PHARMACHOLOGY

Lecture 15

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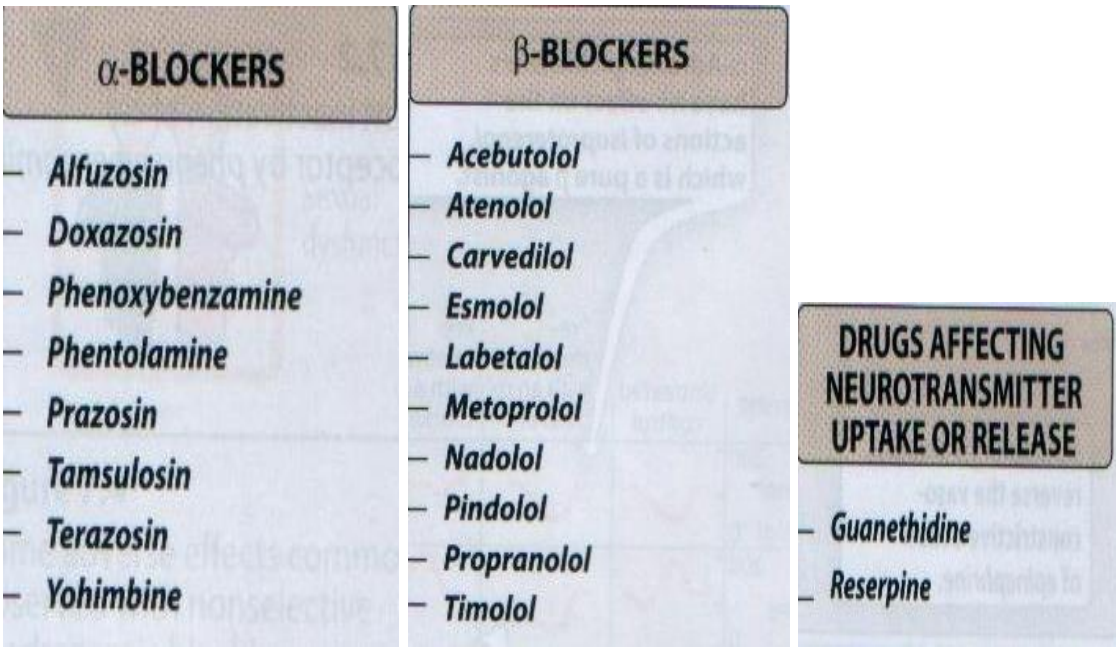
Underlined sentences refer to anything that was mentioned in the record but not in the slides.

The adrenergic antagonists:

- **Also called adrenergic blockers or sympatholytic agents**
- **Bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects.**
- **α-Adrenergic Blocking Agents**
- **β-Adrenergic Blocking Agents**
- **Drugs affecting Neurotransmitter Release Or Uptake**



We have three types of blockers:

1. Alpha blocker
   This drug (blocker) for example will be used for a hypertension .

2. Beta blocker
   This drug is mainly targeted to the heart and it will reduce atrial fibrillation , arrhythmia, decrease the heart rate and sometimes the blood pressure.

3. Alpha and beta blocker(mainly inhibit releasing)
   Inhibit releasing adrenalin or noradrenalin so will affect all receptors (because they acts on synaptic receptors) so no action at these receptors.
   This type of blockers is therapeutically less important for example reserpine was used until 1996 it was used for hypertension disease but they noted that it has a very very side effect because it's not selective rather than it inhibits adrenaline releasing so it will affect many receptors

In each case I have to know what the target receptor and which one is blocked because that action is different from one to another.

A. α-Adrenergic Blocking Agents:

Importance of alpha1 receptors:

1. For example it's found in the sphincters of the kidney → it makes a contraction so it will decrease the size of urinary bladder and reduces pressure on the prostate gland so we can use it for benign prostate hypertrophy
2. Found in the smooth muscles in blood vessels and leads to vasoconstriction

a) selective α- adrenergic blocker:

- They are selective competitive blockers of the α1 receptor.
- prevents vasoconstriction of peripheral blood vessels and decreased peripheral resistance

1) **Prazosin, terazosin, doxazosin (**for hypertension and congestive heart failure)
   - By dilating both arteries and veins, these agents decrease preload and afterload, leading to an increase in cardiac output

2) **tamsulosin, and alfuzosin (for** benign prostatic hypertrophy BPH)
   - Blockade of the α1- receptors decreases tone in the smooth muscle of the bladder neck and prostate and improve urine flow.

