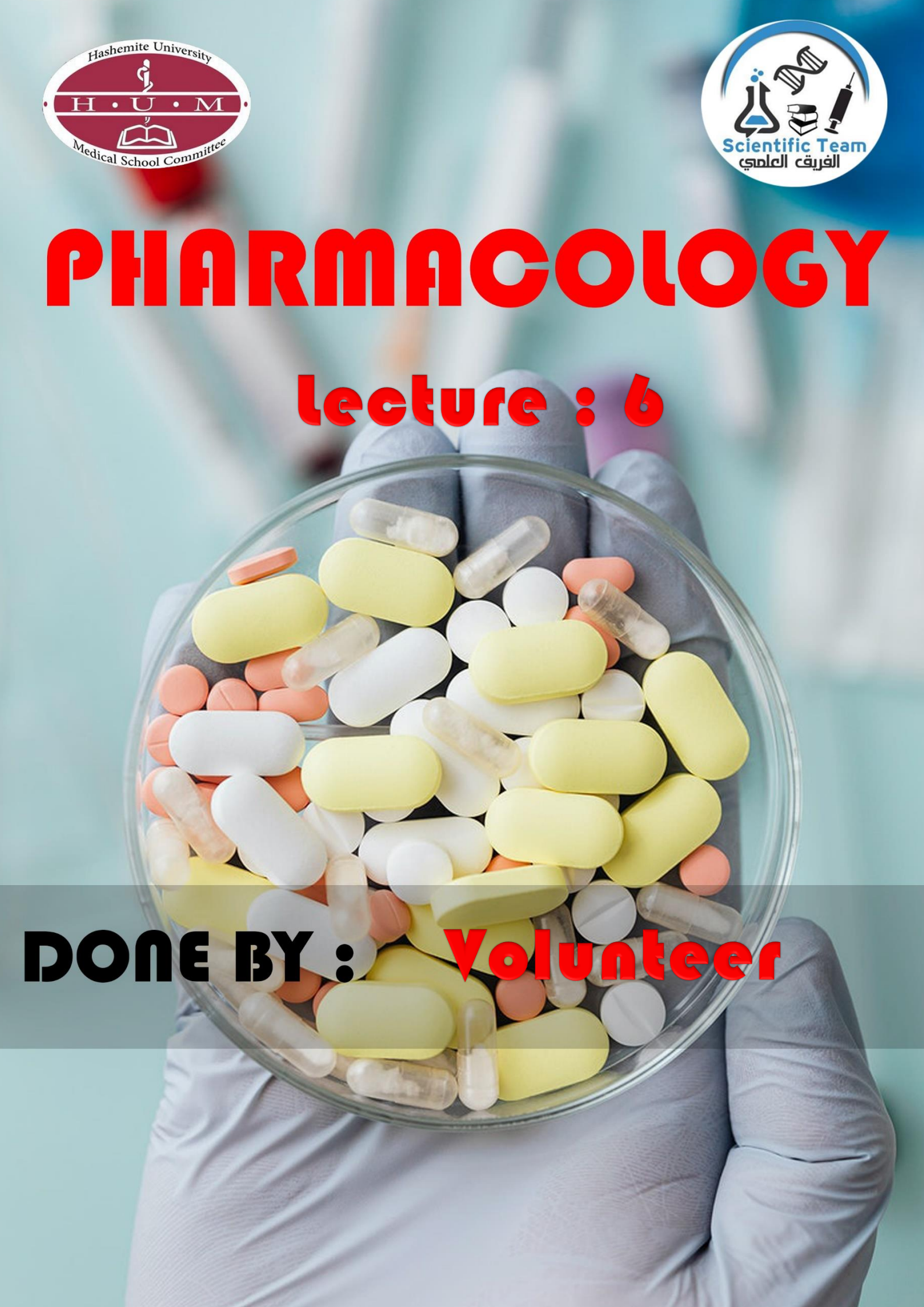
Hashemite University
H · U · M
Medical School Committee

Scientific Team
الفريق العلمي

PHARMACOLOGY

Lecture : 6



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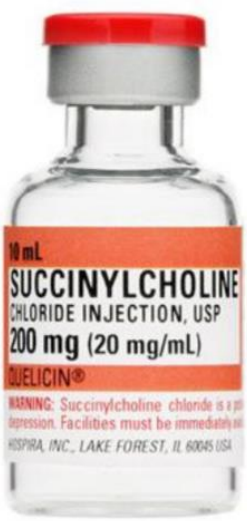
Lecture 6

Therapeutic Uses of Neuromuscular Blockers

◆**Main Therapeutic Use:** Adjunct to General Anesthesia

◆الاستخدام الرئيسي **كمساعد** اثناء التخدير الكلي عشان ما اعطي جرعة كبيرة من ال general anesthetics.



