PHARMACOLOGY

◉ Sheets ○ Slides

Number: 11

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Subject: Autonomic Nervous System

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◘ This sheet will cover the rest of slide number 2 (Cholinoceptor-Activating Drugs) from slide number 37 till 48 + the beginning of slide number 3 (Cholinoceptor-Blocking Drugs) from slide number 1 till 4 .
◘ Note that the doctor during this lecture has stick to what his slides have; most of the lecture.
◘ For a better understanding for the material that will be discussed below; you can refer to ' Basic and Clinical Pharmacology ... By Katzung ... 12th edition ' from pages 108 till 116. *P.S: You will notice that the doctor's slides are taken directly from there, and so will be a lot of this sheet!

- Previously we have talked about some of the clinical uses of **cholinomimetics** ; as their therapeutic use to treat diseases of the eye (like ; Glaucoma) and the gastrointestinal and urinary tracts (like ; Postoperative ileus & Neurogenic bladder) .
- We shall proceed talking about their clinical uses now for the neuromuscular junction & the Central nervous system (CNS).

Neuromuscular Junction:

- A major disease related to neuromuscular junctions is ***Myasthenia gravis*;** which is an autoimmune disease (Autoimmune disease is what happens when your immune system starts attacking healthy cells .) affecting the skeletal muscle neuromuscular junctions .
Antibodies produced during this disease are detected in 85% of patients .The main damage is that those antibodies *reduce the nicotinic receptor function* by several means (like distortion of the structure of the motor end-plate; Cross-linking receptors & lysis of the postsynaptic membrane & binding to the receptor and inhibit its function .) . THE NUMBER OF RECEPTORS REMAINIG IS LOW>>>LOW TRANSMISSION>>>WEAK MUSCLES.

- Main symptoms include the following :

1) **Ptosis** : dropping of the eyelid due to paralysis or a disease .
2) **Diplopia** : the double vision of subjects .
3) **Difficulty in speaking and swallowing .**
4) **Extremity weakness in muscles.**

- NOTE THAT :

●In some severe cases of the disease ; it may affect all the muscles including

those needed for respiration ! Which could put such a risk on life .

● The disease is a resemble to the neuromuscular paralysis produced by d-tubocurarine (competitive blocker of the nicotinic receptors in the muscles, it prevents the action of acetylcholine and nicotinic receptors and it's given during anesthesia to produce muscle relaxation).

● Patients with such disease are very sensitive than normal people to neuromuscular blockers and drugs that interfere with neuromuscular transmission (like aminoglycoside antibiotics such as gentamycin, streptomycin) . If someone with myasthenia took an aminoglycoside, the result that he might die due to the sensitivity to them.

- Patients with **Ocular myasthenia** (related to eyes) can be treated with cholinesterase inhibitors alone.

- When patients have more widespread muscle weakness in body; they are treated with immunosuppressant drugs (: Drugs that can lower the body's ability to resist; which in our case lowering the production of the antibodies), (like; steroids & cyclosporine & azathioprine). Moreover; in severely affected patients; the Thymus gland is removed(because it produces T-lymphocytes that are attacking the receptors) !

- **Edrophonuim** is used as a diagnostic tool for myasthenia .
●it's a short-acting drug ,because it only binds electro statically (doesn't form covalent bonds) ,so it last's 2-10 minutes only.

● If an individual is suspected of having myasthenia due to observed muscle weakness ; he is given a 2 mg dose of endrophonuim intravenously (IV).
If the patient has myasthenia gravis ; then an improvement in muscle strength that would last for about 5 minutes can be observed m So after the confirmation of the condition of having the disease ; the individual is given an appropriate treatment ; given neostigmine or pyridostigmine .

So why are we using edrophonium and not any other drug?
Because if the patient doesn't have myasthenia gravis and has another disease and we give him a long-acting drug, he might suffer from side effects for hours.

●Another condition where edrophonuim is needed for it to be established ; whether the dose is adequate or if the dose is excess . If the dose is not adequate ; then the muscles are not fully strong . So you inject edrophonuim again! If there is an enhancement ; further strength in muscle contraction ; this means the dose of cholinesterase inhibitors is a small dose ; so increase the dose to get the full benefit.

●In other cases , a patient could come to you with muscle weakness though he's been taking neostigmine or pyridostigmine as assigned ; then he should have one of two conditions :

• Either the dose is **very small** ; so he still suffer from muscle weakness.