- It's the first choice for hyper tension. Why?

- Because Alpha blocker can be alpha 1 blocker or alpha 1,2blocker. What choice is better?

- To understand clearly let's take this example :

  You gave an alpha 1,2 blocker what will happen? As we said alpha1 is located in the smooth muscles in blood vessels if we block it that will inhibit or inverse vasoconstriction → that leads to decrease resistance and blood presser.

At the same time alpha2 which is inhibitory for sympathetic will be blocked → stimulation for sympathetic→ releasing of adrenaline → alpha2 now is stimulatory

- So these two actions are antagonist to each other

- We understood that you can't use these drugs in hypertension because you decreased it by alpha1 blocker but after that you increased it by alpha2 blocker (inhibition for inhibition leads to stimulation)

- This type of effect called contradictive effect.

- Now let's talk about the cases in which these type of drugs are given :

As the doctor mentioned above in the slides:

1) Prazosin, terazosin, doxazosin (for hypertension)

- These drugs are mainly used for hypertension.. But why we don't use beta1 blocker in this case? Simply if you have a patient who has hypertension with congestive heart failure which means that he doesn't have good heart contractility if we give beta blocker this is one of the contraindication cases.
- Why Prazosin is considered as an excellent drug for this case?

Because it's decrease the hypertension without affecting the heart.

2) tamsulosin, and alfuzosin (for benign prostatic hypertrophy BPH)

- why we give these drugs in this case? Because they are more directed means that they are more selective to alpha1A receptor in smooth muscles of urinary bladder.

- So it can do more smoothing in urine flow → decreasing prostate gland pressure on the bladder →smoothly urinate.
- Alpha1 receptors have two subunits alpha1A and alpha1B and these drugs are more selective to it so we can use them in hypertension with prostate hypertrophy cases.

b) Non-selective α- adrenergic blocker:

1) Phenoxybenzamine

- Link covalently to both α1- and α2-receptors
- Irreversible, non-competitive
- Action last 24 hours
- Action: prevents vasoconstriction of peripheral blood vessels, decreased peripheral resistance, provokes a reflex tachycardia
- This drug is unsuccessful in maintaining lowered blood pressure in hypertension, why?
- Used in the treatment of pheochromocytoma, a catecholamine-secreting tumor of cells derived from the adrenal medulla.

