MED438
KING SAUD UNIVERSITY

pharmacology
Team 438

- Red : important
- Black : in male / female slides
- Pink : in female's slides only
- Blue : in male's slides only
- Green : Dr's notes
- Grey: Extra information, explanation

Editing File

LECTURE 2: MUSCLE RELAXANTS

OBJECTIVES:

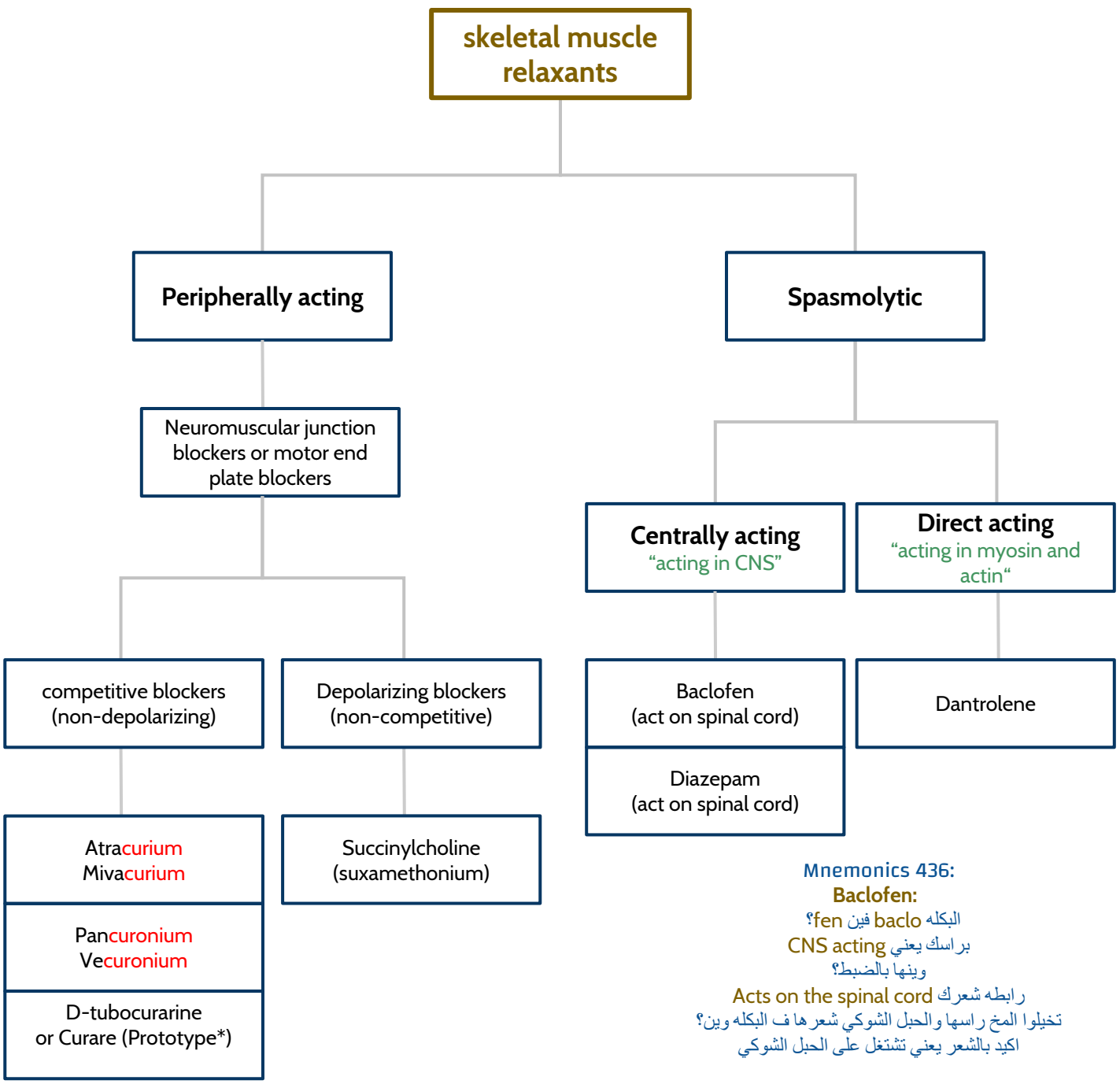
By the end of this lecture, students should be able to:

- ✓ 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

Skeletal Muscle Relaxants :

Are drugs used to induce skeletal muscle relaxation

- They are classified according to the mechanism of action into:



*Prototype is the first drug to be discovered in a particular class. Related drugs are compared to it.

