Urogenital System

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Subjects to be Covered

- **Pharmacological properties of:**

- Diuretics

- Antifungal agents

- Oxytocin (drugs acting on uterus) & ADH

- GnRH; LH; FSH

- Estrogens; antiestrogens; progestins; antiprogestins; contraception

Diuretics (Saluretics)

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 its pH as well as the ionic composition of the urine and blood.

- Water, digitalis, caffeine and theophylline have diuretic activity, but are not diuretics.

Diuretics

- **General clinical uses:**

- Hypertension
- Edema of heart, renal or liver failure
- Pulmonary edema
- ↑ intracranial pressure (Mannitol)
- ↑ intraocular pressure=glaucoma (CA inhibitors) (acetazolamide)
- Hypercalcemia (Furosemide=Frusemide)
- Idiopathic hypercalciuria (Thiazides)
- Inappropriate ADH secretion (Furosmide)
- Nephrogenic diabetes insipidus (Thiazides)

Diuretics

- **General consideration**

- Basic knowledge of renal physiology particularly salt and water movements (absorb., reabsorb and tubular secretion) and cotransporter systems is mandatory

- 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

- Diuretics are highly effective, relatively safe and cheap
- Diuretics are considered first-line therapy for most hypertensive patients.
  - Initial antihypertensive therapy without compelling indications
  - JNC 6: Diuretic or a beta-blocker
  - JNC 7: Thiazide-type diuretics

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

Diuretics

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

- **ALLHAT** study:

(**A**ntihypertensive and **L**ipid **L**owering treatment to prevent **H**eart **A**ttack **T**rial)

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

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

Diuretics

- **<u>Diuretics MOA:</u>**

- 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

- Thiazides are also believed to have direct vasodilating effect

Diuretics

- **Diuretic therapy cautions**

- Excessive diuretic usage may lead to a compromise of the effective arterial blood volume with reduction in perfusion of 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

Diuretics

Cont. diuretic cautions,

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

- Blood viscosity rises due to an increase in erythro-and thrombocyte concentration, which could lead to an increased risk of intravascular coagulation or thrombosis

Diuretics

- **Diuretics**

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

- Other diuretics exert osmotic effects that prevent water reabsorption (mannitol),

- Still others inhibit enzymes (acetazolamide),

- Some others interfere with hormone receptors in renal epithelial cells (spironolactone)

Diuretics

- **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

- **Osmotic diuretics**

Mannitol

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

↑ osmotic pressure in kidney tubules → withdraw H_2O → ↑ urine excretion by ↓ H_2O reabsorption with little ↑ in NaCl excretion

Osmotic Diuretics

- Mannitol increases urine volume & can be used to maintain urine volume and to prevent anuria
- Reduces intraocular pressure before ophthalmologic procedures
- Promotes removal of renal toxins
- Facilitates clearance of mucus in patients with bronchiectasis

Site of action: Proximal convoluted tubule

Major clinical use: ↑ intracranial pressure, given I.V

Osmotic Diuretics

- **Mannitol toxicity**

- Extracellular volume expansion

Mannitol is rapidly distributed in the extracellular compartment and extracts water from cells

- Headache, nausea, and vomiting are commonly observed in patients treated with osmotic diuretics

- Dehydration, hyperkalemia and hypernatremia

Carbonic Anhydrase Inhibitors

- **Carbonic anhydrase inhibitors**

Acetazolamide

Carbonic anhydrase enzyme is important enzyme responsible for reabsorption of Na^+HCO_3 from proximal convoluted tubules and for formation of aqueous humor (fluid of the eye)

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

Carbonic Anhydrase Inhibitors

- Acetazolamide inhibits the enzyme carbonic anhydrase → ↓ Na^+HCO_3 reabsorption and thus H_2O → ↑ urine outflow
- Site of action: Proximal convoluted tubules
- Major clinical use: glaucoma
- Acetazolamide is effective orally and as an ophthalmic drops
- Dorzolamide & Brinzolamide are other available
- topically (ophthalmic drops) active carbonic anhydrase inhibitors

