

Indirect acting cholinomimetics

Dr. Saed M Al-daiaen

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Mutah University

Cholinesterase enzymes

- ❖ CE is a protein
 - In cholinergic synapses & RBC
 - Metabolizes Ach into choline & acetate
 - Specific for Ach in cholinergic synapses
- ❖ Pseudocholinesterase in plasma & liver
 - Not specific to Ach
 - Metabolizes other drugs (suxamethonium, procaine)

Classification of indirect-acting cholinomimetics

Classified into:

- ❖ Reversible cholinesterase inhibitors
- ❖ Irreversible cholinesterase inhibitors

Uses of indirect-acting cholinomimetics

- ❖ Diagnosis of MG (Edrophonium)
- ❖ Treatment of MG (Pyridostigmine)
- ❖ Reversible NMB intoxication (Neostigmine)
- ❖ Alzheimer's disease (Donepezil)
- ❖ Irreversible CEI: insecticides

Myasthenia gravis (MG)

- ❖ Autoimmune (autoantibodies to N_M in NMJ)
- ❖ Reduction in receptor number
- ❖ Muscle weakness, fatigability, Ptosis, diplopia, difficult speaking & swallowing
- ❖ Treatment:
 - Reversible CEI
 - Thymectomy
 - Immunosuppressant (CS, cyclosporine)





Reversible ChE inhibitors

- ❖ Inhibit reversibly CE enzyme
- ❖ Accumulation of Ach
- ❖ Electrostatic bonds
- ❖ Stimulate nicotinic & muscarinic receptors
- ❖ Useful in myasthenia gravis

Neostigmine

- ❖ Synthetic CEI, does not cross BBB
- ❖ Duration of action (4 hrs)
- ❖ Mainly in MG & also in:
 - Antidote to competitive NM blocker tubocurarine poisoning
 - Paralytic ileus, urinary retention
- ❖ Given orally, SC

Physostigmine

- Tertiary amine alkaloid.
- Lipid soluble
- well absorbed orally.
- Cross CNS and cornea.
Predominant effect on the Muscarinic receptors ,autonomic ganglia and CNS

Neostigmine

- Quaternary ammonium compound.
- Poorly absorbed orally
- doesn't cross CNS.
- Predominant effect on the skeletal muscles (direct & indirect action).

Pyridostigmine

- ❖ Similar to neostigmine
- ❖ Has longer duration of action (6 hrs)
- ❖ Useful orally in myasthenia gravis

Edrophonium

- ❖ Similar to neostigmine
- ❖ IV, short duration of action (10-20 min)
- ❖ Useful in diagnosis of MG
- ❖ To differentiate between weakness due to myasthenic crisis or cholinergic crisis:
 - Myasthenic crisis → improvement
 - Cholinergic crisis → aggravated

Adverse effects of CEI

- ❖ Excessive salivation
- ❖ Flushing and hypotension
- ❖ Abdominal colic and diarrhoea
- ❖ Bronchospasm

CEI useful in Alzheimer's disease

❖ Tacrine

- Reversible CEI used in treatment of Alzheimer's disease; hepatotoxic

❖ Donepezil

- New selective CEI
- Once daily
- Lacks hepatotoxicity of tacrine
- Useful in Alzheimer's disease

Irreversible CE Inhibitors

- ❖ Organophosphorous compounds
- ❖ Irreversibly inhibit CE
- ❖ Covalent bond in Enzyme-inhibitor complex
- ❖ Used as insecticides:
 - Parathion, malathion
- ❖ As nerve gases in chemical warfare:
 - Tabun, Sarin, Soman

Isoflurophate (DFP)

- ❖ OP compound
- ❖ Irreversibly inhibits CE
- ❖ Insecticide
- ❖ Toxicity: excessive cholinergic stimulation
- ❖ May be used topically in glaucoma
- ❖ Duration of action about a week

Echothiophate

- ❖ New agent
- ❖ Similar to isofluorophate
- ❖ Long duration of action (week)

Differences between direct & indirect-acting cholinomimetics

- ❖ Actions on receptors:
 - Direct
 - Indirect
- ❖ Pharmacodynamic effects:
 - Similar
- ❖ Central effects with indirect:
 - Cross BBB

Organophosphorous Insecticide Poisoning

- ❖ Agricultural or industrial accidents
- ❖ Excessive cholinergic manifestations
- ❖ GIT (diarrhoea, colic)
- ❖ Respiratory (dyspnoea, bronchospasm)
- ❖ CV (bradycardia, hypotension)
- ❖ Micturition, excessive sweating, M. paralysis
- ❖ Miosis (pin-point pupil), convulsions & death

Treatment of OPI Poisoning

- ❖ General measures
- ❖ High doses atropine IV or IM
- ❖ Mechanical ventilation
- ❖ Diazepam for convulsions
- ❖ Enzyme reactivation by pralidoxime IM