◆Muscle relaxation: orthopedic, abdominal surgeries

◆في اي عملية بنحتاج relaxant muscle و خاصة عمليات البطن والعظام

◆Facilitation of intubation, mechanical ventilation

◆-تسهيل التهوية الميكانيكيةventilator mechanical وهذا الشي شائع الان لأنها تستخدم للحالات الصعبه لمرض COVID-19

◆**Succinylcholine** during electroconvulsive therapy

◆-تقليل تشنجات العضلات(convulsions) مش كثير بنستخدمه بهالحالة.

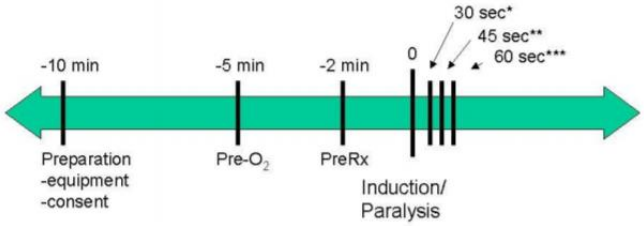
RSI: Rapid Sequence Intubation

تسهيل وضع tracheal tube .

rapid sequence induction and intubation
اول اشي بنعطيه oxygen و بعدين ketamine الي هو anesthetics و بعدين (**succinylcholine**او rocuronium)و بعدين بتحط tube (كل العملية بتستغرق ١٠ دقائق)

◆ Preferred method of endotracheal tube intubation (ETTI) at the ER

◆ results in rapid unconsciousness (induction) and neuromuscular blockade (paralysis)



◆ Give ketamine → followed by succinylcholine (alternative rocuronium).

Cholinergic Agonists

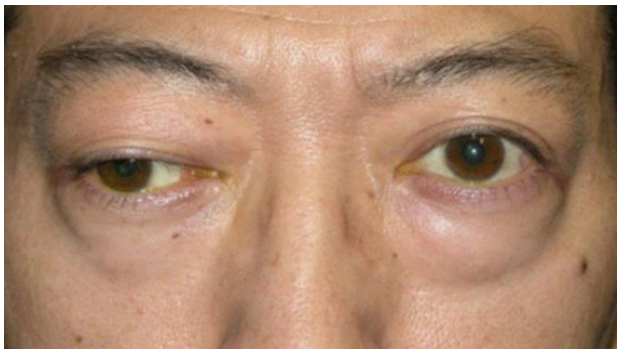
okay so next we will be discussing a separate group of drugs that are called **indirect cholinergic agonists** meaning that these drugs provide cholinergic activity but in an indirect way and these can be either reversible or reversible anti-colonoscopies agents

Myasthenia Gravis

◆ Rare, autoimmune disorder

◆ Autoantibodies directed against the muscle-nicotinic acetylcholine postsynaptic receptors specifically in the neuromuscular junction

◆ Fatigable muscle weakness that worsens with activity



◆ Ptosis(dropping of the eyelid because of weakness in the upper eyelid muscles)

◆sometimes Myasthenia Gravis can be severe enough to result in the paralysis of respiratory muscles and in this case the patient is at risk of respiratory failure and death

◆كيف بدنا نعالجه؟

بنعطي ادوية تزود ال ability Achداخل ال synapse

◆عنا نوعين من الادوية

-Direct agonist

بتشتغل عال R nicotinic بس ما حنحكي عنهم

-Indirect agonist

ما بتشتغل ع ال R بتثبط ال AchE الموجود في ال parasympatheticوganglia autonomic

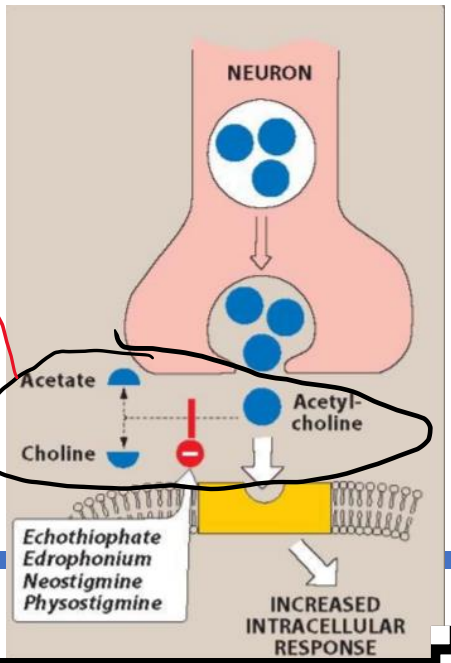
NMJو innervation فاله less specific effect .

