



Cholinergic Drugs (Cholinomimetics)

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1

Cholinergic Drugs

Acetylcholine is a widespread chemo transmitter in the body, mediating broad range of physiological effects acting via two distinct classes of receptors for acetylcholine defined on the basis of their preferential activation by alkaloids, nicotine (from tobacco) and muscarine (from *Amanita muscaria*)

Cholinergic drugs (acetylcholine agonists) mimic acetylcholine at all sites with variable nicotinic and muscarinic effects.

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2

Cholinergic Drugs

These drugs act on postsynaptic acetylcholine receptors (cholinoceptors) at all the sites in the body where acetylcholine is the effective neurotransmitter.

They initially stimulate and later block transmission.

They act on non innervated receptors that relax vascular smooth muscle in peripheral blood vessels.

Classification

Direct-acting (receptor agonists)

- Choline Esters: Acetylcholine-natural, Methcholine, Carbachol and Bethanechol – synthetic.
- Alkaloids: Pilocarpine, muscarine, arecholine.
- Synthetic: Oxotremorine

Classification

Indirect-acting

- **Cholinesterase inhibitors or reversible anticholinesterases:** Physostigmine – natural, neostigmine, pyridostigmine, distigmine, rivastigmine, donepezil, gallantamine, edrophonium, ambenonium, demecarium – synthetic.
- **Irreversible anticholinesterases:** Organophosphorous compounds and carbamates.

Irreversible anticholinesterases

Organophosphorous Compounds (OPC)

- ❖ Diisopropyl fluorophosphate (DFP)
- ❖ Ecothiophate
- ❖ Parathion, malathion, diazinon (insecticides and pesticides)
- ❖ Tabun, sarin, soman (nerve gases in war)

Carbamate Esters (insecticides & pesticides)

- ❖ Carbaryl.
- ❖ Propoxur.

Site of Action of Acetylcholine

- **Autonomic Nervous System**
 - 1) Parasympathetic division: ganglia and all postganglionic endings.
 - 2) Sympathetic division: ganglia and sweat glands.
- Neuromuscular junction
- Central nervous system
- Noninnervated blood vessels: arterioles.
- Placenta and ciliated epithelial cells (autacoid)

PILOCARPINE

- Alkaloid from leaves of *Pilocarpus microphyllus*.
- Prominent muscarinic actions.
- Profuse salivation, lacrimation, sweating.
- Dilates blood vessels, causes hypotension.
- On Eyes it produces miosis and spasm of accommodation.
- Lowers intraocular pressure (IOP) in Glaucoma when applied as eye drops.
- Too toxic for systemic use.

Pilocarpine

- Used as eye drops in treatment of narrow angle and wide angle glaucoma to reduce IOP.
- Used to reverse mydriatic effect of atropine.
- To break adhesion between iris and cornea/lens alternated with mydriatic.
- Pilocarpine nitrate eye drops (1 to 4%).
- CNS toxicity after systemic use.
- Atropine used as antidote in acute pilocarpine poisoning (1-2 mg IV 8hrly).

MUSCARINE

- Alkaloid from mushroom Amanita muscaria.
- Only muscarinic actions.
- No clinical use.
- Cause mushroom poisoning due to ingestion of poisonous mushroom.
 - = Early onset mushroom poisoning.
 - = Late onset mushroom poisoning (neurogenic).

Early Onset Mushroom Poisoning

- ❖ Occurs ½ to 1 hour.
- ❖ *A. muscaria* cause mild cholinergic symptoms like nausea, vomiting, salivation, lacrimation, headache, bronchospasm, diarrhoea.
- ❖ Antidote is Atropine sulphate (0.5-1 mg IM twice daily)
- ❖ *Inocybe* or *Clitocybe* – severe cholinergic symptoms like bradycardia, dyspnoea, hypotension, weakness, cardiovascular collapse, convulsions and coma.
- ❖ Antidote is Atropine sulphate (2-3 mg IM hrly till improvement)

Late Onset Mushroom Poisoning

- Occurs within 6-15 hours.
- *Amanita phalloides* – irritability, restlessness, nausea, vomiting, ataxia, hallucination, delirium, sedation, drowsiness and sleep.
- Maintain blood pressure, respiration.
- Inj. Diazepam 5 mg IM
- Atropine contraindicated as it may cause convulsions and death.
- Gastric lavage and activated charcoal.

Reversible Anticholinesterases

Drugs that inhibit **cholinesterase** which destroys acetylcholine. They act indirectly through acetylcholine on cholinergic receptors at different sites. Duration of action is longer. They cause accumulation of acetylcholine by preventing its destruction.

Mechanism of Action

Physostigmine and neostigmine bind with cholinesterase at two sites – anionic and esteratic forming carbamylated cholinesterase which undergoes slow hydrolysis to form carbamate, choline and cholinesterase.

Physostigmine

- Alkaloid from dried ripe seed (Calabar bean) of African plant *Physostigma venenosum*.
- Tertiary amine, lipid soluble, well absorbed orally and crosses BBB.
- Hydrolyzed in liver and plasma by esterases.
- Long lasting action (4-8 hours).
- Reversible anticholinesterase drug.
- It indirectly prevents destruction of acetylcholine released from cholinergic nerve endings and causes ACh accumulation.

...Physostigmine

- Muscarinic action on eye causing miosis and spasm of accommodation on local application.
- Antagonises mydriasis and cycloplegia produced by atropine and anticholinergic drugs.
- Salivation, lacrimation, sweating and increased tracheobronchial secretions.
- Increased heart rate & causes hypotension.

Clinical Uses and ADRs

- Used as miotic drops to decrease IOP in Glaucoma.
- To antagonise mydriatic effect of atropine.
- To break adhesions between iris and cornea alternating with mydriatic drops.
- Belladonna poisoning, TCAs & Phenothiazine poisoning.
- Alzheimer's disease- pre-senile or senile dementia.
- Atropine is antidote in physostigmine poisoning.
- ADRs – CNS stimulation followed by depression.

Neostigmine

- Synthetic reversible anticholinesterase drug.
- Quaternary ammonium compound and lipid soluble.
- Cannot cross BBB.
- Hydrolysed by esterases in liver & plasma.
- Short duration of action (3-5 hours).
- Direct action on nicotinic (N_M) receptors present in neuromuscular junction (motor end plate) of skeletal muscle.

...Neostigmine

- Antagonises (reverses) skeletal muscle relaxation (paralysis) caused by tubocurarine and other competitive neuromuscular blockers.
- Stimulates autonomic ganglia in small doses.
- Large doses block ganglionic transmission.
- No CNS effects.

Clinical Uses and ADRs

- Used in the treatment of **Myasthenia Gravis** to increase muscle strength.
- Post-operative reversal of neuromuscular blockade.
- Post-operative complications – gastric atony, paralytic ileus, urinary bladder atony.
- Cobra snake bite.
- Produces twitchings & fasciculations of muscles leading to weakness .
- Atropine is the antidote in acute neostigmine poisoning.

Uses of Cholinergic Drugs

- ❖ **Myasthenia gravis:** Edrophonium to diagnose and Neostigmine, Pyridostigmine & Distigmine to treat.
- ❖ **To stimulate bladder & bowel after surgery:** Bethanechol, Carbachol, Distigmine.
- ❖ **To lower IOP in chronic simple glaucoma:** Pilocarpine, Physostigmine.
- ❖ **To improve cognitive function in Alzheimer's disease:** Rivastigmine, Gallantamine, Donepezil.
- ❖ **Physostigmine in Belladonna poisoning.**

THANK YOU