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بسم الله الرحمن الرحيم

Diuretics Pt.2

FINAL | Lecture 2

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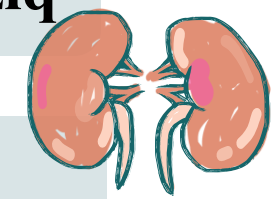

﴿قُلْ بِفَضْلِ ٱللَّهِ وَبِرَحْمَتِهِۦ فَبِذَٰلِكَ فَلْيَفْرَحُوا۟ هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ﴾

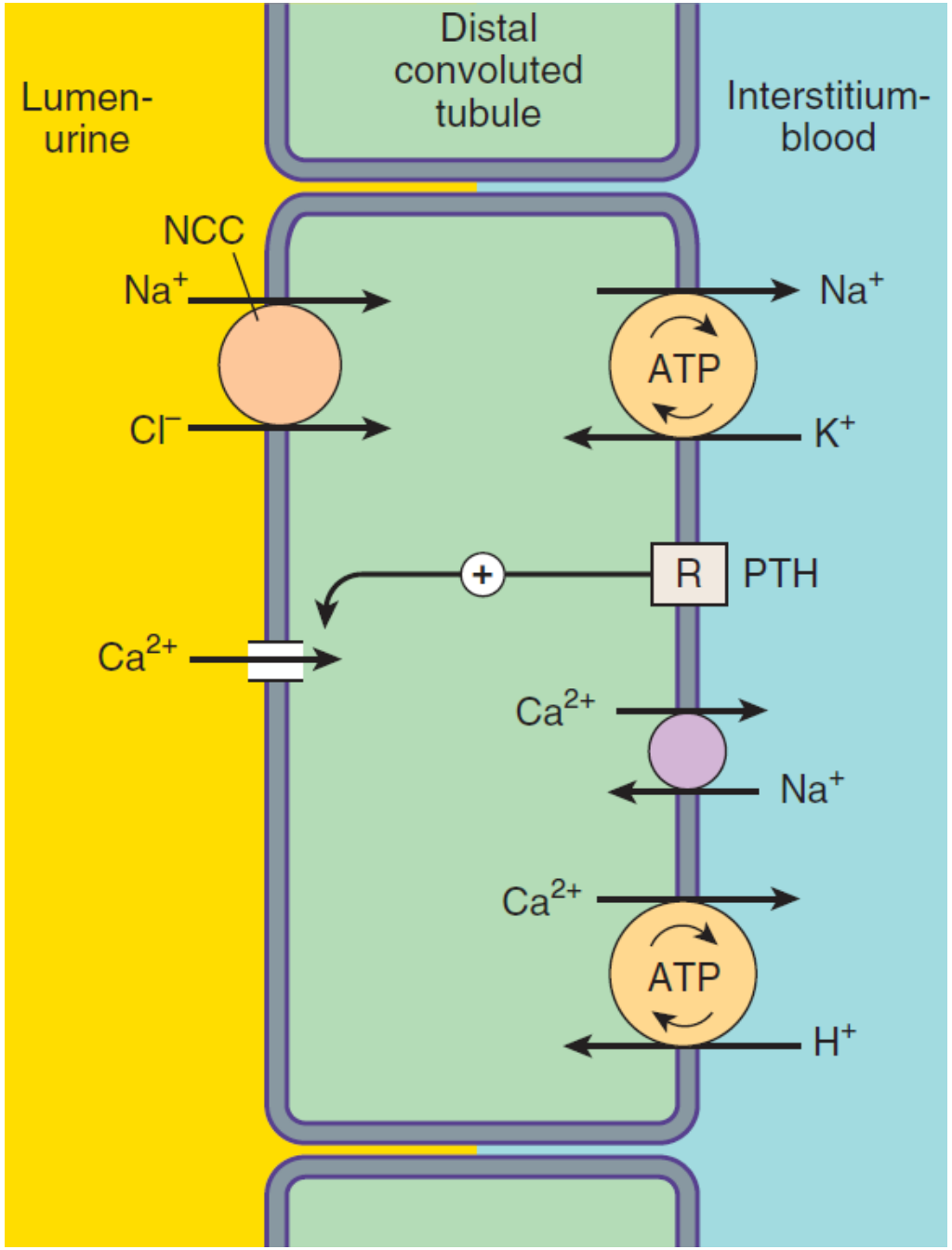

FIGURE 15–4

- **Ion transport pathways across the luminal and basolateral membranes of the distal convoluted tubule cell.**
- **As in all tubular cells, Na^+/K^+-ATPase is present in the basolateral membrane.**
- **NCC is the primary sodium and chloride transporter in the luminal membrane.**
- **R, parathyroid hormone (PTH) receptor.**

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Thiazide Diuretics

These drugs act in distal convoluted tubules, we have 4 transporters in DCT :

Found on the **luminal side**:

- Na^+/Cl^- cotransporter which are the site of action of thiazide diuretics .

