DIURETICS

CAE: Carbonic anhydrase enzyme

Diuretics

Extrarenal
1. H₂O & Ethylacohol
2. Digitalis only in C.H.F.
3. Albumin only in Hypoalbuminemia
4. Dobutamine
5. Methyl xanthines

Renal

Osmotic electrolyte
1. High efficacy ➔ Loop
2. Moderate efficacy ➔ Thiazide
3. Low efficacy ➔ C.A inhibitors ➔ K-sparing

Osmotic non-electrolyte
- Mannitol

Acidifying
- Glucose
- Urea

NB: Diuretics in common use: Loop - Thiazide - K-sparing - Mannitol
### Kidney

#### Thiazide diuretics

<table>
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<tr>
<th>Moderate efficacy</th>
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1. **Mechanism:**
   1. Must be secreted in P.C.T to act as diuretic from luminal side (inhibited by probenecid).
   2. Act mainly on **proximal part of distal convoluted tubule** → ↓ NaCl reabsorption.
   3. Less extent → ↓ carbonic anhydrase enz by their sulphonamide radicle.
   4. Excess NaCl will reach the distal part of D.C.T where part of Na⁺ is reabsorbed in exchange for K⁺ mainly & some H⁺.

2. **Result:**
   Urine will contain:
   1. Excess H₂O → Diuresis
   2. Excess Na⁺ → Hyponatremia
   3. Excess Cl⁻ → Hypochloremia
   4. Excess K⁺ → Hypokalemia
   5. Excess H⁺ → Alkalosis
   6. Excess Mg²⁺ → Hypomagnesamia
   7. **But ↓ Ca²⁺ in urine** → Hypercalcemia

3. **↓ R.B.F**

| Loop diuretics |

| High efficacy |

1. **Mechanism:**
   1. Must be secreted in P.C.T to act as diuretic from luminal side (inhibited by probenecid).
   2. Act mainly on **thick ascending loop of henle** → ↓ Na⁺ / K⁺ / 2Cl⁻ symport.
   3. Less extent → ↓ carbonic anhydrase enz (sulphonamide derivative).
   4. Excess NaCl will reach the distal part of D.C.T where part of Na⁺ is reabsorbed in exchange for K⁺ mainly & some H⁺.

2. **Result:**
   Urine will contain:
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   6. Excess Mg²⁺ → Hypomagnesamia
   7. Excess Ca²⁺ → hypocalcemia

3. **↑ R.B.F** may be through PGE₂ & PGI₂ inhibited by indomethacin.

| Dynamic |

#### (1) Diuretic

#### (2) Antidiuretic

Only in Neohrogenic Diabetes insipidus [↓GFR] **No anti diuretic effect**

#### (3) Anti hypertensive

1. Mainly due to **Direct V.D** effect due to:
   a-Depletion of Na⁺ & H₂O from arterial wall → ↓ oedema
   b-PGs may play a role. NSAID may ↓ V.D effect of thiazide.

2. Less important due to diuretic effect

| (4) Hyper uricemia |

↓ tubular secr. Of urica.

| (5) Hyper glycemia |

↓ insulin release

| (6) Hyper lipidimia |

↑ Bl. Cholesterol & TG
### Uses

| 1) **Edema:** [Cardiac – Hepatic – Renal] |
| - Drug of choice in mild & moderate CHF |
| 2) **Hyper tension** [mild & moderate] |
| 3) **Idiopathic hyper calcuria & Ca++ calculi**; hypocalcemia & osteoporosis |
| 4) **Pre-menstrual tension syndrome** |
| 5) **Diabetes insipidus** |

| 1) **Edema:** [Cardiac – Hepatic – Renal] |
| 1. Acute pulmonary edema |
| 2. Cerebral edema |
| 3. Refractory edema |
| 2) **Hyper tension** [severe or with R.F] |
| 3) **Hypercalcemia** |
| 4) Acute Renal failure |

### Side Effects

| 1) **Hypokalemia** |
| 2) **Hyponatremia** |
| 3) **Hypomagnesemia** |
| 4) **Hypochloremic alkolosis** |
| 5) **Hyper uricemia** |
| 6) **Hyper glycemia** |
| 9) **↓ RBF** |
| 10) **↑ Ca++ [Hypercalcemia]** |
| 11) **GIT Disturbance** |
| 12) **Blood Dyscrasia** |
| 13) **Fetotoxic** |

- **↑ Effect & toxicity of:**
  - i. Warfarin (displacement from plasma protein)
  - ii. Lithium (↓ its renal excretion)
  - iii. Digitalis (due to hypokalemia)
- **↑ Ototoxicity & nephrotoxicity of Aminoglycosides**
- **Its effect is ↓ by:**
  - i. Propenicid ➔ ↓ its renal tubular secretion
  - ii. NSAID ➔ ↓ its diuretic effect.

