pharmacology

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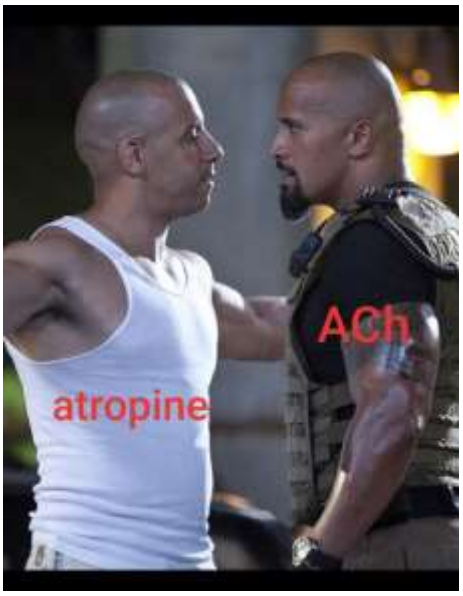
المحاضرة ٣

كلام الدكتور مكتوب بالأزرق

الميم الي تحت مهم جدا ركزوا فيه واحفظوه لأنه مفتاح لفهم كثير شغلات بالمحاضرة وبدون مبالغة الي مش هيفهمه هيفقد المحاضرة وهيفقد الامتحان



We will start by reviewing some points from the previous lectures:

*we talked about a family of drugs which is called cholinomimetics/ parasympathomimetics i.e. drugs that produce the same effect as ACh.

* These drugs are devided to two groups: A) direct acting i.e. acts directly on the muscarinic receptors B) indirect acting i.e. act by increasing the concentration of the ACh and the ACh will act on the receptor.

*we started with the direct group and talked about the first type of them (choline esters)

Now we will talk about another type of the direct acting group which is (natural alkaloid)

طبعا زي ما حكينا قبل هيك انه هاي الأسماء هي مجرد تصنيف كيميائي للأدوية وما بهمنا انه نعرفهم احنا النا بس باسم الدواء

A.Natural alkaloid

- **Pilocarpine**: - 3ry ammonium → **well absorbed orally, pass BBB**

3ry ammonium means it will be absorbed by the tissues faster

Quaternary ammonium means it has a charge and it won't be absorbed (like the first type drugs)

- **Not** affected by Cholinesterase enzyme

All the drugs in the direct acting group are not affected by AChE enzymes except for the methacholine which will be affected by the true choline esterase only.

- More selective on M_3

اذا بتتذكروا الدكتور حكى انه اكثر **receptor** رح يكون اله دور وتأثير هو **M3** وبما انه الدواء **selective** اله رح يكون الـاثير عن طريقه

ملاحظة: لما يكون الدوا **selective** لمستقبل معين هاد لا يعني انه ما رح يشتغل عالمستقبلات الثانية بس التأثير عهاد المستقبل رح يكون اوصح وتأثيره أكبر.

a. Eye:Miotic (the preferred miotic due to M_3 selectivity, rapid action and short acting)

We talked about many drugs that will produce miotic effect on the eye but, Pilocarpine is the preferred on to be used this is because:

A) The M3 selectivity i.e. when the drug is selective for one receptor the adverse effects on the other receptors will be less than in other drugs.

B) Rapid action لما بكون بعمل فحص للعين بحتاج انه لما احط القطرة التأثير يصير بسرعة مشان ابلش افحص بدون ما استنى وقت طويل

C) Short acting نفس النقطة الي فوق تقريبا لما اخلص الفحص ما بدي هاد التأثير يضل موجود عالعين فترة طويلة لأنه ممكن يأثر عالنظر عالمستوى البعيد

used for:

1. Glaucoma

The most important use is for glaucoma

We know that glaucoma is caused by increase the secretions or decrease in the drainage so when I give a drug that cause miotic effect this will increase the angle of the eye and increase the drainage of the aqueous humor

هاي استخدامات كانت موجودة زمان بس استغنوا عنها لأنه صار في حلول افضل واكثر تطور

Was used in

2. After fundus examination→ counteracting mydriatics.

Fundus examination: examination of the retina by a microscope, to do this examination the doctor needs to expand the iris (to see clearly) and he will use drug that cause mydriatic.