Carbonic Anhydrase Inhibitors

** Other uses to acetazolamide:

- Urinary Alkalinization

Renal excretion of weak acids can be enhanced by increasing urinary pH with carbonic anhydrase inhibitors

- 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 3000 m (mechanism unknown)

Carbonic Anhydrase Inhibitors

- **Side effects to CA inhibitors:**

- Hyperchloremic metabolic acidosis

Acidosis results from chronic reduction of body bicarbonate stores

- Renal Stones

Calcium salts are relatively insoluble at alkaline pH

Thiazide Diuretics

- **Thiazides and thiazide-like diuretics**

= Least expensive

= Low to moderate efficacy diuretics

= The most frequently used diuretics

= Differ in their $t_{1/2}$, DOA and potency, have similar MOA

Thiazide Diuretics

Bendroflumethiazide
Benzthiazide
Chlorthiazide
Hydrochlorothiazide
Hydroflumethiazide
Methyclothiazide
Polythiazide
Trichlormethiazide

Chlorthalidone
Indapamide
Metolazone
Quinethazone

Thiazide Diuretics

- **Thiazide MOA:**

a. Inhibition of thiazide-sensitive Na^+/Cl^- transporter in distal convoluted tubule, thus inhibiting Na^+ reabsorption $\rightarrow\uparrow Na^+$, K^+, Cl^-, HCO_3^- and H_2O excretion

Thiazides ↑ Ca++ reabsorption

b. Little carbonic anhydrase (CA) inhibitory effect

Thiazide Diuretics

c. Direct vasodilating effect (Indapamide has been observed for its pronounced vasodilating effect)

d. ↓ 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

Thiazide Diuretics

- **Most widely used thiazides:**

  Hydrochlorothiazide

  Chlorthalidone

  Indapamide

Thiazide Diuretics

Thiazides lead to ≈ 5-10% loss of filtered Na^+

↑ in dose will not lead to further increase in their diuretic effect (low ceiling)

They are ineffective in patients with impaired renal function or patients with GFR< 20 ml/min

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

Thiazide Diuretics

- **Thiazides kinetics:**

Thiazides are usually given orally (Chlorthiazide may be given I.V), strongly bind plasma albumin, reach kidney tubules via a specific secretory mechanism (not filtered) and eliminated mostly unchanged by the kidney (small fraction biliary excretion)

Thiazide Diuretics

- **Thiazides site of action:**

DCT

- **Clinical uses to thiazides:**

- Hypertension

- Edema of HF; liver cirrhosis…etc

- Nephrogenic diabetes insipidus

- Hypercalciuria

Thiazide Diuretics

- **Side effects to thiazides:**

- Weakness; muscle cramps

- Erectile dysfunction

- Hyperglycemia

- Hyperlipidemia (↑ LDL, ↑ TG's)

- Hypercalcemia

- Pancreatitis

Thiazide Diuretics

- Hypokalemia & hypomagnesemia

Most frequent and dangerous side effect → muscle weakness and serious cardiac arrhythmias

patients at high risk are those with:

LVH; previous hx of MI; previous hx of cardiac arrhythmias & patients who are on digoxin therapy

Thiazide Diuretics

- Hyperuricemia

Thiazides could precipitate gout

The effect of thiazides on uric acid is dose dependent:

Low doses → hyperuricemia

Large doses → ↓ uric acid reabsorption

Loop Diuretics

- **High ceiling, loop, high efficacy diuretics:**

Furosemide (Frusemide) O; I.V

Bumetanide O; I.V

Ethacrynic acid O; I.V

Torsemide O; I.V

The strongest diuretics, have rapid OOA and short DOA

- **Site of action**

Thick segment of ascending loop of Henle

Loop Diuretics

- **Loop diuretics MOA**

Inhibition of $Na^+/K^+/2Cl^-$ transporter leading to 10-25% loss of filtered Na^+

↑ dose → ↑ diuretic effect; over-treatment → dehydration

Effective even at GFR below 10 ml/min (loop diuretics are most effective in patients with renal insufficiency = creatinine level > 2.5 mg/dl) or resistant cases to other diuretics

