The Cardio-VASCULAR System

- ○ Anatomy
- ○ Histology
- ○ Pathology
- ● Pharmacology
- ○ Physiology
- ○ Microbiology

Lec #: 2

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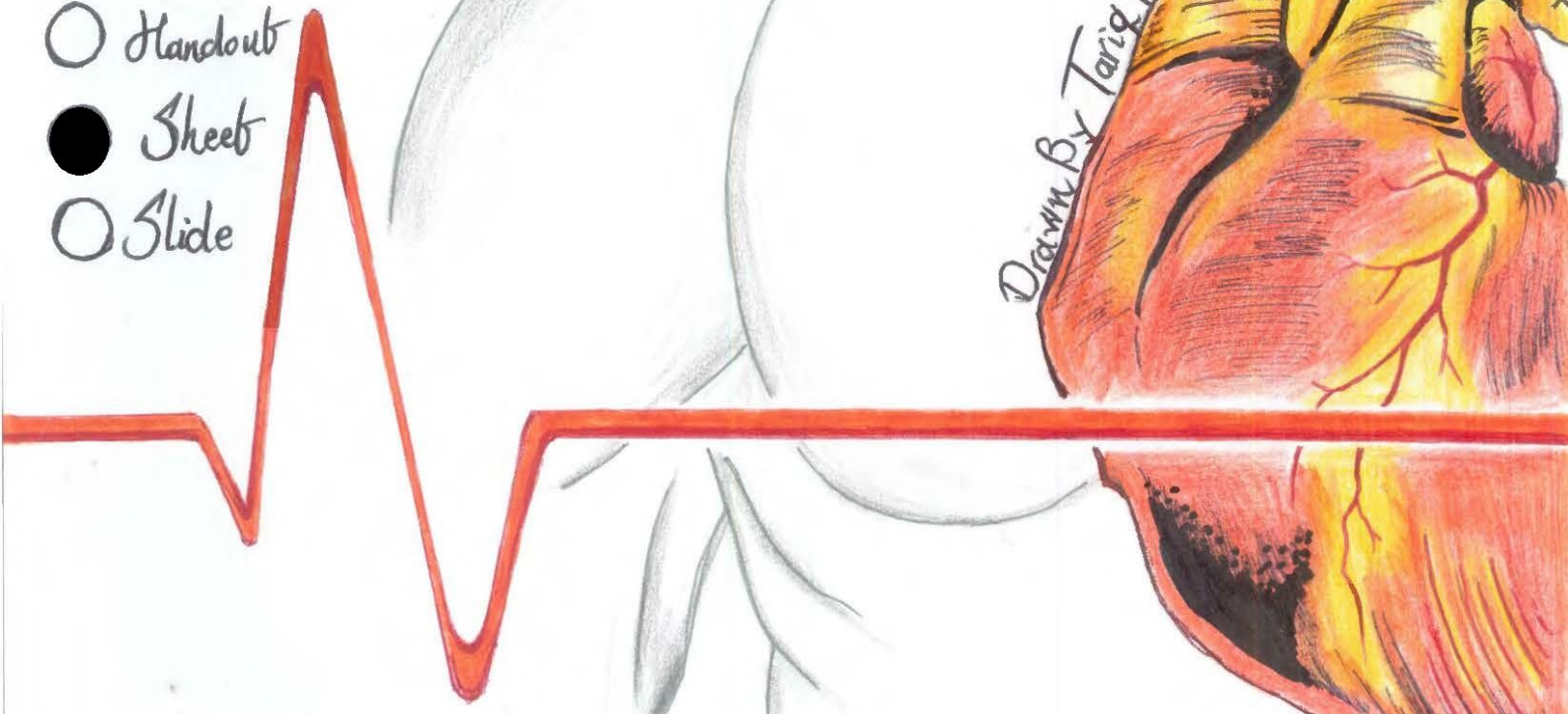
- ○ Handout
- ● Sheet
- ○ Slide



