Medical Committee
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PHARMACOLOGY

Lecture No.: 19

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Antimuscarinic drugs and Sympathomimetics

Peace be upon you my friends , this is the 1st lecture after the midterm week but the 2nd lecture after the midterm material , I hope you all did great in your exams ☺ and bl tawfeg insha'a Allah .

Today's lecture will be a continuation for the previous lecture "cholinoceptors blockers " and a new subject " sympathomimetics " .

Antimuscarinic drugs

We talked in the previous lecture about antimuscarinic drugs, some of their sources, their pharmacodynamic and pharmacokinetic. And we started talking about their effects on body organs systems:

1. The central nervous system CNS
2. The eyes
3. Cardiovascular system CVS

And today we will continue with:

4. Respiratory system
5. Gastrointestinal tract
6. Genitourinary tract
7. Sweat glands (sympathetic cholinergic fibers)

4. Respiratory system: Antimuscarinic drugs will produce the reverse effect of the cholinomimetics. What will happen to the bronchi is dilatation, secretion will decrease, in addition to that there will be prevention of laryngospasm.

What is laryngospasm: it is an uncontrolled contraction of the laryngeal muscles which will result in narrowing the airway and thus suffocation so the patient will not be able to breathe.

** Another premedication use of Atropine and Scopolamine (we talked about amnesia as premedication use affecting CNS) is that they prevent laryngospasm during anesthesia; general anesthetic agents induce laryngospasm so the patient will not be able to breathe, so Atropine and Scopolamine are used in such cases.

5. Gastrointestinal tract GIT: cholinomimetics increase the secretions and contractions of the wall and relax the sphincter, now the reverse will occur with Atropine and Scopolamine and other antimuscarinic drugs; relaxation of the wall, decrease the secretions and contraction of the sphincter. These effects can be modified (reversed) by:

1. Local **hormones** secreted in the GI tract.

2. **Non-adrenergic** neurons present in GI tract.

3. **Enteric nervous system**

***Enteric nervous system:**

They call it **GUT BRAIN** because the GI tract can be controlled by a collection of nerves found in plexus (neuronal plexus) that are isolated from the autonomic nervous system ANS and CNS , it can be considered as a third classification of the nervous system ; 1. ANS 2.CNS 3.Enteric nervous system, and the three of them are inter-related.

People say "I have a gut feeling that (e.g.) something bad is going to happen" and they mean that they have an instinct or intuition (idiomatic) and they don't know that there is a nervous system found in the gut .

As we said, one of the effects of antimuscarinics is the reduction of secretions in the gut wall, if we traced the gut wall from the mouth to the colon we will find:

* Reduction in salivary secretions →dry mouth

* Reduction in gastric secretion

* Reduction in intestinal secretion

* Reduction in the Pancreatic secretion

(these reductions are up to different extents)

Antimuscarinic drugs block the part of parasympathetic secretion which is **the baseline secretion.** Now you are sitting and you have secretions in your mouth, intestine, stomach that is called basal secretion which is a parasympathetic function. If you are chewing gum you will have a lot of secretions in your mouth we call this **stimulated secretion** and not reduced by Atropine or scopolamine or any other antimuscarinic drugs.

Relaxation of the gut wall muscles : if you relaxed the wall of the stomach then the emptying time of the stomach (gastric emptying time) will be prolonged (the time needed for the food from ingestion till leaving the stomach will be longer) so the propulsive movement of the stomach will be slower which may lead to food rotting and for the drugs that are absorbed in the stomach (especially **acidic drugs**) longer time means **more absorption** , but in case of **basic drugs** which are absorbed in the intestines their absorption will be **delayed**. In intestines emptying time is called **intestinal transit time** (at least 6 hours in normal individuals), prolonged transit time and dry of secretions will lead to constipation (more solid stool), propulsive movement is responsible for the expulsion of feces and gases and when this movement is reduced, constipation will happen.

