CHOLINERGIC DRUGS

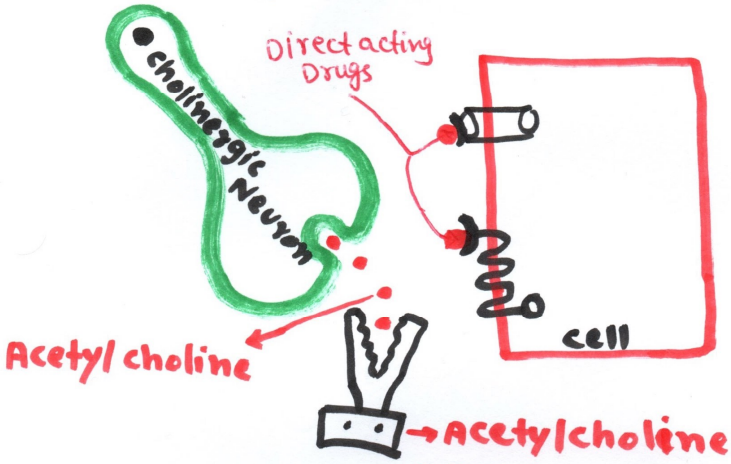
By: ZAKIR ULLAH YOUSUFZAI

DIRECT Acting

These drugs directly acts on the receptor, b/c these are structrally & functionally same like Acetyl choline

Indirect Acting

Basically these drugs inhibit the action of acetylcholinesterase or butylcholinesterase, so whatever Acetylcholine is released and not destroyed, & cause its action on receptor,



→ Acetylcholinesterase (destroy the Acetyl choline) present on both sympathetic & parasympathetic membrane (Plasma have abundant of this enzyme)

DIRECT ACTING Cholinergic Drugs

MUSCARINIC

- Cholin Esters
  - → Acetyl choline (M+N) (Muscarinic, Nicotinic)
  - → Methacoline (M)
  - → Carbacol (M+N)
  - → Bethenicol (M)
- ALKALOIDS
  - → Muscarine (Mushroom)
  - → Pilocarpine

NICOTINIC

(Detailed later)

① ACETYLCHOLINE (M+N)

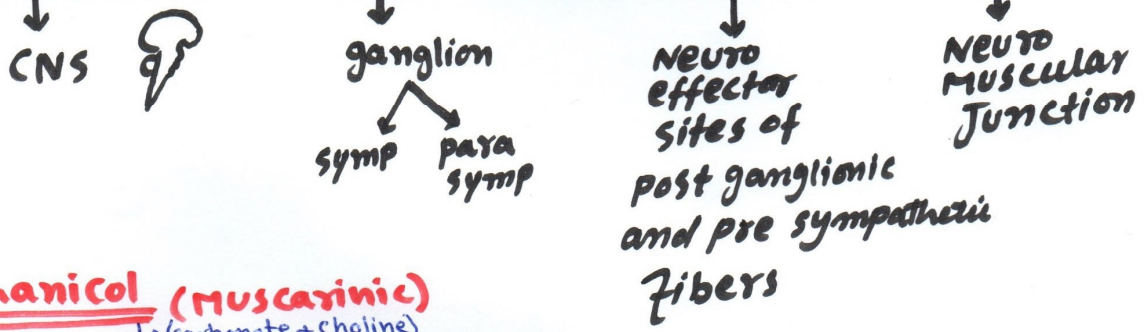
Usually not used pharmacologically because:

① it has shorter half life, & destroyed very soon by Butylcholinesterase, & Acetylcholinesterase.
* It is destroyed in 5—30 seconds

② Acetylcholine have diffuse action on → Nicotinic as well as Muscarinic receptor

③ Can't cross Biological membranes (such as BBB, GIT Mucosal barrier placental membrane)

sites of cholinergic RECEPTORS



② Bethanicol (MUSCARINIC)

↳ (carbonate + choline)

Pnemonic: Beth activate Bowel & Bladder.

this drug is slowely destryed by AChE (Acetyl choline Esterase), and Buteryl choline esterase.
so, it have longer duration of action.
its half life is >60 minutes

* This Drug not acts on Nicotinic receptor
It has special action on GIt & bladder

* This drug are used in hypofunctional bowel & bladder, But make sure, there not be any obstruction.
In case of hypofunction bladder (non obstructive urinary retention)
Such as:

URINARY →
① Post operative urinary retention
② postpartum urinary retention
↳ after child delivery
③ hypotonic, Myogenic & neurogenic bladder

} instead of cathetater we use these drugs b/c cathetater cause infection.