Found on the **interstitial side**:

- Parathyroid hormone receptor in DCT that acts on calcium reabsorption but this function isnt related to the diuretic effect .
- Ca2+ , Na+ exchange
- Ca2+ , H+ ion exchange

The **action** of thiazides leads to **loss of NaCl**, because they inhibit Na^+/Cl^- cotransporter, in combination with water.

Thiazide Diuretics

First line treatment for Hypertension

1.Hydrochlorothiazide, Chlorthiazide, Chlorthalidone.

After 4 or 5 days, **tolerance to diuretic action** develops, but they maintain their effect on the electrolyte balance, as a result they **produce vasodilation** because the ion change under the influence of thiazide diuretics makes the blood vessels not susceptible to the circulating vasoconstrictors like epinephrine, catecholamines, angiotensin || and others.

2. Indapamide, Metolazone.

More recent thiazide diuretics **(newer generation),** there feature is **more urine output** than the old generation thiazide diuretics

- **All have unsubstituted sulfonamide group.**

This structural feature is responsible for allergic reactions and photosensitivity. (All drugs that contain an unsubstituted sulfonamide group such as antimicrobial sulfonamides, loop diuretics, and sulfonylureas used in type 2 diabetes, can produce these adverse effects).

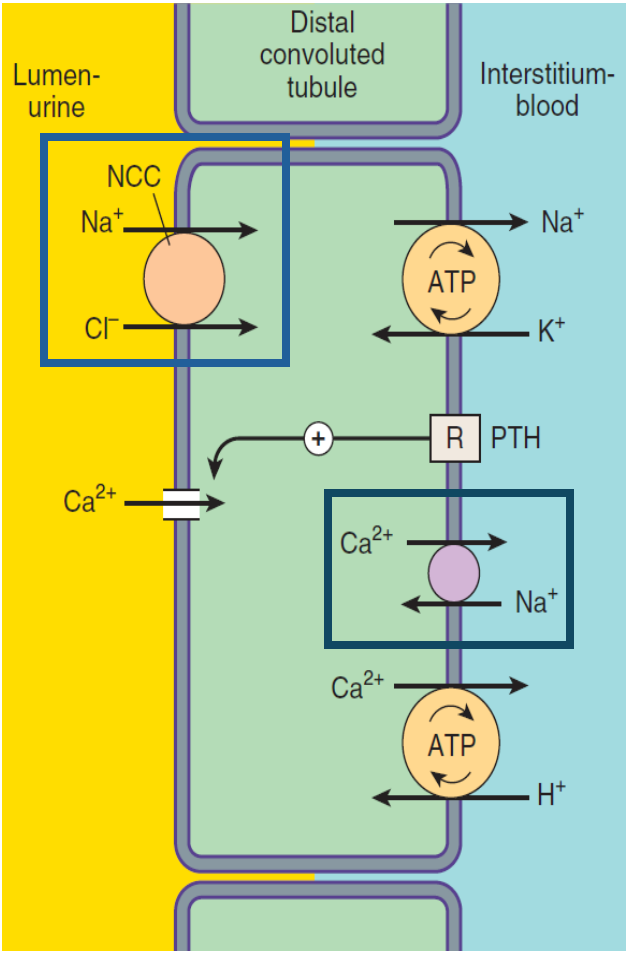
Thiazide Diuretics

Pharmacological Actions:

1. **Inhibit NaCl reabsorption form the distal convoluted tubule by blocking the electrically neutral, thiazide-sensitive Na^+/Cl^- co-transporter.**

2. **Enhance Ca^{2+} reabsorption in the distal convoluted tubule** this is **different** from calcium reabsorption from the effect of parathyroid hormone receptor**. May be due to lowering of intracellular sodium which enhances Na^+/Ca^{2+} exchange in the basolateral membrane.**

   Inhibition of Na^+/Cl^- exchange leads to an increase in NaCl in the urine, which lowers intracellular Na^+. This low intracellular Na^+ enhances Na^+/Ca^{2+} exchange (driving Na^+ into the cells and Ca^{2+} into the interstitium), resulting in calcium retention. On the other hand, loop diuretics cause calcium loss.