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

Peripheral Acting Drugs

Neuromuscular Blockers

Mechanism of action: Act by blocking neuromuscular junction or motor end plate leading to skeletal muscle relaxation **both competitive and depolarizing drugs are taken parenterally (injection)** مهم جدًا

❖ Classification according to the mechanism of Action:

	1-Competitive (Non-depolarizing) Blockers	2-Depolarizing (non-competitive) Blockers
Mechanism of action	• Competes 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). No Na influx • Action can be reversed by increasing Ach concentration cholinesterase inhibitors can reverse blockade (neostigmine)	Phase 1: combine with nicotinic receptors in post-junctional membrane of neuromuscular junction → initial depolarization of motor end plate →muscle twitching → Phase 2: persistent depolarization → Skeletal Muscle relaxation
Drugs	❖ According to the duration of action: **-Long acting:** D-tubocurarine(Prototype not used anymore) Pancuronium **-Intermediate acting:** Atracurium, Vecuronium **-Short acting:** Mivacurium	Succinylcholine (Suxamethonium)
Pharmacokinetics	• **Polar compound** -Inactive orally, taken parenterally -Don't cross Blood brain barrier (No central acting) -Don't cross placenta (Can be used with pregnant women) -Metabolism by either liver(intermediate duration of action) or kidney(long duration of action) **EXCEPT :** •Mivacurium->degraded by Acetylcholinesterase •Atracurium->Spontaneous degradation in blood (without the effect of any enzyme)	• 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). Note : We have two types of acetylcholinesterase 1- true Acetylcholinesterase > found in neuromuscular junction 2- pseudo-cholinesterase > found in plasma
Pharmacological actions	**1-Skeletal muscle relaxation.** -small rapidly contracting muscles of: face and eyes, fingers, neck, trunk muscle, intercostal muscles*, diaphragm* -Recovery comes from REVERSE MANNER starting with diaphragm. Last is face and eyes. **2-They produce different effects on CVS** **3-some release histamine and produce hypotension;** o d-Tubocurarine (Severe release) o Atracurium (Moderate release) o Mivacurium (Mild release) **4-Others produce tachycardia (↑ H.R);** o Pancuronium (No release of Histamine) *Relaxation of these two causes serious respiratory problems	• Skeletal muscles: twitching → relaxation (Usually used before surgery). • Hyperkalemia: Cardiac arrest. Due to the release of K+ into the blood • CVS: arrhythmia. • Eye:↑ intraocular pressure (due to contraction of extra-ocular muscle).
Uses of NM blockers	• control convulsion → electroshock therapy in psychotic patients. • Relieve of tetanus and epileptic convulsion. • As adjuvant in general anesthesia to induce muscle relaxation (main use) • Facilitate endotracheal intubation, endoscopy • Orthopedic surgery	
Modify the effects of NM blockers	**Diseases: (since it enhances the activity it cannot be used in this conditions)** **Myasthenia Gravis & parkinson** increases the response to muscle relaxants. **Drugs:** As Aminoglycosides (e.g. *Streptomycin*), Magnesium Sulphate and General anesthesia can potentiate or enhance the effects of NM blockers. Cholinesterase inhibitors enhance the effect of depolarizing relaxants but decreases the effect of nondepolarizing relaxants	