Indirect-acting Cholinergic Agonists: Anticholinesterase Agents (Reversible)

• AChE cleaves ACh to acetate and choline
• Inhibition of AChE results in_____??

Increase Ach

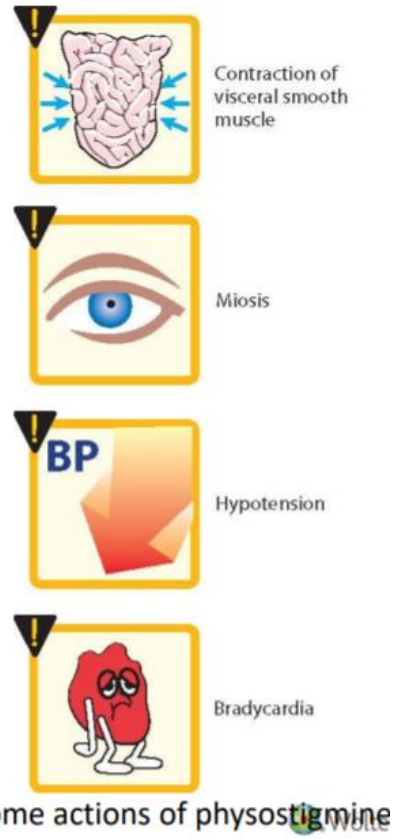
• Which receptors are affected?
• Anti-AChE agents are either short- or intermediate acting



Edrophonium

- Short-acting
- Reversibly binds to the active site of AChE - - - -» increase Ache
- Rapid onset: 1-2 minutes
- Short duration: 10-20 minutes
- Used in the diagnosis of myasthenia gravis (Tensilon test)
- Used to reverse the effects of NMJ blockers
- It's use is limited because it does not have therapeutic save profile
- Excess drug → cholinergic crisis (what is the antidote)?
- Cholinergic crisis means increase of Ach in gap junction and over stimulation
- The antidote is Atropine

Physostigmine



Some actions of physostigmine

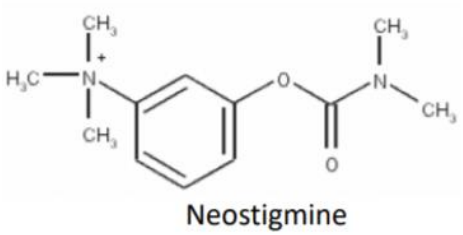
- Found naturally
- Substrate for AChE; forms stable intermediate with the enzyme (reversible)
- Stimulates nicotinic receptors both N and M
- Used in autonomic NS
- Benet rate BBB
- Very bulky
- Stimulate both muscarinic and nicotinic receptor in the ANS and peripherally
- Duration of action: 30 mins to 2 hours
- Used to increase intestinal/bladder motility (have parasympathetic effect)
- Used to treat atropine overdose (because atropine increase HR and Heart contractility)
- Possible adverse effects?
- Contraction of visceral sooth muscle • Bradycardia • Hypotension • Miosis
- Convulsion

Neostigmine

• Synthetic , very large drug

• Reversible AChE inhibitor

• Poorly absorbed from GI; does not cross BBB.
Which means? Its effect is peripheral