6. Genitourinary tract:

Relaxation of the bladder wall due to antimuscarinic drugs will lead to **urinary retention,** we said that the muscarinic (cholinergic) stimulation will lead to contraction of bladder wall and thus urination (voiding) will occur, but here the reverse will occur. **Urinary retention** is the case where the urine stays in the urinary bladder which leads to urinary tract infections, and as the doctor said if you bring a glass of water and leave it for a day or two on the table after that try to drink it, you will not even try because you will find that it has a bad smell and that smell is due to bacterial growth since it is static (no movement). In the case of urinary tract infections, it will spread to the kidneys and cause infections too.

7. Sweat glands (sympathetic cholinergic fibers): sweat glands are sympathetic but we mention them here because the thermoregulatory sweat glands are innervated by cholinergic nerves. As we know that sweating help in reducing the body temperature, blocking cholinergic receptors will elevate body temperature.

*Some animals like dogs don't have thermoregulatory sweat glands and that's why they keep their mouth open to lose heat from the surface of the tongue, otherwise their body temperature will be elevated.

Therapeutic uses of antimuscarinic drugs

Antimuscarinic drugs inhibit the muscarinic receptors, and they are **not specific** in their actions thus they have very limited therapeutic uses .Atropine is modified to perform functions that are specific to some extents.

1. Linking a benzene ring with atropine makes it more lipid soluble **Benztropine** and that aids in crossing the blood brain barrier and can be used in treatment of Parkinson's disease.

2. Motion Sickness: we use a drug called **Scopolamine** (PO, parenteral and transdermal patch) which can be used for prevention and treatment.

*__motion sickness__: the state of being dizzy or nauseated because of the motions that occur while traveling in or on a moving vehicle.

3. To produce mydriasis for eye examination and to prevent adhesions in inflammatory conditions in the eye: **Tropicamide** (given as eye drops in the conjunctival sac not orally) which has smaller action duration than Atropine and thus more favorable, it causes blurry vision and people go to work or schools and don't want long duration of action that's why it's favorable.

4. To prevent airway secretions and laryngospasm associated with general anesthesia (premedication): **Atropine**, **scopolamine** (also produces amnesia).

5. Bronchial asthma and chronic obstructive pulmonary disease (COPD): **Ipratropium** by inhalation and its action is only in the lungs that makes it more specific than Atropine.

6. Bradycardia associated with excessive vagal stimulation**: Atropine**

7. Peptic ulceration**: Pirenzepine** which is more specific for gastric secretion.

8. Diarrhea ,diarrhea is not a disease it is a symptom of diseases and to be a good physician you should treat diseases not symptoms , so never try to treat diarrhea except if you know the cause and after you treat the cause , but you should treat diarrhea because it can lead to electrolytes and fluids imbalance in the body .

9. Urinary incontinence (involuntary urination, disability to control urination)**,** we said antimuscarinic drugs cause urine retention by relaxing bladder wall so they give the patient time to control urination and have the time to go to the bathroom and not urinate on himself **: Tolterodine**

10. Cholinergic poisoning (insecticides "carbamates and organophosphates", mushrooms, chemical warfare "part of organophosphates"): **Atropine**, for any mushroom poisoning that has cholinergic symptoms you can use Atropine.

- We said before that soldiers carry with them physostigmine injections in case they got attacked by nerve gas. Physostigmine is a reversible inhibitor of cholinesterase while organophosphates (nerve gas) are irreversible inhibitors, so by administrating physostigmine you'll occupy some of the active sites of the enzyme and prevent organophosphate from binding to them. Which results in converting the irreversible block of the enzyme into a partial block(less harmful effect), but to cure nerve gas poising; Atropine is the used medication.

Adverse effects of animuscarinic drugs

(exaggeration of the pharmacological effects)

1. Mydriasis that lead to blurring of vision (more light will enter and the patient will not be able to see) and cycloplegia (paralysis of the ciliary muscle of the eye) that inhibits accommodation for near vision.
2. Hallucinations, agitation, delirium.

   *delirium and hallucinations are different ; hallucination is perception of not existing things but the sensorium (الوعي) is intact and people who hallucinate they know that this is dr. Yacoub for example and this is a pharmacology lecture for 2nd year med students so they are in full sensorium, delirium is a hallucinations with being disoriented or confused , the patient may be in the classroom and tell you that he is in Aqaba and President Barack Obama is the one he is talking to at the moment .
3. Dry mouth, dry secretions, constipation.
4. Tachycardia (abnormal increase of heart rate).
5. Hot flushed skin; these drugs are vasodilators they block the vasodilatation of Ach in the parasympathetic but at the same time they do vasodilatation by their action.
6. Fever because of the block of thermoregulatory sweat glands.