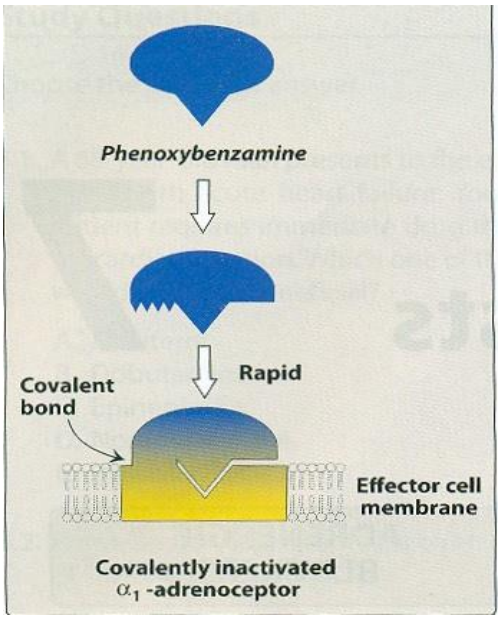
2) Phentolamine

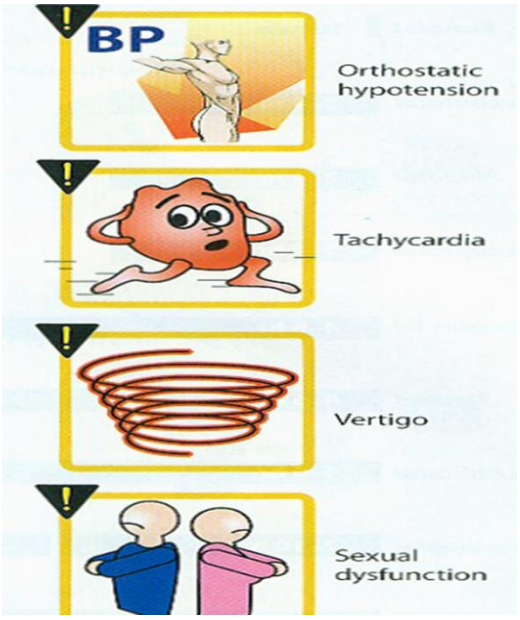
Furthermore, the ability to block presynaptic inhibitory α2 receptors in the heart can contribute to an increased cardiac output. [Note: These receptors, when blocked, will result in more norepinephrine release, which stimulates β receptors on the heart, increasing cardiac output.]

- Why we use these drugs in pheochromocytoma?
- We have two types of tumors :
  1. Functioning : do its functions like normal cells

2. nonfunctioning : don't do the function like cancerous hepatocytes in liver

- so in pheochromocytoma the tumor cells can release adrenaline like normal cells but in big amount(more cells are working)
- how can I treat it : these drugs will be given as supportive treatment (you have to treat cancer firstly) so you give the two drugs above … they will block all the over action.





About the first picture:

Notes about Phenoxybenzamine:

- It smoothly released from the drug and makes a covalent bond with the receptor(strong bond) and it last for 24 hours .
- This is bad for treatment of hypertension because after it lowers the pressure it doesn't released.
- But that is better for pheochromocytoma to inhibit as many receptors as possible.

About the second picture: side effects of these drugs:

- orthostatic hypotension :

هلأ كل الأشخاص الي بياخدوا alpha blocker ما بصير يقوموا فجأة لانه مباشرة رح يصير عندهم postural hypotension Or orthostatic hypotension
ففجأة بدوخ وبينزل ضغطه وهالشي بصير مع أي حدا بياخد vasodilator ولازم يقوم ب step wise يعني اذا كان نايم يقعد بعد ما يقعد يقوم وهكذا ...

- tachycardia :

The vasodilator drugs cause two things:

1. throbbing headache
2. reflex tachycardia (palpitation)

- sexual dysfunction:

mainly in males because of rectal dysfunction.

B. β-adrenergic blocking agents:(for cardiovascular system)

a) nonselective β antagonist:

mean it can block beta1 and beta2

1) Propranolol

- Antagonist both β1 and β2 receptors action:

1. Negative inotropic effect : reduced cardiac output
2. Negative chronotropic effects: depresses sinoatrial and atrioventricular activity cause Bradycardia
3. Peripheral vasoconstriction (prevents β2-mediated vasodilation)

4. Bronchoconstriction: contraindicated in patients with COPD or asthma
5. decreased glycogenolysis and decreased glucagon secretion.— Hypoglycemia

- non selectivity effect on beta2 receptors by this drug:
- For a patient without asthma is good but with one who has increased heart rate and asthma it will make a bronchoconstriction more than what he need →sever asthmatic attack. Means you can't give this drug(contraindicated not with caution) because you will kill the patient even if you gave him salbutamol .
- when you give salbutamol with Propranolol you are giving beta2 agonist with beta2 antagonist
- in this situation the antagonist one will work causing bronchoconstriction→ after the half-life it will start releasing → salbutamol will attach to the receptors بس بوقتها يكون المريض مات قبل ما يشتغل

- a patient with diabetes :
- beta2 increase glycogen degradation and increases blood glucose levels
- if we block this receptors sever hypoglycemia will happen
- if you give this drug to a patient who have a hypertension with diabetes it will mask the hypoglycemic effect(mask the symptoms)
    - at a normal situation a person with hypoglycemia will feel headache and he will have reflex tachycardia but in the case above he will not so it's contraindicated.

- A patient with high levels of triglyceride:
- It will inhibit lipolysis.
- Causes triglyceridemia.

