SHEET NO.

19

PHARMACOLOGY

DOCTOR 2019 | MEDICINE | JU

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مهم تقرأوا هاد البوكس:
1) صفحة ١٠ عدلنا كلمة ظللناها بالأصفر شوفوها
2) صفحة ٦ اسم الإبرة مش أكيدين منه، كلام الدكتور ما كان واضح كتير،، :(

❤️ **سبحانك لا علم لنا إلّا ما علمتنا إنك أنت العليم الحكيم**

Alpha Adrenoceptor Antagonists

Pharmacologic Effects Of Alpha-Receptor Antagonists:

1. miosis -> alpha receptors of the ires muscle are blocked

2. nasal stuffiness(as if you have common cold) -> alpha receptors on nasal mucosa

3. decreases resistance to the flow of urine (reduce urinary urgency).

*As long as Alpha1 receptors are expressed in the base of the bladder and the prostate

*Note: Alpha blockers are used for the treatment of urinary retention due to prostatic hyperplasia **like terazosin, doxazosin, prazosin and tomsulosin**

4. cardiovascular effects:

Alpha receptor antagonists block A1 receptors on vascular beds —> So this removes the sympathetic tone on the blood vessels and this causes vasodilation.

🌸 vasodilation -> ↓ peripheral vascular resistance and blood pressure.

🌸 Prevent the pressor effects of α agonists (by phentolamine)

🌸 often cause orthostatic hypotension (hypotension within three minutes of standing when compared with blood pressure from the sitting or supine position)

➔ When you stand up your pressure goes down because A1 receptors on big veins on your legs are blocked —> this inactivates sympathetic reflex in legs —> blood pooling in legs —> decreasing the central blood volume —> less blood going to the brain causing dizziness and faintness

🌸 reflex tachycardia; nonselective (α 1 = α 2,) blockers cause tachycardia if blood pressure is lowered below normal.

*remember: nonselective alpha blockers —> block alpha-1 and alpha-2 equally

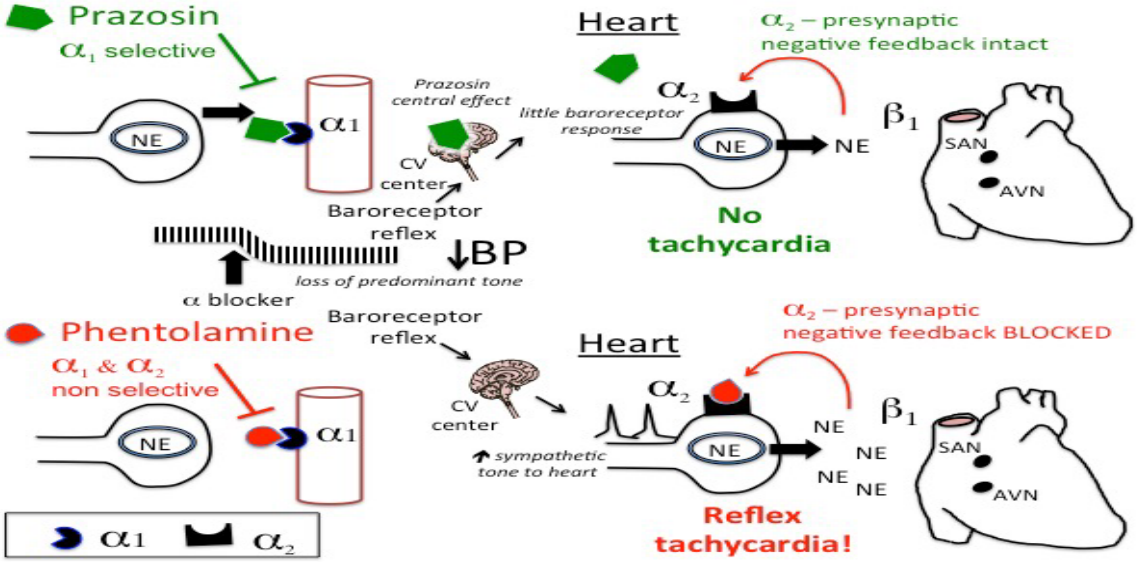
Effects of selective & Non selective alpha blockers on HR

Prazosin (A1 selective) blocks A1 on blood vessels -> decreases peripheral resistance:

1) decrease blood pressure

2) evokes baroreceptor so cardiovascular center activates sympathetic nerve to the heart (the aim is producing tachycardia in order to maintain homeostasis in the body) ***But:***

In The heart we see a little baroreceptor response because when norepinephrine is released in excess (due to the increased sympathetic tone to the heart) it stimulates presynaptic alpha-2 receptors that maintain negative feedback of releasing NE, so no tachycardia.