ANTI-HYPERTENSIVE DRUGS

First group of anti-hypertensive drugs are **diuretics**, these are divided into 5 major groups of drugs only 3 groups of those are used in the treatment of hypertension, these groups include :

1- Thiazide diuretics : most commonly used
2- Potassium sparing diuretics
3- Loop diuretics

Thiazide Diuretics

Mechanism of action

- Thiazide diuretics decrease the blood pressure primarily by depleting the body's Sodium stores through inhibition of Na+ reabsorption in the distal convoluted tubules of the kidneys .

- In the **first 4 weeks** of administration of thiazide diuretics the patient blood pressure will decrease by **decreasing the blood volume** and consequently decreasing the cardiac output so in this time period the patient will experience **frequent urination .**

- After 4 weeks the body will adapts to the drug and the patient's blood volume and cardiac output gets back to normal but the anti-hypertensive effect of the drug persists. How ??

  Since thiazide drugs decrease Na+ stores in the body this will decrease sodium stores within the vessels which results in **vasodilation** because sodium is a major contributor to vascular resistance by increasing vessel stiffness and neuronal activity . Vasodilation will lower the peripheral resistance which will lower the blood pressure .

- The highest efficacy in reduction of blood pressure by thiazide drugs is about 15 mmHg , because of this low efficacy thiazide diuretics are not the first line of management of hypertension , they are used in combination with other drugs (it is an add on drug)

- From slides : thiazide reduces blood pressure in supine and standing position , postural hypotension is rarely observed except in elderly

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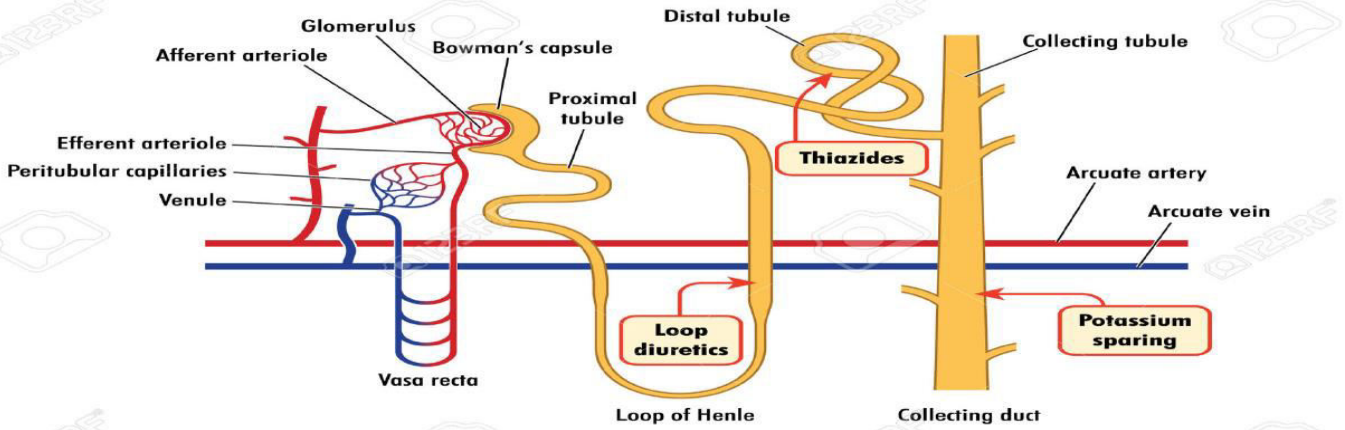

- In the kidneys there are millions of seminiferous tubules , each tubule is divided into proximal tubule →Loop of Henle → Distal tubules →Collecting ducts . each of these tubules has a specialized function of either reabsorption or excretion of minerals and electrolytes .