- Therapeutic Uses

A. Hypertension

Blood pressure = cardiac output * heart rate

When the heart rate id decreased the cardiac output decreased→ volume of blood decreased→ the blood pressure decreased.

This is the main mechanism not the vasoconstriction or vasodilation.

B. Migraine

Used as a prevention and they found that it helps to decrease the attack (the mechanism is on the blood vessels.)

C. Angina pectoris

- decrease in heart rate, Cardiac output, work, and oxygen consumption

- In this case this drug is very important for prevention
- For anyone who has MI or angina he must be given a beta blocker
- This is one of American Heart Association (AHI) guideline
- What do we mean by angina? There is no enough blood supply to the heart because of the coronary artery blocking
- This depend on something called oxygen demanding → depending on how many contraction happened → more contraction more oxygen demand → once the demand less than the need for the heart rate even if there is no blocking in the artery the attack will occur .
- This drug will slow down heart rate → so slowing down oxygen demand
  - أشياء حكتها الدكتورة عن ال angina ..

الجلطات بتصير أكتر شي وقت ال efforts فشي اسمه angina of efforts وفي كمان angina at rest

The angina at rest happened because of vasoconstriction in coronary artery

At effort: because the oxygen demand is more than supply …

D. Myocardial infarction

E. Hyperthyroidism

- Means over secretion of thyroxin which causes many metabolism
- One of the effecting is arrhythmia and hypertension
- This drug block the symptoms of arrhythmia and doesn't treat the over secretion of this hormone.

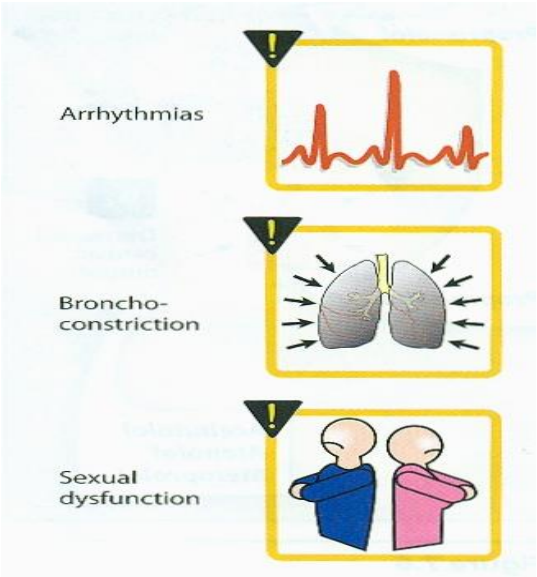
- **Pharmacokinetics**

1. oral administration
2. completely absorbed
3. Highly lipophilic.

- This drug has a high lipophilicity which means it can enter the BBB
- Maybe it causes hallucination

4. It is subject to first-pass effect.

- Side effects of propranolol:



1. **Bronchoconstriction:** so it must never be used in treating any individual with COPD or asthma (C/I)

   It's one of the major side effects.

2. **Arrhythmias? HOW? Up-regulation of receptor? Tapered dose?**
3. **Sexual impairment**

   Mainly in males(male rectal dysfunction)

4. **Metabolic disturbances:** Fasting hypoglycemia
5. **CNS effects:** depression, dizziness, lethargy, fatigue, weakness, visual disturbances, hallucinations, and others

- Remember:

- Treatment with β blockers must never be stopped quickly because of the risk of precipitating cardiac arrhythmias,
- The β blockers must be tapered off gradually for at least a few weeks.
- Long-term treatment with a β antagonist leads to up-regulation of the β receptor.

- A very important point that the doctor said:
- How to stop beta blocker (how to stop taking this drug) ? This point will be explained by this case:

- A 35 years old patient with a hypertension and he was taking beta blocker (for example propranolol) for one year but after that the disease can't be controlled by this drug → now as a doctor you want to use a different drug with different mechanism to control this disease for example ACE inhibitor.

