*Cholinomimetic Drugs part-2-*

**Indirect cholinomimetics :**

**Mechanism of action :**

Inhibiting acetylcholinesterase thus increase the ACH concentration at the cholinergic receptors (both nicotinic & muscarinic ) .

**Degradation of ACH by acetylcholinesterase :**

1. ACH binds to enzyme's active site & is hydrolyzed🡪choline & acetylated enzyme (Binding)

2. Acetylated enzyme’s bond is broken by hydration🡪cholinesterase enzyme + Acetic acid (Hydration) .

3. Anticholinesterase replaces ACH🡪accumulation of ACH.

**Cholinesterase has 2 binding sites:** 1. Anionic🡪N+

2. Estratic site 🡪ester link

*(Fig)*

**Pharmacological effects of anticholinesterase :**

1. Nicotinic action

2. Muscarinic action

3. Action on CNS: excitation, convulsion, respiratory failure, coma.

**Nicotinic actions of cholinomimetics** : ( the same action of ACH + direct + indirect ) :

1. **Skeletal muscle :** stimulation🡪 muscle fasciculation (twitching)🡪 high concentration persistent of depolarization and paralysis .
2. **Ganglia:** stimulation of sympathetic and parasympathetic ganglia.
3. **Adrenal medulla: release** of catecholamines ( A , NA ) .

**Muscarnic action: TABLE**

**Classification of anticholinesterase :**

**1. Reversible indirect cholinomimetics :**

a)**Edrophonium** (quaternary alchohol ) .

b) **Carbamates** (esters) : Physostigmine , Pyridostigmine , Neostigmine , Ambenonium .

**2. Irreversible indirect cholinomimetics :**

- phate means phosphate derivatives

Organophosphorous compounds (esters) : Ecothiophate , Isoflorophate .

**Edrophonium :**

* Simple alcohol.
* Polar – quaternary.
* Reversible anticholinesterase .
* Not substrate for enzyme (not degraded by cholinesterase).
* Attach mainly to anionic site.
* Has very short duration of action (5-15 mins , more than ACH but less than the others).
* **pharmacokinetics :**
* Polar.
* Not absorbed orally (should be given by injection).
* Not hydrolyzed by cholinesterase (because it doesn't have ester so it cannot bind properly to cholinesterase).
* Excreted unchanged in urine.
* **Uses:** Diagnosis of Mysthenia gravis (weakness of skeletal muscle).

**Carbamates :**

* **Mechanism of action :**
* Attach at both sites of cholinesterase enzymes (have ester group ) .
* Hydrolyzed at slower rate than ACH.
* Substrate for TRUE cholinesterase enzyme & non specific esterases .
* Long half life (4-8 hours).
* All are polar except Physostigmine .

*fig ( reversible anticholinesterase ) .*

**Physostigmine :**

* Tertiary ammonium compound.
* **Pharmacokinetics :**
* Not polar.
* Good lipid solubility.
* Good oral absorption.
* Good BBB penetration.
* Hydrolyzed by cholinesterase (true + pseudo).
* **Pharmacodynamics :**
* attatch at both sites of the enzyme .
* Has intermediate duration of action.
* Has indirect action (reversible anticholinesterase) .
* Has muscarinic (see table of ach) and nicotinic action.
* Has CNS stimulant action.

*mydriatics :are drugs thatcause eye mydreasis which is dilatation of the pupil of the eye .*

* No direct action on NMJ.
* **Uses :**
* Glaucoma.
* To counteract the effect of mydiatrics .
* Atropine intoxication ( muscarinic blocker) (I.V) .

**Neostigmine :**

* Reversible anticholinesterase .
* Quaternary ammonium compound.
* **Pharmacokinetics :**
* Polar compound.
* Poor lipid solubility.
* Can be used orally.
* No BBB penetration (no CNS effect).
* Has intermediate duration of action.
* Hydrolyzed by cholinesterase (true + pseudo).
* **Pharmacodynamics :**

1. **Indirect action:**

* Has both muscarinic and nicotinic action.
* More prominent on GIT and urinary tract than CVS.

1. **Direct action** on NMJ.

* **uses :**
* Treatment of myasthenia gravis when it's combined with atropine.
* Paralytic ileus + urinary retention .

*Curare is a skeletal muscle relaxant .*

* Curare intoxication.

**Ambenonium and Pyridostigmine :**

* + Reversible anticholinesterases .
  + Similar to neostigmine .(In pharmacodynamics-kinetics)
  + Used for treatment of myasthenia gravis.

**Organophosphorous compounds:**

**Ecothiophate and Isoflurophate :**

* Irreversible drugs .
* Toxic and has no clinical application.
* **mechanism :**
* Indirectly by inhibition of cholinesterase.
* Binds to esteratic site of cholinesterase forming covalent bond (the phosphorus atom).
* Have long duration of action .
* Aging make the bond extremely stable .(Cannot be cleaved)
* **All** are highly lipid soluble except ecothiophate .
* Used only for glaucoma.

**pharmacological effects of organophosphorus compounds :**

1. **Muscarinic action .(**table)
2. **Nicotinic action**. (Ganglia, NMJ).

* Therapeutic dose >>> increase action of ach
* Toxic dose:muscle twitching and paralysis.