- The main site of action of thiazide diuretics is on the distal tubules inhibiting the reabsorption of sodium . **About 3-5 % of Na++ reabsorption is inhibited** that's why thiazide drugs don't produce hypovolemia because minimum amount of Na+ reabsorption is inhibited , consequently minimum amount of water is lost from the body since water reabsorption generally follows sodium reabsorption .

- Thiazide diuretics is not really a good drug for the treatment of edema since minimal amount of sodium and water is lost by the action of this drug. The main drug of choice of the treatment of hypertension with signs of edema is **loop diuretic** , unfortunately loop diuretics are associated with hypovolemia and electrolyte imbalance (hypocalcemia , hypomagnesemia , hypokalemia) since these electrolytes are mainly reabsorbed in the loop of henle , that's why loop diuretics are not used in the management of hypertension EXCEPT in a case of patients with **hypertension + edema** .

Dosing

- There are many prototypes of thiazide diuretics but the most important ones are :

1- Chlorothiazide : given orally 1-2 times a day

2- Hydrochlorothiazide : 1-2 times a day

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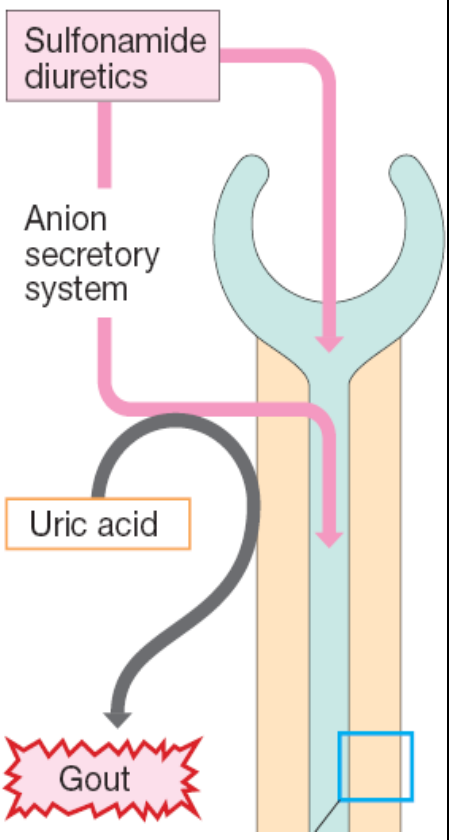
- **Thiazide is usually administered under low dose of 12.5-25 mg (or up to 50 mg in extremes) because this low dose exerts an antihypertensive activity of minimal side effect , when the dose exceeds 50 mg we start to see side effects . From slides : low doses of thiazide exert as much antihypertensive effect as higher dose . (IMPORTANT)**

Side effects (Always remember that these side effects appear in doses higher than 50 mg)



1- Hypokalemia : Because normally the reabsorption of Na+ is coupled with the reabsorption of K+ so when you inhibit the reabsorption of Na+ , the reabsorption of K+ will also decrease . Is this hypokalemia significant ? No because as we said 3-5% of Na+ reabsorption will be inhibited which also means that 3-5 % of K+ will be lost so this is not that much EXCEPT if thiazides were used in combination with drugs that depend on K+ like digoxin (I didn't understand what the doctor mean in this).

   Note : The risk for hypokalemia increase drastically with high salt diet because high salt intake means high Na+ intake -> More Sodium excretion -> more K+ loss following sodium .So you should tell your patient to stick with a salt free diet .

2- Hyperglycemia : due to inhibition of K+ dependent insulin release

3- Hyperlipidemia : rise in total LDL level which increases the risk for strokes

4- Hyperuricemia : this is due to drug-drug interaction (competition) between thiazide and uric acid at the site of excretion , this will inhibit the excretion of uric acid causing it to accumulate in the body, resulting in gout. This side effect is really prominent in patients taking thiazide over a long time (about 10 years) even under low doses (IMPORTANT). In your clinical life you will always face elderly people complaining about pain in their toes , the first question you ask them is if they take thiazide ? if they do you ask them for how long ? if it is more than 10 years then it is a side effect of the drug .