- The reason that why this drug can't control this disease is because during the time the human body starts producing new receptors to maintain the normal number of them after the older ones was blocked.(over expressed new receptors or up regulation of receptors)
- Now when the patient stop taking the blocker his body has big amount of adrenergic receptors(more than he needs) which will attach with adrenalin and noradrenalin (released normally from the body) → leading to over stimulation → leading to rebound hypertension and tachycardia.
- So what is the exact mechanism to stop this drug?
- By something called tapering dose which means down the dose gradually

يعني كان ياخد حبتين باليوم بصير حبة لمدة أسبوعين بعد الأسبوعين بنصير نخفف الجرعة تبعة الحبة يعني بدل 500 بتصير 250 وكل مرة بنقللها by half لحتى يوصل لل minimum بياخدها كل يوم بعديها مرة كل أسبوع بعديها بيوقف الدواء.

- If you stopped the drug suddenly you will cause angina to the patient …how?
- Because you increased the heart load → increased the oxygen demand→no enough oxygen → angina.

2) **Timolol and nadolol:**

- They are more potent than *propranolol*
- Block β1- and β2-adrenoceptors
- Nadolol *has a very* long duration of action
- Timolol reduces the production of aqueous humor in the eye.
- It is used topically in the treatment of chronic open-angle glaucoma
- The doctor mentioned a case that there was a patient with Bradycardia, after she checked the types of drugs that the patient was taking she notes that there is an eye drop (Timolol) which can block beta1 and bet2 two

receptors even if it's an eye drop it can be absorbed by 10-20% to the blood.

- The patient also has congestive heart failure so small amount of Timolol leaded to Bradycardia
- In these type of cases instead of using Timolol use one of the cholinergic agonist if the disease can be cured by them.

b) Selective β1 antagonists

- **Metoprolol, Atenolol, Bisoprolol, Betaxolol, Esmolol**
- They are cardio selective β1 blockers
- Cardio selective at low doses and is lost at high doses

- Therapeutic use

1) in hypertension, post MI and post angina.

- useful in hypertensive patients with Asthma and COPD Like asthmatic patients because it doesn't affect bet2
- Are useful in diabetic hypertensive patients who are receiving insulin or oral hypoglycemic agents.
- Are useful in high cholesterol levels with hypertension.
- They aren't sever lipophilic so the don't cross the BBB and don't make problems in the CNS
- Less sexual dysfunctions than the nonselective ones.

c) Antagonists of both α and β (novel drugs):

- **Labetalol and carvedilol:**

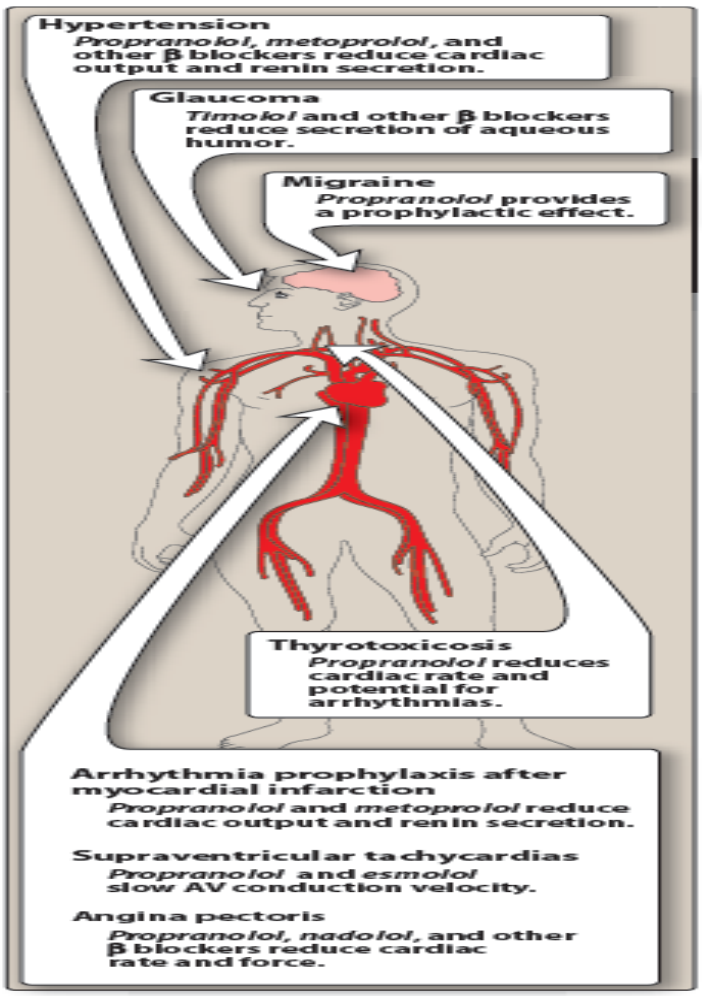
- α1-blocking actions that produce peripheral vasodilation, thereby reducing blood pressure
- Blocking alpha1 and beta1

