



- 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 4: INDIRECT ACTING CHOLINERGIC DRUGS

OBJECTIVES:

-By the end of this lecture student should be able to:

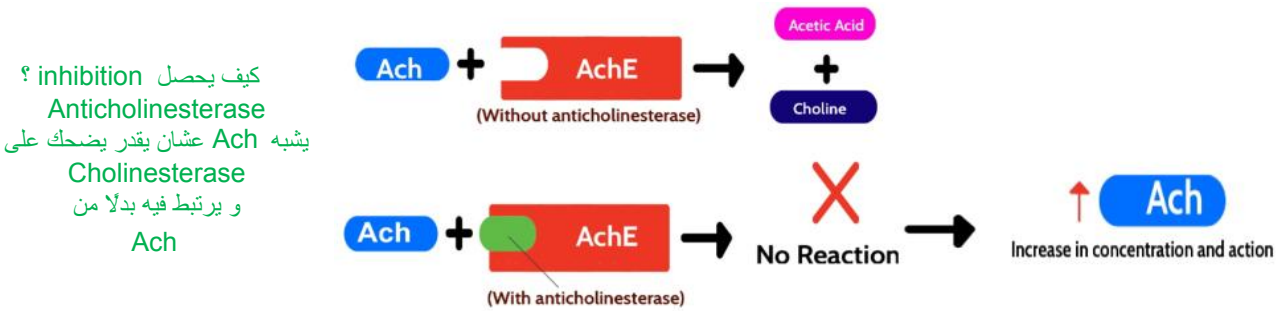
- ✓ Classification of indirect acting cholinomimetics
- ✓ Mechanism of action, kinetics, dynamics and uses of anticholinesterases
- ✓ Adverse effects & contraindications of anticholinesterases
- ✓ Symptoms and treatment of organophosphates toxicity.

Indirect cholinomimetics (Anticholinesterases)

Mechanism of action: prevent the hydrolysis of acetylcholine by inhibiting Acetylcholinesterase ; thus increasing acetylcholine concentration and action at the cholinergic receptors (both nicotinic and muscarinic).

Anticholinesterases are similar in structure to Ach to combine with cholinesterase enzyme (2 sites: Anionic **polar** and esteratic sites) instead of Ach.”

عنده يدين يد ترتبط بالجزء البولار من الاسيتايل كولين واليد الثانية بالجزء الاستر من الاسيتايل كولين



Classification of Anticholinesterases

According to the duration of action

Drug	Reversible 4-8 hours		Irreversible forever
	Alcohols	Carbamate esters	Phosphate esters
Duration	Short acting ليش؟ لان اذا جا يرتبط بالاستريز بيمسك بيد وحده البولار بينما يد الاستر بتصير فاضية لانه كحول	Intermediate Acting	Long acting
Binding with Ach esterase	Forms weak hydrogen (electrostatic) bond with acetylcholinesterase enzyme (Reversible)	binds to two sites of cholinesterase enzyme (covalent bond) (Reversible)	Form very stable covalent bond with cholinesterase, resistance to hydrolysis (Irreversible)
Examples	Edrophonium	Physostigmine neostigmine Pyridostigmine	e.g. insecticides, gas war e.g. Echothiophate & Isoflurophate. Very toxic drugs but they are the only exception used medically (topical eye drops)
Further features		All polar and synthetic EXCEPT physostigmine “lipid soluble “	All phosphates are lipid soluble EXCEPT Echothiophate which is polar . well absorbed from the skin.

Pharmacological effects of Anticholinesterases

- They act on both muscarinic and nicotinic receptors .
- Some have CNS effects (only the lipid soluble drugs) e.g. physostigmine & phosphate ester

CNS actions: [diffused activation of EEG](#) → [alerting response](#), excitation, convulsion, respiratory failure and coma.

	Site	Action
Nicotinic Actions	Neuromuscular junction	- Therapeutic dose : muscle contraction - Toxic dose : relaxation or paralysis of skeletal muscles. Depolarization
	Ganglia	stimulation of sympathetic and parasympathetic ganglia
	Adrenal medulla	release of catecholamines (adrenaline and noradrenaline)
Muscarinic Actions	Eye	-Contraction of circular muscle of iris (also called constrictor pupillae or iris sphincter muscles)(miosis) M3 -Contraction of ciliary muscles for near vision M3 - Decrease in intraocular pressure
	Heart endothelium	-bradycardia (decrease heart rate) M2 -Release of NO (EDRF) EDRF: Endothelium-derived Relaxing Factor NO: Nitric Oxide
	Lung	- Constriction of bronchial smooth muscles. - Increase bronchial secretion M3
	GIT	-Increased motility (peristalsis) -Increased secretion -Relaxation of sphincter M3
	Urinary bladder	-Contraction of muscles -Relaxation of sphincter M3
	Exocrine glands	-Increase in secretion of sweat, saliva, lacrimal, bronchial, intestinal secretions M3