### Contraindications

| 1) Digitalis toxicity |
| 2) with steroid |
| 3) Gout |
| 4) DM |
| 5) Renal disease (for thiazide) |
| 6) Liver disease |
| 7) Pregnancy |

### Preparations

| 1) **Short acting** |
| - Chlor thiazide |
| - Hydrochlo-thiazide 25 – 100 mg / d |
| - Hydroflumethiazide |
| - Polythiazide |

| 2) **Long acting** |
| given once daily |
| - Chlorthalidone 50-100 mg / d |
| - Quinathazone |
| - Metolazone |

| 3) **Indapamide** [Natrilex]: |
| - Long acting 2.5-10 mg once/d |
| - Diuretic |
| - Depend on Biliary excretion, so safe in RF |

| 1) **Sulfa-containing:** |
| 1- **Furosemide** (or Frusemide) (Lassix) |
| 2- **Bumetanide** [More potent] |
| 3- **Torsemide** (or Torasemide) |

| 2) **Non-sulfa containing:** |
| Ethacrynic acid |
| (highly ototoxic, used only when the patient is allergic to sulfa compounds) |

**N.B:** There is a synergistic effect, if thiazide combined with loop
**N.B: Hypokalemia: ** *Worsens:* Digitalis toxicity- Liver disease- Kidney disease

*Avoided by:* 
1- Intermittent use of the least effective dose 
2- Fruit Juice 
3- KCl supplement 
4- Add K⁺ sparing diuretic

**Potassium sparing (retaining, conserving) diuretics**

1- They inhibit Na⁺ / K⁺ exchange in the late D.C.T. (weak diuretics = low efficacy)

2- They produce hyperkalemia, so:
   a. Never add KCl supplement. 
   b. Not combined with ACE inhibitors or Losartan 
   c. Never use in renal insufficiency => fatal hyperkalemia.

3- They do not ↓ carbonic anhydrase enzyme & cause slight alkalinization of urine.

4- Drugs ↓ aldosterone synthesis (e.g.: Metyrapone & Amphenone) => Na⁺ loss & K⁺ retention

*Classification:*

A) Aldosterone antagonists: Spironolactone & Eplerenone  
B) Non-aldosterone antagonists: Triamterene & Amiloride.

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**A) Aldosterone antagonists  
(Spironolactone “Aldactone” & Eplerenone)**

*Kinetic:*

1- Absorbed orally  
2- In liver: Spironolactone (active) => Canrenone (active metabolite)

*Dynamic:*

1- They compete with aldosterone for its specific receptors in late D.C.T. and collecting tubules ↓ Na⁺ / K⁺ & Na⁺ / H⁺ exchanges, leading to:
   a. ↑ excretion of Na⁺ in urine with its iso- osmotic water => weak diuretic effect. 
   b. Retention of K⁺ in blood => hyperkalemia. 
   c. Retention of H⁺ excretion in blood => metabolic acidosis.

2- Spironolactone ↑ Ca²⁺ excretion in urine by a direct effect.

*Uses:*

1- Hyperaldosteronism: 
   a- Primary: tumour of adrenal cortex (Conn’s Syndrome). 
   b- Secondary: to hypovolemia & stimulation of rennin-angiotensin system as in: Cogestive heart failure - Nephritic syndrome - Liver cirrhosis. 

2- Refractory edema: Cogestive heart failure - Liver cirrhosis with ascites. 

3- Essential hypertension
4- In combination with thiazide & loop diuretics to:
   a- Synergize their diuretic effect.
   b- Correct their resulting hypokalemia.
   “Aldactazide = spironolactone 25 mg + hydrochlorothiazide 25 mg”
5- Instead of thiazide & loop diuretics when they are contraindicated, e.g.: in hypokalemia, hyperuricemia, hyperglycemia & hypersensitivity.

