Clinical Pharmacology

Dr. Bassim I Mohammad,
MBChB, MSc, Ph.D
Professor and Consultant Physician
Dept. of Pharmacology & Therapeutics
College of Medicine
University of Al Qadisiyah, Iraq

Diuretics

- **Diuretics:** are drug that increase urine volume excreted. They are inhibitors of renal ion transporters that decrease sodium reabsorption at different sit in renal tubules thereby by causing sodium and water excretion.
- As a result of diuretic effect, decrease volume of the urine, change its pH, as well as ionic composition of the urine and the blood.

Classification of Diuretics

They are classified according to the percentage of loss of sodium (or inhibition of tubular sodium reabsorption) in urine into:

1. High efficacy (loop or high celling) diuretics
2. Medium efficacy diuretics
3. Low efficacy (Weak or adjuvant) diuretics

Loop Diuretics

Loop diuretics; this type of diuretics leads to excretion of 15-25% of filtered Na:

- Frusemide or furosomide
- Bumetanide
- Toresmide

} **sulphonamides**

- Ethecrynic acid (non-sulpha)

LD- Mechanism of action

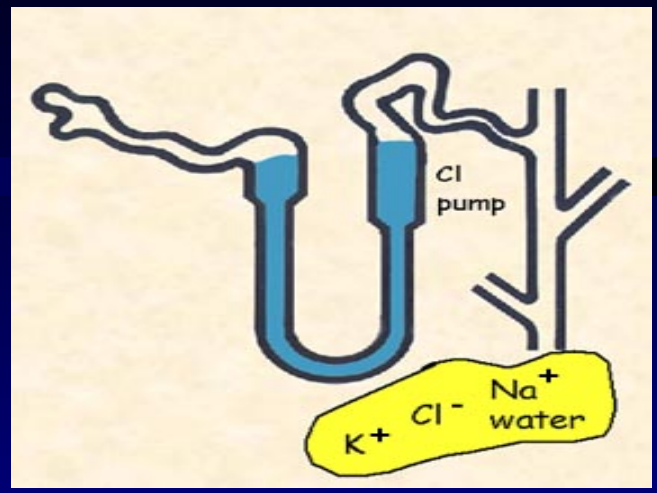
- They inhibit the Na+ K+ 2Cl Co-transport in thick Ascending loop of Henle (major site of action). Therefore they decrease reabsorption of these ions and water causing diuresis.
- Prior to their diuretic action (subdiuretic dose), LD cause venodilation. Thus increase venous capacitance and reduce left ventricular filling by enhanced PG synthesis.
- Hemodynamic effect:

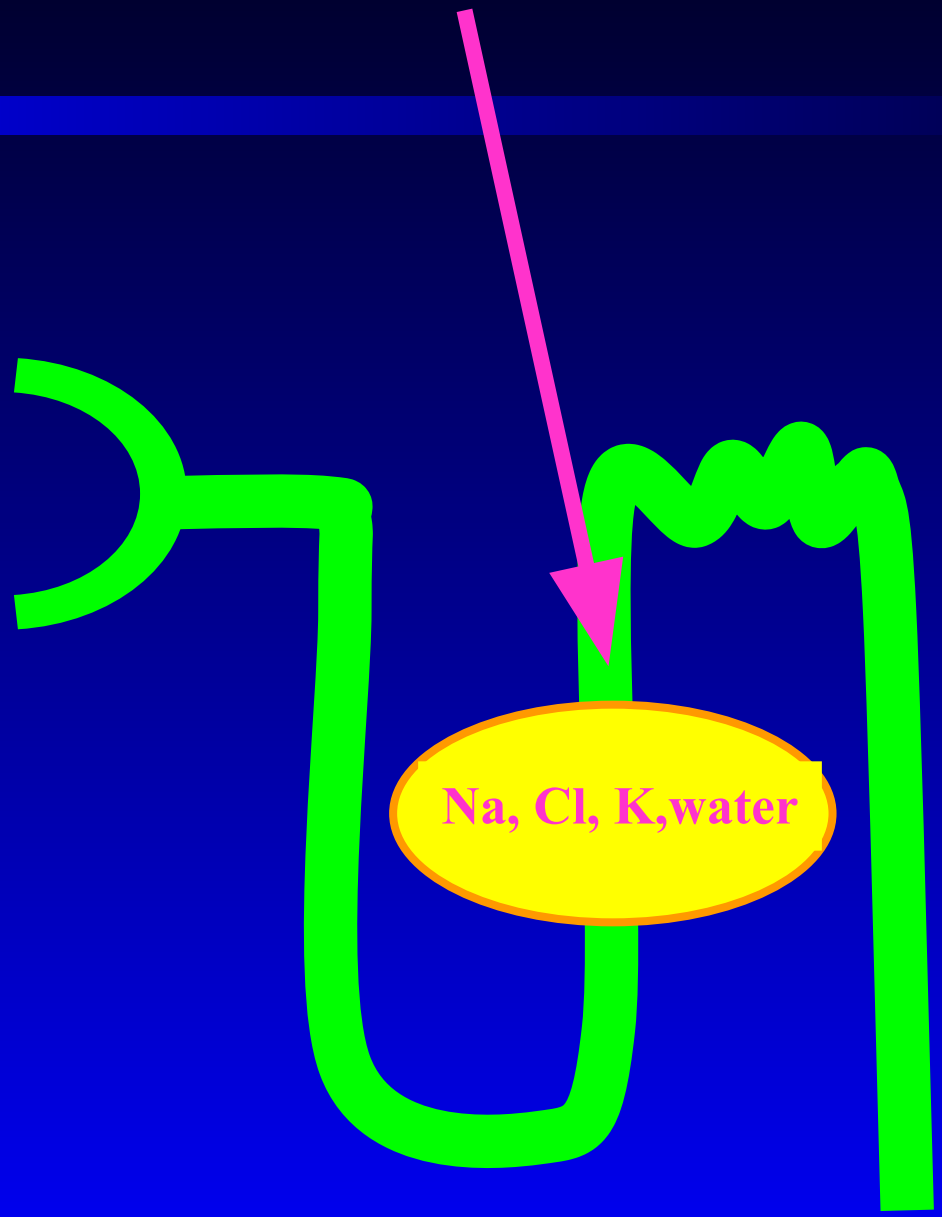
1. Duiresis: increase water lose and so decrease Blood volume = decrease preload
2. Venodilation: increase venous capacitance and reduce left ventricular filling by enhanced PG synthesis.