Reversible indirect Cholinergic Drugs

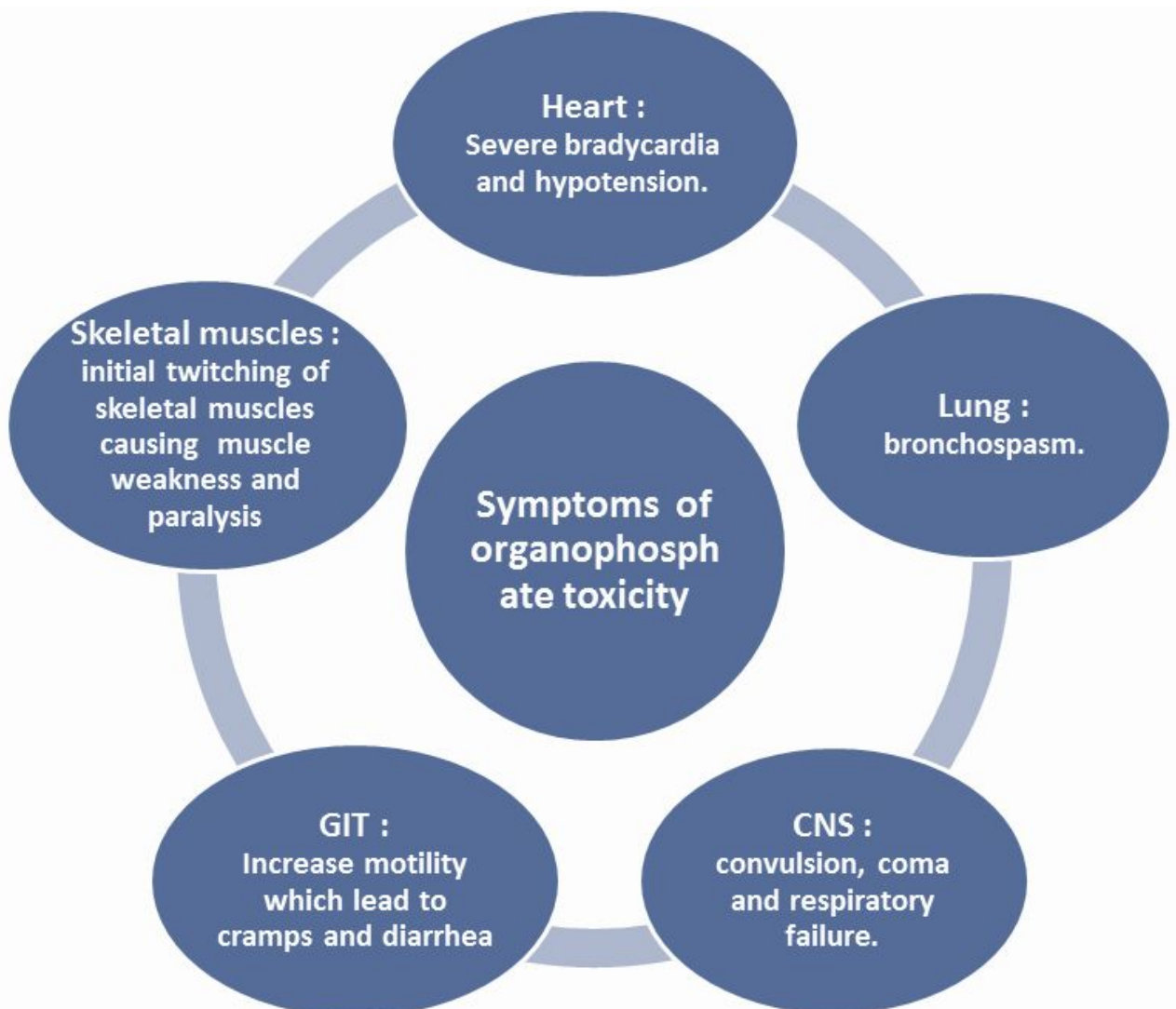
Drug	Actions	Pharmacokinetics	Uses	Chemical structure
Edrophonium	muscarinic and nicotinic actions	<ul style="list-style-type: none"> -NOT absorbed orally must be given by injection. -polar (alcohol). -Very short duration of Action(5-15 mins) - Esters prolong the effect of the drug. 	<ul style="list-style-type: none"> -Used to diagnose myasthenia gravis) -Used to assess the adequacy (كفاءة) of longer acting cholinesterase inhibitors (not used for treatment) 	Quaternary
Physostigmine	<ul style="list-style-type: none"> -Muscarinic and nicotinic action -has CNS effects 	<ul style="list-style-type: none"> -Good oral absorption -non polar (lipid soluble). -short duration of action(0.5-2 hrs) -Cross BBB (has CNS effects) 	<ul style="list-style-type: none"> -Glaucoma. -Atropine toxicity (anticholinergic drug) (Atropine can cross BBB therefore we use Physostigmine which also can cross BBB to block the muscarinic receptor in the brain resulting in treating the toxicity) 	Tertiary ammonium compound
Neostigmine	<ul style="list-style-type: none"> muscarinic & nicotinic actions (prominent on GIT & urinary tract) (has a very similar uses to bethanechol, a direct cholinergic agonist which is prominent on GIT and UT) 	<ul style="list-style-type: none"> -Can be used orally -polar compound -short duration of action(0.5-2 hr) - NO CNS effect. 	<ul style="list-style-type: none"> -Treatment of myasthenia gravis. -Paralytic ileus & Urinary retention. (bethanechol provides same effect) -Competitive neuromuscular blockers intoxication (curare toxicity) مثال: لو اعطينا دواء يقفل الريسبتور مثل Atracurium، وحصلت تنسم كيف أعالجه؟ ازيد Ach عند الريسبتور عبر anticholinesterase والأفضل هو Neostigmine 	Quaternary ammonium compound
Pyridostigmine	Nicotinic & muscarinic	<ul style="list-style-type: none"> -Polar -short duration of action (3-6 hr) 	Treatment of myasthenia gravis.	Quaternary
Ambenonium	Nicotinic & muscarinic	<ul style="list-style-type: none"> -Polar -short duration of action (4-8 hr) 	Treatment of myasthenia gravis.	Quaternary
Donepezil	Is a centrally acting reversible acetyl cholinesterase inhibitor M4, M5	<ul style="list-style-type: none"> -Given orally -Lipid soluble 	Treatment of dementia of Alzheimer's disease	-

