Doctor.021

no. 2

CVS PHARMACOLOGY

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Loop diuretics

Furosemide, ethacrynic acid, and bumetanide, produce greater diuresis than thiazides, but they have weaker anti-hypertensive effect and cause severe electrolyte imbalance.

Typically, only beneficial in patients with:

1- resistant HTN (hypertension) **and evidence of fluid**

- Fluid=edema; lung fluid especially, this is close to the idea of heart failure, the circulation in the body isn't enough; therefore, fluid accumulates in the chest and the patient could have resistant hypertension. We need stronger diuretics, so, instead of inhibiting 5-7% reabsorption of sodium in the proximal duct, we would target the loop of Henle and inhibit 20% of reabsorption of sodium.

2- effective if CrCl <30 ml/min (creatinine clearance)

- The patient has chronic renal failure already; giving thiazide would constrict the kidneys and worsen the case further.

- furosemide (most famous one; aka lasix) /ethacrynic acid/ bumetanide; these three are called loop diuretics.
- Some people have sulfur hypersensitivity we don't give them furosemide because it contains sulfur, we give them bumetanide instead. 99% of people take furosemide, we are going to use it a lot in heart failure due to the presence of fluid.
- **MUST be dosed at least twice daily (Lasix = Lasts six hours);** due to their small half-life
- **Administer AM and lunch time to avoid nocturia**→ it's a very strong diuretic; we don't want the patient going to the toilet a lot at night.

Adverse effects of the loop diuretics summarized in:

- **Ototoxicity** (type B side effect), **especially when used with a** predisposition agent **such as:**

1- **aminoglycosides** (Gentamicin, tobramycin, amikacin—> these are antibiotics that cause ototoxicity and lymphotoxicity)

Types of side effects	
A	**B**
Pharmacological	**Non-pharmacological**
Dose dependent	**Dose independent**
	Example: penicillin allergy happens at any dose
We also have types c,d,e…not important	

2- cisplatin

- **hyperurecemia:** reabsorption and retention of uric acid
- **Loop→ Hypocalcemia**
  - Loop diuretics inhibit reabsorption of Na, Mg, K, Ca
  - The hypocalcemia isn't remarkable though because calcium is controlled by many things including hormones and many body systems.
- **Thiazide→ hypercalcemia**
  - It causes retention of calcium; used in reduction of urinary stones.

β-adrenergic blocking agents

The various β blockers all appear to be equally effective for the treatments of hypertension.

- **Propranolol, Timolol, Nadolol, Pindolol, Penbutolol, carvedilol, are nonselective.**
  - Carvedilol is not selective at all because it acts as β1, β2 and α1 receptors.
  - Propranolol is used in arrythmia to reduce heart pulses.
- **while Metoprolol, Acebutolol, and Atenolol, Esmolol are cardioselective, sotalol.**

- We can use them for asthmatic and diabetic patients unlike the previous ones.
- Esmolol is used in surgeries and emergency cases because its effect begins and ends quickly. Why do we need that though? This is called titration; aka seeing the effect of this drug quickly and the difference it makes. Carvedilol needs 4hrs to leave the body which is inconvenient.
- Sotalol is used as a grade 3 antiarrhythmic drug.

➢ **Adverse effects:**

- **Dizziness**
- **sudden weight gain**
- **irregular heart- beat**
- congestive heart failure

The patients have bad chronotropic and inotropic activities; previously, we wouldn't give such patients β blockers. There is a compensatory mechanism that happens in the body where β1 receptors get pressured and the heart hypertrophies as a result; this can lead to heart failure. Nowadays, we can give patients a low dose to prevent the compensatory mechanism from happening. Doses given in cases of heart failure are very low unlike the ones given in angina pectoris. There is a lack of oxygen in angina pectoris; there are two types: stable and unstable (even worse), we don't want the heart to pump too fast and cause myocardial infarction.

- **asthma (non-selective)**
- **hypoglycemia (non-selective) in patient with diabetes mellitus.**
- Patients could have nightmares due to the change in the sympathetic flow and fatigue.

Beta blockers

- Used to treat migraine, and as stage drugs to decrease stress and heavy breathing.