   Keep in your mind that the only side effect that you should worry about with low dose of thiazide is **hyperuricemia** and it happens after 10 years of use .

Loop Diuretics

- These groups of drugs work on loop of henle and they facilitate the excretion of 20% of Na+ from the body along with water and many electrolytes , so when you use these drugs you will worry about hypovolemia , hypomaganesemia , hypocalcemia ,hypokalemia , hyponatermia .

- These drugs are not usually prescribed for the treatment of hypertension and the only cases that they are used in are :

  1- In Patients who have resistant hypertension with signs of edema : resistant hypertension is defined as a hypertension that is not responsive to medications

  2- Patients with edema caused from **congestive heart failure**

- The prototype drug of loop diuretics is **furosemide** commonly known as **Lasix** and you are going to hear about it a lot in the urogenital pharmacology .

Extra notes from the slides :

- Lasix must be dosed at least twice daily (lasix activity lasts for 6 hours)

- Lasix must be administered during the day or at lunch to avoid nocturia

- Adverse effect of loop diuretics is summarized in :

1- Ototoxicity especially when using them with aminoglycosides

2- Hyperurecemia and hypocalcemia

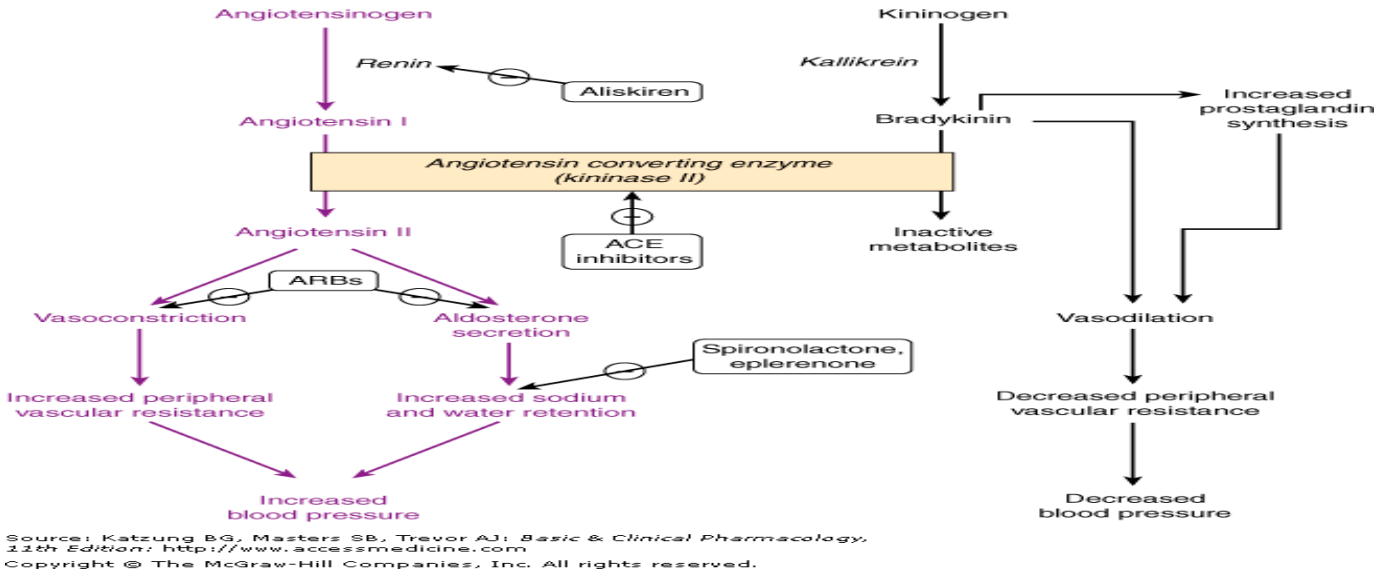
ACE inhibitors

- These are the best drugs ever in the treatment of hypertension for everything (with diabetes , kidney failure , heart failure … الخ)