- They do not alter serum lipid or blood glucose levels
- **Therapeutic use** in hypertension in elderly and heart failure
- IV Labetalol as an alternative to methyldopa in the treatment of pregnancy-induced hypertension.(in emergency)

- they are not completely blocker (partial agonist antagonist) means that they don't cause severe hypotension or sever Bradycardia. **So they are excellent at emergency cases .**
- hypertensive crisis: an emergency cases in which the blood pressure is 220/180 or around that in this case you use nitroprusside(IV infusion) which releases NO which is a vasodilator. Then it decrease the pressure to 100

- note that if the pressure was 150 this drug is contraindicated because it will cause severe hypotension and death. So You give IV labetalol for him

- Question : pregnancy woman has gestational hypertension in the 26 weak what is best drug for her? Methyldopa which is alpha2 stimulator is the main drug used in this case →stimulation for inhibitor→inhibition for adrenaline.
- Methyldopa is very safe for the pregnant woman and given in any time in pregnancy.
- Instead of methyldopa you can use IV labetalol just at emergencies (a sudden hypertension which causes endometrial toxemia)



C) Drugs affecting neurotransmitter release or uptake(antagonists):

a) Reserpine

- blocks the transport of norepinephrine, dopamine, and serotonin from the cytoplasm into storage vesicles in the adrenergic nerves of all body tissues

- it was used for hypertension but they note that it causes obesity because this drug is centrally working in the brain so it increase the hepatitis and it change lipid distribution profile in the body

b) Guanethidine

- Blocks the release of stored norepinephrine from storage vesicles

- Guanethidine we can use it in the cases of pheochromocytoma and cancer but not in hypertension because it's non selective
- Reserpine Guanethidine are antagonists for neurotransmitter release or uptake but at indirect mechanism

- Summary:

DRUG	RECEPTOR SPECFICITY	THERAPEUTIC USES
Propranolol	β_1, β_2	Hypertension Glaucoma Migraine Hyperthyroidism Angina pectoris Myocardial infarction
Nadolol *Timolol*	β_1, β_2	Glaucoma Hypertension
Acebutolol[1] *Atenolol* *Esmolol* *Metoprolol*	β_1	Hypertension
Pindolol[1]	β_1, β_2	Hypertension
Carvedilol *Labetalol*	$\alpha_1, \beta_1, \beta_2$	Hypertension Congestive heart failure

Questions

Choose the correct β-blocker???

- The best treatment for hypertensive patients with Asthma is ----------

  Selective beta1 and Labetalol and carvedilol but the selective are better.

- The best treatment for hypertensive patients with hyperlipidemia is ----------

  Alpha and beta blockers : Labetalol and carvedilol

- The best treatment for hypertensive elderly patients is ----------

  Alpha and beta blockers : Labetalol and carvedilol أفضل شي لإلهم

  ملاحظة مهمة: دائماً دائماً الكبار بالعمر حاول ابتعد عن ال receptors قد ما نقدر يعني ما تعطيهم شي full antagonist لانه ال sensitivity for them is very high

- The best treatment for hypertensive patients with Diabetes is ----------

  Selective beta1

  هون الدكتورة حكت انه كل شي بينفع عدا ال propranolol

- The best treatment for hypertensive patients with angina -----

  We can use all

  But here if you want to use propranolol you have to chick all the history … there is no diabetes Asthma hyperlipidemia … etc.

- The best treatment for hypertensive pregnant lady is------

  Methyldopa is not beta blocker so the answer is labetalol

DONE