Irreversible Indirect Drugs

Drug	Actions	Pharmacokinetics	Uses
(Organophosphorous compounds) ex : Ecothiophate "Organic = lipid soluble"	<ul style="list-style-type: none"> •Irreversible anticholinestrases •Bind to cholinesterase by strong covalent bond. 	<ul style="list-style-type: none"> •very long duration of action (100 hours). •Aging makes the bond extremely stable and makes the treatment difficult from toxicity. •All the Organo-phosphorous compounds are highly lipid soluble EXCEPT Ecothiophate (polar). 	<ul style="list-style-type: none"> •Used for glaucoma. •Used as pesticides and veterinary vermifuge.

- Aging: long time exposure to Organophosphates makes the covalent bond between the drug and the enzyme stronger.
- Used rarely due to adverse effects but used safely in glaucoma because it has local effect when applied by eye drop.

organophosphate toxicity **"important"**



Treatment of organophosphate toxicity

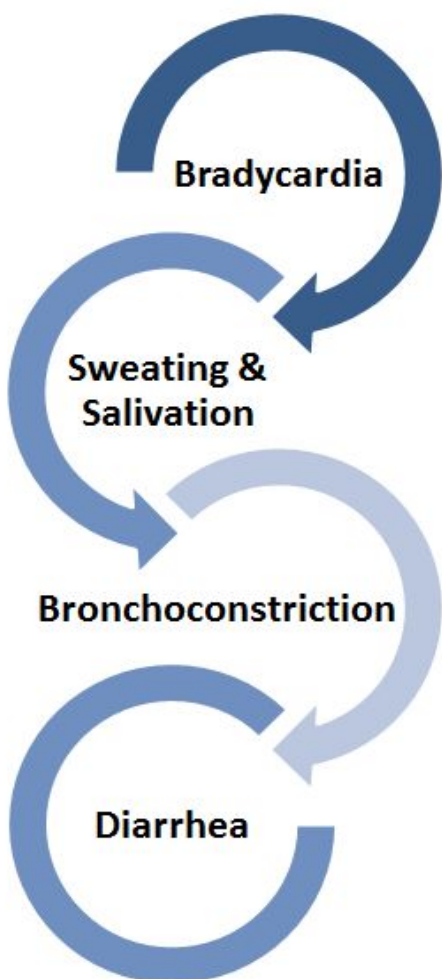
Support respiration.

Cholinesterase reactivators (Oximes).