Loop Diuretics

- LD by venodilation reducing venous return to the heart with the resultant decrease in pulmonary congestion. This explain the effectiveness of these drugs at subdiuretic dose in relieving pulmonary congestion (in APO) and reducing BP before diuresis.
- These drugs are *effective even when GFR are is <20 ml/min* and this mean that these drug are effective even in renal failure.
- LD *increase Ca excretion in the urine*.
- Frusemide and Bumetanide have same efficacy while ethecrynic acid is less efficcious. Bumetanide is 40 times more potent than furosemide.

Loop Diuretics





Loop Diuretics - Pharmacokinetics

- GI absorption torsemide and bumetanide is more rapid (1 hr) than that of frusemide (2-3 hrs)
- Also given i.m. and i.v.
- Extensively protein bound in plasma
- Diuresis started within 10-20 minutes (1V) and one hour (oral).
- Generally, short half-lives
- They are eliminated by the kidney, tubular secretion and glomerular.

Loop Diuretics – Clinical Uses

- Acute pulmonary edema
- Edema due to CHF, nephrotic syndrome or cirrhosis
- Hypocalcaemia and Hypokalemia
- Forced diuresis and anion overdose, they are usefule in treating toxic ingestion of bromide, flouride, iodide which are reabsorbed in TAL
- Not in widespread use for the treatment of hypertension (except in a few special cases e.g. *hypertension in renal disease and hypertensive emergencies*)

Loop Diuretics – Side Effects

1. Sulphonamide Hypersensitivity: Ethecrynic acid is only non-sulph diuretics and used in patient allergic to other diuretics.
2. Electrolytes and acid-base:
   - Hypokalemia (so combine with K-sparing, ACEIs, ARBs)
   - Hyponatremia
   - Hypocalcemia (in contrast to thiazides)
   - Hypomagnesemia
   - Metabolic alkalosis

Loop Diuretics – Side Effects

3. Metabolic:

- Hypercholesterolemia
- Hyperuricemia (decreasing renal excretion – interference with tubular secretion of UA and secondary to compensatory water reabsorption)
- Hyperglycemia (secondary to hypokalemia, decrease insulin release and peripheral utilization of glucose, GLUT-4 receptors need I

Loop Diuretics – Side Effects

4. Dehydration and postural hypotension
5. Ototoxicity: Dose related, could be transient with frusemide or permanent with EA

- Rapid IV bolus
- Ototoxic drugs (aminoglycoside, amphotericin-B)
- Renal impairment),.

6.
8. Urine retention (elderly and nursing mother).