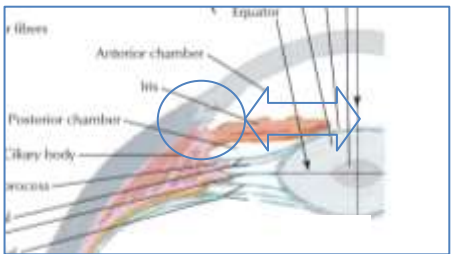
After the examination I use this drug to reverse it.

3. Iridocyclitis→ alternating with mydriaticsto prevent adhesions.

Iridocyclitis: inflammation in the ciliary body of the iris

After the inflammation the inflammatory cells might accumulate and forms fibrous tissue or adhesions in the eye and this will lead to the closure of the angle.

بالصورة تحت بتشوفوا صورة العين (مشان تذكركم بالاناتومي شوي) هلأ اذا صار inflammation in the ciliary body رح تبلش الخلايا تتجمع في المنطقة الي معينة (angle of the eye) وهاد الاشي على المدى البعيد رح يكون اله اضرار كثيرة زي مثلا انه رح يمنع الIOP drainage of aqueous humor and increase in the طيب كيف رح يساعدني هاد الدوا بالموضوع الي رح يعمله انه رح يصير يعمل توسيع وتضييق ورا بعض لحدقة العين (السهم الي مرسوم) وهاد الاشي رح يؤدي لتكسير ال adhesion ومنع تكوينها



b. Exocrine glands: ↑ secretion → in dryness of eye & mouth (xerostomia).

The fluid on the eye is protective and it will prevent ulceration or inflammation of the cornea so I need to preserve this fluid all the time

c. Scalp blood vessels: VD→ used as hair tonic.

It will increase the blood supply of the hair and will help in hair growth

B. Cevemiline

- More Selective on **M_3** → used in **dryness of eye & mouth**.

Adverse effects are the same like other direct acting drugs but, with less effect on M1 and M2 effects.

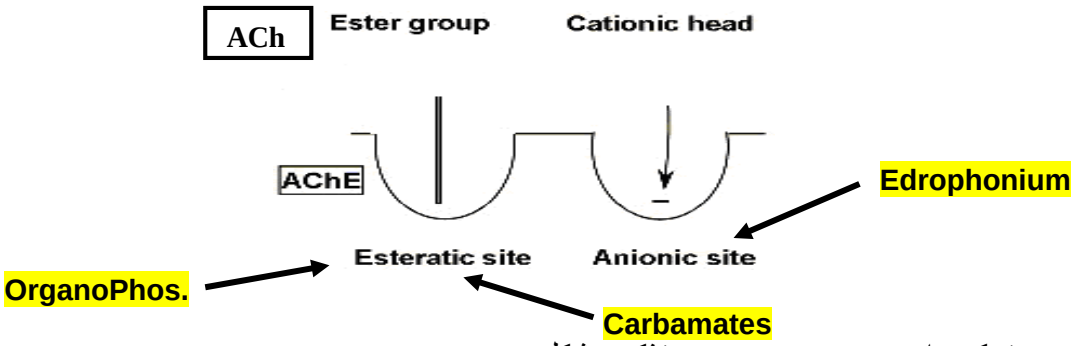
CHOLINE ESTERASE INHIBITORS (ChEIs)

ANTI-CHOLINESTRASES

It is called indirect because it doesn`t act on the receptor instead it increase the ACh by inhibiting the choline esterase enzyme

Mechanism of Action

- ChEIs act indirectly by inhibiting choline esterase → accumulation of ACh.



حكينا قبل هيك عن تركيب انزيم **AChE** بس نرجع نتذكره بشكل سريع

The enzyme has two binding sites: A) esteratic site which will bind with the ester group of ACh (covalent bond)

b) Anionic site which will bind with the cationic head of the ACh (ionic bond)

Now the drugs that inhibit the enzyme will act on different sites:

A) **Endophorium: this drug will bind with the anionic site of the enzyme (ionic bond) and we know that the ionic bond is weak and could be broken easy and will be short duration drug.**

B) **Carbamates/ organoPhos: these drugs will bind with esteratic site of the enzyme (covalent bond) and we know that this bond is strong so the drugs will be long acting**

Reversible Ch.EIs

1. Simple Alcohols: Edrophonium

- Weak, **short-acting** (2-10 min) 4ry compound

Because it is 4ry compound this means it won't be absorbed orally

- Binds electrostatically to the **anionic site** of enzyme
- **Uses:IV, short acting** used in

1. **Diagnosis of myasthenia gravis** → muscle improvement

Myasthenia gravis: disease that cause weakness of the muscles.