• Or he is taking a **large dose** which is related to **cholinergic crisis** because – as you know – excessive acetylcholine can cause a neuromuscular blocking which causes muscle weakness .

In order to distinguish between **myasthenic crisis** – due to low dose – and **cholinergic crisis** – due to excessive drug therapy - , we also inject edrophonium . If the patient improves then is taking a low dose so we must increase it (myasthenic crisis) ! But if his condition doesn't improve or get worsen then he has a high dose so just reduce it(cholinergic crisis) !

- The use of its drugs like **pyridotigmine** ,**neostigmine** &**ambenonium** cause muscarinic effects (like ;salivation, Diarrhea , bronchospasm) . So we need atropine to control these effects .However , the muscarinic effect after a while, could exhibit tolerance so that atropine wouldn't be needed .

- Another use of neuromuscular blockade is frequently used as an adjunct to **surgical anesthesia** .

When a surgeon wants to operate on the patient ; he needs the muscles to be at complete relaxation ,which he gets be reducing the concentration anesthetic agent and complement it with neuromuscular blocker so it's safe .

Muscle relaxation is produced by general anesthesia ,which has **4 stages:**

The 4th is irreversible ,reaching it means the death of the patient.

The 3rd stage is called **the stage of surgical anesthesia**, the danger usually in surgeries is mostly due to anesthesia ,high concentrations of the anesthetic can be lethal ,so to make a safe anesthesia ,the physician tries to give the minimal concentration of the anesthetic agent ,this concentration will make the patient unconscious but he/she might still feel pain with incomplete muscle relaxation .so the physician combines the anesthesia with drugs,

giving the patient neuromuscular blockers so that he has full muscle relaxation .
Reversing the effect after the operation can be done by giving the patient anticholinestrases: neostigmine or endrophonuim.

Central Nervous System :

- **Tacrine** ; is a new drug that is used for Alzheimer disease (it is the condition where certain cholinergic nerves in the brain go through atrophy or dry or die , thus the amount of acetylcholine is decreased in these areas which explains its observed signs like forgetting the place and people by the patient) ●It is an anticholinesterase used for the treatment at mild or moderate conditions .
●It has a modest efficacy .
●it shows a significant side effect, which is the hepatic toxicity . (It shows improvement for the patient but cannot go back normal as before having the disease).

- **Donepezil** ; a newer drug(longer acting) with no hepatic toxicity & is used in the treatment of cognitive dysfunction in Alzheimer disease .

♦Toxcity

Cholinergic toxicity varies depending on absorption(well or not well-absorbed) of the cholinoceptors stimulants , access to the CNS (if it reaches the brain or not) and metabolism .

Direct-Acting Muscarinic Stimulants :

●Such drugs (like ; Pilocarpine& Choline esters) can cause excessive parasympathetic effect (like ; excessive sweating , salivation , diarrhea , urinary urgency , cutaneous vasodilation , bronchial constriction & so on) .
●All these effects can be controlled by atropine ; atropine can remove all these effects.

Also ; certain mushrooms like *Amanitamuscaria ;* they contain

muscarinic alkaloids , the ingestion of these mushrooms can cause toxicity within 15-30 minutes , the treatment is by atropine of 1-2mg parenterally (: giving the drug by another mean than swallowing) . (P.S : *Amanita muscaria*is considered to be the first muscarine source .

* Direct-Acting Nicotinic Stimulants :

- Nicotine is a very poisonous material. In fact ; it is used as rat poison .

1. Acute Toxicity :

A fatal dose of nicotine is 40 mg which equals 1 drop of pure liquid-alkaloid ,This dose is present in two regular cigarettes .
Luckily ; not all nicotine is inhaled into the body system when smoking such 2 cigarettes as most of it is destroyed by burning or escapes via "side-stream" smoke !
If infants or children ingest nicotine insecticides or tobacco , it is followed by vomiting in order to reduce/limit the amount of the alkaloid that is absorbed .

What could happen if someone took a large dose of nicotine ?(The toxic effect)

• CNS is affected ; it causes convulsion and may progress into coma and respiratory arrest, Because even in the brain there is depolarizing blockade !

• Skeletal muscle end plate depolarization ; which leads up to depolarization blockade and respiratory paralysis .