Neostigmine

• Similar duration of action as physostigmine

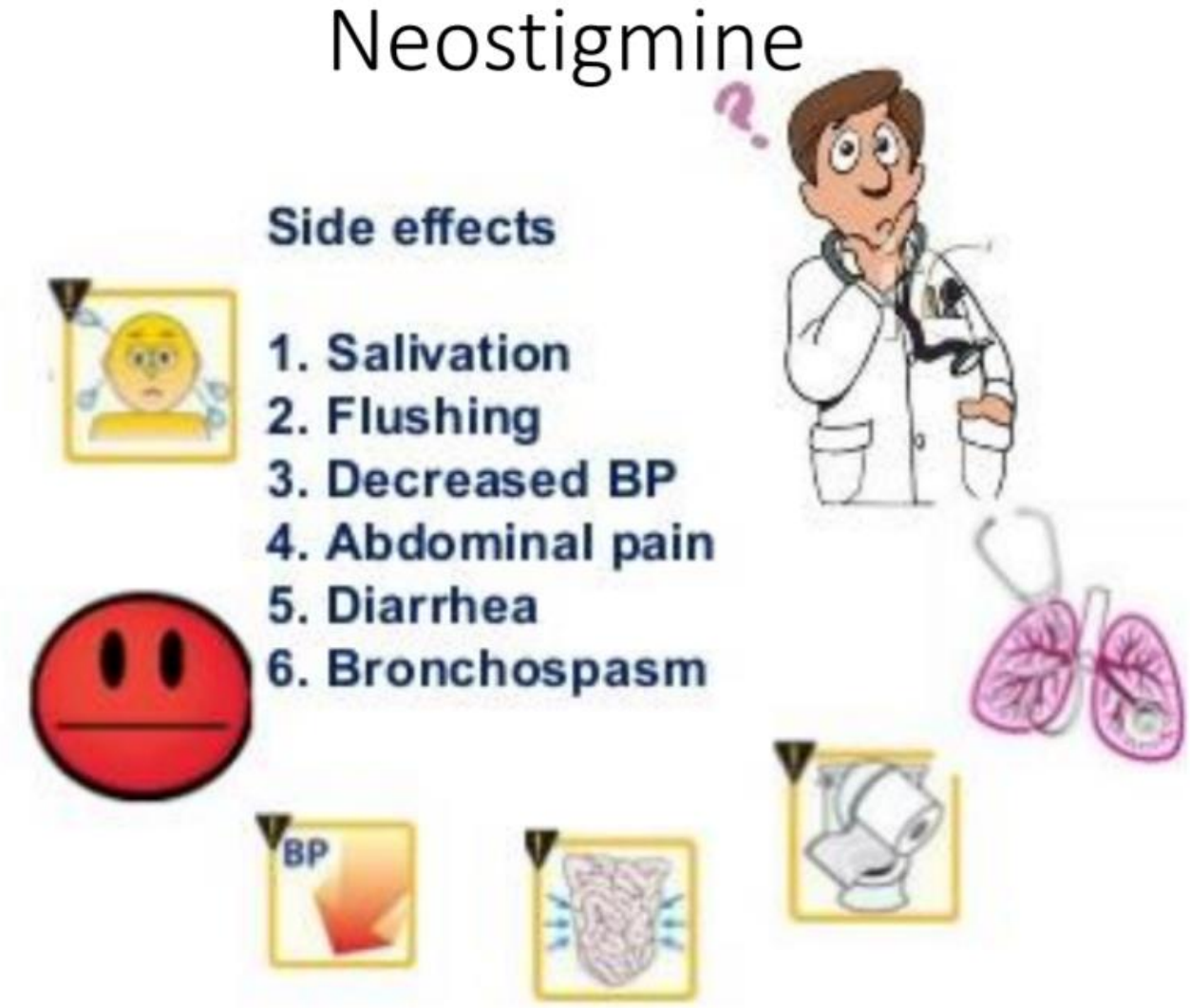
• Used to stimulate gut/bladder

• Used as antidote for NMJ blockers

• Used for myasthenia gravis

• Can you use neostigmine to treat atropine overdose?
it is not a good choice because it is poorly absorbed and does not cross BBB

•Parasympathetic like side effects



Pyridostigmine

• AChE inhibitor

• Used for the chronic management of myasthenia gravis

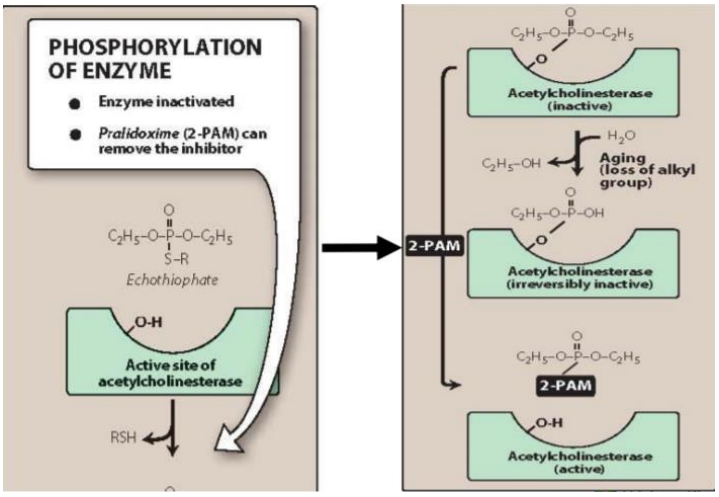
• Duration of action: intermediate 3 to 6 hours