It is used only for diagnosis and not for treatment because it is short acting

2. **Differentiation between myasthenic & cholinergic crisis**

2. <u>Carbamate esters</u> Physostigmine – Neostigmine & its substitutes

- medium-duration (3-4 hours)
- The carbamyl group binds <u>covalently</u> to **esteratic site** of enzyme (active site) → carbamylated enzyme

Carbamylated means that the enzyme is linked with carbamate group

	Physostigmine (Eserine)	**Neostigmine(Prostigmine)**
Nature:	Natural – 3ry amine	Synthetic – 4ry ammonium
Kinetics:	- Well absorbed **orally** - Pass **BBB & conjunctiva** **It can be used localy on the eye**	- **Poor oral** absorption - **NOT** Pass BBB & conjunctiva **No CNS action and can`t be used as eye drop**
Dynamics:	- **Mainly muscarinic**& weak nicotinic effects **ACh will accumulate in all sites of the cholinergic system but mainly this drug will act on the muscarinic receptors** - **CNS stimulation** **It passes the BBB**	- **Muscarinic & Nicotinic**effects - **Direct skeletal ms. Stimulation** **It will act on skeletal muscles with two ways:** **A) indirect way by increasing ACh in the motor end plate** **B) direct by stimulating the motor end plate**

Uses:	1. **Miotic**: eye dropsAs pilocarpine **but with lid twitches** **this drug has the same uses as pilocarpine but with extra adverse effect which is lid twitches and this adverse effect is caused by the nicotinic effect of the drug that will affect the smooth muscles** 2. **Atropine toxicity** (correct central & peripheral effects) **Atropine is competitive inhibitor of the muscarinic receptor i.e. if the conc. Of atropine is high I need to give the patient drug that act on the receptor to antagonise the effect of atropine** **And it cross the BBB so it will reverse the peripheral and central effect of atropine**	**1. Non-obstructive paralytic ileus &urine retention** **Increase the movement of the intestine wall and the bladder wall** حكينا قبل انه شرط استخدام الأدوية لهاي الحالات انه ما يكون في **obstruction** لأنه بكون هيك عم بحرك الأمعاء عالفاضي ورح يصير ضرر بعد مدة **2. Myasthenia gravis**(preceded by **atropine** to ⊖ muscarinic side effects): **diagnosis and treatment** **I aim to increase the muscle strength by ACh** **Long acting drug so can be used for treatment** **3. Antidote to neuromuscular blockers** (Nicotinic + Direct) (preceded by **atropine**) **In MSS we studied the neuromuscular blockers (skeletal muscle relaxants) which act by blocking the nicotinic receptors of the muscle to relax it** **So in cases of toxicity by these drugs I use neostigmine to reverse the relaxation and cause contraction** ***when I use it for myasthenia gravis or as antidote (2+3) I inject the patient with atropine first.why? because in these two cases I use the drug for its nicotinc effect and I don't want it to act on muscarinic receptors to avoid adverse effects so I inject him atropine to block the muscarinic receptors**
Toxicity:	1. **Exaggerated ACh. Like actions** → treated by **Atropine** **I have a competition between the atropine and ACh if one get high I will use the other one to reverse its effect**	

	2. **Convulsions** → treated by **Anticonvulsants** *it crosses BBB	NO convulsions → NO need for Anticonvulsants *it doesn't cross the BBB

Neostigmine substitutes:

- **Pyridostigmine & Ambenonium :** in **myasthenia gravis** (long acting - ↑ selectivity on skeletal muscles - fewer visceral side effects).

Cant be used for any other disease

It is better than neostigmine in:

a) long acting: rather than taking the drug many times a day the patient can take it once only.

b) Selective on muscles : so I will avoid adverse effects on muscarinic receptors.

c) I don't have to use atropine before them.

