Diuretics agents II

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Objectives

- Discuss other types of diuretics: Carbonic anhydrase diuretics and osmotic diuretics
- Describe the drugs for reducing urine volume in nephrogenic diabetes insipidus.
- Describe a therapy that will reduce calcium excretion in patients who have recurrent urinary stones.
- Discuss the principle of force diuresis.

Carbonic anhydrase inhibitors

- **Prototype drugs include:**
- **Acetazolamide and methazolamide.**
- **These agents are sulfonamide derivatives, forerunners of thiazide diuretics.**
- **Thiazides separate natriuresis from carbonic** anhydrase inhibition

Carbonic anhydrase inhibitors

- ***MOA:***
- ***Carbonic anhydrase inhibitors inhibit carbonic anhydrase in all parts of the*** body.

- In the kidney, the effects are predominantly in the proximal tubule.

a. **These drugs reduce HCO3-** reabsorption and concomitant Na+ uptake.

b. They also inhibit excretion of hydrogen (H+) (acidosis)

c. **Carbonic anhydrase inhibitors are absorbed from the GI tract and are secreted by the proximal tubule**

d. **Urine pH changes are observed within 30 minutes**

Carbonic anhydrase inhibitors

- ***Therapeutic uses.***
  - ***Carbonic anhydrase inhibitors are rarely used as diuretics.***
  - **These drugs are most useful in the treatment of glaucoma. They serve to decrease the rate** of HCO_3^- formation in the aqueous humor and consequently reduce ocular pressure.
  - **These agents may be used to produce a desired alkalinization of urine to enhance renal secretion of uric acid**
- ***Adverse reactions and contraindications***
  a. **metabolic acidosis** due to reduction in bicarbonate stores.
  b. **Urine alkalinity** decreases the solubility of **calcium salts** and increases the propensity for **renal calculi formation**.
  c. **Hypokalemia**

c. The use of these drugs is contraindicated in the presence of hepatic cirrhosis

Osmotic agents

- **Include mannitol, glycerin, urea, and hypertonic saline.**
- **MOA: These agents are** easily filtered, poorly reabsorbable solutes that alter the diffusion of water relative to sodium by “binding” water. As a result, net reabsorption of Na is reduced.
- **Therapeutic uses**

1. **Mannitol is used in prophylaxis of acute renal failure resulting from physical** trauma or surgery. Even when filtration is reduced, sufficient mannitol usually enters the tubule to promote urine output.
2. **Mannitol may also be useful for reducing cerebral edema and intraocular pressure**.
3. **Parenteral urea is approved for the reduction of intracranial and intraocular** pressure.

3) Forced diuresis in drug poisoning

- ✓ (FAD in barbiturate poisoning

Osmotic diuretic - Preparations

Drug	Daily dose
Mannitol I.V. 10% or 20% soln.	1-2 gm/kg 100 – 300 ml rapid infusion Over 30 to 90 min
Glycerol oral	1-1.5 gm/kg metabolized to glucose
Isosorbide oral	1.5 gm/kg

Osmotic agents

1. **Mannitol and urea are administered intravenously**
2. **Glycerin is administered orally. This drug is used primarily for ophthalmic procedures.**
3. Topical anhydrous glycerin is useful for **corneal edema**

- **Adverse effects and contraindications.**

1. Minor adverse effects include headache and nausea.

1) **If overdose → dehydration → hypernatremia**

Nephrogenic diabetes insipidus.

- Nephrogenic diabetes insipidus occurs when there's a defect in the kidney tubules the structures in your kidneys that cause water to be excreted or reabsorbed. This defect makes your kidneys unable to properly respond to ADH.
- The defect may be due to an inherited (genetic) disorder or a chronic kidney disorder.
- Certain drugs, such as lithium or the antiviral medications cidofovir and foscarnet (Foscavir), also can cause nephrogenic diabetes insipidus.