• Is the best to treat chronic Myasthenia Gravis Because it has a longer duration than others and can be given less frequently

Indirect-acting Cholinergic Agonists: Anticholinesterase Agents (Irreversible)

• **Organophosphates**

• **Longer increase in junctional Ach**



Echothiophate

• Organophosphate

• Covalently binds a phosphate group at the active site of AChE

• Phosphorylated AChE releases one of its ethyl groups (aging)

• Impossible for chemical activators such as pralidoxime to break bond between drug and enzyme

• Uses: cholinergic activation, muscle paralysis, ophthalmic uses

MOA of this drug has 2 steps :

1st step is binding of drug via its phosphate group at the active side of AchE this causes phosphorylation of the enzyme and until now its reversibly inactivated that means if the drug pralidoxime cameto reverse the action if he drug it can work by breaking the phosphate bond

2nd step called aging ----» release of ethyl group from phosphorylated AchE right now the enzyme became irreversibly inhibited and thre drug pralidoxime cant work

How about some toxicology?

• Irreversible AChE inhibitors (organophosphates) are used as insecticides

• Possibility for accidental poisoning

• Suicide/homicide

• Warfare/chemical terrorism (nerve gas)

Reactivation Of Acetylcholinesterase

Pralidoxime

• reactivate inhibited AChE

• displaces the phosphate group of the organophosphate (e.g., echothiophate)and regenerates the enzyme

• Does not cross BBB. What does this mean?
That means it can only be used to reverse the action of the enzyme if it was in the reversiable stage and peripheral

• Would it overcome the toxicity of reversible AChE inhibitors?
Pharmacological antidote for oregano phosphate is Atropine because it's action on the receptor not the enzyme and can cross CNS.

QUESTION

A 44-year old male patient works as an ICU nurse at a university hospital. He was brought to the emergency room suffering from unconsciousness, muscle paralysis and severe apnea. The patient has a history of severe depression and previous suicidal attempts. After successful intubation the patient was further examined to determine the cause of his condition and his muscles were found to respond to direct electrical stimulation. Which of the following drugs might be useful to give this patient immediately?

<A>Atropine
<B>Neostigmine
<C>Succinylcholine
<D>Acetylcholine
<E>Rocuronium

ANSWER IS B

QUESTION

Which of the following scenarios will mostly attenuate the neuromuscular blockade of cisatracurium?

<A>If cisatracurium was administered with atropine simultaneously.
<B>If cisatracurium was administered after succinylcholine.
<C>If cisatracurium was administered with gentamicin simultaneously.
<D>If cisatracurium was administered with desflurane simultaneously.
<E>If cisatracurium was administered before physostigmine

ANSWER IS E

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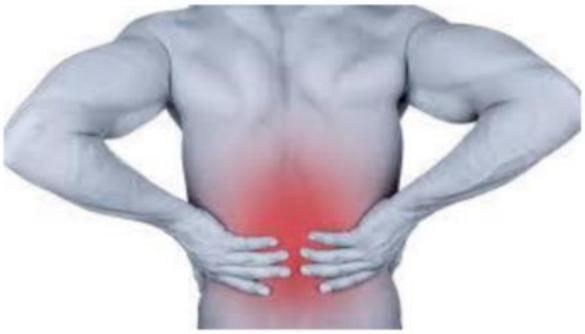
Skeletal Muscle Relaxants

Overview



• Low back pain is ranked amongst top causes of pain

• Mainstay of symptomatic treatment includes NSAIDs and acetaminophen (paracetamol)

• Skeletal muscle relaxants are an alternative

Subdivided into central which acts on brain and peripheral which used for pain associated with neuron disorders as multiple sclerosis

