

The Cardio-

VASCULAR

System

- Anatomy
- Histology
- Pathology
- Pharmacology
- Physiology
- Microbiology

Lec #: 4

Dr. Name: **Malik**

Done By: **Ebraheem Al-Abdali**

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Drawn by Tariq Bushnaq



ANTIHYPERTENSIVE DRUGS CONTINUED

Please refer to the table at the end of this sheet that summaries the main points about each drug.

-Review from last lecture

Last lecture we started talking about beta blockers ...

We talked about propranolol and that it crosses the blood brain barrier. And that it has **beta 2 antagonist effect** that's why its **contraindicated in asthmatics and patients with diabetes mellitus** (because it interferes with insulin release).

We talked about atenolol which is selective to B1 and it can be safely given to asthmatics, **so it is the drug of choice for hypertension.**

Remember that beta blockers work on beta-receptors (B1 receptor) on the juxtaglomerular apparatus which releases renin. So beta blockers block renin release from the juxtaglomerular apparatus and this is the main mechanism of action how beta blockers reduce blood pressure. So although they decrease cardiac output (by blocking B1 receptors on heart and reducing heart rate and contractility) this is NOT the mechanism how they reduce blood pressure. Rather, it's by suppressing renin release from the juxtaglomerular apparatus.

The above mechanism explains why when you give beta-blockers they don't reduce blood pressure immediately. Rather they need 10-15 days; because they reduce hypertension by inhibiting renin release and not by reducing cardiac output (beta-blockers reduce cardiac output in one to two days but remember again, this is NOT how they reduce blood pressure).

How is this applied in the clinical world?

Beta-blockers are used for reducing blood pressure by working on the renin angiotensin system (and they don't produce the hypotensive activity immediately by this mechanism). Also they are used for other diseases like angina pectoris by reducing cardiac output and heart rate. This is determined by the DOSE, that's why we use different dosing.

For example, the Atenolol dose for hypertension is 25mg, it reduces the blood pressure by 10 mm Hg. But for angina pectoris, we give 100 mg to reduce the heart rate mainly.

-Pindolol, acebutolol and penbutolol

Pindolol and acebutolol are the **drugs of choice for hypertensive patients with bradyarrhythmia or Peripheral vascular disease**. Why? Because they are **partial beta agonists** which means they have some intrinsic sympathomimetic activity so they depress cardiac output LESS than other beta-blockers.

What is a peripheral vascular disease? It is a poor perfusion in the peripheral

-Labetalol and carvedilol

Are totally nonselective; **alpha 1, beta 1 and beta 2 blockers**. So in addition to their beta blockade effect they cause **vasodilation by blocking the alpha 1 receptors**. That's why they are useful in the management in **pheochromocytoma** and **hypertensive emergencies** (more on hypertensive emergencies later in this lecture)

Also they are good in patients with **peripheral vascular disease** since they cause vasodilation by blocking alpha-1 receptors.

-Esmolol

Esmolol has a rapid onset of action and **short half-life** 9-10 minutes (administered through constant I.V infusion). That's why it "works fast and finishes fast" which makes it a good **drug of choice** In management of **intraoperative and postoperative hypertension** because it can be *titrated* and monitored carefully.

Also it can be used with **hypertensive emergencies** especially when associated with tachycardia.

During operations, hypertension may occur because most of anesthetic drugs that are used are vasodilators and muscle dilators (result in relaxation). In this case, baroreceptors are activated and cause tachycardia & hypertension.

-Don't stop beta-blocker suddenly

Because sudden withdrawal may cause rebound hypertension

Why? Because when we give beta-blockers for a long time, our bodies respond by up-regulating the number of beta receptors so they become more sensitive toward adrenaline. So when you stop beta blockers the increased number of beta receptors will cause hypertensive crisis that's why you need to stop beta-blockers gradually by tapering the dose.

-Selective alpha1 blockers

Examples: Alfuzosin, doxazosin, prazosin, terazosin

Remember that alpha 1 receptors cause vasoconstriction. Alpha 1 blockade causes vasodilation and reduces blood pressure.

Generally speaking, alpha1 blockers are **not great drugs** for treatment of hypertension.

However, because they block alpha receptors on the prostate they are the **first line therapy** for management of hypertension in patients with prostatic hyperplasia (benign prostatic hyperplasia BPH). In those patients, the urethra is compressed which makes the urination difficult and thus urinary retention. They are used also for naïve hypertensive patients.

One side effect is hypotension.

Another important side effect of alpha blockers is **first dose syncope**, which means the patient experiences syncope after the administration of the first dose of the drug (because the body is not used to the mechanics of this new drug). **To avoid this** you start the drug with one-third the dose instead of the full dose.

Now if the patient has prostatic hyperplasia **but does not have hypertension** then you can use alpha blockers **selective for alpha1-A which is only found on the prostate** and not on blood vessels (alpha1-B is found on blood vessels). Drugs that only block alpha1-A and are used for normotensive patients with prostatic hyperplasia are **silodosin**.