Agents that influence the action of ADH (vasopressin)

- Agents that **elevate or mimic ADH are antidiuretic; agents that lower or antagonize ADH action are diuretic.**
- **MOA:** Agents that influence the permeability of the luminal surface of the collecting duct to water by causing water-specific water channels called aquaporin II to be inserted into the plasma membrane
- Under conditions of dehydration **ADH levels increase** to conserve body water.
- **Vasopressin binds to three receptors: V1a in the vasculature, V1b in the brain, and V2 in renal collecting ducts.**

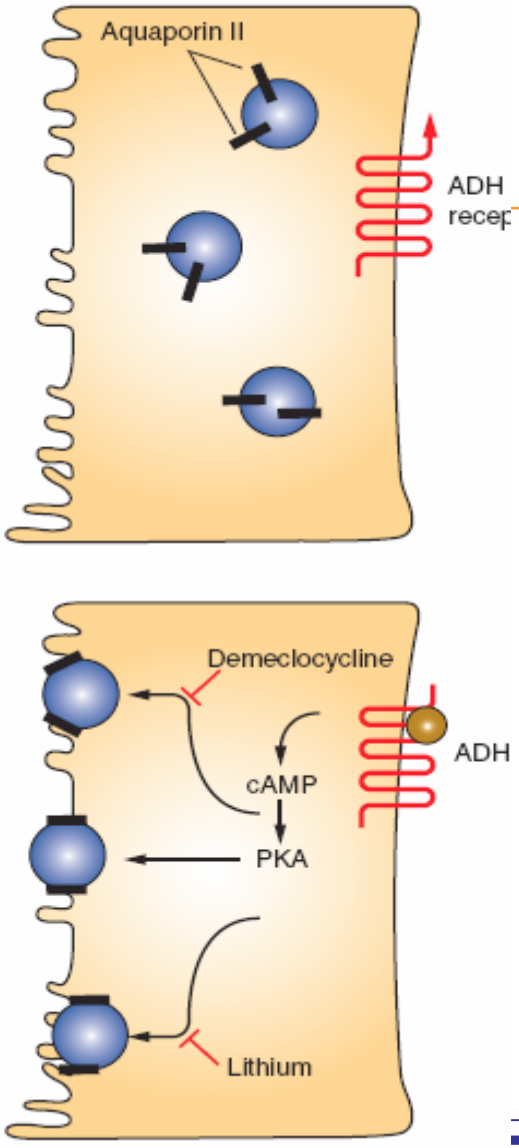
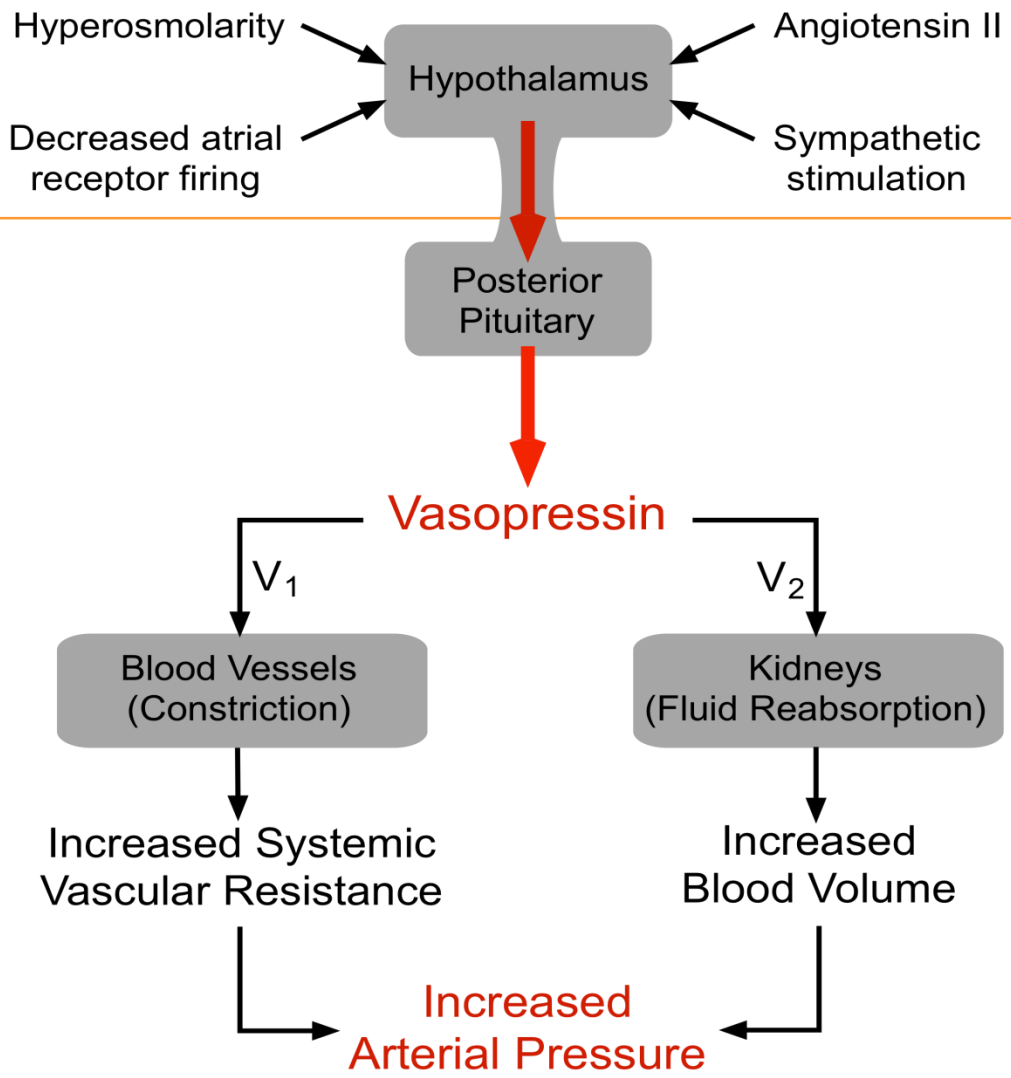