Loop Diuretics

- Loop diuretics ↑ excretion of Na^+, Cl^-, K^+, H^+, H_2O and HCO_3^- (weak CA inhibitory effect)
- They are effective orally (OOA 30-60 min ; DOA ≈ 6 hrs) and parenterally (OOA 5 min; DOA ≈ 2 hrs)
- They are albumin bound, eliminated in urine by filtration and tubular secretion and 1/3 rd of oral dose is excreted in bile

Loop Diuretics

- **Clinical uses to loop diuretics:**

- Acute pulmonary edema
- Edematous states (ascitis; CHF; renal failure…etc)
- Considered 1st line therapy in patients with CHF
- Hypertension
- Hypercalcemia
- Inappropriate ADH secretion

Loop Diuretics

- **Side effects to loop diuretics:**

- Hypokalemia; hypomagnesemia

- Hypocalcemia

- Irreversible ototoxicity (usually dose related and more common with I.V administration)

- Dehydration; hyperglycemia; hyperuricemia

- Headache; dizziness (due to ↓ in BP)

- Allergic reactions; alkalosis

Potassium-sparing Diuretics

- **potassium-sparing, low efficacy diuretics;**

a. Aldosterone antagonists

Spironolactone; Eplerenone

Aldosterone → ↑ synthesis of Na^+-K^+ ATPase → ↑ Na^+ reabsorption, ↓ reabsorption of K^+ (↑excretion of K^+ & H^+)

Aldosterone antagonists →↑ Na^+ excretion & ↓ K^+ excretion

Potassium-sparing Diuretics

- **Site of action of potassium-sparing diuretics**

DCT, collecting ducts

Only effective in presence of aldosterone (competitive antagonists)

Given orally; have delayed OOA

Weak diuretics, usually combined with other antihypertensives or thiazides

Have great benefit in improving myocardial function in patients with heart failure

Eplerenone is more potent than Spironolactone

Potassium-sparing Diuretics

- **Clinical uses to potassium-sparing diuretics:**

- Hypertension

- CHF

- Hyperaldosteronism (1° or 2°)

- Hypokalemia

- Hirsutism (antiandrogenic effect)

Potassium-sparing Diuretics

- **Side effects to potassium-sparing diuretics:**

- Hyperkalemia → cardiac arrhythmias

More common in patients with diabetes, chronic renal disease or patients on ACE inhibitors

More severe with eplerenone

- Gynecomastia in ♂'s (rare with Eplerenone)

- Breast tenderness in ♀'s (rare with Eplerenone)

Potassium-sparing Diuretics

b. Nonsteroidal potassium-sparing diuretics:

Amiloride; Triamterene

- **Site of action: DCT**
- **MOA**

Blockade of epithelial Na^+ channels $\rightarrow\downarrow$ Na^+ reabsorption, $\downarrow$ K^+ excretion

Orally effective and available alone or combined with thiazides

Potassium-sparing Diuretics

- **Clinical uses:**

- Hypertension

- Hypokalemia

- **Side effects:**

- Hyperkalemia

- Renal tubular damage especially reported following the use of Triamterene + Hydrochlorothiazide

Potassium-sparing Diuretics

- **The problem of diuretic-induced hypokalemia:**

- Thiazide or loop diuretic + oral K^+ supplement

- Combine thiazide or loop diuretic with a K^+ sparing diuretic

**** Unlike thiazide diuretics, loop and K^+ sparing diuretics have no effects on blood lipids**

Diuretic Resistance

- **Diuretic resistance or refractoriness (Therapeutic Failure):**

- Continued ingestion of salt

- Impairment of organic acid secretion mechanisms in the proximal tubules due to: diseases or drugs