Muscle Relaxant Use

• Used more than expected

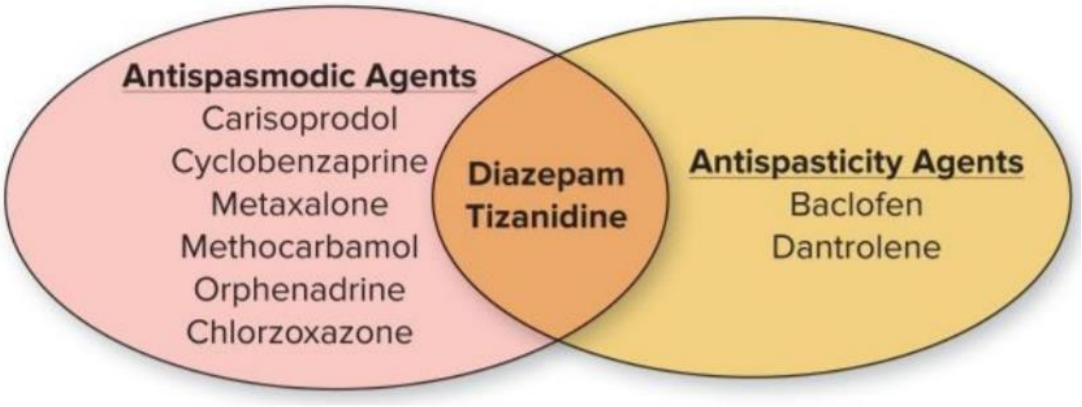
• 35% of patients use muscle relaxants for nonspecific back pain and of those, 18.5% use them as first-line

• Make up 45% of total prescription for musculoskeletal pain

• Conflicting evidence of their benefits and adverse effects

• Short-term vs. long-term use

Drug Classes



Central

- Act on CNS
- Not used interchangeably with antispasticity

Peripheral

- Act on Spinal chord/muscle
- Spasticity/rigidity
- CP, MS spine injuries

Baclofen

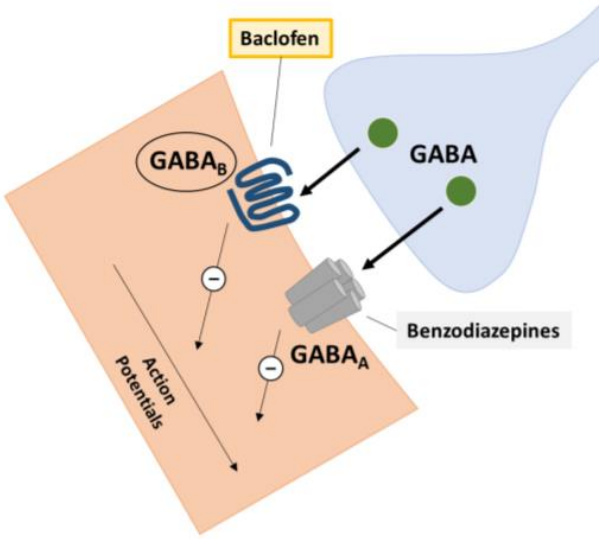
• Chemistry: structurally similar to γaminobutyric acid (GABA)

• MOA: GABAB agonist→ Inhibits transmission at spinal level → CNS depression

• Indications: MS, spinal chord lesions

• Kinetics: oral or intrathecal

• Adverse Effects: drowsiness, fatigue, nausea, dose adjustment in renal disease



Ach is a stimulatory neurotransmitter once it binds to post synaptic receptor it cause AP. But GABA is an inhibitory molecule binds to 2 receptors GABAa or GABAb

GABAa - - -» is a ligand gated ion channel, allows Cl- to go inside which lead to increase the negativity of the membrane and become difficult to be stimulated.

GABAb----» is a G-protein signalling pathway its effect is CNS depression.

