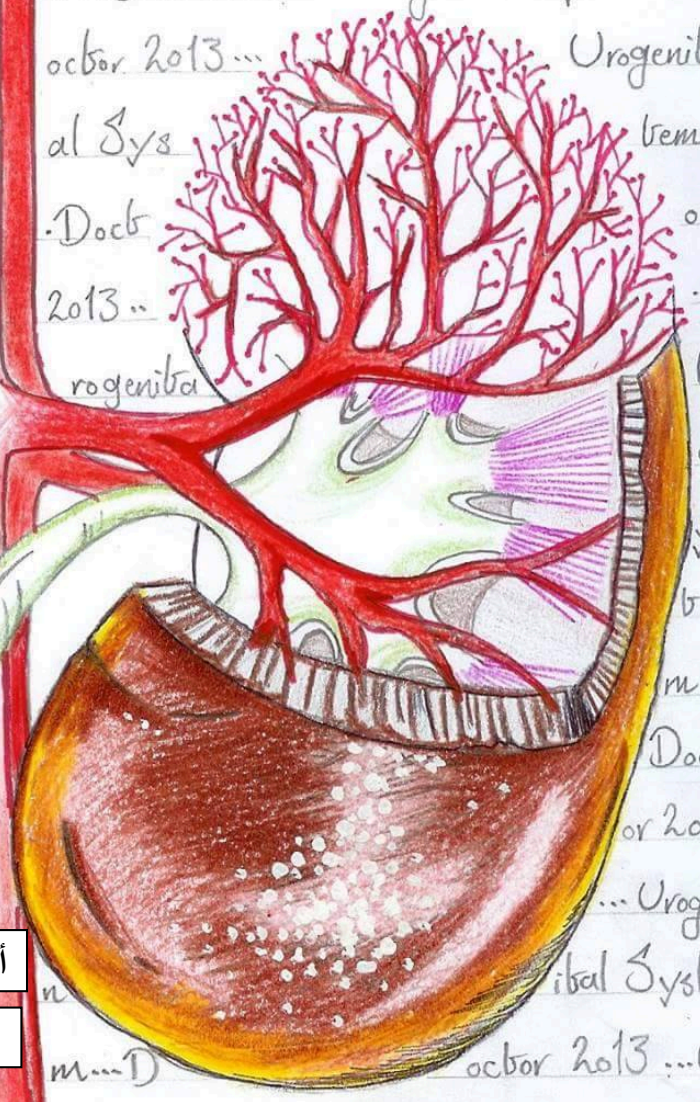
URO-GENITAL SYSTEM

- Handout
- Sheet
- Slide

- Anatomy
- Physiology
- Pathology
- Biochemistry
- Microbiology
- Pharmacology
- PBL



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بسم الله الرحمن الرحيم

Diuretics(Saluretics)

This sheet was written according to section 2's record, and includes the entire slide. Good luck.

In this course we will discuss:

1- **Diuretics**
2- **Antifungal agents**
3- **Oxytocin (drugs acting on uterus) & ADH**
4- **GnRH; LH; FSH**
5- **Estrogens; antiestrogens; progestins; antiprogestins; contraception**

Diuretics:

Diuretics increase urine excretion mainly by ↓reabsorption of salts and water from kidney tubules.

These agents are ion transport inhibitors that decrease the reabsorption of Na+ at different sites in the nephron, thus increasing the volume of the urine, and often change the pH of urine, as well as the ionic composition of the urine and blood.

Remember that there are certain substances that have diuretic effect but are not considered diuretics by definition such as: Water, digitalis, caffeine and theophylline.

-General clinical uses:

1-Hypertension: thiazides are the first line therapy for treatment of hypertension.

(There are a huge number of drugs that act by different mechanisms to lower blood pressure, such as β-blockers, angiotensin converting enzyme inhibitors and many others.)

2- Edema of heart, renal or liver failure

3- Pulmonary edema: this is a severe condition that needs medical intervention and a very strong diuretic is used.

4- ↑ intracranial pressure (Mannitol): mannitol is the most effective diuretic for treatment of increased intracranial pressure.

5- ↑ intraocular pressure=glaucoma (CA inhibitors, such as acetazolamide):

All diuretics can be used to treat glaucoma, but the most effective one is acetazolamide.

6- Hypercalcemia (Furosemide=Frusemide'loop diuretic')

7- Idiopathic hypercalciuria (Thiazides):

Certain diuretics will increase the excretion of $Ca^{2+}$and so are used for the management of hypercalcemia while other diuretics will increase the reabsorption of Ca^{2+}, so we use them for the management of hypocalcaemia "hypercalciuria".

8- Inappropriate ADH secretion (Furosemide)

9- Nephrogenic diabetes insipidus (Thiazides):

Diabetes insipidus characterized by frequent urination and bloody urine>>> thiazides act as paradoxical antidiuretic in this condition.