-Alpha 2 receptor agonist (Centrally acting adrenergic drugs): Clonidine and Methyldopa

Remember that alpha 2 receptors cause feedback inhibition on the sympathetic system and noradrenalin release. So Alpha 2 agonists reduce sympathetic activity and decrease blood pressure as a result.

Clonidine

- **Used to treat mild to moderate hypertension that has not responded adequately to treatment with diuretics alone.**
- **Does not reduce renal blood flow**, thus it is useful in the treatment of **hypertension complicated with renal disease**. (Remember that ACEI are good for patients with renal diseases but **they are contraindicated in patients**

with bilateral renal artery stenosis in that case you can give clonidine or Calcium channel Blocker)

- Clonidine lowers heart rate and cardiac output more than methyldopa.
- Withdrawal of clonidine after protracted use, particularly with high dosages (more than 1 mg/d), can result in life-threatening hypertensive crisis mediated by increased sympathetic nervous activity. Patients exhibit nervousness, tachycardia, headache, and sweating after omitting one or two doses of the drug. **So stop the drug gradually.**
- If the patient stops the drug suddenly, this will over-activate α_1 & α_2 . We need to block them in this emergent situation by Labetalol.

Methyldopa:

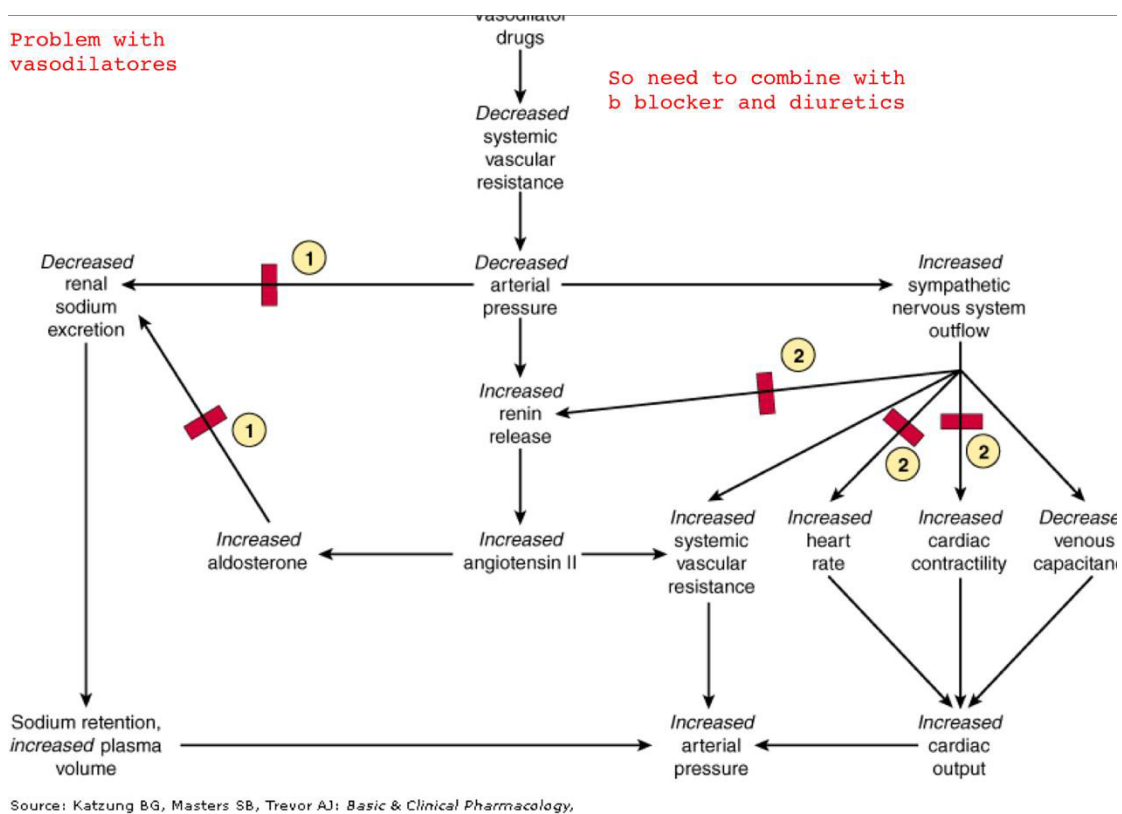
- The most important thing you need to know about this drug is **the drug of choice** used in **pregnant women** with hypertension since it does not reduce cardiac output and perfusion to the baby.
- Cardiac output is not decreased, and so the blood supply to the vital organs, such as kidney, which makes Methyldopa especially valuable in treating hypertension with renal insufficiency. Still clonidine is more preferred. Methyldopa is only used for pregnant hypertensives today.
- Firstly we give the pregnant woman minerals; it is known that magnesium reduces the blood pressure, so we give $MgCl_2$. If she doesn't respond well, we give methyldopa.
- The most common side effect is **sedation** (remember it is centrally acting)
- Side effects of clonidine and methyldopa include: dry mouth and nasal mucosa, and **sedation**, hallucination, depression (remember it cross the blood brain barrier and act on the CNS)

-Vasodilators: fenoldopam, nitroprusside, hydralazine, diazoxide, minoxidil

- When talking about vasodilators they are explained concurrently with hypertension emergency.
- These agents are smooth muscle relaxants
- They produce **reflex stimulation** of the heart resulting in increasing the myocardial contractibility, heart rate, and oxygen consumption, so they may prompt angina, myocardial Infarction in predisposed individuals .
- They increase plasma renin concentration, which resulting in sodium and water retention.

