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بسم الله الرحمن الرحيم

Diuretics (Pt.3)

FINAL | Lecture 3

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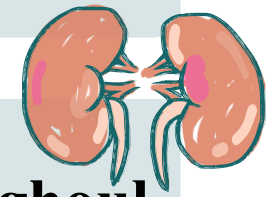
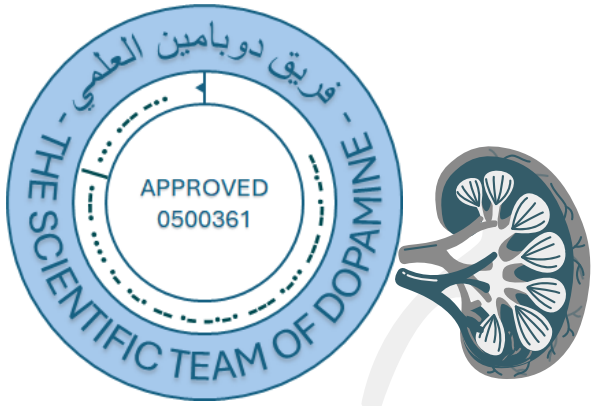


﴿قُلْ بِفَضْلِ ٱللَّهِ وَبِرَحْمَتِهِۦ فَبِذَٰلِكَ فَلْيَفْرَحُوا۟ هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ﴾



Osmotic Diuretics

Mannitol, Urea, Glycerin and Isosorbide.

- **Agents that are filtered and NOT reabsorbed.**
- **Act within the proximal tubule and descending limb of Henle's loop – which are freely permeable to water.**
- **Also oppose ADH action in the collecting tubule.**

- Once they are filtered, they attract huge amount of water with them inducing **diuresis**.
- Some **osmotically active** substances **can in fact be reabsorbed** such as **glucose** in patients with uncontrolled diabetes mellitus. In these patients, **glucosuria** leads to **polyuria** because filtered glucose retains water within the renal tubules. However, since glucose is normally reabsorbed, it is not used as an osmotic diuretic.
- **Mannitol** is the commonly used one.

Osmotic Diuretics

- **They attract water from cells into the bloodstream (dilutional effect)→hyponatremia**

➢ Those agents are given **IV**, attracting water from the intracellular compartment into the blood, leading to unfavorable consequences such as **dilutional hyponatremia** and **intracellular dehydration**. The latter results in more concentrated intracellular potassium, increasing K^+ gradient and thus leaking of K^+ outside the cell causing **hyperkalemia**.

- **In the renal tubules, the nonreabsorbable solute prevents the normal absorption of water, thus reducing Na^+ and counter-ions as well as water reabsorption**
- **The resulting natriuresis is of lesser magnitude than the water diuresis (Disproportional H_2O and Na^+ loss, more H_2O loss than Na^+), leading eventually to excessive water loss and hypernatremia.**

Osmotic Diuretics

Summary:

- **Osmotic diuretics typically cause an initial, often temporary, decrease in serum sodium (hyponatremia) by pulling intracellular water into the extracellular space.**
- **However, as the drug induces significant water loss over sodium loss in urine, it can eventually lead to dehydration and hypernatremia.**

Osmotic Diuretics

- **Attracting water in the lumen of renal tubules – increase urine volume and flow.**
- **Mannitol can increase renal blood flow through a prostaglandin- mediated, resulting in partial washout of normal medullary hypertonicity. It decreases net sodium reabsorption in Henle's loop.**

➢ Most of the diuretics mentioned so far actually **increase prostaglandin synthesis** and **RBF** such as **loop**, **thiazide**, **potassium-sparing** as well as osmotic diuretics like **mannitol**)

Osmotic Diuretics

Mannitol

Pharmacokinetics:

- **Not absorbed orally, may cause osmotic diarrhea if given orally.**
- **Not metabolized.**
- **Excreted by glomerular filtration.**
- **No tubular secretion or reabsorption.**

➢ Remember, osmotic diuretics are -by definition- **only filtered, without reabsorption or secretion**.

Osmotic Diuretics

Therapeutic Uses:

1. **To increase urine volume, to prevent acute renal failure from large pigment load to the kidney (from hemolysis and rhabdomyolysis). Some oliguric patients do not respond to osmotic diuretics in such conditions. (Why?), in cases of profound kidney damage, severe dehydration, or inability of the drug to reach its site of action (lumen) due to necrosis, obstruction or profoundly decreased GFR.**

- **Remember** that **loop diuretics** are used as well in **acute renal failure** to increase the rate of **urine flow** and enhance **potassium excretion** and ameliorate **intratubular obstruction. (return to lecture 1)**
- **Heme pigment-induced acute kidney injury** due to **rhabdomyolysis** or **hemolysis**. The **nonprotein heme pigment**, that is released from either **myoglobin** or **hemoglobin** during rhabdomyolysis or hemolysis respectively, causes **toxicity** and **obstruction** to renal tubules.