Paradoxical effect: is an effect of medical treatment,usually a drug,opposite to the effect which would normally be expected.

■ General consideration

- Basic knowledge of renal physiology is essential to understand the mechanism by which different diuretics act, particularly salt and water movements (absorption, reabsorption and tubular secretions) and cotransporter systems.

It's your job to look for the sequence by which the drugs work.

Diuretics, in short, are widely used in the management of any condition associated with salt and water retention.

- Diuretics act at different sites of the nephron (the basic unit of the kidney).

- Diuretics are highly effective, relatively safe and cheap.

- Diuretics are considered first-line therapy for most hypertensive patients >>>>**The evidence is:**

1)JNC 7=The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

- JNC 6: Diuretic or a beta-blocker
- JNC 7: Thiazide-type diuretics

2)ALLHAT study:

(Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial)

{Involved more than 40,000 hypertensive pts; 8 yrs study started in 1994}

Accumulating evidence proves that in hypertensive patients, diuretics, particularly thiazides, decrease the risk of cardiovascular disease, fatal and nonfatal MI and stroke.

- Many other antihypertensive agents are combined with diuretics in the same tablet

The mechanism of action:

*Simply by increasing urine output →↓ plasma and stroke volume →↓ CO →↓ BP

The initial ↓ in CO leads to ↑ peripheral resistance, but with chronic use extracellular fluid and plasma volume return to normal and peripheral resistance ↓ to values lower than those observed before diuretic therapy

*Some thiazides are also believed to have direct vasodilating effect.

*Many diuretics (loop diuretics, thiazides, amiloride, and triamterene) exert their effects on specific membrane transport proteins in renal tubular epithelial cells.

*Other diuretics (mannitol) exert osmotic effects that prevent water reabsorption >>>this causes increasing osmotic pressure in tubules leading to increased secretion of water and salt

*Others diuretics inhibit enzymes>>>acetazolamide inhibits carbonic anhydrase

* Some diuretics interfere with hormone receptors in renal epithelial cells >>>spironolactone is a potassium-sparing diuretic that inhibits the action of aldosterone.

(The normal function of aldosterone is reabsorption of water and Na+ and secretion of K+, so we need to antagonize its effect.)

■Classification of diuretics:

Diuretics are usually categorized by their site of action in the kidney, their MOA and, to a lesser extent, by their potency.

■ Diuretic therapy cautions

-In some courses, excessive diuretic usage may lead to a compromise of the effective arterial blood volume with reduction in blood perfusion to vital organs.

Therefore, the use of diuretics to mobilize edema requires careful monitoring of the patient's hemodynamic status and an understanding of the pathophysiology of the underlying condition.

The decrease in blood volume can lead to hypotension and collapse.

- Blood viscosity rises due to an increase in erythrocyte and thrombocyte concentration, which could increase the risk of intravascular coagulation or thrombosis.

We will start with **Osmotic diuretics:**

Mannitol……

It is a sugar that is not absorbed by kidney tubules, has no systemic effects and is not metabolized.

↑osmotic pressure in kidney tubules → withdrawal of H_2O into the tubules→↑ urine excretion by ↓ H_2O reabsorption with little ↑ in NaCl excretion.

- Mannitol increases urine volume & can be used to maintain urine volume and to prevent anuria.

-It reduces intraocular pressure before ophthalmic surgeries.

-It Promotes removal of renal toxins

-It facilitates clearance of mucus in patients with bronchiectasis (a condition characterized by excessive production of mucus due to enlargement of the airways of the lung).

The Site of action: Proximal convoluted tubule

Major clinical use: it is mainly used in management of increasing intracranial pressure, and usually given I.V.

Mannitol toxicity

-Mannitol toxicity is common and the main side effect is extracellular volume expansion because mannitol is rapidly distributed in the extracellular compartment and extracts water from cells.

Other side effects are really not that specific to mannitol as most of the drugs could cause it, such as: Headache, nausea, and vomiting.

- Dehydration, hyperkalemia and hypernatremia are other side effects of mannitol.

Carbonic anhydrase inhibitors :

Acetazolamide.....-

Carbonic anhydrase is an essential enzyme for reabsorption of $NaHCO_3$ from proximal convoluted tubules and also for formation of aqueous humor (fluid of the eye), which if builds up may lead to glaucoma. Acetazolamide decreases the amount of aqueous humor that builds up in the eye.

Inhibition of carbonic anhydrase enzyme increases urine outflow and decreases formation of aqueous humor.

Site of action: Proximal convoluted tubules

Major clinical use:

1-in management of glaucoma.

2--Alkalinization of urine:- in management of toxicity from weak acids >>> Renal excretion of weak acids can be enhanced by increasing urinary pH with carbonic anhydrase inhibitors.