• Hypertension and cardiac arrhythmias ; both are potentially fatal !

So the treatment of acute poisoning is symptom-directed (We give the treatment for the symptom that arises from the condition we have) .
Example ; if there is convulsions ; we give anticonvulsants as Diazepam !So ; as follows :
• Muscarinic excess (Its effects) resulting from parasympathetic ganglion stimulation can be controlled with atropine !

• Central stimulation is usually treated with parenteral anticonvulsants such as diazepam !
• Neuromuscular blockade is not responsive to pharmacologic treatment and may require mechanical respiration **!**
(Note that there is no pharmacological for depolarizing neuromuscular blockade , but there is treatment for the NON-depolarizing ones .)

So, what can we do ?
We can give assistant respiration (respiration by machines) till the paralysis goes away .
Fortunately, nicotine in cells is metabolized and excreted relatively rapidly . Patients who survive the first 4 hours (he is not dead yet or no severe brain damage) usually recover completely if hypoxia and brain damage have not occurred.

2. Chronic Nicotine Toxicity :

For smokers , It's well-known now that tobacco smoking is a cause of sudden coronary death and heart-attack .

- Also , high incidences of ulcer recurrences in smokers with peptic ulcer .

One way to help smokers to stop smoking , is to give them nicotine in a form of gum , transdermal patch, nasal spray or inhaler which should help them to overcome smoking .

Varenicline ; is a drug that is developed to help smokers to quit!
How come ?
Because it's a partial agonist **(P.S : refer to Pharmacology book .. Lippincott ..page 33 for a better understanding of partial agonist which is from Doc.Omar's material**) at a central nicotinic receptor . It also has antagonist properties that persist due to its long half-life .
The main idea ; is that it blocks the central nicotinic receptors whom (the receptors) cause the release of dopamine .Dopamine gives the smoker the feeling of pleasure ; so by blocking dopamine release , we cut that pleasure!
It's use is limited by some side effects :
• Nausea .
•Insomnia ; which is habitual sleeplessness or inability to sleep .
• Exacerbation of psychiatric illness like ; anxiety & depression .

*Toxicity of Cholinesterase Inhibitors :

- Its toxicity comes usually from the use of pesticides in agriculture and in homes . Pesticides can cause slowly or rapidly developing symptoms which would persist for many days or even weeks .

- The chemical warfare agents (like ; soman , sarin& VX) , they produce very rapid effects .
They produce parasympathetic symptoms (like ; Miosis, salivation, sweating, bronchial constriction, vomiting and diarrhea) .
Also ; several symptoms in the CNS (like ; Cognitive disturbances ' this is a mental-health disorders related to memory , learning and perception ' , convulsions and coma) usually follows rapidly , accompanied by peripheral nicotinic effects , especially depolarizing neuromuscular blockade that affects muscles such as the ones in the respiratory system ; so you can expect a respiratory-failure !

-THERAPY ; it always includes :
1) Maintenance of vital signs ; especially respiration ; mechanical respiration is very important !
2) Decontamination to prevent further absorption ; like removing all the clothing or washing the skin if contaminated !
3) Atropine parenterally in large doses (intravenously) , sometimes we inject the patient every 15 minutes until we see that the patient is about to have toxicity due to atropine ; like until the pupil is very wide .
So basically , it is given as needed to control signs of muscarinic excess .
Therapy often also includes treatment with pralidoxime (used to regenerate the enzyme) and benzodiazepines (to stop seizures) .

-Preventive therapy for cholinesterase inhibitors :

If soldiers are going to the battlefield , and chemical-weapon agents are expected to be used ; we can prevent the effect of nerve gases by auto-injection syringes !
It usually contains a mix of drugs (most commonly pyridostigmine& atropine),So if he sensed that a gas is thrown ; he can immediately inject himself .
These drugs (mainly pyridostigmine) reversibly bind to cholinesterase ; so when the nerve gas inters the body and circulates there ; it cannot bind to the

cholinesterase enzyme (phosphorylates it) due to the presence of these drugs . (*Remember that atropine will handle the excessive muscarinic effect*) .