① Atonic Stomach / Gastroparesis
② post operative Adynamic ileus (paralysis of GIT)
③ ileus due to any Toxic reasons.
④ Congenital Megacolon.
(sometime ganglion are absent in short segement of Colon, & this part become adynamic, & become enlarges)

sideffects of Bethenicol

all side effects produced by generalized cholinergic system such as:
① lacrimation ② sweating ③ salivation ④ Abdominal cramps
⑤ Miosis ⑥ Thightness of chest ⑦ Bradycardia
⑧ Urination ⑨ defecation ..... etc.

Contraindication of Bethenicol

① It is not used in peptic ulcer
② COPD
③ IHD (Ischemic heart disease)
④ Hyperthyroidisim) in hyperthyroidism there is palpitation, these drugs also increase Atrial flutter.
⑤ Parkinson's disease → b/c in this disease Dopaminergic ganglions are destryoed, & there is ↑ cholinergic activity, by this drug the cholinergic activity increase more.

③ Carbacol: (Carbonate + Choline)

It has Muscarinic & some nicotinic action.
* in these days this drug is not used, systemically b/c it activate ganglion and than inhibit them. due to this reason it stimulate the CVS & than inhibit it, & stimulate GIT & than inhibit it.
* it is only used in Miosis] ↓ Intraocular pressure in glucoma.
for contraction of cilliaris
So, this drug is used when pilocarpin not work.

④ METHACOLINE (M)

This drug is not used systemically.

* It is used in patient with hyper reaction bronchial system.

i.e * any irritation of bronchial tree will cause spontaneously to check asthma, we give very little inhalation of methacholine.

For E.g: to check respiratory function.

⑤ Pilocarpine (M) it is tertiary amine

It is not destroyed easily by Acetylcholinesterase.

It has a long duration of action.

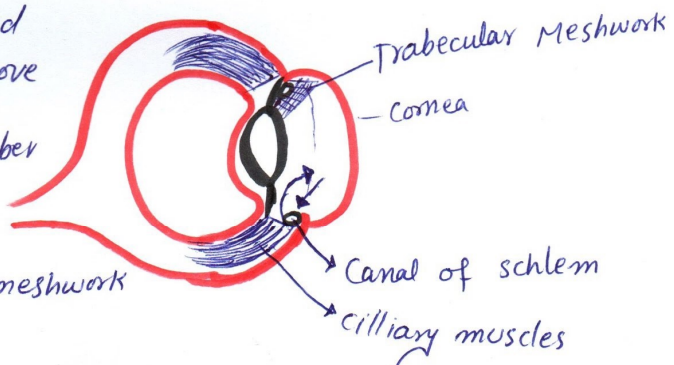
opthalmic uses

It is used in glucoma topically: ie applied directly to Cornea & absorbed.
- open angle
- close/narrow angle

*It acts on Muscarinic receptor of sphencter. pupili and muscarinic receptor on cilliaris, it reduce Intra occular pressure.

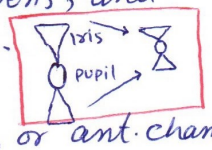
The angle present B/w corneoscleral Junction.

acqueous humour produced by cilliary process and move toward the anterior chamber



This angle Contain trabecular meshwork through which Aq. humor pass.

when cilliaris muscles Contract it will have pull the trabecular meshwork, & the trabecular meshwork opens, and aqueous humor flow through it & pressure goes down.



* some people Congenitally have small eyeball, or ant. chamber shallow, so they have relatively narrow angle. These people have one problem. ie: when pupil dialate they develop glucoma.

when pupil dialate root of iris is fit into corneoscleral ~~angle~~ Junction So, angle become narrow, & slower the drainage, so Intra ocular pressure become high, so aq. humor accomudate in post. chamber & push the iris anteriorly, that further narrowing the angle

Red eye with high Intra occular pressure is a sign of acute narrow angle glucoma.

In this case we add Pilocarpine drops; It cause contraction of pupil & intense contraction will pull zest. of Iris away from Cornea (ie: centerally) and angle become opened & drainage occur.