FIGURE 3.3. The mechanism of action of ADH includes ligand binding to the V_2 receptor, which is coupled to increased cAMP production. This ultimately causes an increase in the insertion of the water-specific transporter aquaporin II into the apical plasma membrane.


Hyperosmolarity
Angiotensin II
Hypothalamus
Decreased atrial receptor firing
Sympathetic stimulation
Posterior Pituitary
Vasopressin
V1
V2
Blood Vessels (Constriction)
Kidneys (Fluid Reabsorption)
Increased Systemic Vascular Resistance
Increased Blood Volume
Increased Arterial Pressure

1. Vasopressin or analogs

- **Desmopressin**
- **Therapeutic uses.**
  - used to treat **nocturnal enuresis.**
  - **useful in the management of** nephrogenic diabetes insipidus (dehydration due to the inability to concentrate urine).
  - **Studies have suggested that vasopressin and** its analogs are useful to maintain blood pressure in patients with **septic shock** and to increase **clotting factor VIII in some patients with Type I von Willebrand's** disease.
- ***Adverse effects and contraindications.***
- ***serious cardiacrelated* adverse effects, and they should be used with caution in individuals with coronary artery disease**.
- **Hyponatremia** occurs in ˜5% of patients

2. Enhancer of ADH

- Chlorpropamide, acetaminophen, indomethacin, and clofibrate
- **Mechanisms**

(a) **Chlorpropamide, acetaminophen, and indomethacin enhance the action of ADH,** at least partially by reducing the production of prostaglandins in the kidney.

(b) **Clofibrate increases the release of ADH centrally**.

- **Therapeutic uses.**
  - **These agents are useful as antidiuretics in diabetic patients.**

3. ADH antagonists

- include the **vaptans: conivaptan**, a mixed V1a and V2 antagonist, and **tolvaptan**, a V2 selective antagonist.
- **Therapeutic uses.**
- **Conivaptan** is approved for the treatment of hypervolemic hyponatremia and syndrome of inappropriate ADH (SIADH).
- Tolvaptan is approved for treating hyponatremia associated with CHF, cirrhosis, and SIADH. The vaptans may be more effective in treating hypervolemia in heart failure than diuretics.

4. Nonreceptor antagonists of ADH action

- **include demeclocycline and lithium carbonate.**
- They may be useful in the treatment of **Syndrome of inappropriate antidiuretic hormone secretion** (**SIADH**) is characterized by excessive release of antidiuretic hormone from the posterior pituitary gland

Thiazide diuretics

- Thiazides can reduce polyuria and polydipsia in patients who are not responsive to ADH.
- This seemingly paradoxic beneficial effect is mediated through plasma volume reduction, with an associated fall in glomerular filtration rate, enhanced proximal reabsorption of NaCl and water, and decreased delivery of fluid to the diluting segments. Thus, the maximum volume of dilute urine that can be produced is lowered and thiazides can significantly reduce urine flow in the polyuric patient.

