



Editing File

Indirect acting cholinergic drugs

Objectives:

- ✓ 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

❖ Also called Anticholinesterases
 Anticholinesterases prevent hydrolysis of Ach by **inhibiting acetyl cholinesterase** thus, increase Ach concentrations and actions at the cholinergic receptors (**both nicotinic and muscarinic**).
 Acetylcholine binds to **acetylcholinesterase** at two sites, **anionic site and esteric site**, then the enzyme somehow breakdown the acetylcholine into acetic acid and choline.
 In order to inhibit this enzyme we need to create a substance that is **similar to acetylcholine either in both sites or even one site. (Similar structure)**

M.O.A

Reversible anticholinesterases			Irreversible anticholinesterases
Duration of action	Short Acting	Intermediate acting	Long Acting
Drugs	(Alcohols) e.g. edrophonium.	(Carbamates esters) e.g. Physostigmine, Neostigmine, Pyridostigmine.	(Phosphates esters) e.g. insecticides, gas war e.g. Ecothiopate & Isoflurophate. Using those drugs leads to death
Features	Forms weak hydrogen bond with acetylcholinesterase enzyme	Binds to two sites of cholinesterase enzyme. All polar and synthetic except physostigmine.	used as insecticides(malathion) or nerve gases (sarin) . Form very stable covalent bond with cholinesterase . All phosphates are lipid soluble except Ecothiopate which is polar

Pharmacological actions

- They act on both Muscarinic and nicotinic receptors.
- Some has CNS effect **“only the lipid soluble drugs”**

CNS actions:
 (excitation leads to convulsion leads to respiratory failure leads to coma).
 e.g. physostigmine & phosphate ester

✓ Revise the nicotinic and muscarinic actions from (Direct Acting) lecture, it is the same!

Reversible indirect drugs:

Drug	Edrophonium	Neostigmine	Physostigmine
MOA	<ul style="list-style-type: none"> Reversible anticholinesterase and forms weak hydrogen bonds. 	<ul style="list-style-type: none"> Reversible anticholinesterase Has muscarinic & nicotinic actions (prominent on GIT & urinary tract) Special action 	<ul style="list-style-type: none"> Reversible anticholinesterase. Has muscarinic, nicotinic action
P.K	<ul style="list-style-type: none"> NOT absorbed orally, given by injection. Bc its polar Alcohol (ionic bonds, not esters), so its polar Short duration of action (5-15 mins) Esters prolong the effect of the drug 	<ul style="list-style-type: none"> Can be used orally Quaternary ammonium comp. Polar compound No CNS effect 	<ul style="list-style-type: none"> Good oral absorption. Tertiary ammonium compound. Non polar. Good lipid solubility. Cross BBB (has CNS effects)
Uses	<ul style="list-style-type: none"> Used only for the diagnosis of myasthenia gravis due to its limited duration of action. Used to differentiate between Cholinergic crisis and Myasthenia Gravis because the drug will make the crisis worse. 	<ul style="list-style-type: none"> Treatment of myasthenia gravis. Longer duration Paralytic ileus & Urinary retention. Competitive neuromuscular blockers intoxication by increasing the level of Ach. Thus prevent the action of NMBs (Neuromuscular Blocking Agents) 	<ul style="list-style-type: none"> Glaucoma. Atropine toxicity (atropine is anticholinergic drug) <ul style="list-style-type: none"> used in atropine toxicity because atropine has an effect on the CNS. Thus, we need a drug that can clean up atropine from all over the body Not used with Myasthenia Gravis because it was not used on MS patients before
Mnemonic	<ul style="list-style-type: none"> Eyelid drop (E) Drop honium Myasthenia gravis 	-	-

Cont. of reversible drugs

Drugs	Donepezil
M.O.A	<ul style="list-style-type: none">Is a centrally acting reversible acetyl cholinesterase inhibitor. M4, M5
P.K	<ul style="list-style-type: none">Given orally
Uses	<ul style="list-style-type: none">Used for treatment of dementia of Alzheimer's disease

Irreversible indirect drugs:

Drug	Ecothiophate (Organophosphorous compound)
M.O.A	<ul style="list-style-type: none">Irreversible anticholinesteraseBinds to cholinesterase by strong covalent bond
P.K	<ul style="list-style-type: none">Have very long duration of actionAging make bond extremely stable and make treatment difficult from toxicityAll are highly lipid soluble except Ecothiophate
Uses	<ul style="list-style-type: none">Used for glaucoma

Cont. of irreversible drugs

Organo phosphate toxicity	Symptoms of organophosphate toxicity	
	Heart : Severe bradycardia and hypotension.	Lung : bronchospasm
	GIT : Increase motility which lead to cramps and diarrhea	CNS : CNS effects convulsion , coma and respiratory failure
	Skeletal muscles : initial twitching of skeletal muscles causing muscle weakness and paralysis.	
	Treatment of organophosphate toxicity	
	<ul style="list-style-type: none"> • Support respiration • Cholinesterase reactivators (Oximes) • Atropine (to block muscarinic action and CNS effect) • Immediate treatment because delaying makes the bonds more stable 	
	Cholinesterase Reactivators (Oximes)	
	Drug	Pralidoxime (PAM)
	M.O.A	<ul style="list-style-type: none"> • Cholinesterase reactivator • Acts by regeneration of cholinesterase enzyme • Reactivates recently inhibited enzymes before aging
	Uses	✓ I.V over 15-30 min for organophosphate intoxication.

