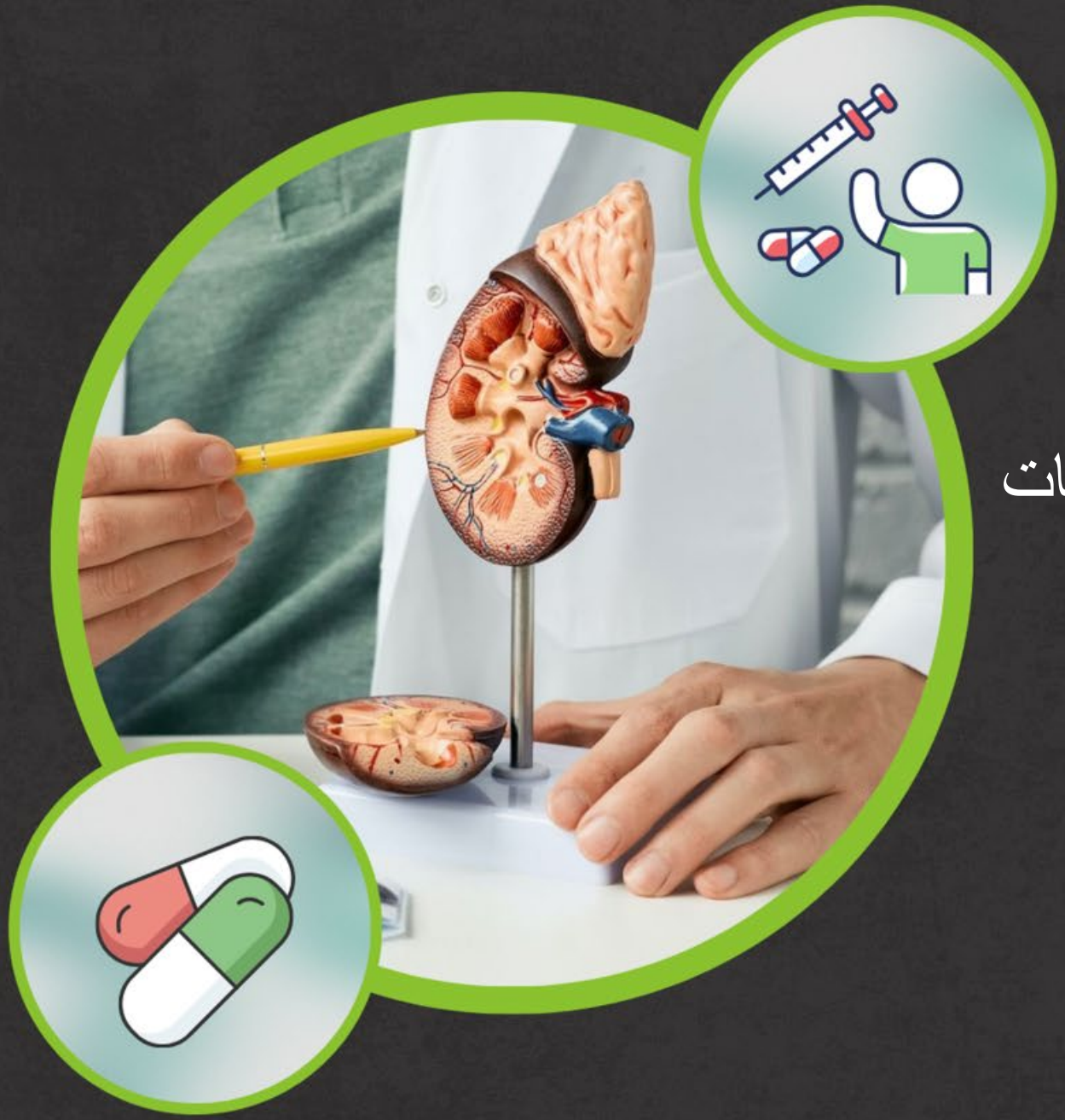


PHARMA

MODIFIED NO. 3

الكُتّاب: صهيب زعيتر و ريناس خريسات

المدققين: إبراهيم الشوابكة

الدكتور/ة: يعقوب ارشيد

Color code

- Slides
- Doctor
- Additional info
- Important

Potassium Sparing Diuretics

We said that there are two types of potassium-sparing diuretics:

1- Aldosterone antagonists
2- Sodium channel blockers — such as **Amiloride** and **Triamterene**. These two drugs block the sodium channels that aldosterone normally acts on through its receptor. However, they block the channel **directly**, regardless of aldosterone's presence (i.e., their action is independent of aldosterone).

