.

6-Muscle pains(myalgia): This is a very common problem in post operative period. These are due to excessive muscle contractions.

7-Malignant hyperthermia

8-Severe Anaphylaxis

9-Masseter Spasm : Sch can cause masseter spasm especially in children & patients susceptible for malignant hyperthermia.

10-myoglobinuria may cause renal insufficiency

CONTRAINDICATIONS of Sch

- 1- **Hyperkalemia**: Serum K > 5.5 is an absolute contraindication for use of Sch.
- 2- **Head Injury** : It increase ICP
- 3- **Newborns and infants**: These have extrajunctional receptors which are sensitive to depolarizing agents & Sch can produce severe hyperkalemia by interacting with these receptors.
- 4- **Glaucoma & eye injuries**.
- 5- Up to 2-3 months after trauma, Up to 6 months after hemiplegia/paraplegia, Up to 1 year after burns. In these conditions the denervated/regenerating nerve develops extra junctional receptors which can produce **hyperkalemia**.

6-renal Failure : If associated with hyperkalemia.

7-Prolonged intra abdominal infection can be associated with hyperkalemia.

8-Diagnosed case of atypical pseudocholinesterase & low pseudocholinesterase.

9-Duchene muscular dystrophy

10-Dystrophia myotonica: Permanent contractures may develop if SCh is given in these patients.

11-Tetanus&Gullian Barre Syndrome

12-Metabolic Acidosis :Acidosis is associated with hyperkalemia.

13-Shock : It is associated with acidosis which in turn is associated with hyperkalemia.

14-Spinal cord injury.

15-in burn(we should decrease the dose)



THANK YOU
Any Questions ?