Competitive (Non-depolarizing) Blockers

Drugs	D-Tubocurarine	Atracurium	Mivacurium	Pancuronium	Vecuronium
		Chemically related			
Duration	1-2 h (Long)	30 min (intermediate)	15 min (shortest one)	1-2 h (Long)	40 min (intermediate)
Metabolism and excretion	Eliminated by kidney 60% & liver 40%.	Spontaneous hydrolysis at body pH, thus goes through non enzymatic chemical degradation in plasma.	-fast onset of action -metabolized by **Pseudo cholinesterase**	Metabolized by liver Excreted by the kidney(80%) Its metabolic products also have some NM blocking activities	Metabolized by liver. Excretion in bile. نقدر نصرفه للمريض الليّ عنده مرض بكليته لانه ماراح يعتمد على الكلية في اخراج الدواء
Side effects	**Not used clinically** due to its side effects. Histamine releaser leading to: -Bronchospasm (constriction of bronchial smooth muscle) -Hypotension -Tachycardia	-Liberates Histamine causing transient hypotension. -Antihistamine Pretreatment may prevent those side effects. No effect on muscarinic receptors nor ganglia	Transient Hypotension due to Histamine release. Mivacuriuam induced prolonged muscle paralysis can be reversed by acetylcholinesterase inhibitors such as Endrophonium.acetylcholinesterase inhibitors increase Ach displacing the drug from the receptor in NMJ	-Hypertension -Tachycardia -Increased Norepinephrine release from adrenergic nerve endings. -Antimuscarinic action (Block parasympathetic effects) Blocks muscarinic receptors in SA node	Has few side effects: -No Histamine release -No Tachycardia (No Ganglionic block nor antimuscarinic effects)
Uses	-	**used in kidney and liver failure (Drug of choice)**	-	-	Given with renal failure patients
Contraindication	-	Asthmatic patients (Because of release of histamine causing bronchospasm)	Longer duration in patients with liver diseases or genetic cholinesterase deficiency (ADR type B) or malnutrition (protein defect)	Patients with coronary diseases امراض القلب التاجية	-
Potency	-	As potent as curare		6 times more potent than curare	

Depolarizing (Non-competitive) Blockers:

Drug	Succinylcholine (Suxamethonium)		
Duration	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 -Elderly -Pseudo-cholinesterase deficiency (liver disease, malnutrition, genetic cholinesterase deficiency, organophosphorus poisoning)	Contraindications	-Glaucoma -Patient with cardiac disease
Side Effects	-Hyperkalemia causing cardiac arrest -CVS arrhythmia - ↑ Intraocular pressure contraindicated in glaucoma **-Can produce malignant hyperthermia** -May cause **succinylcholine apnea** due to deficiency of pseudo-cholinesterase.	Pharmacodynamics	**-Skeletal muscles:** twitching → relaxation **-Hyperkalemia:** cardiac arrest **-CVS:** arrhythmia **-Eye:** ↑ intraocular pressure (due to contraction of extraocular muscle) GIT: increased intragastric pressure –> regurgitation of gastric content to esophagus

Malignant Hyperthermia

Is a rare bizarre inherited condition of having a body temperature greatly above normal.
Is an example of Idiosyncrasy. (ADR type B)

❖ **occurs upon administration of drugs as:**

- 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
- muscle rigidity (spasm)
- Metabolic acidosis
- Tachycardia
- Hyperthermia (Hyperpyrexia)

❖ **Treatment of the disease:** Dantrolene

Spasmolytics

Muscle Relaxants	Action	Act On	Clinical Uses
Baclofen	Centrally	GABA* agonist (acts on spinal cord)	Reduce muscle spasm in spastic states produced by neurological disorders such as: -Spinal cord injury -Cerebral stroke -Cerebral palsy
Diazepam (Benzodiazepines)	Centrally	Facilitate GABA action on CNS	
Dantrolene	Direct	-	All the above + **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.

Mechanism of Action of Dantrolene:

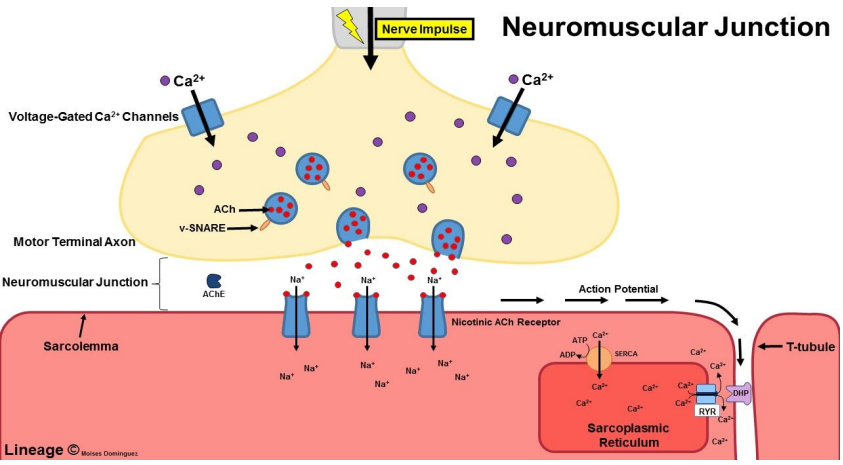
- It acts directly on skeletal muscles.
- It interferes with the release of calcium (inhibit the release) from its stores in skeletal muscles **(sarcoplasmic reticulum)**
- It inhibits **excitation-contraction coupling** in the muscle fiber.Ca releases from the sarcoplasmic reticulum via Ca channels, Dantrolene blocks these channels.
- Given orally or IV (t ½ = 8-9 h)