While **phentolamine** (not selective):

1) Blocking alpha one receptors decreases the peripheral resistance and evokes baroreceptors so cardiovascular center activates sympathetic nerves to the heart (excess norepinephrine)
2) But alpha-2 receptors are blocked now so no negative feedback for releasing norepinephrine which causes tachycardia so not useful for patients with hypertension.

Now let's discuss:

Non selective alpha blockers: **Phenoxybenzamine, Phentolamine**

Selective α 1 blockers: **Terazosin, Doxazosin, Prazosin, Tamsulosin**

Selective α 2 blockers: **Yohimbine**

🐼🐼 *Non selective alpha blockers:*

1) Phenoxybenzamine: related to nitrogen mustard (mustard gas)

Germans used it n the First World War as if it's given it changes in the body blood and then the new form of it actively binds to alpha receptors then: …

**Blocks α1& to less extent α2 receptors

**Binds covalently to α receptors, causing irreversible blockade of long duration (14–48 h)

Inhibits reuptake of **NE and blocks **histamine (H1)**, **ACh**, and **serotonin** receptors

**Causes little fall in BP in normal supine individuals, it reduces BP when sympathetic tone is high, e.g., as a result of upright posture.

في حالة الاستلقاء بكون ضط الدم أساسًا منخفض بسبب هاد الدواء بالتالي لما يوقف الشخص ما رح ينزل ضغطه فجأة، يعني ما رح يصير عنده: orthostatic hypotension

**Absorbed poorly but usually given orally.
preoperative to control hypertension

**Uses: treatment of: 1) inoperable or metastatic pheochromocytoma, 2)peripheral vascular diseases

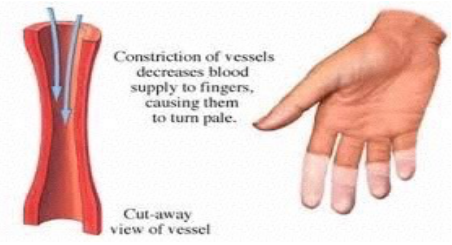
Pheochromocytoma is a tumor that usually starts in the cells of one of adrenal glands(chromophil cells: that produce NE and EPN), often cause the adrenal gland to make too many hormones. This can lead to: intermittent or sustained hypertension (vasoconstriction), headaches, palpitations & increased sweating

Peripheral vascular disease = Raynaud's phenomenon
(excessive reversible vasospasm in the peripheral circulation). Due to vasoconstriction of the arterioles and arteries of the hands and feet causing pain, pale and cold fingers

Prazosin or phenoxybenzamine are used but calcium channel blockers are preferable for most patients

🌸 palpitations can be felt by the patient as strong heart beat, but he cannot feel tachycardia

**Adverse effects:
1)orthostatic hypotension (most common), 3)tachycardia, 4)nasal stuffiness, 4)inhibition of ejaculation.



🌸note that in inoperable or metastatic pheochromocytoma we also use **Metyrosine** (α -methyltyrosine) a competitive inhibitor of tyrosine hydroxylase (the rate limiting step in chatecolamines synthesis)
Which decrease the releasing of EPN, NE from the tumer, but metyrosine decreases the releasing of dopamine also, and that can cause extrapyramidal effects (like parkinson disease) due to reduced dopamine levels

2) Phentolamine:

**Competitive α1 and α2 antagonist.

**Rapidly acting α blocker with short duration t½ 19 min.

**Reduces peripheral resistance (α1) and causes cardiac stimulation (α 2 receptors blockade enhances release of NE) .

Minor ***inhibitory* effects at ***5HT receptors***
(5-HT receptors = 5-hydroxytryptamine receptors, or serotonin receptors)

****Agonist*** effects at ***muscarinic receptors*** (salivary, sweat, lacrimal) and ***H1 and H2 receptors in the stomach*** (Increase acid secretion).