3- Prophylaxis and Rx of Acute Mountain Sickness characterized by weakness, dizziness, insomnia, headache, nausea, cerebral and pulmonary edema that can occur in mountain travelers who rapidly ascend above 2000m. Mountain sickness is not a common condition.Acetazolamide alleviates mountain condition by unknown mechanisms, but it is proposed that it stimulates the respiratory center due to the metabolic acidosis that occurs in response to the use of this drug.

Acetazolamide is effective orally and as ophthalmic drops.

We have similar agents:-

Dorzolamide&Brinzolamide are available topically (as ophthalmic drops) and they are active carbonic anhydrase inhibitors. .

Side effects to CA inhibitors:

1- Hyperchloremic metabolic acidosis: Acidosis results from chronic reduction of body bicarbonate stores.

2- Renal Stones: Calcium salts are relatively insoluble at alkaline pH.

Thiazides diuretics :-

-Thiazides and thiazide-like diuretics:-

1- Are the least expensive diuretics.

2- Have low to moderate efficacy.

3–Are the most frequently used diuretics.

4- Differ in their pharmacokinetic properties: we have many thiazide agents that have similar structure and mechanism of action, but they different in their t1/2, duration of action and potency.

5-If you increase the dose you will not get further increase in urine and salt excretion.

6-- They are ineffective in patients with impaired renal function/have renal failure or patients with creatinine level more than 2mg/dl or with GFR< 20 ml/min.

7-They are highly effective in lowering BP when combined with other antihypertensive drugs (synergistic effect).

Thiazides include :- (you have to memorize them!)

Bendroflumethiazide, Benzthiazide, Chlorthiazide, Hydrochlorothiazide, Hydroflumethiazide, Methyclothiazide, Polythiazide, Trichlormethiazide, Chlorthalidone, Indapamide, Metolazone, Quinethazone.

And the most commonly used are:

Hydrochlorothiazide, Chlorthalidone and Indapamide.

Thiazide mechanism of action:

We have proposed 4 mechanisms:

#1: The major mechanism is by inhibiting of thiazide-sensitive Na^+/Cl^- transporter in distal convoluted tubule, thus inhibiting Na^+ reabsorption leading to ↑Na^+, K^+, Cl^-, HCO_3^- and H_2O excretion.

Thiazides ↑Ca++ reabsorption.

#2: Little carbonic anhydrase (CA) inhibitory effect.

#3: Direct vasodilating effect (Indapamide has the best vasodilating activity among the thiazide drugs.

#4: Decrease the response of blood vessels to NE.

Their early hypotensive effect is related to a reduction in blood volume, their long-term effect is related to a reduction in peripheral vascular resistance.

Important notes about thiazide diuretics:

- The most important thing about these drugs is that they have low efficacy since they lead to only 5-10% loss of filtered Na+ and water.

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Thiazides kinetics:

Thiazides are usually given orally (Chlorthiazide may be given I.V), strongly bind plasma albumin, reach kidney tubules through a specific secretory mechanism (they are not filtered) and are eliminated mostly unchanged by the kidney (small fraction is excreted in bile).

Thiazides site of action: DCT

Clinical uses to thiazides:

1- Hypertension.
2- Edema of HF; liver cirrhosis...etc
3- Nephrogenic diabetes insipidus
4- Hypercalciuria: because they increase the reabsorption of Ca^{2+}.

Side effects of thiazides:

1- Weakness and muscle cramps.

2- Erectile dysfunction: Hypertensive patients who are treated with any type of antihypertensive drugs experience erectile dysfunction. It's not really known if the thiazides causes it or not, but if the patient develops erectile dysfunction once you stop using the thiazide agent, the erectile function will get back to normal.

3- Hyperglycemia: you should monitor the glucose blood level in diabetic patients who used thiazides or you can use another type of diuretics.

4- Hyperlipidemia (↑ LDL, ↑ TG's)

> **Wiki...**..Lipid and lipoprotein abnormalities are common in the general population, and are regarded as a modifiable risk factor for cardiovascular disease due to their influence on atherosclerosis. In addition, some forms may predispose to acute pancreatitis.

5- Hypercalcemia

6- Pancreatitis

7-The most dangerous and frequent side effect is hypokalemia and hypomagnesemia>>> causes muscle weakness and sometimes serious fatal cardiac arrhythmias. So with any patient being treated with thiazide diuretics, you should monitor the potassium levels in the blood carefully.

8- Patients with high risk of hypokalemia are those with:
Left ventricular hypertrophy, previous history of MI, previous history of cardiac arrhythmias & patients who are on digoxin therapy (because it increases the severity of hypokalemia).

9- Hyperuricemia:
The effect of thiazides on uric acid is dose-dependent, they found that:
Low doses will lead to hyperuricemia while large doses lead to hypouricemia by decreasing uric acid reabsorption.

10-Thiazidesare usually used in low doses, and so cause hyperuricemia which may lead to gout.

THE END

Dedicated to: Our best friend Ghydaa Alnajdawi
and to Reem Hyari , Heba Al-Amouri and Tasneem Suheil.
Special Thanks to Lujain Alomari ☺