1. **CNS.**

**Organophosphorus compounds toxicity:**

* Sever bradycardia , hypotension .
* Bronchospasm .
* Increased GIT motility 🡪cramps and diarrhea.
* CNS effects 🡪convulsions, coma and respiratory failure.
* Twitching of skeletal muscles 🡪 depolarization block 🡪muscle weakness,fatigue,paralysis

**Treatment of organophosphorous toxicity:**

1. Prevent further absorption
2. Support respiration
3. Cholinesterase reactivation
4. Atropine (block muscarinic & central actions)

**Cholinesterase reactivation (Oximes)**

**Pralidoxime (PAM)**

* Accelerate the hydrolytic regeneration of cholinesterase enzyme
* They activate recently inhibited enzymes before aging
* **Uses:** IV → over 15-30 min for organophosphorous intoxication (cannot be used as a single dose, must be a multiple because it duration is long)

**New cholinergic drugs:**

**Cevimeline**:

* Direct acting cholinomimetics
* Given Orally
* Used for treatment of dry mouth symptom associated with Sjogren’s syndrome
* increases Salivation

**Anticholinesterase drugs: (reversible indirect)**

* Donepezil.
* Tacrine.
* Given orally.
* Treatment of dementia of Alzheimer disease.

*Indirect Cholinomimetics: Figure*

**Anticholinergic drugs: (Cholinorecptor blockers)**

1. **Nicotinic blockers:**

* Ganglionic blockers
* Neuromuscular blockers

1. **Muscarinic blockers (Parasympatholytics)**

**Classification of Antimuscarinic:**

1. Naturally occurring alkaloids : Atropine – hyoscine
2. Synthetic Atropine substitutes
3. **Naturally occurring alkaloids:** Atropine – hyoscine

* **Pharmacokinetics:**
* 3°(tertiary) amine
* Metabolized in liver & excreted in urine(acidification will increase the excretion).
* Orally absorbed (Crosses BBB)-Non polar
* Has short duration of action on most organs (except eyes:7days)
* **Mechanism of action:**
* Reversible competitive blockade of all muscarinic receptor (NOT SELECTIVE)
* Block muscarinic actions of Ach & other parasympathomimetics
* **Pharmalogical effects :**

1. CNS

* Initial stimulation followed by CNS sedative action .
* Vagal nucleus ( **CIC** stands for **C**ardiac **I**nhibitor **C**enter ) : initial bradycardia ( central action ) & tachycardia .
* Antimimetic effect ( block vomiting center )
* Antiparkinsonian effect ( block basal ganglia )
* Toxic dose: hyperthermia - excitement - hallucination .

1. Eye

* Passive mydriasis (paralysis of circular muscle)
* Cyeloplegia (loss of accommodation ) Paralysis of ciliary muscle
* Loss of light reflex
* Inc. I.O.P ( intra-ocular pressur ) contraindicated with glaucoma
* Decrease lacrimal secretion🡪sandy eye

1. CVS
2. Heart

* Initial bradycardia followed by tachycardia.
* Inc. in AV conduction ( +ve dromotropic effect )

1. Blood vessel

* Therapeutic dose: Dec. vasodilatation induced by cholinomimetics (M3)
* Toxic dose : cutanous vasodilatation 🡪atropine flush

1. Secretions

* Dec. salivary secretion 🡪 dry mouth
* Dec. sweating 🡪 dry skin 🡪fever in infants & children
* Dec. bronchial secretion 🡪 increase viscosity
* Dec. lacrimal secretion 🡪 sandy eye
* Dec. gastric secretion 🡪dec. gastric motility

1. GIT

* Relaxation of smooth muscle ( constipation )
* Dec. GIT motility 🡪 antispasmodic effect.
* Increase sphincter contractions.

1. Urinary tract

* Relaxation of the ureter smooth muscles.
* Sphincter concentration.
* Urinary retention

1. Bronchial muscles

* Bronchial relaxation.
* dec. bronchial secretion 🡪 inc. viscosity \

**Uses:**

1. Preansethetic medication to:

* Decrease salivary and bronchial secretion.
* Protect the heart from excessive vagal tone.

1. Antispasmodic in renal and intestinal colics.
2. Choilnomimetics or organophosphorous poisoning.
3. Bradycardia (myocardial infarction).

**Adverse effect and toxicity:**

* Blurred vision:mydriasis.
* Tachycardia-atropine flush.
* Urinary retention-constipation.
* Dryness of the mouth –sandy eye.
* Malignant hyperthermia.
* Hallucination ,excitation (toxic dose).

**Treatment:**

* Gastric lavage.
* Anticonvulsant.
* Cooling blanket.
* Antidote-physostigmine(IV slowly).

**Contraindiations:**

* Glaucoma.
* Tachycardia.
* Prostate hypertrophy in old patients.
* Constipation and paralytic ileus.
* Children (hyperthermia).
* Asthma patients (increased viscosity).

**Hyoscine(scopalamoine):**

* **Differences between hyoscine and atropine:**

1. Rapid onset of action.
2. Short duration.
3. Less mydriatic action (2-4 days)
4. More CNS depressant action (Increased sedation-inhibition of vomiting center)
5. Has amensic action.
6. Less CVS effect.

* **Uses:**
* Preansthetic mediacation.
* Antimimetic action (motion sickness).

**Synthetic atropine substitutes:**

1. **Eye**: for fundus examination of the eye.

* Atropine :7days .
* Homertropine:24 hours.
* Cyclopentalate:12 hours.
* Iropicamide:6 hours.

1. **GIT:**
2. Peptic ulcer🡪pirenzepine(selective M1 blocker).
3. Antispasmodic🡪Hyoscine butyl bromide,oxyphenonium.
4. **Parkinsonism:**

* Benztropine.
* Trihexphenidyl.

1. **Bronchial asthma:**

* Ipratropium bromide
* Qauternary (no CNS action),
* taken by inhalation (bronchodilator)
* local action.
* little effect on viscocity.

Uses of antimuscarinics(printed slides)+Table+Drug formulation(printed slides)