**Uses: To counteract vasoconstriction due to alpha agonists (Treatment of overdose of α1 agonist) + counteract hypertension:

1)Cheese reaction (+ monoamine oxidase inhibitors) -> hypertnsion

🌸 الدكتور فقط ذكر السطر اللي فوق بدون توضيح، بس ازا حدا بحب يفهمه:
An acute attack of hypertension that can occur in a person taking a monoamine oxidase inhibitor (MAOI) drug who eats cheese, caused by an interaction of the MAOI with tyramine, formed in ripe cheese when bacteria provide an enzyme that reacts with the amino acid tyrosine in the cheese.

2)Control of hypertension due to clonidine withdrawal (alpha-2 receptor agonist -> using for a long time causes depression in sympathetic activity),

3)Diagnostic of pheochromocytoma:

Due to the high amount of circulating EPN, NE -> patients will have symptoms of hypertension, anxiety, arrhythmia.. -> it's difficult to determine the cause of hypertension according to these common symptoms so we use phentolamine:

Remember: in pheochromocytoma hypertension happens due to alpha-1 receptors stimulation, so if you give the patient (phentolamine with mesylate Injection), alpha receptors will be blocked and immediately you will see decreasing of hypertension, this confirmed that the hypertension was caused by pheochromocytoma

**Adverse effects: severe tachycardia, arrhythmias, and myocardial ischemia. Due to the powerful stimulation of the heart.

🐼🐼*Selective α 1 blockers:*

1) **Terazosin:**
   High bioavailability.
   The half-life is 9–12 hours.
   Reduces urinary urgency and improves urine flow

2) **Doxazosin:** Has a longer half-life of about 22 hours, a preferred drug according to its long half life, one dose a day is enough
   Reduces urinary urgency and improves urine flow

3) **Prazosin:**

**Highly selective α1 blocker & less potent at α 2 receptors.

**Relaxes both arterial and venous vascular smooth muscle & smooth muscle in the prostate, due to blockade of α 1 receptors *with no or little tachycardia*

**Extensively metabolized, only 50% is available after oral administration. The half-life is 3 hours. -> short acting drug

**Favorable effect on plasma lipids: increase HDL/LDL ratio which is good for health, while beta blockers do the opposite
High/Low density lipoproteins

Used as Antihypertensive (but not very popular, not recommended as monotherapy, ***other* antihypertensive agents are ***more preferred*** because they provide protection against heart failure)

**Used in benign prostatic hyperplasia (BPH) common in elderly men : Blocks α1 in bladder trigone & prostate -> reduced contraction of smooth muscle in the bladder neck and prostatic capsule -> Reduces urinary urgency and Improves urine flow .

Used in treating **Peripheral Vascular Disease

Adverse effects: ***First dose phenomenon* i.e. postural hypotension with initial doses -> taking the first dose makes patients feel dizzy because of the blood pooling to the legs -> so they take the **first dose (also the first time after **increasing** the dose) before going to the bed

يعني عشان ما ينزل ضغطهم بياخدوا الدواء قبل ما يناموا

4) Tamsulosin:

Uroselective α1A blocker. **α 1A are predominant in bladder base & prostate so it reduces urinary urgency and improves urine flow. preferred in patients who have orthostatic hypotension with other α 1-receptor antagonists.

يعني المرضى العندهم Urinary Obstruction بعطيهم terazosin or doxazosin or parazosin ولكن ازا كان بسببلهم orthostatic hypotension كأثر جانبي، ساعتها لازم أعطيهم tamsulosin

🌸uroselective means that it's effect on prostate and bladder base is higher than its affect on blood vessel

🌸remember : alpha1 receptor subtypes are: Alpha1 A, Alpha1 B, Alpha1 **D**
While : alpha 2 receptor subtypes are: Alpha2 A, Alpha2 B, Alpha2 **C**

**30 times high affinity for α1A

**High bioavailability and a half-life of 9–15 hours.

**It is used to treat BPH.

****No effect on BP and heart rate.**

**Side Effects: Dizziness & retrograde ejaculation (ejaculation into the bladder)
Note that now we have four drugs that Reduce urinary urgency and improve urine flow: **terazosin, doxazosin, prazosin and tamsulosin**

🐼🐼*Selective α 2 blockers:*

Yohimbine:

