Doctor.021

no. 3

# CVS PHARMACOLOGY


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# Angiotensin II-receptors antagonists

• These agents are alternatives to the ACE Inhibitors, and can be used in patient who cannot tolerate ACE Inhibitors. Losartan being the prototype.

• Their pharmacologic effects are Similar to ACE Inhibitors (vasodilation, block aldesterone secretion), however they do not increase the bardykinin levels.

• Their adverse effects are similar to ACE Inhibitor, although the risks of cough and angioedema are significantly decreased.

• Candesartan, eprosartan, irbesartan,telmisartan, and Olmesartan. End with SARTAN.

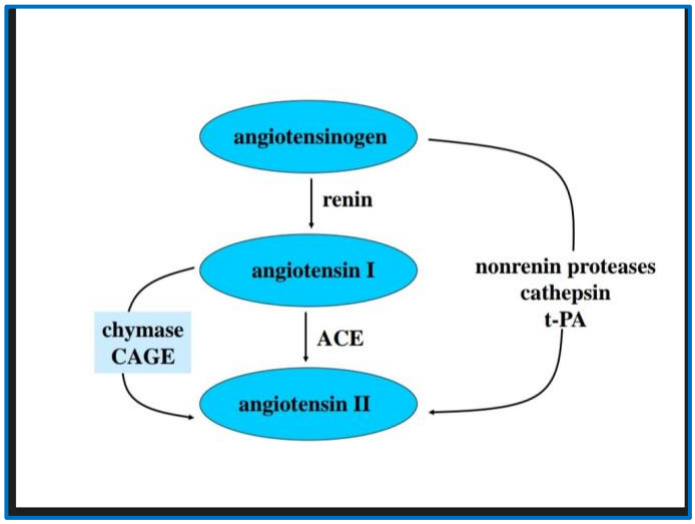
- ACEIs&ARBs are changeable drugs, each of them can be used as first line therapy ACEIs or ARBs.
- ACEIs is the drug of choice for patient having hypertension with diabetes

➢ these drugs lower blood pressure as the ACE inhibitors and have the advantage (for each agent: ACEs "pril" and ARBs "sartan") of much lower incidence of adverse effects. resulting from accumulation of bradykinin (cough, angioneurotic oedema)

➢ they cause fetal renal toxicity (like that of the ACE inhibitors) TERATOGENIC!

- ➢ these drugs reduce aldosterone levels and cause potassium accumulation (attainment of toxic levels-hazardous in patients with renal impairment).
- ➢ Mild hyperkalemia rebalanced with the hypokalemia produced by thiazide

- **Do we combine ACEIs with ARBs?**
- **Its relative contraindicated (combination is allowed only in late stage heart failure)**
- **99% we should NOT do that as hyperkalemia increases**
- **But, in some cases we have to combine these two drugs together and that is because angiotensinogen can be converted to angiotensin II indirectly by cathepsin t-PA, as well as angiotensin I can be converted to angiotensin II by chymase enzyme.**




- **In term of hypertension no need to that combination, however in late stages of heart failure it is used, as in heart failure we need to shut off angiotensin II as much as we can.**
- **In heart failure the patient is treated by ACEIs or ARBs or both to increase the blocking activity.**
- **In case of using both drugs you have to have access to potassium level, otherwise do NOT do this as hyperkalemia will develop (uncontrollable hyperkalemia).**
- **Keep in your mind, in pharmacology you should NOT combine to drugs having the same MOA unless in severe cases as we see here.**
- **Remember that Black patient don't respond well toward ACEIs&ARBs explaining why its not used as first line therapy with them, except in case they have DM**
- **However, if your patient is black with hypertension only, you need to start with calcium channel blockers**

# Calcium channel blockers

- **Direct vasodilators.**

- **In many places they are The best anti-hypertensive drugs in terms of efficacy(stronger than ACEI), but with more significant side effects**
- **They are used when first line therpay-that we discussed in previous two lectures- are ineffective.**

**• Like ACE Inhibitors, they are recommended agents when the preferred first-line agents are contraindicated or ineffective.**
**• They are effective in patient with angina and diabetes.**
**• They exerts their antihypertensive effect by their vasodilation effect.**

**• They divided into three chemical classes:**
**a. Diphenylalkylamines, *Varapamil*.**
**b. Benzothiazepines, *Diltiazem***
**c. Dihydropyridines** (the main class that we will talk about)**, Nifedipine.**

- **Any drug finish with "dipine" is a dihydropyridines calcium channel blocker.**
- **We deal with dihydropyridines and non-dihydropyridines (mainly two drugs: verapamil, Diltiazem).**