Thiazide Diuretics

Thiazide-induced volume depletion leads to enhanced Na^+ and passive Ca^{2+} reabsorption in the proximal tubule.

When you loose sodium and water, proximal sodium and calcium reabsorption occurs, so calcium is retained because of two mechanisms:

- Increased proximal sodium reabsorption as a reflex compensatory mechanism,Ca^{+2} reabsorption follows passively
- Calcium reabsorption that occurs in DCT which was discussed in the previous slide

3. **Significant carbonic anhydrase inhibitory activity.**

   (More than that of loop diuretics)

4. **Actions depend, in part, on renal prostaglandin synthesis.**

   Less than loop diuretics, increasing renal blood flow, perfusion of the tissue, nutrition and protect against damage of the kidney

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Thiazide Diuretics

Pharmacokinetics:

- **Can be used orally.**
- **Have differences in metabolism.** (They aren't identical in the way of elimination)
- **Chlorthiazide is the only thiazide used parenterally. Not very lipid soluble.**

  Drugs administered intravenously (IV) or intramuscularly (IM) should be water soluble. Although there are cases where an IM injection is given so that the drug precipitates in the muscle and then gradually diffuses into the circulation, in this case we want a fast effect.

- **Chlorthalidone is slowly absorbed and has a long duration of action.** However, its adverse reactions are difficult to manage because they also have a long duration.

Thiazide Diuretics

- **Indapamide is primarily excreted by the biliary system.**
- **All are actively secreted by the organic acid secretory system in the proximal tubule** (diuretics have to be actively secreted or filtered to the lumen of tubules)**, and compete with uric acid for that system** so they can cause hyperuricemia**.**

Thiazide Diuretics

Adverse Effects:

1. **Hypokalemic metabolic alkalosis.** Mechanism is discussed more in slide 17,18

- **By inhibiting salt reabsorption in the distal convoluted tubules, thiazide diuretics increase Na^+ delivery to the collecting duct** and tubules **. Increased Na^+ delivery** to the collecting tubules and duct **leads to increased secretion** (loss) **of K^+ and H^+ by the duct, causing hypokalemic metabolic alkalosis.**
- Note: an adverse reaction does not refer to any potassium retention. Only when potassium retention is too much and causes hypokalemia, we list it as an adverse reaction. Adverse reaction here means exaggerated pharmacological effect
- All acid-base disturbances are emergency problems and need treatment

Thiazide Diuretics

2. **Hyperuricemia.** Because these drugs compete with uric acid for active secretion
3. **Hyperglycemia – due to hypokalemia- induced inhibition of insulin release.**
4. **Weakness, fatigue and parasthesia (effect CAI)** due to carbonic anhydrase inhibitors effect
5. **Impotence (probably related to volume depletion)** occurs with loop diuretics as well
6. **Hyperlipidemia (increase cholesterol and LDL).**

More details on this point in the next slide…

Thiazide Diuretics

- Why do we treat a patient with hypertension?

  To prevent complications as it is a risk factor of atherosclerosis, hypercholesterolemia, cardiovascular diseases ...

- The first line treatment of hypertension : **thiazide diuretics** , ACE inhibitors , angiotensin receptor blockers , Ca channel blockers

- How can we treat a patient with hypertension by giving a thiazide which causes hyperlipidemia?

  To solve this problem, we monitor the level of cholesterol in the patient when it starts to increase, we combine thiazide with cholesterol lowering agents.

Any preventable Adverse reaction should not happen (all adverse effects due to exaggerated pharmacological effect are preventable).

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Thiazide Diuretics

7. **Hyponatremia: is significant, due to:**

- **hypovolemia-induced elevation of ADH** compensation to the fluid loss through aldosterone and ADH
- **reduction in the capacity of the kidney to produce dilute urine**
- **increased thirst** because of loss of fluids (the patient will drink water without sodium which results in hyponatremia)
- **extension of pharmacological action of nacl loss as exaggerated action**

Thiazide Diuretics

8. **Allergic reactions** due to sulfonamide group, this group is also present in sulfonamide antimicrobials, sulfonyl urias, loop diuretics.