- **Metoprolol and atenolol, which are cardioselective, are the most widely used blockers in the treatment of hypertension.**
- **Pindolol, acebutolol, and penbutolol are partial agonists, ie, blockers with some intrinsic sympathomimetic activity. They lower blood pressure by decreasing vascular resistance and appear to depress cardiac output or heart rate less than other blockers. This may be particularly beneficial for patients with bradyarrhythmia or peripheral vascular disease.**
  - Pindolol and acebutolol have intrinsic sympathomimetic activity, they act on the receptor and stimulate it partially (partial agonism) unlike noradrenaline and adrenaline which stimulate the receptor greatly. As a result, pulse rate decreases and so do chronotropic and inotropic effects. The effect isn't as strong as metoprolol and propranolol as these are antagonists not partial agonists. So, why do we need drugs with intrinsic sympathomimetic activity? Because some patients have bradycardia, and we don't want their heart rate decreasing any further. Therefore, we would give them pindolol (nonselective) and acebutolol (selective).
- **Labetalol, Carvedilol because of its combined - and -blocking activity, labetalol is useful in treating the hypertension of pheochromocytoma and hypertensive emergencies** (need to block α1 quickly).
  - There is a lot of norepinephrine, so we need to block β and α receptors. Labetalol and carvedilol are used in peripheral diseases such as Raynaud's phenomenon where fingers become purple in color due to constriction. These drugs act on α1 and β2 and cause vasodilation.

- Labetalol is also used as a 3rd line therapy for managing hypertension in pregnancy.

- **Esmolol has a short half-life (9–10 minutes) and is administered by constant intravenous infusion. It is used for management of intraoperative and postoperative hypertension (Titration effect), and sometimes for hypertensive emergencies, particularly when hypertension is associated with tachycardia.**

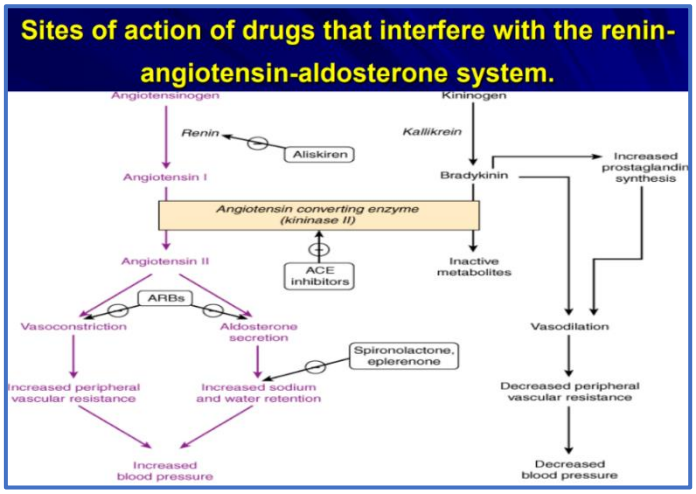
- **Indications for beta blockers include** (Not required; the important ones are mentioned in the lecture)**:**
  - **Angina pectoris.**
  - **Atrial fibrillation.**
  - **Cardiac arrhythmia.**
  - **Congestive heart failure.**
  - **Essential tremor.**
  - **Glaucoma.**
  - **Hypertension.**
  - **Migraine prophylaxis.**
  - **Mitral valve prolapses.**
  - **Phaeochromocytoma, in conjunction with α-blocker.**
  - **Symptomatic control (tachycardia, tremor) in anxiety and hyperthyroidism.**
- **β-adrenergic blocking agents; sudden withdrawal of these agents may cause rebound hypertension and this withdrawal syndrome may involve up-regulation or super sensitivity of beta receptor adrenoceptors So the removal should therefore be gradual to avoid precipitation of arrhythmia.**
  - When blocking the beta receptors for a long period of time, the body will start forming more receptors to compensate (up-regulation). This is why when we stop the drug suddenly, the norepinephrine in the body will find many receptors to bind with causing rebound hypertension.
- Patients who become unresponsive to thiazide after taking it for a while or the ones who come with a BP value of 180/95.

- These are given two drugs- should be given ACEIs or ARBs as the first drugs to begin with.

