Pharmacology - Diuretics (Saluretics)

Diuretics introduction

-Diuretics increase urine excretion mainly by ↓ reabsorption of salts and water from kidney tubules.

-These agents are ion transporter inhibitors that decrease the reabsorption of Na+ at different sites of 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.**

Clinical uses of diuretics

- 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)

-They're used in the **management of any condition associated with salt and water retention**, by acting at different sites of the nephron (The basic unit of the kidney). They're **highly effective**, **relatively safe, and cheap**.

-Diuretics are the first-line therapy for most hypertensive patients. And without any compelling indications, the JNC reports say:

-JNC 6th report recommends **Diuretics or a beta-blocker.**
-JNC 7th report recommends **Thiazide-type diuretics.**

-(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. This is according to the ***ALLHAT*** *study. (**A**ntihypertensive and **L**ipid **L**owering treatment to prevent **H**eart **A**ttack **T**rial) which involved 40,000 hypertensive pts for 8 years, (1994)*

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

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

Diuretics therapy cautions

-Excessive diuretic usage may lead to a **compromise of the effective arterial blood volume** with reduction in perfusion of vital organs. (**This can lead to hypotension and collapse!**) 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.

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

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.

- 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)

- Others **inhibit enzymes** (acetazolamide)

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

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Family	Osmotic diuretics	Carbonic anhydrase inhibitors	Thiazides and Thiazide-like diuretics
Drugs	**Mannitol**	**Acetazolamide**	**Hydrochlorothiazide, Chlorothalidone , Indapamide**
Notes	*It is a sugar, not absorbed by kidney tubules, has no systemic effects and not metabolized. **MAO**:↑ osmotic pressure in kidney tubules → withdraw H2O → ↑ urine excretion by ↓ H2O reabsorption with little ↑ in NaCl excretion. **Site of action**: Proximal convoluted tubule	*Carbonic anhydrase enzyme is important enzyme responsible for reabsorption of Na+HCO3 from proximal convoluted tubules and for **formation of aqueous humor (fluid of the eye),** inhibition of carbonic anhydrase increases urine outflow and decreases formation of aqueous humor. **Site of action:** Proximal convoluted tubules *Acetazolamide is effective orally and as an ophthalmic drops Dorzolamide & Brinzolamide are other available topically (ophthalmic drops) active carbonic anhydrase inhibitors	*they are the most frequently used, least expensive, has low to moderate efficacy *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) **MAO:** by Inhibition of thiazide-sensitive Na+/Cl- transporter in **distal convoluted tubule**, inhibiting Na+ reabsorption →↑Na+,K+, Cl-, HCO3 and H2O excretion (5-10% loss of filtered Na+) * **↑ Ca++ reabsorption** (that's why it is used in idiopathic hypercalciuria) *Little carbonic anhydrase (CA) inhibitory effect *Direct vasodilating effect (especially Indapamide) * ↓ 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 *↑ 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 have synergistic effect with other lowering BP drugs
Clinical use	**Major clinical use**: ↑ intracranial pressure, given I.V. *Facilitates clearance of mucus in patients with bronchiectasis. *Promotes removal of renal toxins *Reduces intraocular pressure before ophthalmologic procedures. *Maintain urine volume and prevent anuria.	*Major clinical use: Glaucoma *Other uses: -**Urinary alkalinization** to excrete weak acids (excretion of weak acids is enhanced by increasing urinary pH) Prophylaxis and treatment of **-Acute mountain sickness** **-Absence seizures and myoclonic seizures**	*Hypertension * Edema of HF; liver cirrhosis…etc * Nephrogenic diabetes insipidus * Hypercalciuria
Side effects	*It's toxicity produces: 1) Extracellular volume expansion (extracts water from cells) 2) Headache, N/V, common in pts on osmotic diuretics 3) Dehydration, **hyperkalemia** and **hypernatremia**	*Hyperchloremic metabolic acidosis which results from chronic reduction of body bicarbonate stores *Renal stones (Increases pH of urine, Calcium salts are relatively insoluble at alkaline pH)	***The most frequent and dangerous**: muscle weakness and serious cardiac arrhythmias (High risk in LVH, previous MI, cardiac arrythmia, on digoxin therapy pts) * Weakness; muscle cramps * Erectile dysfunction * Hyperglycemia * **Hyperlipidemia (↑ LDL, ↑ TG's)** * Hypercalcemia * Pancreatitis *Hypokalemia & hypomagnesemia *Hyperuricemia (could precipitate gout) The effect of thiazides on uric acid is **dose dependent**: Low doses → hyperuricemia Large doses → ↓ uric acid reabsorption

Family	loop diuretics	Aldosterone antagonists	None steroidal potassium sparing diuretics
Drugs	Furosemide (Frusemide), Bumetanide, Ethacrynic acid (prodrug) ,Torsemide (active metabolites) all can be given orally and IV	Spironolactone, Eplerenone (more potent form)	Amiloride; Triamterene
Notes	*The strongest diuretics, have rapid OOA and short DOA **Site of action:** Thick segment of ascending loop of Henle **MAO:** Inhibition of Na+/K+/2Cl- (transporter leading to 10-25% loss of filtered Na+) * High ceiling effect unlike thiazide, so ↑ dose → ↑ diuretic effect; over-treatment → dehydration * Effective even at GFR below 10 ml/min (they are most effective in patients with renal insufficiency = creatinine level > 2.5 mg/dl) or resistant cases to other diuretics (unlike thiazides) *Loop diuretics ↑ excretion of Na+, Cl-, K+, H+,H2O and HCO3- (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 1/3rd of oral dose is excreted in bile	**MAO:** Aldosterone antagonists ↑ Aldosterone → ↑ synthesis of Na+-K+ ATPase → ↑ Na+ reabsorption, ↓ reabsorption of K+ (↑excretion of K+ & H+) **Site of action**: Collecting ducts *Only effective in presence of aldosterone (competitive antagonists) *Given orally; have delayed OOA *Weak diuretics, usually combined with other antihypertensives or thiazides	**MOA:** Blockade of epithelial Na+ channels → ↓ Na+ reabsorption, ↓ K+ excretion * Orally effective and available alone or combined with thiazides **Site of action:** DCT, collecting duct
Clinical use	* Considered 1st line therapy in patients with CHF *Acute pulmonary edema * Edematous states (ascitis; CHF; renal failure…etc) * Hypertension * Hypercalcemia *Syndrome of Inappropriate ADH secretion	*Hypertension *CHF * Hyperaldosteronism (1° or 2°) * Hypokalemia *Hirsutism (antiandrogenic effect)	* Hypertension * Hypokalemia
Side effects	*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	* Hyperkalemia → cardiac arrhythmias (More common in diabetes, chronic renal disease pts or patients on ACE inhibitors) (More severe with eplerenone) * Gynecomastia in ♂'s (rare with Eplerenone) * Breast tenderness in ♀'s (rare with Eplerenone)	*Hyperkalemia * Renal tubular damage especially reported following the use of Triamterene + Hydrochlorothiazide

Diuretic-induced hypokalemia is a serious problem among most of pts on loop diuretics or thiazides . However, we can solve it by:

- Combining 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

Reasons for 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 (post diuretic salt retention)

- Lowered bioavailability of the drug

Management of diuretic resistance

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