The result is the same: by blocking this channel, sodium and water excretion increases, while **potassium and hydrogen ions are retained**.

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^+.

Potassium Sparing Diuretics

4. **The action may depend on renal prostaglandin production.**
5. **Also inhibit H^+ secretion in the distal nephron.**

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. It has a shorter t½ than amiloride.**

- Triamterene is metabolized in the liver, and one of its metabolites is active. This active metabolite acts similarly to triamterene by blocking the sodium channel and is eliminated in the urine.

- As we mentioned earlier, metabolites usually have a longer half-life—but not always. It depends on the rate of metabolism. In the case of triamterene, its half-life is actually shorter than that of amiloride. Amiloride is excreted unchanged in the urine. Despite the fact that renal excretion is generally rapid, the half-life of the parent compound (triamterene) is still shorter than that of amiloride.

Potassium Sparing Diuretics

Adverse effects:

For both:

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

Hyperkalemia and metabolic acidosis occur due to the retention of potassium and hydrogen ions.

Potassium Sparing Diuretics

Adverse effects for triamterene

also:

1. **Leg crambs, azotemia.**

- Leg cramb is a pain or muscle cramps (contractions) in the calf muscles
- Azotemia refers to elevated levels of urea and creatinine in the blood.

2. **Nephrolithiasis (poorly soluble, may precipitate).**
3. **Interstitial nephritis.**
4. **Acute renal failure (when given in combination with indomethacin).**
5. **Glucose intolerance.**
6. **Photosensitivity.**

- **Interstitial nephritis**, we mentioned that this condition is a **drug-induced allergic reaction in the kidney**.
- **Indomethacin** is a **nonsteroidal anti-inflammatory drug (NSAID)** that **inhibits prostaglandin synthesis**, and we noted that **prostaglandin synthesis may contribute to this reaction** by prevent vasodilation leading to renal failure.

•**Some diuretics** as **thiazides** and **loop diuretics**, can lead to **hypokalemia** leading to impair **insulin secretion** causing **glucose intolerance.** However, **triamterene increases potassium levels**, any **glucose intolerance** observed with triamterene **cannot** be attributed to **hypokalemia-induced insulin secretion impairment**.

Potassium Sparing Diuretics

Therapeutic Uses:

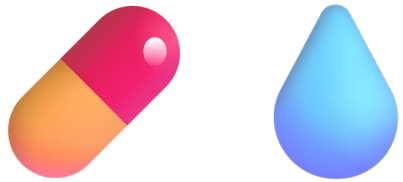
1. **Mineralocorticoid Excess (1^o , 2^o or ectopic).**
2. **In conjunction with other diuretics to reduce potassium loss.**
3. **Hypokalemia (?)**

1- When aldosterone levels are high, there is **sodium and water retention**, along with the **loss of hydrogen ions and potassium**. It's important to **preserve potassium** in such situations.

2- The **most important therapeutic use** of potassium-sparing diuretics is in **combination with other diuretics** (such as amiloride with chlorothiazide in ditide tablet) to **reduce potassium loss** and **prevent hypokalemia**.

3- They may also be used in cases of **hypokalemia**, but this is **questionable**, as **potassium supplements** can often be given directly **without the need for medication**.