Dantrolene

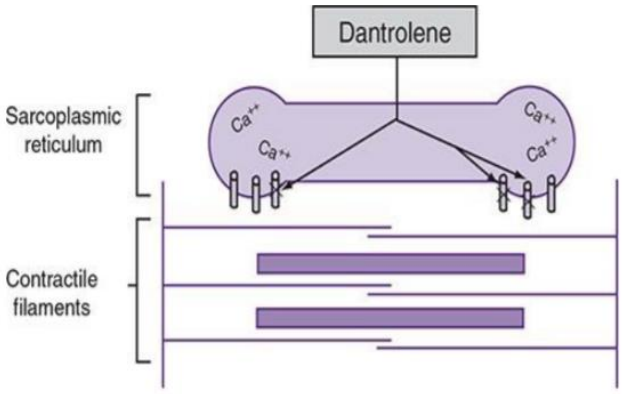
Anti Spasticity

• Chemistry: structurally related to phenytoin

• MOA: Inhibits Ca+2 release from sarcoplasmic reticulum in skeletal myocytes

• Indications: MS, CP, malignant hyperthermia

• Adverse Effects: risk of hepatotoxicity, not used for low back pain



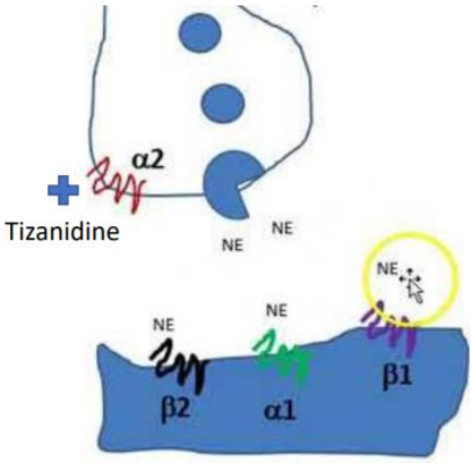
Tizanidine

• Chemistry: related to clonidine

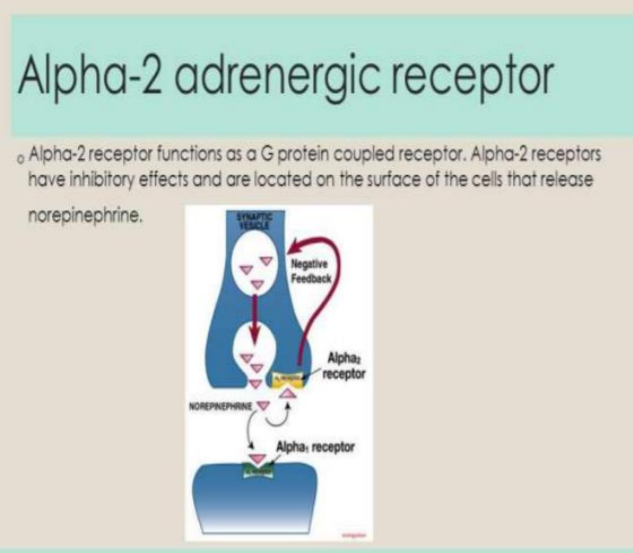
• MOA: α2 -adrenergic agonist→ presynaptic inhibition of motor neurons/excitatory interneurons

• Indications: MS, Spinal chord disease & hypertension

• Adverse Effects: dry mouth, somnolence, hypotension, avoid in hepatic impairment



Alfa 2 receptor is found on presynaptic membrane, it's function is to bound with excessive NE and decrease the production of neurotransmitters and decrease motor signalling



Orphenadrine

Antihistamines

• Chemistry: analog of diphenhydramine

• MOA: antimuscarinic (central atropine-like effects)

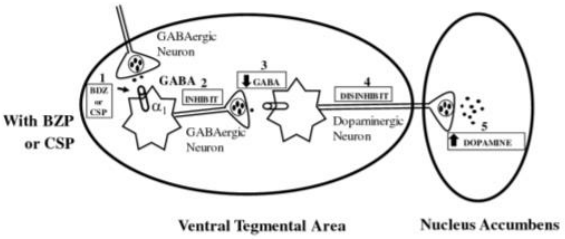
• Indications: muscle spasm, Parkinson's disease

• Adverse Effects: Dry mouth, urinary retention, blurred vision, mydriasis

Carisoprodol

• Chemistry: analog of diphenhydramine

• MOA: unknown. CNS depression?
By binding to GABA b

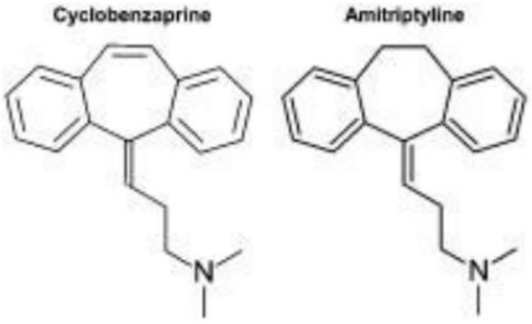


• Indications: acute treatment of musculoskeletal pain

• Adverse Effects: possible abuse potential (due to GABAA modulation)

Cyclobenzaprine

• Chemistry: similar to tricyclic antidepressants (TCA)