   (hemolytic anemia, thrombocytopenia & acute necrotizing pancreatitis, necrotizing alveolitis, bone marrow suppression, exfoliative **dermatitis** (fatal, could progress to Steven Johnson Syndrome)**, cholestatic hepatitis** drug induced allergy of the liver, in the kidney it's called interstitial nephritis**).**

   Note: To avoid exfoliative dermatitis, you should monitor your patient, if the adverse effect starts to appear on the patient you have to change the drug.

9. **Photosensitivity.** Due to histamine release under the influence of UV light, or due to a chemical like morphine / muscle relaxants they release histamine by themselves. This adverse effect is also common in sulfonamide containing groups.

Thiazide Diuretics

Therapeutic Uses:

1. **Hypertension** (most common use)
2. **Edema of:**
   - **a. mild-moderate congestive heart failure**

     Indapamide &Metolazone –the new"**strong**" generation drugs
   - **b. hepatic and renal insufficiency**

     Hydrochlorothiazide, the old "**weak** sgurd noitareneg " SEE THE NEXT SLIDE
3. **Nephrolithiasis due to hypercalciuria**

Thiazides reduce urinary calcium loss In contrast to loop diuretics

Thiazide diuretics & Edema

- Although the main therapeutic use of thiazide diuretics is Hypertension, in some cases we use them to get rid of excess fluids in different parts of the body, with caution, monitoring for electrolyte and fluid levels:

  - For edema caused by **congestive heart failure** esu ew ,**strong** thiazide diuretics because we need to get rid of excess fluids **rapidly** and efficiently.

  - For **ascites and lower limb edema** caused by hepatic and renal insufficiency respectively, **slower** and more cautious diuresis is preferred to avoid complications such as dehydration and renal hypoperfusion, so we should use **weak** edizaiht diuretics.

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Thiazide Diuretics

4. Nephrogenic diabetes insipidus (where the kidney is NOT responding to ADH)**: NaCl & water loss in the distal nephron** (Thiazides MOA) **enhances NaCl & water absorption by the proximal nephron** as a paradoxical compensatory mechanism**, and decreasing delivery of fluid to the diluting segment** (ascending limb of henle) to decrease urine dilution effect of thiazides .

- **Dietary sodium restriction can potentiate this effect.**

Less dietary sodium →Less sodium needs excretion →Less obligatory water loss occurs →Thiazide-induced volume contraction becomes more effective So:low sodium diet potentiates the antidiuretic effect of thiazides.

Golden rule from Dr. Yacoub:
When there is diuretic effect in any distal part of kidney tubules, the proximal parts always try to compensate this effect.