**An indole alkaloid

🌸ملاحظة مش كتير مهمة (للتذكير فقط بإشي أخدناه بالميتا شيت ١١ صفحة ١٩) :

How does **viagra** work? It inhibits the phosphodiesterase leading to cGMP elevation and for muscle relaxation

**Blocks other receptors also – 5HT, DA
5HT= 5-hydroxytryptamine receptors, or serotonin receptors
DA= dopamine receptors

**Increases ADH release

**Enhances sexual activity – aphrodisiac
Was widely used to improve male erectile dysfunction but has been superseded by **phosphodiesterase-5 inhibitors** like **sildenafil (viagra)**.

**Sometimes used in the treatment of orthostatic hypotension because it promotes NE release through blockade of presynaptic α 2 receptors.

β- Adrenoceptor Antagonists(lol)

The first beta receptor antagonist was synthesized in early 60s late 50s

🌸First generation: non selective (β1 and β2)
🌸Second generation: Cardioselective (β1)
🌸Third generation: Vasodilator β blockers: ***additional effect -> directly dilate blood vessel either by blocking also alpha receptors, or by releasing nitric oxide which is a vasodilator***.

The selectivity is dose-related; it tends to diminish at higher drug concentrations.

Most drugs are well absorbed after oral administration;
peak concentrations 1–3 hours after ingestion.

Other major differences relate to their:
🦜**local anesthetic** (membrane-stabilizing) effects. However, the concentration in plasma when taking the drug is too low for the anesthetic effects
🦜**lipid solubility**
➔ Lipid soluble drugs have shorter half life than water soluble drags.

• Lipophilic β blockers

– readily absorbed from GI, metabolized in liver
– large volume of distribution, and penetrate BBB well reaching the brain and having central effects or central side effects
– **hepatic failure** prolongs their t1/2.

- metoprolol,
- oxprenolol,
- carevdilol,
- timolol: no local anesthetic activity used topically to treat glaucoma, nonselective
- propranolol: Prototype, nonselective, high lipid soluble drug

*Has low and dose-dependent bioavailability (first-pass metabolism) -> bioavailability improves with time

*First-pass effect varies among individuals: so we start with a very low dose then increase it according to the patient response

*A long-acting form of propranolol is available; prolonged absorption of the drug may occur over a 24-hour period.

*No effect on α and M receptors but may block some serotonin receptors in the brain, though the clinical significance is unclear.

*It has no partial agonist action at β receptors.

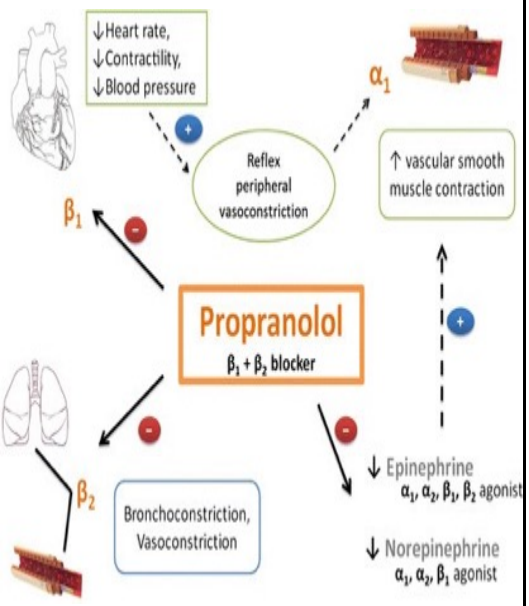
• Hydrophilic β blockers

– less readily absorbed, not extensively metabolized
– long plasma half-lives which are prolonged in **renal failure**.

- acebutolol,
- atenolol,
- bisoprolol,
- nadolol: Has a very long duration of action, nonselective
- sotalol: exhibits Class III antiarrhythmic properties, Is a calcium channel blocker, nonselective

1)Effects on the Cardiovascular System(propranolol)

Very valuable in: **hypertension**, **angina** and **chronic heart failure** and following myocardial infarction (MI).



1)by blocking B1 it: *decreases heart rate, *decreases contractility, *decreases cardiac output so decreases blood pressure

🌸because of decreasing HR there will be a reflex peripheral vasoconstriction by activating A1 receptors (to maintain homeostasis) -> which cause vascular smooth muscle contraction -> increasing peripheral resistance and increasing BP

Subsequently BP will remain constant.