• MOA: reduces tonic somatic motor activity (alpha and gamma motor neurons), others similar to TCA

• Indications: acute treatment of musculoskeletal pain, muscle spasm

• Adverse Effects: drowsiness, dry mouth

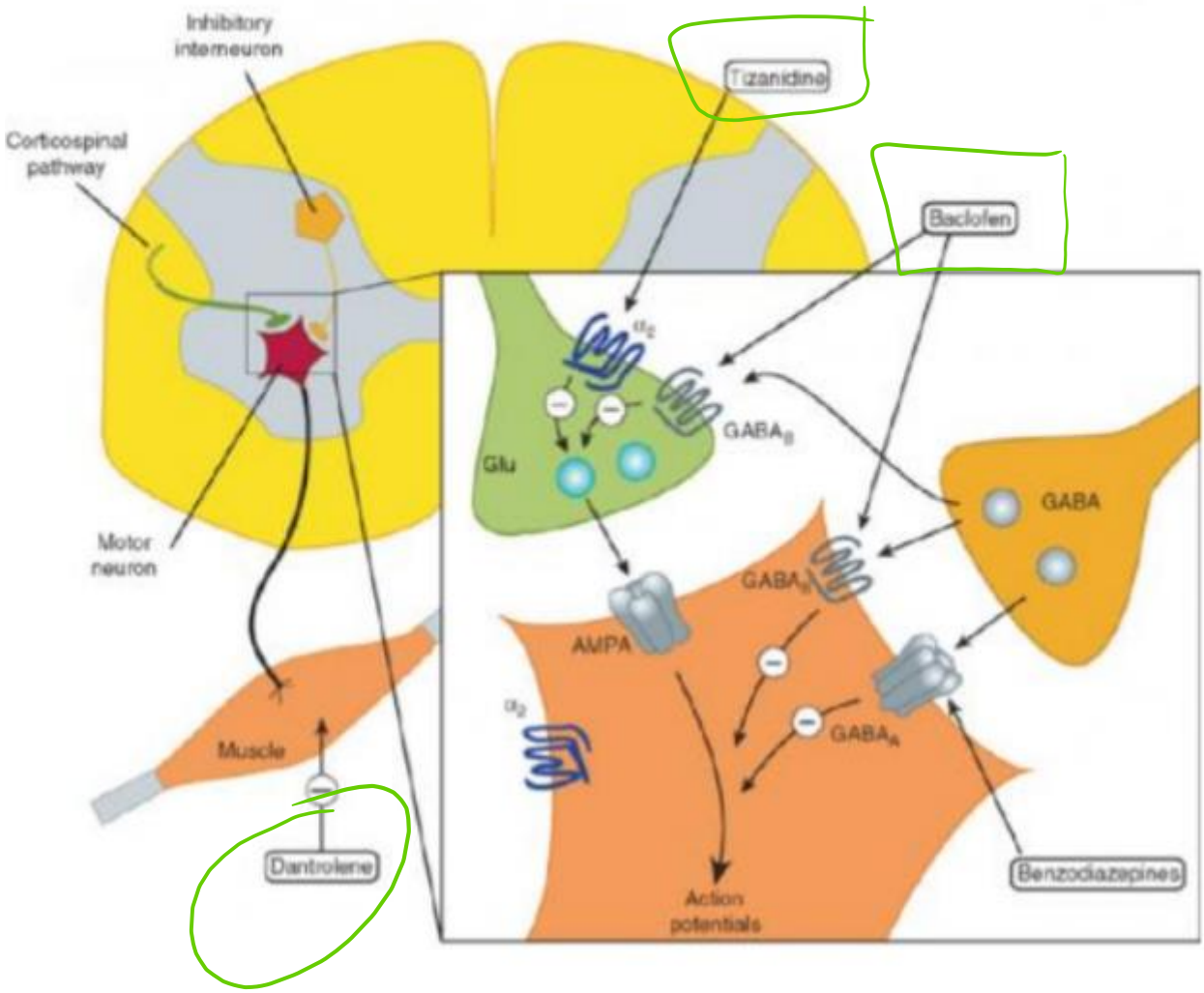
Metaxalone

• MOA: General CNS depression, sedation, no direct effect on muscles

• Indications: acute treatment of musculoskeletal pain, muscle spasm

• Adverse Effects: GI disturbance, nausea, vomiting, dizziness

Summary



THANK YOU

AND

GOOD LUCK