Clinical Uses:

- Spastic states
- Malignant hyperthermia (the first choice)

Extra explanation

❖ Mechanism of action of Neuromuscular Blockers:



Extra explanation From 436:
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 and then the muscle will contract. The Neuromuscular blockers basically will block the nicotinic receptors so the acetylcholine can not bind with the receptors and produce its action (muscle contraction) and if the muscle will not contract it will relax.

❖ Mechanism of action of Depolarizing Blockers:

Extra explanation from 437:
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 is called **hyperpolarization** so no more contractions will occur.
e.g of depolarization NMB is: ***succinylcholine*** **They are agonist drugs**

Mnemonics 436:
Mivacurium
Pseudo-cholinesterase كذابين miva نيفيا curium جربت كريم
Short duration of action مره مو زين ما يطول بالجسم بسرعه يروح اثره

Pancuronium (Tachycardia)
عشان اربط ان هالدواء له علاقة معدل ضربات القلب
بنك panc الدم بالجسم هو القلب

*taken from prof. Hanan's lecture

SUMMARY

(# = contraindicator)

Drug	Duration	Side Effects	Notes
Tubocurarine	Long 1-2 h	Hypotension	# Renal Failure
Pancuronium	Long 1-2 h	Tachycardia	# Renal Failure
Atracurium	Short 30 min	Transient hypotension Histamine release	Spontaneous degradation Used in liver and kidney failure
Vecuronium	Short 40 min	Few side effects	# Liver failure
Mivacurium	Short 15 min	Similar to atracurium	Metabolized by pseudocholinesterase # Cholinesterase deficiency
Succinyl choline	Short 10 min	Hyperkalemia Arrhythmia Increase IOP	# CVS Diseases # Glaucoma # Liver disease

QUIZ

Quiz (MCQ) :

Q1.Which one of these is an example of depolarizing Blockers ?

A)Pancuronium B)Suxamethonium C)Vecuronium

Q2.The metabolism of Atracurium ocurre in ?

A)Blood B)Liver C)Kidney

Q3.Which one of these NM blockers hydrolysis at body pH ?

A)Pancuronium B)Atracurium C)Vecuronium

Q4.Which one of these act on the spinal cord?

A)Atracurium B) Dantrolene C) Diazepam

Q5.Which one of these has a long duration of action ?

A)Mivacurium B)Vecuronium C)Tubocurarine

ANSWER : 1)B - 2)A - 3)B - 4)C - 5)C

Quiz (SAQ) :

Q1.Define the skeletal Muscle Relaxants ?

Q2.What is the mechanism of action of Peripheral Acting Drugs ?

Q3.Give an example of a disease and drug that change the effect the NM blockers ?

4-5.A patient came to the emergency with high fever, after examinations the diagnose was Malignant Hyperthermia.

Q4.What is the possible causes of this condition ?

Q5.What is the suitable treatment ?

Q6.Why does D-tubocurarine drug not favor to use clinically ?

Q7.What is the pharmacodynamics effect of Suxamethonium in the eyes ?

Q8.What is the main mechanism of action of Spasmolytic ?

Q9.Why using muscle relaxant during caesarean surgery doesn't affect Uterus?

QUIZ

1.Drugs used to induce skeletal muscles relaxation.

2.Act by blocking neuromuscular junction or motor end plate leading to skeletal muscle relaxation

3.Diseases: Myasthenia Gravis - Drug: Streptomycin

4.administration of drugs as: (general anesthesia e.g. halothane) (neuromuscular blockers e.g. succinylcholine)

5.Dantrolene

6.due to its side effects

7.increase intraocular pressure

8.Reduce muscle spasm in spastic states

9.Because it doesn’t affect smooth muscle.

pharmacology

Team 438

GOOD LUCK

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