- **Donepezil:**in **Alzheimer disease** (3^{ry} → crosses BBB -long acting).

It cross the BBB so I can use it on the CNS
We talked about the M1 receptor which has a role in short term memory

- **Demecarium:** eye drops in **Glucoma**

Neostigmine doesn't cross the conjunctiva so I cant use it to treat glaucoma and I use demecarium instead.

باختصار هاي الادوية الثلاثة هي عبارة عن اني باخذ عيوب ال **neostigmine** وبحاول اعمل دوا بشملها مشان يكون احسن منه

Myathenia gravis

- Autoimmune disease of skeletal muscles → antibodies → ↓ number of Nm
  → weakness of extraocular, neck, followed by other muscles)

We studied it in immunology last year as a quick recap the body will produce antibodies that block the nicotinic receptors in the NMJ and this will lead to weakness of the muscles

- **Diagnosis:**

  1. IV Edrophonium

When I give it to the patient he starts to move his muscles normally this means he has the disease

***can't be used as treatment because short acting**

الأمراض الي بتأثر على العضلات كثيرة بس الي بميز هاد المرض هو انه التأثير ما بكون عال **innervation** بالعكس
العصب بكون واصل عالعضلة طبيعي ما في اشي بس المشكلة بال **receptor**

2. IM Neostigmine 0.5 mg (preceded by 0.5 mg atropine)

***use very small dose if want to diagnose the disease**

*** inject atropine first to block muscarinic receptors and avoid adverse effect.**

3. Antibody titre *will be high

- **Treatment:**

  1. Neostigmine, Pyridostigmine, Ambenonium العلاج الأساسي

  2. Ephedrine & Caffeine are adjuvants أشياء إضافية

The drugs above will cure the symptoms but, it is also important to cure the cause which is the antibodies.

3. Immunosuppressants: Corticosteroids &Antimetabolits e.g. Azathioprine

4. Thymectomy (thymus gland→ antibodies)
*surgical removal of the thymus gland to stop producing antibodies

5. Plasmaphoresis (purify plasma from antibodies)

- **Drugs contraindicated in Myasthenia gravis:** ***any drug that will relax the muscles**

  1. Skeletal muscle relaxants
  2. Aminoglycosides: curare-like effect
  3. Beta-blockers (↓ blood flow to skeletal ms.)
  4. Quinidine (sk.ms. relaxant effect)

     Antiarrhythmic drug but has relaxant effect on skeletal muscles

Myasthenic crisis **In this case the patient will be tacking the treatment but he isn't getting better because the dose might not be enough**	Cholinergic crisis **In this case the patient will be tacking high dose of the drug so he has excessive ACh in his body**
- due to **ineffective or insufficient treatment**→ ↓ ACh→ sever muscle weakness - Edrophonium→ **muscle improvement**	- due to **excessive treatment**→ ↑ ACh→ maintained depolarization → muscle exhaustion and weakness in normal cases depolarization should be followed by repolarization but with high conc. of ACh the depolarization will last for long time and this means elongated refractory period which will lead to block the neuron and prevents it from receiving any impulse - Edrophonium→ **more muscle weakness**

In both cases the patient will suffer from muscle weakness how I will know which one of them he has?

By edrophonium

Edrophonium will increase ACh so if the patient improved this means he has low ACh (myasthenic crisis) if he get worse this means he has high ACh (**Cholinergic crisis**)

طبعا في حال المرميض كان بعاني من cholinergic crisis وأعطيته edrophonium هل رح يشكل خطر عليه؟ لأ لأنه الدواء تأثيرا ما بكون لمدة طويلة

Irreversible Ch.EIs

Organophosphorous compounds

- Very long duration
- The phosphate group binds covalently **to the esteratic site** of the enzyme.
- The **covalent phosphorous enzyme bond** is extremely stable and hydrolyzes in water at a very slow rate (hundreds of hours)→ reactivation time of phosphorylated enzyme > the regeneration time of the enzyme→ **irreversible inhibition**

Why this drug is the only irreversible drug although carbamates will also bind with the enzyme with myasthenia gravis? This is because the bond that will be formed between the phosphate group of the drug and the estreratic site of the enzyme is very very very very stable and will need very^{4} long time to be hydrolyzed and this time is enough for the phosphorylated enzyme to be formed again

- **Ageing** occurs in the phosphorylated enzyme bond within 2 min-12hrs → strengthening of covalent bond →recovery of enzyme cannot occur. Thus, choline esterase regenerators in organophosphate toxicity should be given early before ageing occurs.