Contraindications of antimuscarinic drugs

They are absolute contraindications not relative; so you can't give these patients these drugs no matter what.

1.Glaucoma: giving Atropine to patient with glaucoma will cause blindness , so even before giving **Tropicamide** for examination of the eye you should measure the intra-ocular pressure , if it was above the range don't ever give him Atropine.

2. Prostatic hyperplasia (benign enlargement of the prostate) with urine retention, when prostate is enlarged it will press the urethra narrowing it and the urine will not be completely excreted, it will be sporadic and always there is retention. if you give antimuscarinic drugs you will cause more urine retention because of relaxation of the bladder wall.

Sympathomimetics ...

Sympathomimetics are drugs that imitate or mimic the action of the sympathetic nervous system →drugs that stimulate the adrenergic receptors, or prevent the reuptake of catecholamines, or displace catecholamines from their synaptic vesicles.

Modes of action:

1. Direct stimulation of adrenoceptors.

2. Inhibition of catecholamine reuptake **(cocaine, tricyclic and tetracyclic antidepressants).**

3. Displacement of stored catecholamines from the adrenergic nerve endings **(amphetamine, tyramine).**

Amphetamine is a CNS stimulant , lipid soluble drug that can cross the blood brain barrier and stimulate the central nervous system , it is used by addicts because it causes euphoria , truck drivers in the western countries also use amphetamine because it keeps them awake during long journeys , but you as medical student you can't use it to stay awake **IT WILL NOT HELP YOU** ; if you usually can study 5-10 pages per hour and you have an exam in the next day and the material is about 40 pages you usually take about 5-6 hours to study but if you use amphetamine you will stay awake all night long but you will not be able to finish at least one or two pages (you can't focus).

Tyramine displaces catecholamines in the **periphery** more that the CNS, it is found in the rotten cheese, in wine, in liver (as a food ; animals liver), in some fruits like banana**, but it isn't available as drug.** When you take tyramine it reaches the synaptic terminals and replaces epinephrine and nor-epinephrine in the synaptic vesicles thus EN and norEN will be discharged and will exert more effect than normal. Usage of tyramine by itself is not a problem because it can be metabolized and its action is temporary, metabolism of tyramine is done by monoamine oxidase (MAO) and if you have a problem with MAO (deficiency or inhibition) tyramine will accumulate in the body and will displace a huge amount of catecholamines and that will lead to what we call **hypertensive crisis**. So MAO inhibitors should be given with food that is not containing significant amount of tyramine.

*the greater the rot in the cheese the higher the amount of tyramine so if you eat this cheese you should not take any MAO inhibitors.

*** tyramine in the body ::**

More MAO means less tyramine accumulation

More MAO inhibitors means more tyramine accumulation

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Sympathomimetics and receptors

Direct stimulation of the receptors (adrenoceptors), α & β.

You should memorize the table (b9m), but as the doctor explained it.

Table 9–2. Relative selectivity of adrenoceptor agonists.

	Relative Receptor Affinities
Alpha agonists	
Phenylephrine, methoxamine	$\alpha_1 > \alpha_2 >>>>> \beta$
Clonidine, methylnorepinephrine	$\alpha_2 > \alpha_1 >>>>> \beta$
Mixed alpha and beta agonists	
Norepinephrine	$\alpha_1 = \alpha_2; \beta_1 >> \beta_2$
Epinephrine	$\alpha_1 = \alpha_2; \beta_1 = \beta_2$
Beta agonists	
Dobutamine[1]	$\beta_1 > \beta_2 >>>> \alpha$
Isoproterenol	$\beta_1 = \beta_2 >>>> \alpha$
Terbutaline, metaproterenol, albuterol, ritodrine	$\beta_2 >> \beta_1 >>>> \alpha$
Dopamine agonists	
Dopamine	$D_1 = D_2 >> \beta >> \alpha$
Fenoldopam	$D_1 >> D_2$

[1]See text.