Osmotic Diuretics

2. **Reduction of intracranial pressure.**
3. **Reduction of intraocular pressure (for high intraocular pressure as in glaucoma) in preparation for surgery.**
4. **To increase water excretion in preference to sodium excretion, when avid sodium retention [heart failure, liver cirrhosis, nephrotic syndrome, drugs (NSAIDS)] limits the response to conventional diuretics.**

- In this condition, the kidney senses **hypovolemia** rather than **hypervolemia** in the presence of **edema and congestion.** Treatment includes either **osmotic diuretics,** or another treatment regimen**. (See next slide)**

Diuretic Resistance

- This concept is related to diuretics in general, and not exclusively osmotic diuretics.
- Some **edematous** patients are **resistant** to loop diuretics, even though they are the most efficacious diuretic agents.
- The reason behind this phenomenon is that the kidney for some reason senses **hypovolemia** even though the clinical presentation is **fluid overload, edema and congestion**.
- In such cases, treatment includes **IV fluids** with **concurrent loop diuretic therapy** initially **,** then IV fluid administration is caseated, and the patient is maintained on loop diuretics.

Diuretic Resistance

- Another related point is that with chronic diuretic therapy especially **loop diuretics**, distal convoluted tubular cells (DCT) undergo **hypertrophy** as part of **nephron remodeling (structural adaptation),** resulting in excessive water and salts reabsorption (more than the usual contribution of the absorptive capacity of DCT) and thus **failure of therapy.** Treatment includes **combination** therapy of **loop** and **thiazide** diuretics.

Osmotic Diuretics

Adverse Effects:

1. **Extracellular volume expansion and hyponatremia (dilutional) prior to diuresis. In vulnerable patient, It causes pulmonary edema and congestive heart failure in pre-heart failure.**
2. **Headache, nausea and vomiting.**
3. **Dehydration and hypernatremia, because of free water loss. Excessive use without adequate water replacement.**

Osmotic Diuretics

4. **Hyperkalemia: due to intracellular dehydration → increase in intracellular K^+ concentration → leak of K^+ into the circulation causing hyperkalemia. (This shift does not change total body potassium – Hyperkalemia affects the heart negatively).**

