Diuretics (Saluretics)
Lecture 1

Objectives

By the end of the 2 lectures on the pharmacology of diuretics all students should be able to understand and know:

- Available diuretics
- Their site of action on the nephron
- Their mechanism of action
- Their clinical uses
- Their side effects
- How to answer questions inserted within the text

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 or increase urine output, but are not considered 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 (Furosemide)
- Nephrogenic diabetes insipidus (Thiazides)

- **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 are highly effective, relatively safe and cheap
- Diuretics are considered first-line therapy for most hypertensive pts
  - 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

- 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 pts; 8 yrs study started in 1994}

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

- **Diuretics MOA:**

- 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

- **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

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**

- 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)

- **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

- 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

- **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**

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

Acetazolamide inhibits the enzyme carbonic anhydrase $\rightarrow \downarrow Na^{+}HCO_3$ reabsorption and thus $H_2O \rightarrow \uparrow$ 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

** 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)

- Absence seizures and myoclonic seizures

- **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

- **Thiazides and thiazide-like diuretics**

= Least expensive

= Low to moderate efficacy diuretics

= The most frequently used diuretics

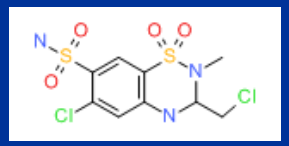
= Differ in their $t_{1/2}$, DOA and potency, have similar MOA

Thiazides

Bendroflumethiazide

Benzthiazide

Chlorthiazide



Hydrochlorothiazide

Hydroflumethiazide

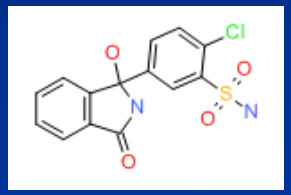
Methyclothiazide

Polythiazide

Trichlormethiazide

Thiazide-like drugs

Chlorthalidone



Indapamide

Metolazone

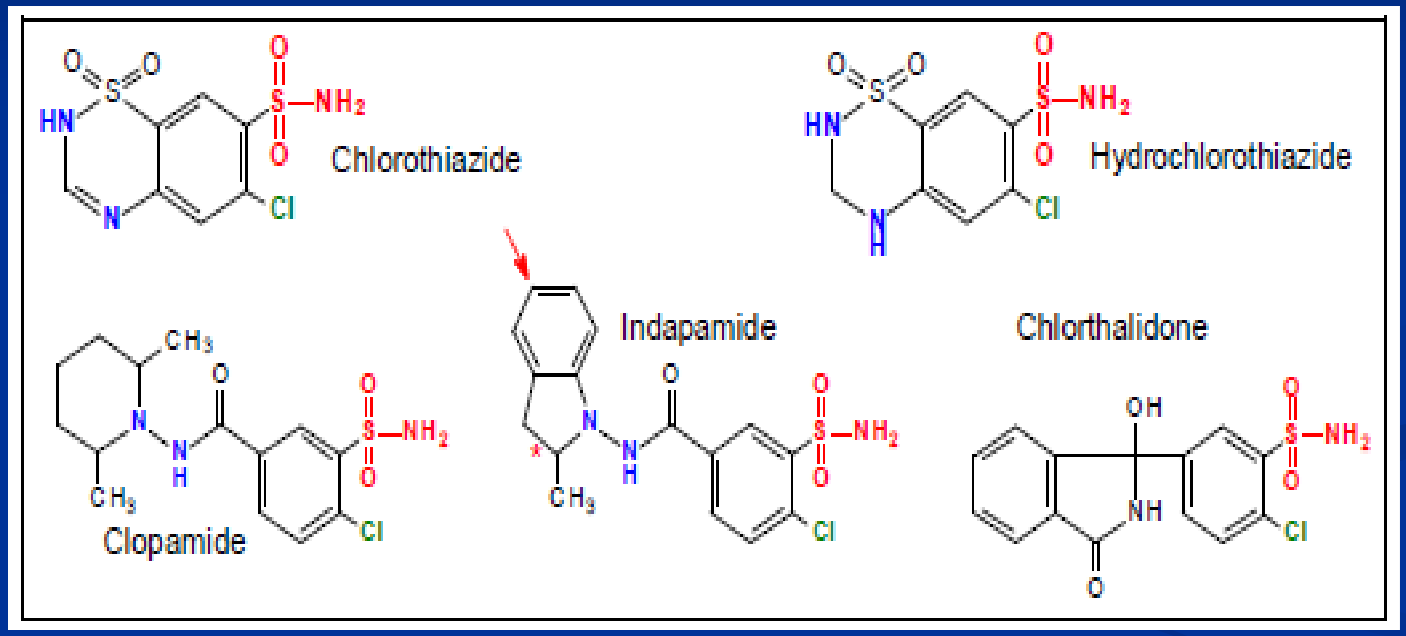
Quinethazone

- **Most widely used thiazides , thiazide-like diuretics:**

  Hydrochlorothiazide

  Chlorthalidone

  Indapamide


Chlorothiazide
Hydrochlorothiazide
Indapamide
Chlorthalidone
Clopamide

- **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

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

- 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 pts with impaired renal function or pts with GFR< 20 ml/min
- They are highly effective in lowering BP when combined with other antihypertensive drugs (synergistic effect)

- **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)

- **Thiazides site of action:**

DCT

- **Clinical uses to thiazides:**

- Hypertension
- Edema of HF; liver cirrhosis…etc
- Nephrogenic diabetes insipidus
- Hypercalciuria

- **Side effects to thiazides:**

- Weakness; muscle cramps
- Erectile dysfunction
- Hyperglycemia
- Hyperlipidemia (↑ LDL, ↑ TG's)
- Hypercalcemia
- Pancreatitis

- Hypokalemia & hypomagnesemia

Considered the most frequent and dangerous side effect to thiazide diuretics → muscle weakness and serious cardiac arrhythmias

Pts at high risk are those with:

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

- Hyperuricemia

Thiazides could precipitate gout

The effect of thiazides on uric acid is dose dependent:

Low doses → hyperuricemia

Large doses → ↓ uric acid reabsorption