Alpha agonists: tens of these drugs are found and as example we took phenylephrine, methoxamine, clonidine and methylnorepinephrine.

***Phenylephrine** and **methoxamine** affect both α1 &α2 receptors but α1 more, forget about β.

* **Clonidine** and **methylnorepinephrine** affect both α1 &α2 receptors but α2 more.

Mixed alpha and beta agonists: epinephrine and nor-epinephrine (the difference between these two agonists is in a methyl group which is linked to epinephrine –nor epinephrine lacks a methyl group (nor = lack)).

* **Norepinephrine** equal effect at α1 & α2 receptors, and more selective relatively to β1 compared to β2.

* **Epinephrine** also act equally at α1 & α2 receptors, but also equally at β1 and β2.

Beta agonists: dobutamine , isoproterenol , terbutaline , metaproterenol , albuterol and retodrine .

* **Dobutamine** works at β1 mainly, more than β2. β1 receptors are found mainly in the heart and juxtaglomerular apparatus in kidneys.

* **Isoproterenol** acts on both β1 and β2 equally, and doesn't work on α receptors.

* **terbutaline , metaproterenol , albuterol and retodrine** work at β2 much more than β1 , and they are relatively selective, which means that selectivity will be lost due to huge amount of the drug (increased dose or increased concentration) and the drug will stimulate the other receptors.

__therapeutic uses of these drugs :__ we talked in the previous lectures about the uterus and the receptors found there are β2 receptors , these receptors increase in number due to pregnancy and in case of premature labor you can give these drugs **(terbutaline , metaproterenol , albuterol and retodrine).** These drugs are used also to treat bronchial asthma, since bronchi have β2 receptors more than α1, β2 relaxes the smooth muscles and α1contracts the smooth muscles.

__Dopamine agonists:__ dopamine and fenoldopam

***Dopamine** dilates the renal vascular bed at __low concentrations__ by D1 receptors, and if you increase the dose it may stimulate the other receptors, increasing the dose stimulates β, and more increase will stimulate α which causes vasoconstriction.

- If we patient took dopamine to dilate the renal vascular bed and it didn't work well, increasing the dose won't be a wise decision, since it'll stimulate α receptors causing vasoconstriction.

***Fenoldopam** is used as a vasodilator to treat hypertensive emergency and hypertensive crises, through D1 receptors.

The actions in the two other tables you should know them from the previous lectures

you should know all alpha 1 actions

about alpha 2 you the doctor commented:

Clonidine can be used to treat hypertension while phenylphrine causes hypertension, the 1st acts on alpha 2 and causes vasodilatation (negative feedback inhibition of catecholamine release), and the 2nd acts on alpha 1 and causes constriction and elevate diastolic pressure.

blood pressure; we have diastolic and systolic blood pressures, systolic reflects the contractility of the heart (when elevated; the heart is pumping stronger), diastolic reflects the resistance of blood vessels to this pumping and we call that **(peripheral vascular resistance).** In cases of vasoconstriction; resistance increases and diastolic pressure increases while in cases of vasodilatation resistance decreases and diastolic pressure decreases. Norepinephrine increases the diastolic and systolic pressures because it simulates alpha 1 and beta1 receptors, while epinephrine increases the systolic and

decreases the diastolic because it works on beta 2 which causes vasodilatation. In the best conditions epinephrine doesn't affect the systolic although it has alpha 1 receptors but because beta 2 receptors are more extended in our body in the blood vessels to the skeletal muscles and we have more blood vessels in the muscles than the skin for example so the net effect is vasodilatation and reduction in the diastolic pressure (no increase in the systolic **relatively**).

beta 1 receptors affect the heart and juxtaglumerular apparatus in the kidneys and increase the contractions.

beta 2 receptors will relaxes the respiratory muscles, in skeletal muscles promote potassium uptake into the cell and can be used to treat hyperkalemia (elevated **[K+]** in the blood) . In human liver glycogenolysis is activated by these receptors too.

beta 3 receptors activate lipolysis

D1 dilate renal blood vessels.

Good Luck All

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