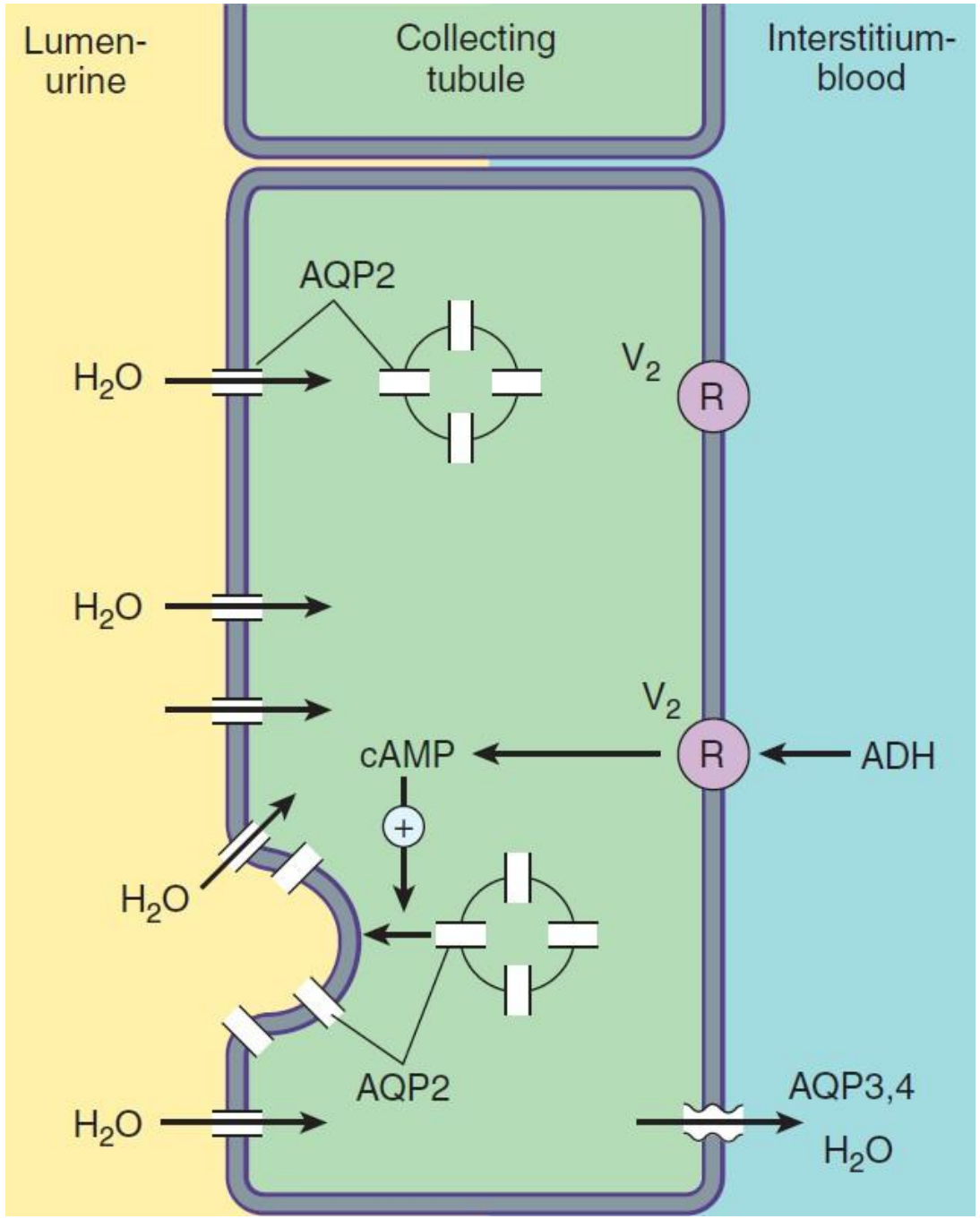


FIGURE 15–6:

- **Water transport across the luminal and basolateral membranes of collecting duct cells.**
- **Above, low water permeability exists in the absence of antidiuretic hormone (ADH).**
- **Below, in the presence of ADH, aquaporins are inserted into the apical membrane, greatly increasing water permeability.**
- **AQP2, apical aquaporin water channels; AQP3,4, basolateral aquaporin water channels; V2, vasopressin V2 receptor.**

Collecting ducts

- In the collecting tubules, there are **apical (2)** and **basolateral (3/4)** water channels **(aquaporins)** for water reabsorption, and basolateral ADH (vasopressin) **V2 receptor**.
- In the absence of ADH stimulation, only a small number of aquaporin channels are present in the apical membrane. ADH increases the number of **apical aquaporins**, leading to increased water reabsorption.
- ADH action is primarily mediated by **cAMP.**

Antidiuretic Hormone (ADH) Antagonists

- **Conivaptan is a nonpeptide ADH receptor antagonist. This is the drug used clinically.**
- **Nonselective agents: Lithium (used for bipolar and never used as ADHR antagonist) & demeclocycline (a tetracycline), is of limited use as both antibiotic and ADHR antagonist.**
- **They inhibit the effects of ADH in the collecting tubule by reducing the formation and action of cAMP.**

Antidiuretic Hormone (ADH) Antagonists

- **Used when ADH is elevated (commonly (SIADH) & other causes).**
  - **SIADH, syndrome of inappropriate ADH secretion, can be drug-induced.**

Pharmacokinetics:

- **Conivaptan can be orally absorbed, but it is used IV (not suitable for chronic use in outpatients as it must be administered via injections).**
- **t½ ~ 5-10 hours.**

Antidiuretic Hormone (ADH) Antagonists

Pharmacodynamics:

- **Inhibits ADH action in the collecting tubules by blocking vasopressin (ADH) receptors.**

Therapeutic uses:

- **Syndrome of Inappropriate ADH Secretion**

Antidiuretic Hormone (ADH) Receptor Antagonists

Adverse Effects: (of conivaptan)

1. **Nephrogenic diabetes insipidus.**

- Not because of **ADH deficiency** (central diabetes insipidus), but rather due to **blockade of ADH receptors** by these drugs, which renders ADH ineffective. This is caused by **exaggerated pharmacological action**.

1. **Severe hypernatremia.**
2. **Dry mouth and thirst**
3. **Hypotension**

PHARMACOLOGY QUIZ LECTURE 3

External Resources

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Versions	Slide # and Place of Error	Before Correction	After Correction
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