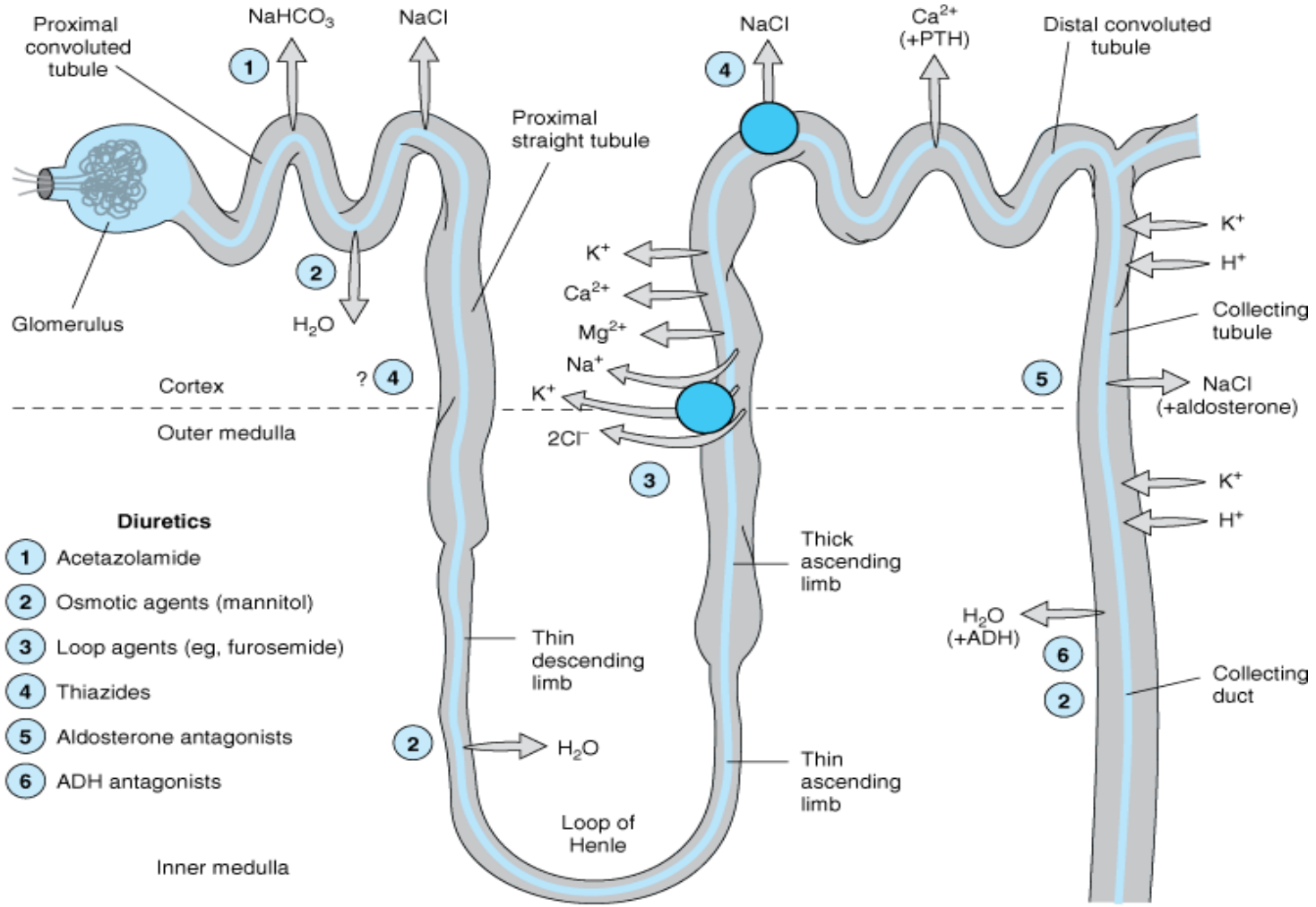
- Secondary hyperaldosteronism

- Lowered renal blood flow $\rightarrow\uparrow$ Na^+ reabsorption (postdiuretic salt retention)

- Lowered bioavailability of the drug

- **Management of diuretic resistance**

Restriction of sodium intake, changes in dose, changes in timing, and combination of diuretic therapy



Source: Katzung BG: *Basic & Clinical Pharmacology*, 10th Edition: http://www.accessmedicine.com