In case of open angle glaucoma, but there resistance present in meshwork. & when cilliaris contract it opens meshwork and facilitate the drainage.

But in case of close angle glaucoma there the angle is physiologically narrow.

pilocarpine strongly stimulate secretions

piles on sweat, tears and saliva

* **XEROSTOMIA** (dry mouth) due to irritation of head & neck.
  ↳ In this condition we use pilocarpine spray/Tablets in mouth to ↑ salivation.

* **XEROPHTHALMIA** (dry eye)
  ↳ In this condition we use pilocarpin topically in eyes.

* **SJogren syndrome**
  This is an autoimmune disease more common in females, where lacrimal and sweat glands are destryoed, so Dry eye & dry mouth, to these patients given pilocarpine or another drug CEVILINE (↑salivation & longer action) a muscarinic drug

pilocarpine as an Alkaloid derived from plants, so stronger Muscarinic

If someone have Mydriosis (dialated pupil) due to Atropine, this also correlated by pilocarpine.

If there is adhesion b/w lens and iris we alternatively give pupiloconstrictive and pupilodialators to break the adhesions, so pilocarpine is used with mydriated.

Cholinergic drugs

- DIRECT
- Indirect Drugs
  - Reversible inhibitors of acetylcholinesterase (ACE)
    These drugs bind with enzyme and than detache after some min/hours
  - Irreversible inhibitors of Acetylcholinesterase
    These drugs never Let the enzyme free and the enzyme activity Lost for many days, even new enzymes produced and may reverse the enzyme activity if patient survive.

(A) REVERSIBLE INHIBITORS OF ACE

(1) Physostigmines:

* It is an Alkaloid derived from plants,
* It is tertiary amine
* CROSS BBB, even cause toxicity in CNS
* easily absorb from GI mucosa
* acts on ganglions, B/c they're lipid Soluble & cross fats.

Tertiary Amines	Quaternary Amines
*less polar *Lipid Soluble *Absorb from membranes easily	* More polar * less lipid soluble * less absorb from membranes

(2) Neostigmine
(3) pyridostigmine
(4) Endrophonium

These are Quaternary Amines, and synthetic drug. So, Cannit cross BBB, & Canit produce toxicity in CNS.

physostigmine, Neo stigmine, pyridostigmine — have Carbonated group
Endrophonium — have Alcohol group

Endrophonium

Bind with ACE losely, so easily detaches, & doesnt make strong covalent bond, so its duration of action is shorter (10–20 min)

Neo/physo/pyridostigmin

They make covalent bond with ACE, but the bond are labile covalent bond (a bond which is eventually break)

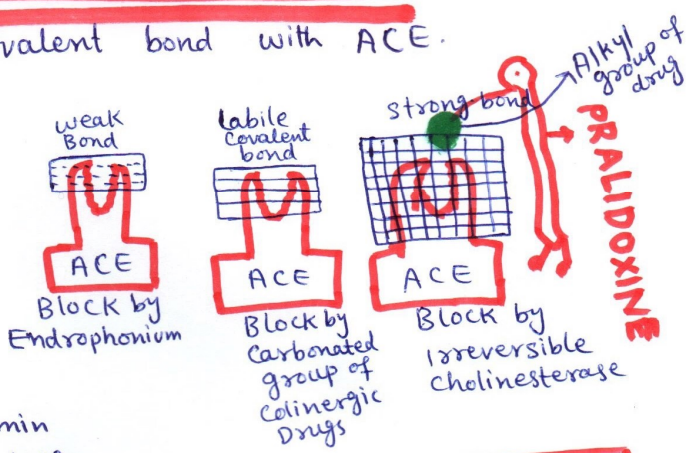
Its duration of action is longer than Endrophonium, (about 30min–2hr)

(B) Irreversible cholinesterases

These drugs make strong covalent bond with ACE.

i.e

1. Isoflurophate
2. Echothiophate
3. Malathione
4. Parathione



once the irreversible cholinergic drugs bind for 30-minutes, after 30min the alkyl group detaches from the drug & it will be for long time, & never antidote work on it. & the drug never detach from ACE.