**• Mechanism of action:**
**Calcium enters muscle cell through special voltage sensitive calcium channel. These agents exert their effect by antagonists block for the inward movement of calcium by binding to the L-type (faster than T-type) channels in the heart and peripheral vasculature.**

- **There are two types of Ca channels, L-type and T-type, responsible about Ca entery into vessels and heart.**
  **If calcium entery into heart and vessels is blocked, vasodilation will take place and cardiac output will be decreased (negative inotropic and chrontropic activity).**
- **The conductivity on AV and AS node depends on calcium, so to decrease their activity and conductivity we block calcium entery into heart.**

- **L-type channels that found on heart differ from those that found on vessels(in configuration), Dihydropyridines bind with the type of channels that found on vessels NOT the type that found in heart→so dihydropyridines called Vasodilators only.**
- **However, non-dihydropyridines binds toward heart type L-channels more than vessel type L-channels→so they are called cardioselective.**

***Very important, note the notes on the table and under it.**

| | NIFEDIPINE* | DILTIAZEM | VERAPAMIL |
|---|---|---|---|
| coronary arteries dill | ++ | ++ | ++ |
| peripheral arteries dill | ++++ The strongest | ++ | +++ |
| negative inotropic | + Very weak | ++ | +++ The strongest |
| slowing AV cond | ↔ No effects | +++ | ++++ |
| Heart rate | ↑↔ No effect | ↓↔ | ↓↔ |
| ↓ blood presure | ++++ High reduction | ++ | +++ |
| depression of SA | ↔ | ++ | ++ |
| increase in cardiac output | ++ | ↔ | ↔ |

* And others dihydropyridines
↓ = decrease
↑ = increase
↔ = without change

***All three drugs have activity as a vasodilator on coronary artery.**
***The effect of Ca channel blockers on arteries more than veins(arteriodilators)→as arteries are more calcium dependent.**
**There is a little effect on veins.**
***Contraindicated to combine beta-blocker with verapamil as both of them decrease heart rate(negative inotropic activity)**

- **Both beta blockers and verapamil are contraindicate in case of heart failure**
- **You can give nifedipine with beta blockers since it have very weak (negative inotropic) effect**

***The increase in heart rate with nifedipine is due to reflux Tachycardia due to arteries dilation**

- **There is not much orthostatic hypotension in nifedipine because they work on arteries.**
- **Patients with arrhythmia, atrial fibrillation, atrial flatter, Hypertension→Verapamil as it reduces AV node conductivity.**

# Adverse effects of calcium channel-blocking agents

| Drug | Effect on heart rate | Adverse effects |
|---|---|---|
| Nifedipine | ↑ | Headache, flushing, ankle swelling |
| Amlodipine | ↑ | Ankle swelling |
| Nimodipine | ± | Flushing, headache |
| Diltiazem | ± | Generally mild |
| Verapamil | ↓ | Constipation, marked negative inotropic action |

- **Calcium channel blockers do not affect concentrations of plasma cholesterol or triglycerides, or extracellular calcium homeostasis.**

- **All vasodilator cause headache in different levels due to its effects on blood circulation and brain perfusion-that's why its used for migraines sometimes-**
- **Amlodipine causes swelling and flushing as the dilation of vessels and capillaries takes place.**

- Note that verapamil cause constipation as a result to its binding on L-type that are found on GI
- Nimodipine crosses BBB thus its used in case of cerebrospinal haemorrhage
- Whenever we deals with calcium channels blockers remember this: (headache, edema and flushing) all due to vasodilation
- Amlodipine: causes gingival hyperplasia

- Some info about Nifedipine:
- It has 2 typed: sustained released and short acting.
- Sustained released means that the drug will reach Cmax then follows gradual elimination not a sudden drop.
- We like to give nifedipine as sustained released only.
- If you have to give nifedipine as short acting (3 times a day) remember to monitor the tachycardia
- The short acting cause high reflux tachycardia, why?
- Remmeber that when we give a drug it will reach Cmax then begins elimination with time, at this point the dilation effect is reduced but the effect on the heart is no longer there (its erased), causing significant reflux tachycardia.
- Note that this only happens when the drug begins to get out of the body, once the other dose is taken, the reflux tachycardia Is reduced.
- That side effect led to sustained released type creation.

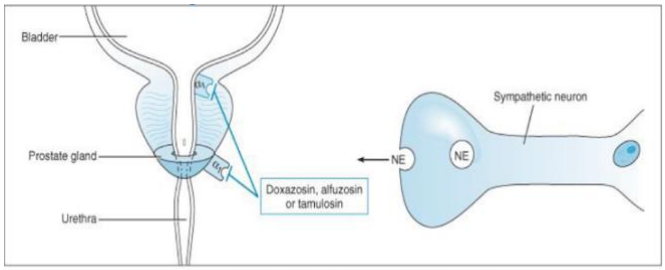
Now let's move to alpha-1 blockers. Alpha-1 blockers are used as a first line therapy in case of prostate hypertrophy.