- These unwanted effects can be blocked by the **combination with a diuretics and a beta blocker** (remember that beta blockers suppress myocardial contractility and block renin release) This is explained in the following diagram.

Explanation: those drugs are hypotensive, they will decrease the arterial pressure which will decrease renal sodium excretion (sodium retention and increased plasma volume) & increase the sympathetic nervous system outflow. This will result in increased arterial pressure. That is why we combine them with β -blockers, diuretics or ACEI.



Nitroprusside

- Works by release of nitric oxide
- It is the **drug of choice** for hypertension emergency
- Why is it the DOC? Because it has activity on **BOTH veins and arteries** (this is an advantage over other vasodilators).
- But it reduces kidney perfusion so use fenoldopam instead if there is kidney injury.

Fenoldopam

- **D1 receptor** agonist (D1 receptor is found peripherally and in kidney; activating D1 causes vasodilation).
- It does not reduce kidney perfusion, thus it is **the drug of choice** for patients with **hypertensive emergency with kidney problem**.

Hydralazine

- A smooth muscle relaxant, produces reflex stimulation of the heart...
- Used to treat moderately severe hypertension, combine with diuretic (to prevent sodium and water retention) and beta-blockers (to prevent reflex tachycardia). It decreases the arterial pressure.
- Hydralazine monotherapy is accepted method of controlling blood pressure in **pregnancy-induced hypertension**. It is the *second choice*. Remember that methyldopa is the drug of choice.
- Main side effects are arrhythmia, precipitation of angina. **Lupus-like syndrome** can occur with high doses, but it is reversible on stopping the therapy.

Minoxidil and diazoxide activate potassium channels and cause vasodilation. Minoxidil causes hair growth and is used to treat baldness **الدكتور قال انه مو مطالبين فيهم**

Hypertension emergency:

- it is rare but life threatening, in which **DBP is > 150 mm Hg with SBP > 210 mm Hg (healthy person)**, OR **DBP of > 130 mm Hg in individual with pre-existing complications**, such as encephalopathy, cerebral hemorrhage, and left ventricular failure, or aortic stenosis.
- Blood pressure should not be reduced rapidly, or hypoperfusion of vital organs would be compromised.
- Drugs used for treatment of hypertensive emergency (remember that you need a drug that “works fast and finishes fast”):
 - Sodium nitroprusside (onset 1-2 min), is **the drug of choice** is administered intravenously as continuous infusion and causes sudden vasodilation and reflex tachycardia, it is effective in all patients regardless the cause. You can *titrates* easily.

- Labetalol (alpha and beta blocker), (onset 5-10 min) does not induce reflex tachycardia, given intravenous bolus or infusion. major, limitation of this agent is the **long half-life**(3-6 hr), that prevent rapid titration. That is why nitroprusside and fenoldopam are better.
- Fenoldopam (onset 2-5 min), peripheral dopamine 1 receptor agonist that also given as an intravenous infusion, does not reduce kidney perfusion, **it is the drug of choice** for patients with **hypertensive emergency with kidney damage**.

Drug	Main points
<i>B-blockers</i>	
Pindolol and acebutolol	Partial beta agonists, so they are the drugs of choice. For patient with brady arrhythmias and peripheral vascular disease
Labetalol and carvedilol	Both alpha and beta blockers, so they are used in pheochromocytoma and hypertensive emergencies in addition peripheral vascular disease
Esmolol	Rapid onset and short half life that's why it's the drug of choice intraop and postop management of hypertension.
<i>Alpha 1 blockers</i>	
Alfuzosin, doxazosin, prazosin, terazosin	Not great for hypertension alone But DOC for htn. with BPH If normotensive with BPH use silodosin and tamsulosin .
<i>Alpha 2 agonists</i>	
Methyldopa	DOC for pregnant
Clonidine	Good for bilateral renal artery stenosis Must stop gradually or hypertensive crisis will occur

Vasodilators

Nitroprusside	Dilates both arteries and veins DOC for hypertensive emergency
Hydralazine	Second line for pregnancy and hypertension Used with b blockers and diuretics Side effects include tachyarrhythmias and drug induces SLE
Fenoldopam	D1 receptor agonist The drug of choice for patients with hypertensive emergency w kidney damage.

Abbreviations

BPH: benign prostatic hyperplasia

SLE: systemic lupus erythematosus.

DOC: drug of choice

Thank you

And I apologize for any mistakes