* within 30 minutes the Antidote work properly,

The Alkyl group are not removed after 30min this process is called **"Aging"**.

the antidote of irreversible cholinergic drugs are **PRALIDOXINE**

when there is high Acetyl choline it causes:

1. If some of these drugs cross BBB & enter to CNS, they inhibit ACE and Acetylcholine store in the CNS, due to that cause convulsion(seizure)
2. Acetylcholine accomudate at ganglia, & there is pathological stimulation of it.
3. Acetylcholine accomudate at neuroeffector site & there is strong stimulation of Muscarinic receptor.
4. If acetyl choline accomulate at neuromuscular Junction they cause stimulation of Nicotinic receptor & paralysis occur.

To solve this problem we give ATROPINE, which block the Muscarinic receptor.
We also give Antidote (Pralidoxine) before Aging.

physostigmine

If physostigmine enter to CNS & cause

① CNS stimulation
② ganglion stimulation
③ Neuronal effector receptor stimulation
④ Neuromuscular stimulation.

Uses of physostigmin

① GIT
② Non-obstructive urinary retention.
③ Glaucoma

Sometime pilocarpine and physostigmine are used togather.
↓ Cause direct stimulation
↓ Cause inhibition of ACE, so ↑ Acetylcholine

④ used in overdose of ATROPINE (ie: Atropin toxicity)

⑤ in Toxicity of PHENOTHIAZINE, the phenothiazine is a psychotic drug, this drug cause anticholinergic activity by blocking Muscarinic receptor, to restore muscarinic receptor action we give physostigmin

⑥ if someone taken high dose of Tricyclic anti deepresant (TCA), we give physostigmine, which ↑ acetylcholine, & the acetylcholine start their action.

side effects of Physostigmine

① CNS over stimulation and eventually convulsion
② paralysis (due to failure of transmition at neuromuscular junction)
③ collaps of CVS.

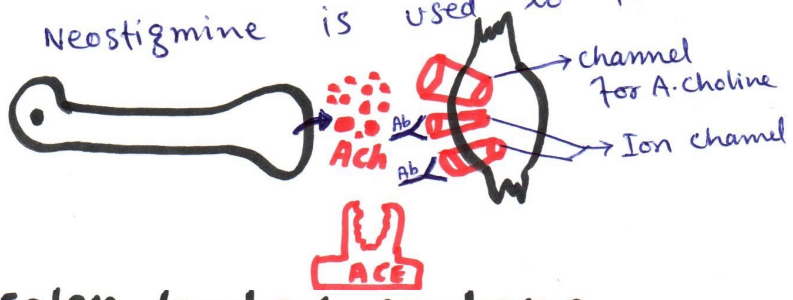
NEOSTIGMINE

NO — CNS

* Neostigmine does not enter to CNS.
* As most of autonomic ganglion are embeded in fats, so neostigmine does not work on ganglion and post neuronal effector sites. B/C it is less lipid soluble.
* Neostigmine can directly stimulate Acetylcholine receptor at neuromuscular junction

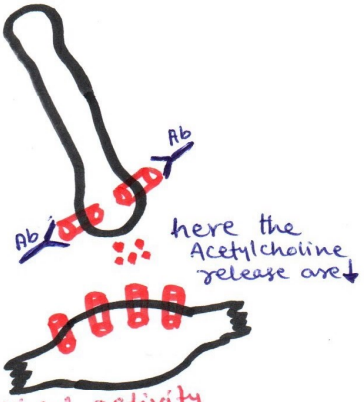
Myasthenia gravis

In this disease Autoantibodies are produced against nicotenic receptor, these antibodies + nicotenic receptor undergoes internalization, so number of receptor on surface is decresed.
Some Ab bind to ion-channel on surface, but not be activated, so no end plate potential is produced, & muscles become weak.
Neostigmine is used to treat this condition.



Eaten lambert syndrome

in This disease Nicotenic receptor are normal But Ab. are produced against Ca^+ chanel, so No Ca^+ chanel release more Acetylcholine, & the muscle become weak.



in both myastenia graves & eaten lambert syndrome muscles are weak, but the difference is that:
* In Myastenia graves Muscles are initially OK, & by physical activity person feel tired.

in Eaten lambert syndrome person initialy are feeling weak, but by physical activity become active later.

* in myastenia graves the Ab are against Postsynaptic.
in Eaten lambert syndrome the Ab are against presynaptic.

in these both diseases the Neostigmin inhibit ACE, so the the Acetylcholine (accomudate in EL-syndrome presynaptic membrane, & activate the chanel & releases), and in (M.g. disease the Acetylcholine amount ↑ in junction & activate the chanel.