LD – Drug/Drug interactions

- With *ototoxic drugs* (like certain aminoglycoside, amphotericine-B….)
- *Pobencid* may interfere with effect of LD or thiazides by blocking their secretion to PCT.
- *NDAIDs* decrease renal response to LD by interfering with formation of vasodilator PGs
- High dose may competitively inhibits the excretion of *salicylate*, thus precipitate to SA poisoning
- *Steroids or ACTH* may predispose to hyperglycemia.
- LD do not alter *digoxin* level nor interact with *warfarin*

Moderate Efficacy Diuretics

1. Thiazides
2. Thiazide-Related agents

Moderate Efficacy Diuretics

1. **Thiazides:**
   - Chlorthiazide
   - Hydrochlorthiazide
   - Bendrofluzide

Moderate Efficacy Diuretics

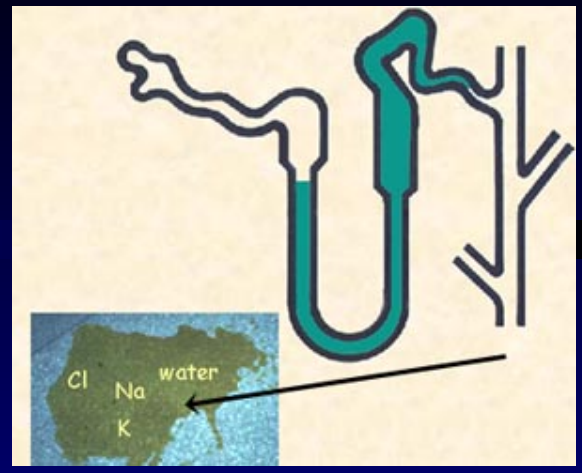
2. **Thiazide-Related agents:**

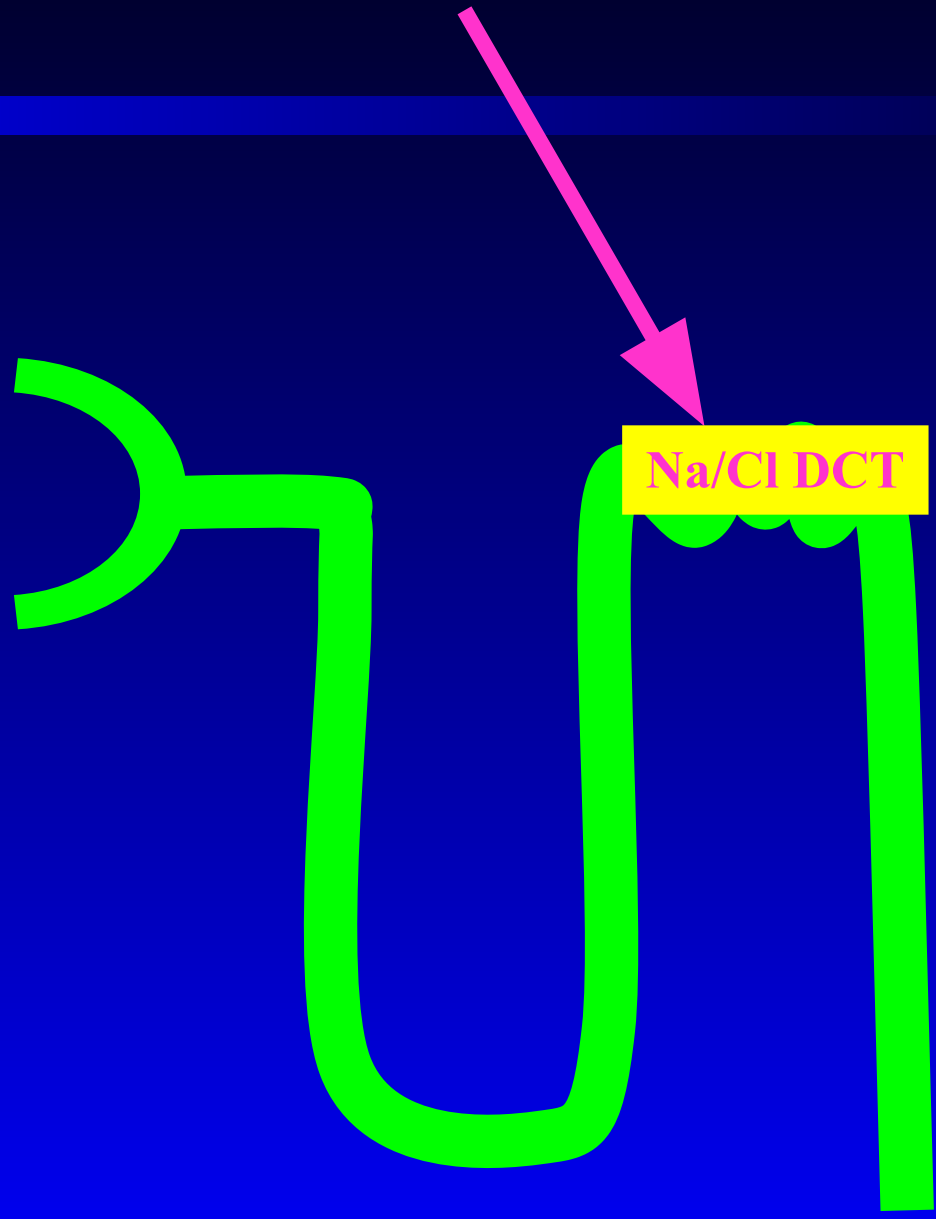
- Metazolone
- Indapamide
- Clopamide
- Chlorthalidone