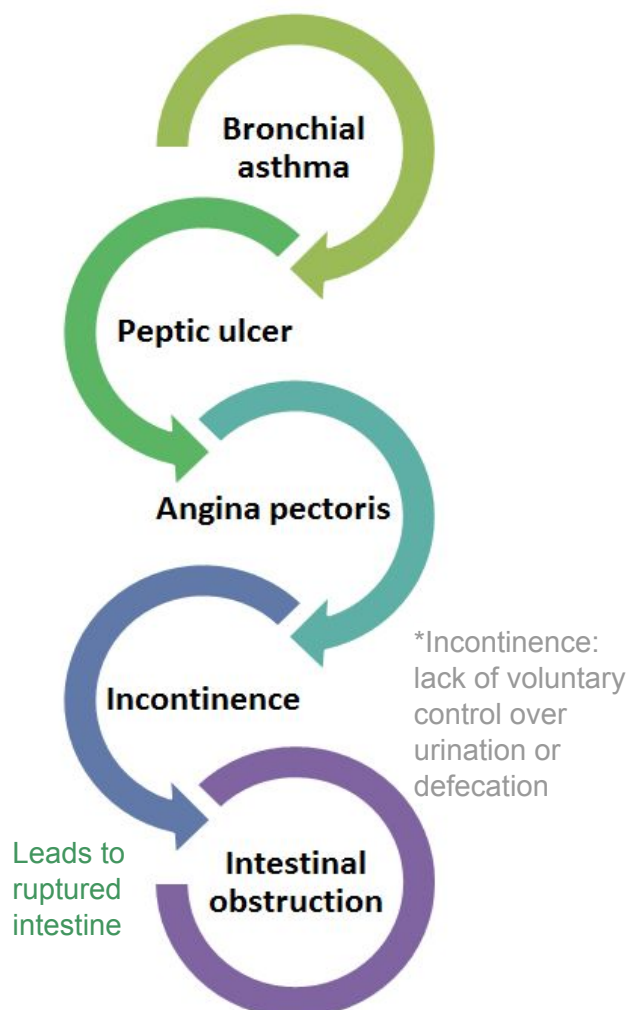
Atropine (to block muscarinic action and CNS effect).

Drug	Actions	Uses
Cholinesterase Reactivators (Oximes) ex : Pralidoxime (PAM)	<ul style="list-style-type: none"> •Cholinesterase reactivator. •Acts by regeneration of cholinesterase enzyme. •Reactivates recently inhibited enzymes before aging. 	<ul style="list-style-type: none"> • (I.V) over 15-30 min for organophosphate intoxication.

Adverse effects of cholinergic drugs:



Contraindication of cholinergic drugs:



Summary of cholinomimetics and their uses

***Important**

Eye : treatment of glaucoma

- **pilocarpine** (direct muscarinic agonist)
- **physostigmine** - ecothiophate (indirect cholinomimetics)

Urinary retention and paralytic lieus

- **bethanechol** (direct)
- **neostigmine** (indirect)

Myasthenia gravis (only indirect cholinomimetics)

- **pyridostigmine , neostigmine , ambenonium**

Xerostomia

- **pilocarpine**
- **cevimeline** (sjogren's syndrome)

Alzheimer disease

- **donepezil**

QUIZ

MCQ's

Q1: Which one of these drugs have an irreversible binding with cholinesterase enzyme :

A-edrophonium

B-Neostigmine

C-isofluorophate

D-Donepezil

Q2: which one of these drugs used as treatment of myasthenia gravis :

A-edrophonium

B-Neostigmine

C-isofluorophate

D-Donepezil

Q3: which one of the following is side effects of cholinergic drugs :

A-Bronchial asthma

B-Incontinence

C-salivation

D-coma

Q4: which one of the following is Pharmacokinetics feature of Ecothiophate :

A-Polar

B-Short duration of Action

C-Cross BBB

D-well absorbed

5-All anticholinesterases have :

A)Nicotinic action.

B)Muscarinic action.

C)Both nicotinic and muscarinic action.

D) α_1 & α_2 action.

Answers:

MCQ,s : 1/C , 2/B , 3/C , 4/C

QUIZ

SAQ

Q1-describe the mechanism of action of indirect acting Cholinergic drugs.

Q2-list 2 ways to treat organophosphate toxicity.

Q3:Mention three reversible indirect parasympathomimetics :

Q4:What are the pharmacological actions of nicotinic receptors in skeletal muscles ?

Answers:

SAQ : 1/slide 3 , 2/slide 7



GOOD LUCK

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Sources:

Team 435

Team 437