Ageing means the longer the drug will last in the body the bond will be stronger and harder to break so if I want to reverse the act of the drug I should do this before ageing occurs.

Members & uses:

1-**Malathion& parathion:** Insecticides.

2- **Sarin**: Nerve gas

Used in wars to increase the ACh in the body and causes toxicity

3- **Echothiophate**: **Eye** drops

a. Antagonizes atropine after fundus exam. b. Glaucoma

4- **Pyrantel pamoate:** Paralysis of round worms

Toxicity of Organophosphorus Compounds

خطورة هاد النوع من الأدوية انه ممكن يعدي من خلال أي اشي "الي يعدي حاجة يعدي كل حاجة" خلص هيك اختصرت عليكم كل الكلام الي تحت وما في داعي تقرأوه أو تزاكروه هتزاكر ليه

- Organophosphorus compounds are highly lipid-soluble &are well absorbed from all sites & cross BBB **(except Echothiophate has 4^{ry} N^{+}→ ↓systemic toxicity).**
- Poisoning occurs due to suicide or accidental exposure to drugs during spraying insecticides or Nerve gases during war.

كل الأعراض تتلخص في كلمتين increase in ACh conc./ AChEI

I- Acute toxicity

- **Excessive muscarinic effects:**
  - Miosis, Bronchospasm, Colic
  - Lacrimation, Sweating, Salivation
  - Vomiting, diarrhea, Urination
  - Bradycardia, Hypotension
- **Nicotinic effects:** Skeletal muscle twitches followed by paralysis.
- **CNS effects**: (stimulation): Excitation, Anxiety, convulsions followed by (depression): coma & respiratory depression.

Everything will be excited at the beginning this will lead to exhaustion of neurons

Death is due to respiratory failure:

- Respiratory center depression.(central effect)
- Paralysis of respiratory muscles due to persistent depolarization block.(nicotinic effect)
- Excessive bronchial secretions with **acute pulmonary oedema**.(muscarinic effect)

Treatment of acute Organophosphorus Toxicity

1. **Maintain vital signs**:

   Aspirate bronchial secretions, endotracheal intubation & artificial respiration.

   As we know that the ACh will increase all the secretions and the bronchi in this case will be full with mucus so the first move I do is aspirating all the secretion and in some cases I will put a tube to help him breath

2. **Decontamination** (to prevent further absorption):

   Remove contaminated clothes - wash skin (Na hypochlorite) - gastric lavage.

بما انه هاد المركب موجود في المبيدات الحشرية ممكن انه الواحد ينصاب وهو برشها بمزرعة فضروري اني اشيل اواعيه عنه واغسل جسمه واعمللله غسيل معدة وابعد اي اشي ممكن يكون متلوث بالمبيد.

3. **Atropine** (large doses) for CNS & muscarinic effects:

   2 -5 mg/ 5 min→ **Full Atropinization**

I start drug therapy with giving the patient large doses of atropine every 5 min and I do this until I achieve full atropinization which means عملت منه جاج محشي بس اتروبين and the signs for this is the opposite signs for the toxicity

Mydriasis, Dry mouth, Tachycardia >80/min, Systolic pr.>80 mmHg,

bronchial secretions & wheezes stop.

4. **Choline esterase reactivators (oximes): PAM** (pralidoxime)

This drug will attach with the phosphorus group of the enzyme and excretes it from the body and the enzyme will be free to act

React with phosphorous → Harmless compounds = Chelation → Regenerates choline esterase (IV infusion 1-2 g over 15-30 minas soon as possible before enzyme ageing).

5. **Diazepam**: for convulsions.

II- Chronic Toxicity: → **delayed neuropathy**.

In some patient after 2 or 3 months of the acute toxicity they will start having symptoms of neuropathy

وفقكم الله لما يحب ويرضى

~عزات ماجد