Uricosuric agents
Probenecid

- **MOA: Uricosuric agents increase excretion of uric acid.**
- Probenecid was developed to **decrease secretion of penicillin** (an organic acid) and thus prolong elimination of this antibiotic.

a. **Other drugs whose secretion is inhibited by probenecid** include **indomethacin and methotrexate.**

- At higher doses, probenecid also **decreases reabsorption of uric acid by inhibiting URAT1, a urate transport protein. This results in a net increase in urate** excretion and accounts for the drug's usefulness in treating gout
- **Therapeutic uses.**

1. **used to prevent gout in individuals with normal** renal function.
2. It is also used as an **adjuvant to penicillin therapy when prolonged** serum levels following a single dose are required or to enhance antibiotic concentrations in the CNS

Nephrolithiasis

- Approximately two thirds of all renal stones contain calcium phosphate or calcium oxalate.
- Many patients with such stones exhibit a renal defect in calcium reabsorption that causes hypercalciuria.
- This can be treated with thiazide diuretics, which enhance calcium reabsorption in the distal convoluted tubule and thus reduce the urinary calcium concentration.
- Salt intake must be reduced in this setting, as excess dietary NaCl will overwhelm the hypocalciuric effect of thiazides.

Drugs for Reducing the Risk of Kidney Stone

- Thiazide diuretics reduce the risk of calcium stone recurrence
- Thiazide diuretics reduce the renal excretion of Ca and the incidence of kidney stone formation in patients with idiopathic hypercalciuria
  - Hydrochlorothiazide, chlorthalidone, and indapamide each reduce the risk of recurrent stones.
  - No trial directly compared different dosages of agents, and no trial assessed the lower thiazide doses often used to treat hypertension.
- Loop diuretics. Agents such as furosemide increase renal excretion of Ca.
- Citrate reduces the risk of calcium stone recurrence
- Allopurinol reduces the risk of calcium stone recurrence in patients with elevated blood and urine uric acid levels

Hypercalcemia

- Hypercalcemia can be a medical emergency.
- Since the loop of Henle is an important site of calcium reabsorption, **loop diuretics** can be quite effective in promoting calcium diuresis..
- However, loop diuretics alone can cause marked volume contraction. Thus, saline must be administered simultaneously with loop diuretics if an effective calcium diuresis is to be achieved.
- The usual approach is to infuse normal saline and furosemide (80–120 mg) intravenously. Once the diuresis begins, the rate of saline infusion can be matched with the urine flow rate to avoid volume depletion. Potassium may be added to the saline infusion as needed

Forced diuresis

- **Forced diuresis:** increased urine formation by **diuretics** and fluid) may enhance the excretion of certain drugs in urine and is used to treat drug overdose or poisoning of these drugs

Forced alkaline diuresis

- Infusion of large amount of NS+NAHCO3
- Used to eliminate acidic drug that mainly excreted by the kidney eg., salicylates
- Serious fluid and electrolytes disturbance may occur
- Need expert monitoring

Forced alkaline diuresis

- One of the commonly used methods to increase the elimination of a toxin is forced diuresis with alteration in urine pH.
- Principle :
- The renal tubular epithelium is relatively impermeable to the ionized molecules. If the urinary pH is changed so as to produce more of ionized form of a chemical, it is trapped in the tubular fluid and is excreted in the urine.
- This is the basis for alkaline diuresis which is useful in salicylates, phenobarbital and lithium intoxication
- Renal excretion of a substance is dependent upon glomerular filtration rate, active renal tubular secretion and passive tubular reabsorption.

Forced alkaline diuresis

- The glomerular filtration is determined:
  - by the molecular weight,
  - the degree of protein-binding
  - the volume of distribution in the body.
- A large volume of distribution means that only a small amount of a chemical is available for filtration and therefore, forced diuresis is of little help.
- Because of these reasons, most of the chemicals (except isoniazid and bromides) are not amenable to removal by forced diuresis alone.

Forced alkaline diuresis procedure

- 5% dextrose in half-normal saline containing 20-35 mEq/L of bicarbonate is administered at a rate so as to produce a urine output of 3-6 ml/kg/hour and a urine pH 7.5- 8.5.
- Diuretics are often needed to maintain high urine flows.
- To prevent hypokalaemia, potassium should be added in every second or third bottle.
- During forced alkaline diuresis, the vitals of the patient along with input/output, electrolytes and acid base status should be closely monitored.
- This procedure is contraindicated in patients with shock, hypotension, renal failure and congestive heart failure.