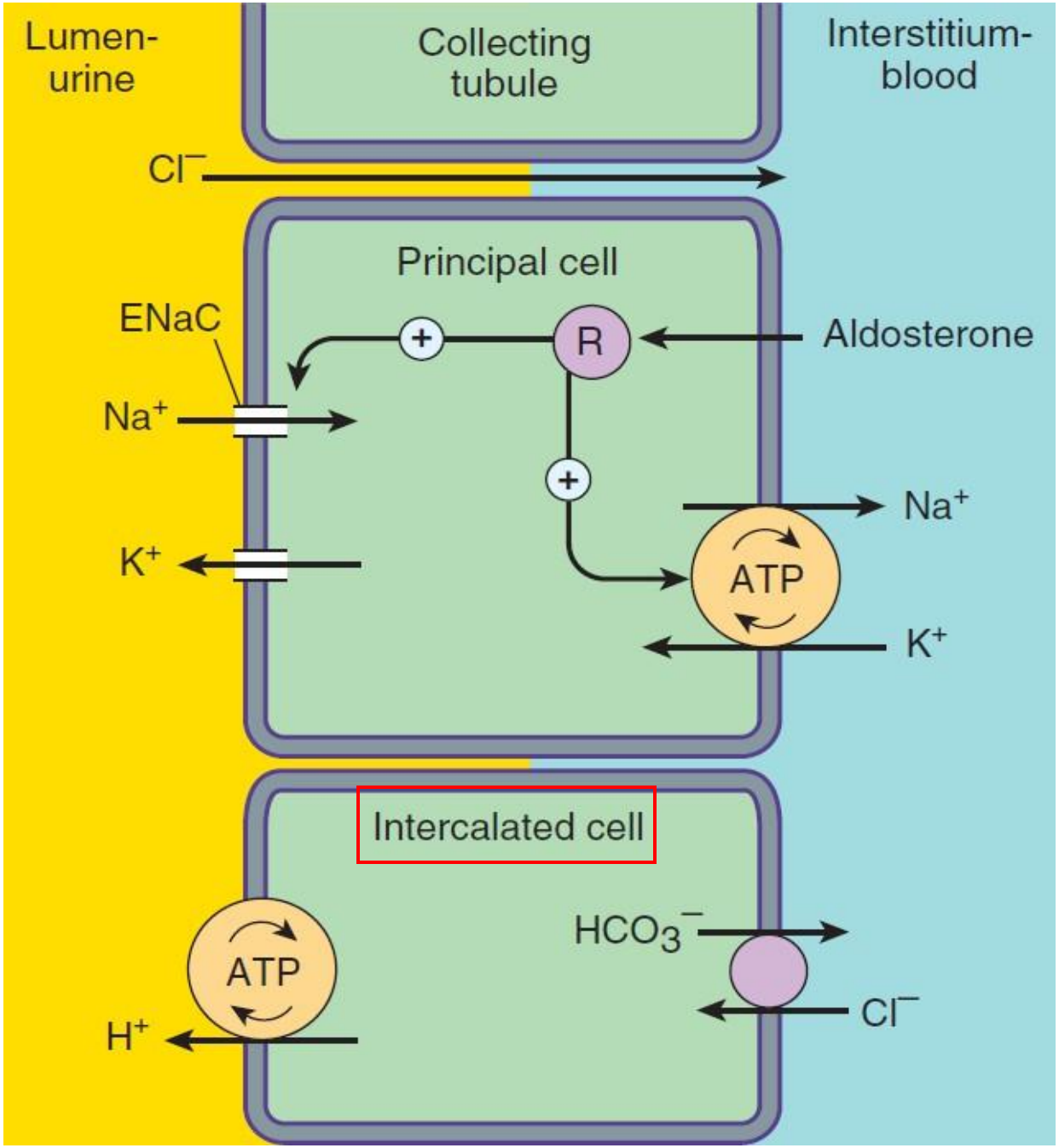

FIGURE 15–5

- **Ion transport pathways across the luminal and basolateral membranes of collecting tubule and collecting duct cells.**
- **Inward diffusion of Na+ via the epithelial sodium channel (ENaC) leaves a lumen-negative potential, which drives reabsorption of Cl– and efflux of K+.**
- **R, aldosterone receptor.**

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Overview of the Normal Physiology in Collecting Ducts

- Normally, in the collecting ducts, aldosterone causes increased sodium and water retention, through inward diffusion of Na+ via the epithelial sodium channel (ENaC) and the sodium potassium pump.
- This results in a decreased positive charge in the lumen, causing chloride to **diffuse between the cells** out of the lumen, and potassium secretion into the lumen to increase.
- Additionally, through the intercalated cells, the decrease in sodium (and the resulting decrease in positive charge) causes hydrogen secretion into the lumen as well.
- However, when we use potassium-sparing diuretics that inhibit sodium reabsorption, there is less potassium and hydrogen secretion, leading to hyperkalemia and acidosis.
- Regarding what was mentioned in slide 9 about thiazide diuretics they cause hypokalemia and alkalosis because the cells of the collecting duct want to reabsorb that extra sodium reached it (to maintain blood pressure and volume), to do so the cell must get rid of another positive ion to maintain electrical balance inside the cell. It does this by secreting potassium (K^+) and hydrogen (H^+) into the urine in exchange for reabsorbing sodium.

■ What's special about collecting tubules is the significant role of their intercalated cells in maintaining acid-base balance via the hydrogen pump, which is crucial with K+ sparing diuretics.

■ Most K+ sparing diuretics exert their effect mainly by working on **Na+ channels inhibition** in the late distal tubule and collecting duct, leading to **mild Na^+ and water loss** while **decreasing K^+ secretion**, thereby causing potassium retention (sparing).

■ **There are 2 <u>main</u> types of potassium-sparing diuretics:** OVERVIEW

The first one are the **<u>Aldosterone Antagonists</u>**, such as Spironolactone and Eplerenone, which block the intracellular aldosterone receptor in principal cells. This decreases the synthesis and activity of ENaC and Na^+/K^+ ATPase pumps, reducing Na^+ reabsorption and consequently decreasing K^+ and H^+ secretion.