Osmotic Diuretics



Explanation two slides ahead

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.**
- **The nonreabsorbable osmotic diuretic prevents the normal absorption of water, thus reducing Na + as well as water reabsorption.**
- **The resulting natriuresis (Na+ loss in urine) is of lesser magnitude than the water diuresis, leading eventually to excessive water loss and hypernatremia.**

Osmotic Diuretics

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

💧 Osmotic Diuretics

- Osmotic diuretics work by drawing water with them. These agents are **filtered through the glomerulus**, enter the **renal tubules**, and are **not reabsorbed**. As a result, they **attract water** into the tubules, leading to **increased water excretion** by the body.

- The most important therapeutic agent in this class is **mannitol**, followed by **glycerin**. Other substances can also cause **osmotic diuresis**, but mannitol is the primary one used clinically.

- These diuretics **act in segments where water is normally reabsorbed**, preventing that reabsorption and increasing water loss. For example, wherever **water is usually reabsorbed**, osmotic diuretics will keep it in the lumen, enhancing diuresis.

- **Mannitol** also **increases renal blood flow** through a **prostaglandin-mediated mechanism**, making it useful in cases of **acute renal failure**.
- The medullary hypertonicity of the kidney is mainly generated in the **thick ascending limb of the loop of Henle**, where **sodium, potassium, and magnesium are reabsorbed without water**.

- This **separation between solutes and water** causes the **medulla to become hypertonic**, which in turn **attracts water from the collecting ducts**.

- **Mannitol decreases net sodium reabsorption** in Henle's loop, interfering with this process.

Osmotic Diuretics

Mannitol

Pharmacokinetics:

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

- This is the criteria for osmotic diuretics:
- They are filtered through the glomerulus, not reabsorbed, not metabolized, and not actively secreted.
- As a result, they **remain in the tubular lumen** and **attract water**, leading to diuresis.

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 this effect .**
2. **Reduction of intracranial pressure.**
3. **Reduction of intraocular pressure in preparation for surgery.**
4. **To increase water excretion in preference to sodium excretion, when avid (intense) sodium retention limits the response to conventional diuretics. ->** explained earlier in slide 11

1) **To increase urine output and prevent acute renal failure:**
Mannitol is used to promote diuresis in conditions where there is a risk of acute kidney injury, especially due to large pigment loads to the kidney, as seen in **hemolysis** or **rhabdomyolysis**. In these conditions, the breakdown of red blood cells or muscle tissue releases **hemoglobin** or **myoglobin**, respectively, which can precipitate in renal tubules, obstructing them and potentially leading to **renal shutdown**.

2) **Reduction of intracranial pressure:**
Mannitol is effective in lowering intracranial pressure in cases of cerebral edema, head trauma, or other conditions associated with elevated ICP.

3) **Reduction of intraocular pressure (IOP) before surgery:**
Mannitol is occasionally used by ophthalmologists to acutely reduce intraocular pressure, particularly in **acute angle-closure glaucoma**, prior to surgical intervention.
It is only beneficial in acute settings to temporarily lower IOP before surgery.

Osmotic Diuretics

Adverse Effects:

1. **Extracellular volume expansion and hyponatremia (dilutional) prior to diuresis, pulmonary edema, congestive heart failure.**
2. **Headache due to blood pressure changes , nausea and vomiting.**
3. **Dehydration and hypernatremia – free water loss . Excessive use without adequate water replacement.**
4. **Hyperkalemia: due to intracellular dehydration → increase in intracellular K^+ concentration → leak of K^+ and hyperkalemia**

- **Adverse Effects of Mannitol:**

1- Extracellular Volume Expansion and Hyponatremia (Dilutional):

Before diuresis occurs, mannitol draws water from the intracellular and interstitial compartments into the extracellular space. This can lead to volume expansion and **dilutional hyponatremia**.

•This fluid shift may **increase the workload on the heart (** More blood volume = **increased preload** on the heart) potentially causing **pulmonary edema** or **congestive heart failure (CHF)**, especially in patients with compromised cardiac function (e.g., **left-sided heart failure**).

2- Headache due to rapid **changes in blood pressure or osmotic shifts**.

3- Nausea and vomiting, often associated with increased intracranial pressure changes or volume shifts.