TD- Mechanism of action

- TD and thaizide like agents act mainly by inhibiting the Na/ Co-transporter in DCT. These drugs inhibit the reabsorption of 10% of filtered Na causing modest diuresis, decrease blood volume and COP.
- Late effect: reduce PVR by relaxation of arteriolar smooth muscle.
- *Decrease urinary Ca excretion (content) by promoting reabsorption of Ca in DCT.*
- *They are not effective in low GFR (20ml/minute)* except metolazone which is useful even when GFR is low (moderate RF).

Thiazide Diuretics





Indapamide- Beyond diuresis

- Vasodilator
- Class I and III antiarrthymic effect

TDs - Pharmacokinetics

- Rapid GI absorption
- Distribution in extracellular space
- Elimination unchanged in kidney
- Variable elimination kinetics and therefore variable half-lives of elimination ranging from hours to days

Thiazide Diuretics – Clinical Uses

1. Hypertension:
   - Usually first line therapy
   - Diuresis and reduction in PVR (decrease in response of resistance blood vessels to circulation catecho. and this explains the effect of Indapamide (as antihypertensive) at subdiuretic dose

Thiazide Diuretics – Clinical Uses

2. Edema (cardiac, liver and renal)
3. Idiopathic hypercalciuria (recurrent renal stone formation due to excess calcium excretion)
4. Diabetes insipidus (nephrogenic)

Thiazide Diuretics – Side Effects

1. Electrolytes and acid-base
   - Hypokalemia *(and risk of arrhythmias):* therapeutic strategy is to avoid hypok in high risk patients (ihds, HF on digoxin, HT with LVH) by k-sparing diuretics (unless contraindicated renal impairment) or cotherapy with ARBS OR ACEIS.
   - Hypomagnesemia
   - Hyprecalcemia
   - Hyponatremia
   - Metabolic alkalosis

Thiazide Diuretics – Side Effects

2. Metabolic:

- *Hyperglycemia* (more diabetogenic potential than LDs), especially when combine with B-blockers. The risk depends on dose of thiazide and type of b-blocker, Patients with family history of DM and metabolic syndrome are more prone for DM (so avoid TD or start low dose.

Thiazide Diuretics – Side Effects

2. Metabolic:
   - *Hyperlipidemia* so frequent check up of lipid profile is required to minimize the atherogenic potential.
   - *Hyperuricemia* (precipitation of gout, so they should be avoided patients with Hx of gout)

3. Impotence: it is a big challenge and frequently cause drug withdrawal and failure of therapy. So changing the drug or using sildenafile (unless contraindicated like in nitrate) may help.

Thiazide Diuretics – Side Effects

4. Hypersensitivity reactions
5. Dehydration and postural hypotension
6. Others; Impotence and acute angle closure glaucoma

Loop vs Thiazide Diuretics

	LD	TD
sulfa	Yes (except EA)	NO
mechanism	TAL (Na/K/Cl cotransporter inhibitor)	DCT (Na/Cl transporter inhibitor)
potency	High (inhibit 25% of filtered Na)	Moderate (inhibit 10% of filtered Na)
ceiling	high	low
Ca excretion	yes	Enhance Ca reabsorption
Efficacy in RF	Effective even when GFR les than 20 ml/min	Not effective when GFR is very low (except metalozone)
Use in HT	Unusual (HT plus RF or hypertensive emergencies	First indication
Diabetogenic potential	less	High
ototoxicity	yes	no

Thiazide vs. Loop D

1. Less potency
2. Different site of action
3. Low ceiling diuretics (max. response reached at relatively low dose).
4. Longer duration
5. Ineffective in low GFR (except metalozone)
6. More diabetogenic potential
7. Reduce Ca excretion

THANK YOU

FOR YOUR ATTENTION