- Chronic exposure to cholinesterase inhibitors happens to those who deals with them frequently as pesticides (like ; farmers) causes other toxic effects that sometimes may not be related to the inhibition of the enzyme .
Such as ; the delayed neuropathy associated with demyelination of axons caused by '**neuropathy target esterase**' (NTE) inhibition ! Its symptoms which appear after 1-2 weeks of exposure (delayed not rapid) ; include :
1) Weakness of upper and lower extremities .
2) Un-steady gait ; which is an abnormality in walking
.

- Another nerve toxicity called **intermediate syndrome** ; which occurs after 1-4 days after exposure to organophosphate insecticides . This syndrome is characterized by muscle weakness . It's worthy to denote that the origin of this syndrome is yet not well-known , but it appears to be related to cholinesterase inhibition .

◘ We now start with a new subject ; with Slide number 3 !

♦ Cholinoceptor-Blocking Drugs :

Those are the drugs that block muscarinic cholinoceptors . They are sub-divided into five types:
1) M1 : found ;
• on CNS neruons • symathotic postganglionic cell bodies • on many presynaptic sites
2) M2 : found ;
• in the Myocardium of the heart • smooth muscle organs • some neuronal sites
3) M3 : found ;
• on effector cell membrane • especially found in glandular and smooth muscle cells
4) M4 : play a greater role in the CNS than in the periphery.

- **5) M5** :play a greater role in the CNS than in the periphery.

Note that all of the 5 types are found in the CNS ; yet only M1 , M2 & M3 are found in the peripheral nervous system .

Absorption :

- We have natural alkaloids and synthetic ones .

- Natural alkaloids comes from **Solanaceae** species (plant family) like; *atropabelladonna* (**atopa** : a Greek God that is thought to strangle people+ **belladonna** : is a beautiful lady ; as this drug was as a cosmetic used to plush cheeks and pupil the eyes) . These natural alkaloids and most tertiary antimuscarinic drugs , so absorption is very good , it reaches everywhere ! Scopolamine is absorbed across the skin (transdermal) .

- We also have quaternary antimuscarinic drugs which are synthetic . They don't cross the Brain-Blood-Barrier (BBB) ; so it's doesn't have a central effects . And only about 10-30% of the drug dose is absorbed after oral administration .

Distribution:

- It depends whether we are talking about natural or synthetic antimuscarinic drugs.

- Natural alkaloids like atropine and other tertiary agents are widely distributed; they can reach the CNS within 30 minutes to 1 hour.

- Scopolamine is rapidly and fully distributed into the CNS where there; it has the greater effects than most other antimuscarinic drugs (at low dose it causes amnesia but at high dose it can cause hallucinations, convulsions and excitation).

-On the other hand; the quaternary derivatives are poorly taken up to the brain as mentioned earlier (because they are polar & not lipid-soluble).

Metabolism & Excretion:

- Elimination of atropine occurs in two phases; one phase is rapid and the other is slow.
-The half-life (*t1/2*) of the rapid phase is 2 hours and that of the slow phase is 13 hours ! Atropine exists as *levo*-hyoscyamine in plants; and when you extract the *levo*- ; half of it becomes *dextro*- ; and that mixture is atropine!
-What happens is that the *levo*- metabolized in the fast phase and the other half which is *dextro*- is excreted in the urine.
- Most of the rest appears in the urine as hydrolysis and conjugation products.
-The drug's effect on parasympathetic function declines rapidly in all organs except the eye.
-Effects on the iris &ciliary muscle persist for 72 hours or more than that and the eye don't go back fully-normal till two weeks!

Mechanism of Action:

- Drugs go with competitive antagonism for muscarinic receptors. Atropine causes reversible blockade (can be overcame by increasing the concentration of the agonist).

- Muscarinic receptors are **constitutively active** (tend to shift into the active form); (remember that receptors are present in active form and inactive form).
Muscarinic blockers are inverse agonists ; agonist with below than zero intrinsic activity , that shift the equilibrium to the inactive state of the receptor , Like ; atropine , pirenzpine , trihexyphenidyl (used in Parkinson disease treatment) & a methyl derivative of scopolamine .
- Tissues most sensitive to atropine are the salivary, bronchial, and sweat glands. (It can cause complete dryness)
- Secretion of acid by the gastric parietal cells is the least sensitive to atropine.
- Antimuscarinic agents block exogenous cholinoceptor agonists more effectively than endogenously released acetylcholine.

GOOD LUCK ;D

P.S : Sorry for any mistakes that were made ; as this is my first time in attempting to write a sheet !.. ~