If a person is exposed to TUBOCURARIN, which block the nicotinic receptor & Muscle weakness occur, such person are exposed to Neostigmine the ACE are inhibited, so Acetylcholine concentration increase and acetylcholine competatively inhibit Tubocurarine & bind with receptor & the muscle are stimulated.

* Neostigmin is strong indirecting inhibitor but also a weak directly acting Nicotenic receptor activator.

Neostigmin Stimulate bowel and bladder.

***If we stimulate Neuromuscular junction Neostigmin is prefered over physostigmine.**

side effects of Neostigmine

Generalized increased of cholinergic system side effects of physostigmin are more dangereous b/c it produce cholinergic crisis in CNS.

Pyridostigmin + Ambenonium

Here ↓ wrot the P larger b/c
↓
prolonged duration of action
4-6 Hours

duration of action
4-8 hr.

So therefor more used in Cholinergic Myasthenia gravis

Remaning is same like as Neostigmine.

Endrophonium (it is like phony person) b/c

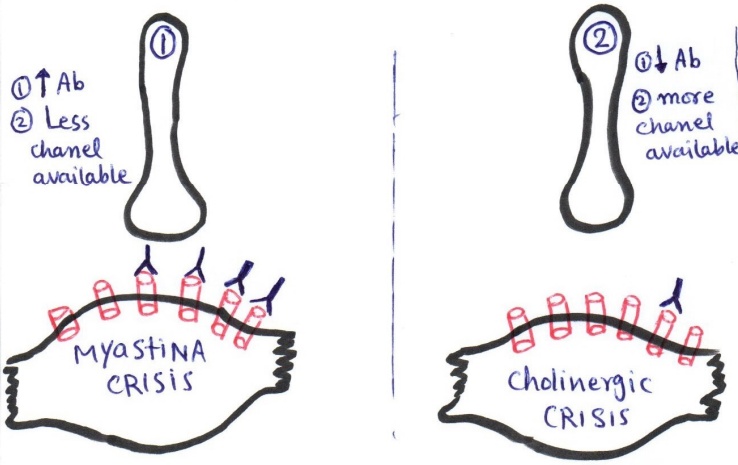
duration of action is 10—20 minutes.

* There are some conditions in which Endrophonium are prefered over Pyridostigmin & Neostigmine.

To confirm myasthenia graves weakness we give short acting cholinergic drug (Endrophonium), if patient recove from weakness after inj of Endrophonium, it indicate the patient is myasthenia gravis.

Tensilon Test

for example: we have two patients, of myastina gravis on Neostigmine treatment



the autoAntibodies fluctuates either increased or decreased.

In patient No:1 we have more Ab, so prescribe dose of Neostigmin will not work, for such a patient we need to ↑ the dose.

in this patient of Myastina graves the disease is aggravated is called Myastina crisis.

But in patient No:2 auto Ab are less, so the prescribed amount of dose is now overloded for such patients, so the Acetyl choline will stimulate the receptor and again Muscle weakness occur. this patient are having Cholinergic cholinergic crisis.

How we check Myastina & Cholinergic crisis?

* we inject Endrophonium, if after inj person become active, he is having Myastina crisis.
* if after inj person feel more weakness it is cholinergic crisis.
* so Endrophonium tell us about initial Myastina, & also differentiate B/w Myastenic/cholinergic crisis

Alzhimers disease

there is deficiency of cholinergic system in CNS.

Mynert nucleus gives alot of Cholinergic fibers stimulation.
In this disease this nucleus is degenerated and person loss Cognitive function (to learn and remembare)
we use drugs which are having anticholinesterase activity so whatever remaning Acetylcholine, & perform its function.

ie ① **Tacrine (produce strong hepatic toxicity)**
② **Donezepil**
③ **Revastigmine**
④ **Galantamine**

These drugs does not reduce the progresion of disease but give releaf from symptoms.

cholinergic drugs Toxicity (crisis) (DUMBBELSS)

Diarrhea
Urination
Miosis
Broncho spasm
Brady cardia
Excitation of → CNS & Muscles
Lacrimation
Sweating
Salivation

End of cholinergic drugs
By: Zakir ullah Yousufzai