4- Dehydration and Hypernatremia, Excessive diuresis without adequate fluid replacement can lead to **significant free water loss**, resulting in **dehydration** and **hypernatremia**.

5- Hyperkalemia, due to **intracellular dehydration**, the intracellular potassium concentration rises, leading to **leakage of K^+ into the extracellular space**, which may cause **hyperkalemia** .

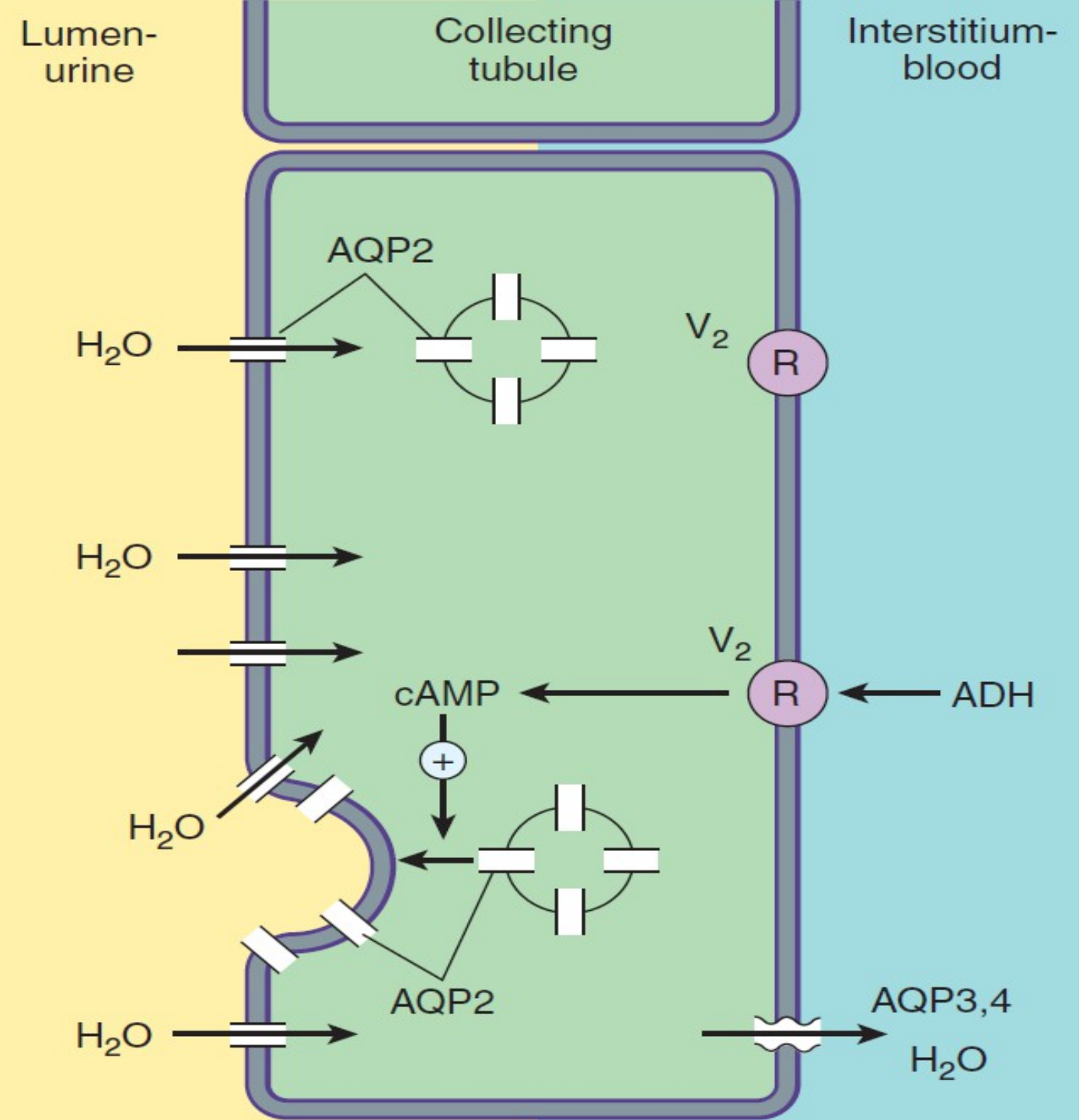


FIGURE 15–6:

- **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.**

Antidiuretic Hormone:

- **ADH (also called vasopressin)** acts on the **collecting ducts** of the kidney.
- It works by stimulating **water channels called aquaporins** to increase **water reabsorption** back into the bloodstream.
- This action **prevents diuresis**, leading to **water retention** and helping maintain **blood pressure and hydration**.

ADH Antagonists:

- Block the action of ADH.
- **Examples of non-selective ADH antagonists: Lithium and Demeclocycline.** However, these are **not preferred** for use as ADH antagonists because of their **significant adverse effects**, such as **nephrotoxicity**.
- Instead, more **selective ADH antagonists** like **tolvaptan** and **conivaptan** are used clinically, especially for conditions like **SIADH (Syndrome of Inappropriate ADH Secretion)**.

Antidiuretic Hormone (ADH) Antagonists

- **Conivaptan is a nonpeptide ADH receptor antagonist.**
- **Nonselective agents: Lithium (never used as ADHR antagonist) & demeclocycline (a tetracycline), is of limited use.**
- **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 (SIADH (Syndrome of Inappropriate ADH Secretion) & other causes).**

Pharmacokinetics:

- **Conivaptan can be orally absorbed, but it is used IV (not suitable for chronic use in outpatients),** given only in a hospital setting under strict medical supervision. They are **not prescribed for home use**.
- **t½ ~ 5-10 hours.**

Antidiuretic Hormone (ADH) Receptor Antagonists

Pharmacodynamics:

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

Therapeutic uses:

- **Syndrome of Inappropriate ADH Secretion**

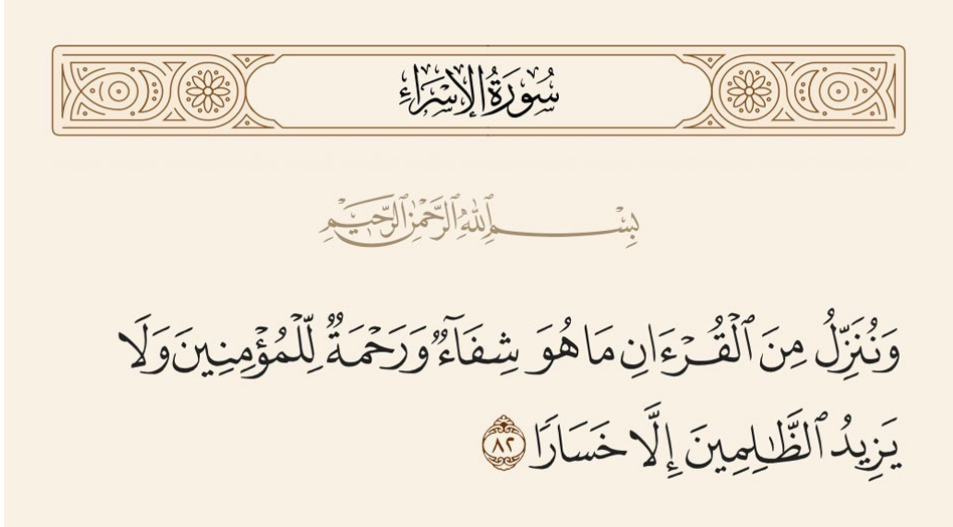
Antidiuretic Hormone (ADH) Receptor Antagonists

Adverse Effects:

1. **Nephrogenic diabetes insipidus**
2. **Severe hypernatremia due to water loss.**
3. **Dry mouth and thirst**
4. **Hypotension (** Lower volume → Lower pressure **).**

Additional sources

1. Book pages
2. Youtube videos
3. Webpages...etc



VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	23	retention	loss
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!