Side effects of Cholinergic drugs:

Those ADRs are of both **INDIRECT** and **DIRECT** acting drugs:

- ❖ Bradycardia
- ❖ Sweating & Salivation
- ❖ Bronchoconstriction
- ❖ Diarrhea

Summary

Uses of some Cholinergic drugs:

Eye:

Treatment of glaucoma

- Pilocarpine (direct muscarinic agonist)
- Physostigmine
- Ecothiophate (indirect cholinomimetics)

Urinary retention and paralytic ileus:

- Bethanechol (direct)
- Neostigmine (indirect)

Myasthenia gravis (only indirect cholinomimetics):

- Pyridostigmine, Neostigmine, Ambenonium

Xerostomia:

- Pilocarpine – Cevimeline (Sjogren's syndrome)

Alzheimer's disease:

- Donepezil. (**Dementia of Alzheimer's disease**)

Drugs	Chemical structure	Actions	Administration	Kinetics	Uses
Neostigmine	Quaternary ammonium compound	Nicotinic muscarinic M, N	Can be used orally	-0.5-2hr -polar	<ul style="list-style-type: none"> •Myasthenia gravis treatment •Paralytic ileus •Urinary retention •Curare toxicity
Physostigmine	Tertiary ammonium compound	Nicotinic muscarinic M, N, CNS	Good oral absorption, can be used topically in the eye	-0.5-2hr -nonpolar (lipid soluble)	<ul style="list-style-type: none"> •Glaucoma •Atropine toxicity
Pyridostigmine	Quaternary	Nicotinic muscarinic M, N	-	-3-6hr -polar	<ul style="list-style-type: none"> • Myasthenia gravis treatment
Ambenonium	Quaternary	Nicotinic muscarinic M, N	-	-4-8hr -polar	<ul style="list-style-type: none"> •Myasthenia gravis treatment
Edrophonium	Quaternary (Attach mainly to acetyl cholinesterase by weak hydrogen bond.)	Nicotinic muscarinic M, N	injection	-5-15 min -Polar	<ul style="list-style-type: none"> •Diagnosis of Myasthenia gravis, not for the treatment.

Questions

MCQs:

1- which one of the following is lipid soluble

- A) Neostigmine.
- B) Physostigmine.
- C) Donepezil.
- D) Ecothiophate.

2-which one of the following has the shortest duration of action

- A) Ambenonium.
- B) Ecothiophate.
- C) Edrophonium.
- D) Neostigmine.

3-Which of the following is an anticholinesterase drug that has an effect on the CNS?

- A) Pyridostigmine.
- B) Isoflurophate.
- C) Physostigmine.
- D) Ambenonium.

4-Which of the following drugs is used in the diagnosis of Myasthenia gravis?

- A) Edrophonium.
- B) Ambenonium.
- C) Neostigmine.
- D) pyridostigmine.

5-All anticholinesterases have :

- A) Nicotinic action.
- B) Muscarinic action.
- C) Both nicotinic and muscarinic action.
- D) $\alpha 1$ & $\alpha 2$ action.

Answers:

- 1-B
- 2-C
- 3-C
- 4-A
- 5-C

Cont..

SAQ:

1)What's the function of indirect cholinergic drugs?

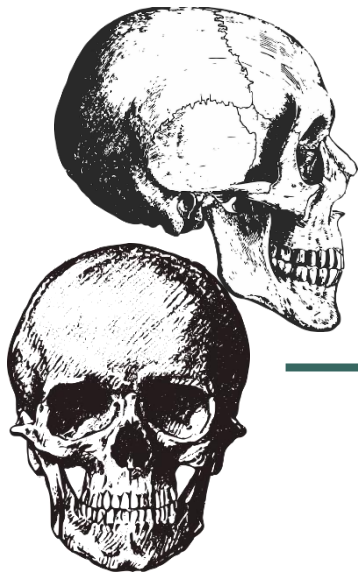
prevent hydrolysis of Ach by inhibiting acetyl cholinesterase thus increase Ach concentrations and actions at the cholinergic receptors (both nicotinic and muscarinic).

2)What is the Drug used in treatment of dementia of Alzheimer's disease?

Donepezil.

3)How the endrophonium inhibit the acetyl cholinesterase?

By attach to acetyl cholinesterase by weak hydrogen bond.



“It is not hard, you just made it to the end!”

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- ✓ Doctors' notes and slides

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