- **ACE Inhibitors, such as Enalapril, Lisinopril, and Captopril are recommended when the preferred first line agents (diuretics or β blockers) are contraindicated or ineffective. They lower the blood pressure by reducing peripheral vascular resistance without reflexively increasing cardiac output.**
- **They block the ACE that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II. Moreover, ACE is also responsible for the breakdown of bradykinin (endogenous vasodilator).**
  - When using ACEIs, we stop the production of Angiotensin II and increase the levels of bradykinin (vasodilator); so, the overall effect will clearly be the decrease of BP. Also, they inhibit aldosterone secretion (aldosterone causes sodium and water retention), and this gives them the ability to work as diuretics.

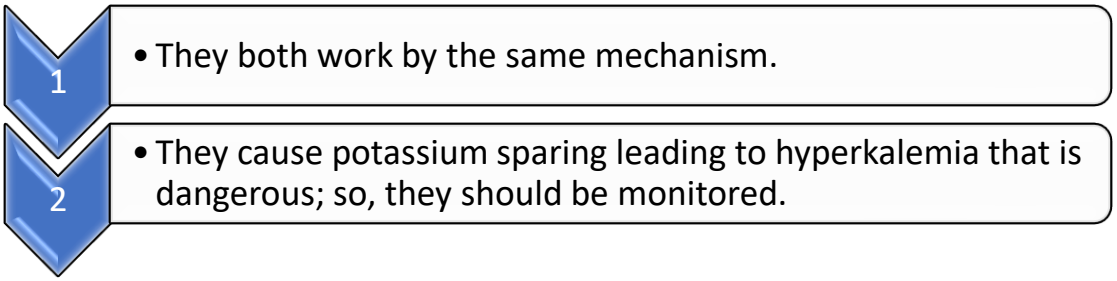
In conclusion, ACEIs work as vasoconstrictor inhibitors, vasodilator enhancers and diuretics.

- **Benazepril, fosinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril**



- After giving ARBs, peripheral vascular resistance, sodium and water retention and blood pressure decrease.

- The efficacy of it is equivalent to the reduction of 20-25 mmHg; they are strong, but not suitable for emergencies.
- Spironolactone and eplerenone are potassium sparing diuretics that cause diuresis without causing potassium loss in the urine.
- We can't give ARBs and ACEIs at the same time for two reasons:



- They can be given together only in one extremely rare case where a patient has congestive heart failure and is unresponsive to all kinds of therapy. To prevent the very low likelihood of angiotensin production in minute amounts and its binding to receptors on the heart (even after giving ACEIs), we give ARBs (you should have access to the potassium levels).
- Thiazides + Candesartan (ARB)=co-diovan; a drug given for hypertension patients to balance potassium levels in blood.
- Only ACEIs are responsible for the bradykinin lane.

- **Dry cough occurs in 10% of patients and thought to be due to increase level of bradykinin in the pulmonary tree. Also, Angioedema is rare but a potential life-threading reaction (may be caused by bradykinin).**
  - Excessive levels of bradykinin due to ACE inhibition can lead to swelling in deeper layers of the skin and mucous membranes, resulting in angioedema. This mechanism is not very well understood though.

- **Because of the risk of first-dose syncope, and the angioedema ACE inhibitors are first administrated under the doctor observation.**
  - First-dose syncope: severe hypotension when taking the first pill.

- **Contraindications: pregnancy.**
  - Very important: ACEIs, ARBs and thiazides (thiazides reduce the blood perfusion towards the placenta) are all contraindicated in pregnancy.

- **ACE inhibitors have a particularly useful role in treating patients with chronic kidney disease because they diminish proteinuria and stabilize renal function (even in the absence of lowering of blood pressure- when there is no hypertension).**
- **This effect is particularly valuable in diabetes, and these drugs are now recommended in diabetes even in the absence of hypertension even in blacks.**
- ACEIs are not the first line therapy in blacks; we give them thiazide and calcium channel blockers.
- ACEIs are contraindicated in the case of bilateral renal stenosis and not in all kidney diseases including unilateral renal stenosis.

- **These benefits probably result from improved intrarenal hemodynamics, with decreased glomerular efferent arteriolar resistance and a resulting reduction of intraglomerular capillary pressure.**
- **ACE inhibitors have also proved to be extremely useful in the treatment of heart failure, and after myocardial infarction.**

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- **The underlined text in pages 5,6 & 8**