🌸 after **continuous treatment**.:**↓BP** both diastolic and systolic
If the patient continuo to take beta blockers for long time, peripheral resistance will decrease causing low BP

➔ So beta blockers are effective in treating hypertention

🌸Do **not** cause hypotension in **healthy individuals** with normal BP.

🌸Heart:↓ HR, ↓SV (stroke volume), ↓COP (cardiac output), ↓AV (atrioventrecular) conduction,↓cardiac work & O2 consumption -> this is the base in using beta blockers for angina and ischemic heart disease

2)by blocking B2: *bronchoconstriction (**unuseful** for bronchial asthma patients)
*vasoconstriction

🌸Nonselective and β1-block → Inhibit renin. Also, an inverse agonist (↓ resting Heart Rate)
Inverse agonist: shifts the receptor format into its active format

Cardioselective β Blockers (β1-selective antagonists)

*less effects on bronchioles, carbohydrate metabolism, lipids -> so more preferred than nonselective beta blockers

*Lower incidences of Cold hands and feet (while nonselective beta blockers block vasodilator beta receptor in skeletal muscles blood vessels -> cold)

*Less liable to impair exercise tolerance because during exercise you need beta-2 receptors to be active -> vasodilation-> more oxygen to the muscles

*Safer in patients who experience bronchoconstriction in response to propranolol, but their β 1 selectivity is modest, so they should be used with great caution in patients with asthma.

*Beta1-selective antagonists are preferred in patients with **diabetes** or **peripheral vascular disease** since β 2 receptors are important in liver (recovery from hypoglycemia which depends on gluconeogenesis that is blocked by beta2 receptor blockade) and blood vessels (vasodilation)

2) Effects on the Respiratory Tract

🌸Increase in airway resistance, particularly in patients with asthma -> blockade of beta2 .

🌸β1 blockers are safer than nonselective β blockers.

🌸β 1-selective blocker are not sufficiently specific to completely avoid interactions with β 2 receptors -> it's dose dependent
Consequently, these drugs should generally be avoided in patients with asthma.

Many patients with chronic obstructive pulmonary disease may tolerate these drugs & the benefits may outweigh or exceed the risks.
e.g., in patients with myocardial infarction.
e.g. in patients with concomitant ischemic heart disease, angina

3)Effects on the Eye

Reduce intraocular pressure in glaucoma by decreasing aqueous humor production.

Glaucoma is treated by:
1- reduction of aqueous humor secretion.
2- enhancement of aqueous out-flow.

Drugs useful in reducing intraocular pressure: Cholinomimetics, α agonists, diuretics, β blockers, prostaglandin F2 analogs
Prostaglandin analogs & β blockers are the most popular

4)Metabolic and Endocrine Effects

🌸Beta-receptor antagonists increases LDL, triglycerides, ↓ HDL by inhibiting lipolysis. —> which is not good for the body

🌸β –blockers should be used with caution in insulin-dependent diabetic patients, for tow reasons:

1)β blockers delay recovery from hypoglycemia due to insulin and oral anti diabetics: Glycogenolysis in the liver is inhibited after β 2-receptor blockade.
2)mask early symptoms of hypoglycemia (tremors, sweating & tachycardia).

In pheochromocytoma we use both phenoxybenzamin (which protect against hepertention) and beta blockers (protect against excessive cardiac stimulation). But phenoxybenzamine should be the fisrt one to use because we need to establish the blockade before givng the beta blocker

Beta-receptor antagonists used to reverse the cardiac effects. Should not be used prior to establishing effective α -receptor blockade

Blocking beta2 receptors in the blood vessels in skeletal muscles causes vasoconstriction and hypertension so we give the patient phenoxybenzamine to make sure we decrease the BP, then we give beta blockers to protect the heart❤️

In **Hypertensive Emergencies**: **Labetalol** (α and β blocker) is used

بجوز ضغط هالفصل أخد منا كتير شغلات حلوة كنا نحب نعملها بوقتنا😊 ، بس إلا ما يكون شغلنا عن ذنوب ما كنا قادرين نتركها لما كنا فاضيين😉
الله يفتح عليكم 🙏❤️

That’s it. Good luck