# Selective alpha1-blockers

- Selectively block alpha1 receptors
- Alfuzosin, doxazosin, prazosin, terazosin
- Silodosin (slightly different than drugs above -note the selectivity of the receptors, the receptor on the prostate differs from the receptors on the vessels-, silodosin works only in prostate receptors)

**So, a patient with prostate hypertrophy <u>without</u> hypertension—> you give silodosin.**
**a patient with prostate hypertrophy <u>with</u> hypertension—> Alfuzosin, doxazosin, prazosin, terazosin**

**•Used in the treatment of chronic hypertension**
**• Also used to treat urinary retention in men with benign prostatic hyperplasia**



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**Are there alpha nonselective blockers? Yes, but not used anymore.**
**Those drugs may cause reflux tachycardia (but not as significant as nitrates and vasodilators) and water retention.**

**Remember that alpha-1 receptor exists on arteries and veins, but these drugs are more selective toward arteries explaining the week tachycardia in comparison to the drugs that cause vasodilation of arteries and veins.**

# Centrally acting adrenergic drugs

- **We finished first line therapy now let's move to Resistant hypertension.**
- **In this case our patient is no longer responding and needs new drugs (<u>alpha-2 agonist</u>, <u>mytheldopa</u>).**

**• Clonidine, an alpha2 agonist diminishes central adrenergic outflow.**
**• Used to treat mild to moderate hypertension that has not responded adequately to treatment with diuretics alone.**

**• Does not decrease renal blood flow, thus it is useful in the treatment of the hypertension complicated with renal disease.**
**• Nonetheless it does produce sodium and water retention, and so usually administered in combination with a diuretic.**
**• This drug (clonidine) works through NE release inhibition, means that it works slowly, that explains why the most important reflux of this drug is water retention not reflux tachycardia -not so important-.**
**• Clonidine causes sedation.**

**• Methyldopa and clonidine produce slightly different hemodynamic effects: clonidine lowers heart rate and cardiac output more than does methyldopa. Why?**
**• Because clonidine is a true alpha 2 agonist, while methyldopa is not a direct alpha 2 agonist, it does bind to the alpha 2 receptors slightly, but it is thought that its main function is to decrease the synthesis of caticolamines (noradrenaline in particular) in the brain and their storage in vessels, which is why it has a milder, smoother, and longer effect than clonidine. It also doesn't cause water retention like clonidine, but it causes sedation.**
**• Because of that, methyldopa is the drug of choice in pregnancy (in gestational hypertension), not clonidine, because in pregnancy we need to keep the mother's hemodynamics as stable as possible to keep the placental perfusion unchanged** (a frequently asked question)**.**
**• Withdrawal of clonidine after protracted طويلًا 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. (This doesn't happen in methyldopa) withdrawal symptoms happen because of the down regulation of the number of receptors, since we are giving alpha 2 agonist, this decreases the feedback inhibition.**
**• All patients who take clonidine should be warned of the**

possibility. If the drug must be stopped, it should be done gradually (to rebuild the number of alpha 2 receptors) while other antihypertensive agents are being substituted. Treatment of the hypertensive crisis consists of reinstitution of clonidine therapy or administration of - and - adrenoceptor–blocking agents.

• Clonidine is used a one of the last solutions for resistant hypertension.

• Adverse effects of clonidine:

– Effects include dry mouth, sedation (the most important, due to decreased flow out of the brain) and drying of the nasal mucosa, water retention.

– Rebound hypertension occur following sudden withdrawal, so should withdraw slowly.

# Methyldopa

• Alpha 2 agonist that converted to methylnorepinihrine centrally to diminish the adrenergic outflow from the CNS, Which lead to reduction in the peripheral resistance and decreased blood pressure. (this is what was said before, but nowadays it's thought that is decreases the synthesis of noradrenaline and it is the reason why sudden withdrawal of methyldopa doesn't cause rebound hypertension or reflux tachycardia).

• Cardiac output is not decreased, and so the blood supply to the vital organs, such as kidney, which make Methyldopa especially valuable in treating hypertension with renal insufficiency (cause reduction in renal vascular resistance) this is a result of the similarity between it and dopamine which has vasodilation effect on kidney vessels.

• Used primarily for hypertension during pregnancy.

• The most common side effect are sedation and drowsiness because it decreases the activation sympathetic nervous system.

# V2

- **Page 7: Amlodipine: causes gingival hyperplasia**

# V3

- **Page 2: Mild hyperkalemia rebalanced with the hypokalemia produced by thiazide**
- **Page 3: late stages**