The second type includes **<u>Amiloride and Triamterene</u>**, which directly block the epithelial sodium channels (ENaC) on the luminal membrane of principal cells, thereby reducing Na^+ entry into the cells and diminishing the electrical gradient that normally promotes K^+ secretion.

Potassium Sparing Diuretics

A. Aldosterone Antagonists

Spironolactone , Eplerenone

Pharmacological Actions:

Rule:
· Aldosterone causes retention of Na+ & Cl-
· Aldosterone antagonists cause retention of K+ & H+ (that's why they belong to the family of K+ sparing drugs)

- **Block aldosterone receptors competitively and thus:**

1. **Interfere with sodium & water reabsorption and potassium excretion in the collecting tubules.**
2. **Also interfere with H^+ handling in the intercalated cells.**

Such actions may depend on prostaglandin production.

As we said in loop and thiazide diuretics!

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Potassium Sparing Diuretics

Spironolactone:

Pharmacokinetics:

- **Absorbed after oral administration.**
  Usually, we don't use them for urgent situations, so oral administration is enough.
- **Extensive enterohepatic cycling;** **thereby increasing the drugs t1/2 & toxicity risk.**
  How could we get rid of this effect? By giving specific positively charged resin (e.g. Cholestyramine) which binds the drug's free metabolite in the intestines and inhibits its reabsorption
- **Extensive binding to plasma proteins.** = interacts (competes) with plasma protein-bound drugs
- **Canrenone is an active metabolite.**

Potassium Sparing Diuretics

Adverse Effects:

1. **Hyperkalemia: can be dangerous especially when combined with other drugs that increase potassium, such as, potassium supplements, NSAIDs, ACEIs, AT-blockers, β-blockers, etc.**

   OR in renal failure.

   !! Hyperkalemia is a medical emergency state which –if not corrected urgently– may lead to cardiac arrest. So, these patients potassium levels must be monitored.

2. **Metabolic acidosis.**

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Potassium Sparing Diuretics

3. **Gynecomastia** which may progress to breast cancer in males**, Impotence & benign prostatic hyperplasia** because of its steroidal structure acts as an androgen **– not seen with eplerenone**
4. **GIT upset.**

CAUTION:

1. **Reduce dose in hepatic disease.** (Due to accumulation of the dose)
2. **Ketoconazole and itraconazole can increase blood levels of eplerenone due to inhibition of CYP3A4.**

Potassium Sparing Diuretics

B. Amiloride and Triamterene

Pharmacological Action:

1. **Do not block aldosterone receptors.**
2. **Directly interfere with Na^+ entry through the selective ion channel in the collecting tubule.**
3. **Since K^+ excretion is coupled with Na^+ entry, the effect is sparing of K^+.**
4. **The action may depend on renal prostaglandin production.** As we said in loop, thiazide, and both classes of potassium sparing diuretics!
5. **Also inhibit H^+ secretion in the distal nephron.**

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Potassium Sparing Diuretics

Pharmacokinetics:

- **Amiloride is excreted unchanged in urine.**
- **Triamterene is metabolized in the liver, but renal excretion is a major route of elimination for the active form and metabolites.**
- **The metabolite has a shorter t½ than amiloride.**

Potassium Sparing Diuretics

Adverse effects:

For both:

1. **Hyperkalemia.**
2. **Significant Nausea, vomiting, headache.**
3. **Metabolic acidosis.**

For triamterene also:

1. **Leg crambs, azotemia.**
2. **Interstitial nephritis.**

Potassium Sparing Diuretics

3. **Nephrolithiasis (crystal formation).**
   Renal stones caused by drug crystallization in urine
4. **Acute renal failure when given in combination with indomethacin**(anti-inflammatory drug)**, indomethacin inhibits renal prostaglandins while triamterene potentially causes tubulointerstitial damage or crystal formation.**
5. **Glucose intolerance.**
6. **Photosensitivity.** Due to UV induced histamine release

Potassium Sparing Diuretics

Therapeutic Uses:

1. **Mineralocorticoid Excess (1^o , 2^o or ectopic).** Hyper-aldosteronism
2. **In conjunction with other diuretics** *e.g. Loop diuretics & thiazide diuretics* **to reduce potassium loss.**
3. **Hypokalemia (?)** In combination with K+ supplements

PHARMACOLOGY QUIZ LECTURE 2

External Resources

رسالة من الفريق العلمي

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقِه من فتنة القبر وعذاب النار، أنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم.

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