Drug prototype

- ACEI drugs end with the suffix **pril** and the main prototype drug is **captopril**

Mechanism of action



- ACE inhibitors inhibit the enzymatic activity of angiotensin converting enzyme found in the lungs and this is going to produce the following actions :

1- This is going to reduce the amount of angiotensin 2 by inhibiting the conversion of angiotensin 1 to angiotensin 2
2- Prevent the conversion of bradykinin to an inactive metabolite by ACE which is going to increase the amounts of bradykinin in the body

Let us go deeply in each one of these points and see what are the outcomes

Inhibition of angiotensin 2 synthesis

Angiotensin 2 has two important functions : it is a potent vasoconstrictor and it stimulates the production of aldosterone from the adrenal cortex which in turn stimulate the reabsorption of Na+ and water from kidney tubules (water and sodium retention) .

So if you inhibit the production of angiotensin 2 you will get :

1- Vasodilatation of vessels

2- Diuretic action by inhibiting the reabsorption of Na+ and water by kidney tubules

-So you can think of ACE inhibitors as they have a double function , first as a **vasodilator** and second as a **diuretic** .

Inhibition of the inactivation of bradykinin by ACE

This will lead to building up of bradykinin in the blood which is also a **vasodilator** . So we got vasodilatation by using ACEI by 2 mechanisms : inhibition of angiotensin 2 and by bradykinin

Side effects

1- The most important side effect related to ACEI is **dry cough** which is caused from the building up of bradykinin in the trachea and it happens in **10% of the patients** . In those patients who develop dry cough we switch them into **angiotensin 2 receptor blocker** (ARB) which we are going to talk about later on this lecture .

2- **Angioedema :** this is a very rare side effect and it is caused from an allergic reaction to bradykinin which leads to excessive vasodilatation and increased vascular permeability , leading to rapid accumulation of fluid in the neck . This fluid accumulation in the neck area creates a huge risk for airway **obstruction and suffocation** which is a medical emergency. That's why when we first administer ACEI we give it under close medical observation in case Angioedema happens.

3- **Hyperkalemia :** since we inhibited the production of aldosterone by angiotensin 2 , we inhibit the reabsorption of Na+ and excretion of K+ from the proximal renal tubules which is the function of aldosterone , This will cause K+ retention in the body and hyperkalemia but again this hyperkalemia is not significant because minimal amount of Na+ is reabsorbed and minimal amount of K+ is excreted in the proximal renal tubules .**The only case when the hyperkalemia becomes significant is when we use spironolactone along with ACEI because spironolactone is an aldosterone antagonist , this will produce an additive action with ACEI which increase the risk for significant hyperkalemia , that's why it is relatively contraindicated to give ACEI with spironolactone .**

Since both thiazide and ACEI inhibit Na+ reabsorption, why do they have different effects on K+ levels?

It depends on their site of action; thiazide works on the distal renal tubule where Na reabsorption is coupled with K+ reabsorption, so it causes hypokalemia. ACEI works on the proximal renal tubule where Na reabsorption is coupled with K+ excretion, so it results in hyperkalemia.

4- **First dose syncope** from Wikipedia : it is a sudden and sever fall in blood pressure when changing from a lying to standing position the first time after using the drug which results in fainting (syncope) . The doctor says that this effect does not happen in reality but it is written in books .

Therapeutic uses of ACEI

- Before talking about the therapeutic uses let us review some of the important actions of angiotensin 2 and use them to conclude the therapeutic uses

1- Angiotensin 2 increases myocardial force of contraction (Ca++ influx promotion) and increase the heart rate by sympathetic activity which increases the cardiac work and reduce the cardiac output which forces the heart toward hypertrophy.

This action is highly linked with **congestive heart failure** , in patients with congestive heart failure they have increased level of angiotensin 2 because of hypovolemia (activation of renin-angiotensin system) caused from the low pumping action of the heart , so in those patients angiotensin 2 makes his condition worse since his heart has already failed.

So the first therapeutic use of ACEI is in patients with congestive heart failure in order to reduce the levels of angiotensin 2 which further damage the heart

2- Vasoconstriction of renal arterioles which rises intra glomerulus pressure and reduces glomerular filtration rate.

The main cause of development of renal diseases is caused from vasoconstriction of renal arterioles which predispose the patient to renal damage. Renal damage mainly happens in Chronic renal disease and diabetes mellitus.

So the 2nd therapeutic use of ACEI is in the treatment of hypertension in patients with diabetes or chronic renal disease to antagonize the vasoconstriction of arterioles , reduce IGP and improve the glomerular filtration rate which reduce the risk of further kidney damage in those patients .

Note : sometimes we prescribe ACEI to diabetic patients **even if they don't have hypertension** in order to protect them from **diabetic nephropathy** .

Angiotensin 2 receptor antagonists

- These agents are alternative to ACEI and are mainly used if the patient can't tolerate the side effects of ACEI especially the dry cough.

- Angiotensin 2 receptor blockers (ARB) are drugs that end with the suffix **sartan** with **Losartan** being the prototype .

- ARB have the same efficacy as ACEI and they have the same therapeutic uses and the same side effects EXCEPT dry cough and Angioedema because they don't increase bradykinin levels.

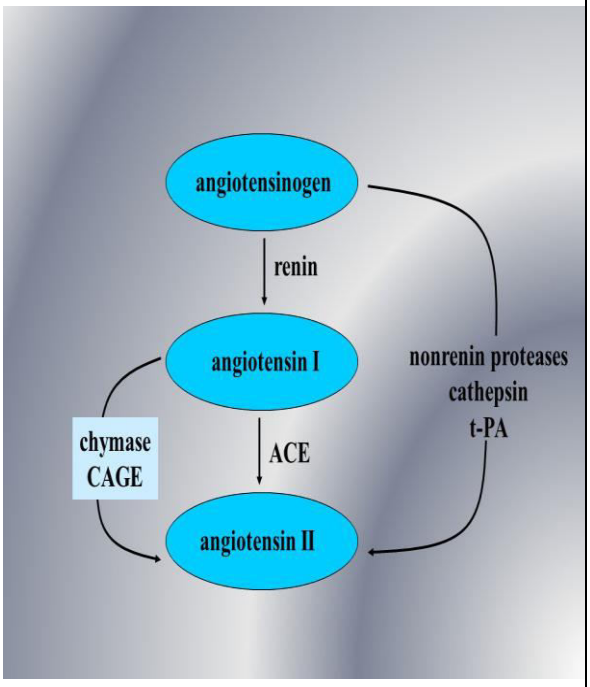
- **ARB and ACEI are teratogenic drugs; so they're absolutely contraindicated to be given to pregnant women and they are in category X.**

Alternative pathways of angiotensin 2 production

There are 2 main alternative pathways that can produce angiotensin 2 other than ACE which are:

1- **Chymase enzyme** which converts angiotensin 1 to angiotensin 2
2- **Nonrenin protease cathepsin t-PA** which converts angiotensinogen to angiotensin 2 directly

- This alternative pathway can sometime overcome the inhibition of angiotensin 2 production by ACEI , in this case we combine ACEI with ARB because even if some angiotensin 2 was produced by chymase it won't act on its receptor because it will be blocked by ARB drug .



Note : normally we should never combine 2 drugs with the same mechanism of action and side effects as in the case of ACEI and ARB but we only do this combination in patients with congestive heart failure because we really don't want any angiotensin 2 to be produced at all . In case of combining the 2 drugs you need to carefully monitor the patient K+ level as the risk for hyperkalemia increases .

The end

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