* Side effect & Toxicity:
  1. Weak. So, usually combined with other diuretics.
  2. Delayed onset (2-3 days).
  3. G.I.T. disturbances
  4. Hypersensitivity & skin rash.
  5. Hyperkalemia especially in patients with renal disease.
  7. C.N.S: mental confusion, drowsiness & headache (due to acidosis).
  8. Hormonal: ➔ Antiandrogenic effect
     - males ➔ gynaeecomastia & impotence
     - females ➔ menstrual disturbances.

NB.: Eplerenone: has less side effects & used mainly in ttt of hypertension & CHF

* Drug interaction:
  1. Antagonize the action of Digitalis & Carbenoxolone
  2. ACEI, beta blockers & NSAID ➔ ↑ Hyperkalemia

B) Non-aldosterone antagonists
1. Trimterene : 100 – 300 mg / day orally.
2. Amiloride : 5-10 mg once / day orally.

*Kinetic:
  - Triamterene is extensively metabolized & bound to plasma protein
  - Amiloride is not metabolized, so excreted unchanged.
  - They have rapid onset than spironolactone.

*Dynamic:
  1- Their action does not depend on the presence of aldosterone. They block directly the Na⁺- channels in DCT ➔ directly Na⁺ / K⁺ exchange in the late D.C.T.
  2- They also ↓ excretion of H⁺ & Ca++ in urine.
      May ↑ uric acid excretion in urine (may be Uricosuric).

*Uses: Usually used + thiazide or loop diuretic to:
  a. synergize their action
  b. correct hypokalemia

*Side effect:
  1) Hyperkalemia   2) Metabolic acidosis
  3) GIT disturbance 4) Hypersensitivity

NB.: Diuretics causing HYPOcalcemia: Loop diuretics - Spironolactone
NB.: Diuretics causing HYPERcalcemia: Thiazide diuretics – Non aldosterone antagonists
Carbonic anhydrase inhibitors

Acetazolamide “Diamox”

* **Pharmacokinetics:**
  1. Absorbed orally (given once daily)
  2. Not metabolized.
  3. Excreted in urine

* **Pharmacodynamics:**

  *Reversible Non-competitive Inhibitor of carbonic anhydrase enzyme.

1- **Kidney:** ➔ weak self-limiting diuretic

   ![diagram]

   1. Acetazolamide inhibits NaHCO$_3$ reabsorption in exchange for H$^+$ mainly in P.C.T & to some extent in D.C.T.
   2. Excess NaHCO$_3$ will reach the late D.C.T where part of Na$^+$ is reabsorbed for K$^+$ only.
   3. The urine will contain:
      a. Excess water ➔ weak diuretic effect.
      b. Excess Na$^+$ ➔ hyponatremia.
      c. Excess HCO$_3^-$ ➔ acidosis
      d. Excess K$^+$ ➔ hypokalemia
   e. ↓ $\text{NH}_4^+$ in urine (due to ↓ H$^+$ secretion which convert NH$_3$ to NH$_4$)

4. H$^+$ is retained in blood ➔ relative hyperchloremic acidosis ➔ ↑ availability of H$^+$ ➔ ↓ its diuretic effect ➔ self-limiting diuretic.

2- **Eye:** ↓ synthesis of aqueous humor ➔ ↓ intraocular pressure.

3- **C.N.S.:** - Anti-epileptic effect in petit-mal epilepsy (absence seizures).
   - Due to either ↑ CO$_2$ or acidosis.

* **Uses:** orally or I.V

1- **On kidney:**
   - As diuretic in edema but weak & self-limiting.
   - As alkalinizer of urine. e.g: to dissolve uric acid crystals

2- **On eye:**
   - Note: Dorzolamide eye drops: better, more specific & used topically.

3- **On CNS:**
   - Treatment of Petit mal epilepsy (absence seizures), when other measures fail.
Kidney

* Side effect & toxicity:
1. Allergy & cross-allergy with other sulfonamides.
2. Metabolic effects:
   - Hypokalemia. “see before”
   - Hyperchloremic acidosis ➔ self-limiting & weak
4. CNS.: inhibition due to acidosis ➔ Drowsiness and paresthesia.

N.B. Other C.A inhibitors: Ethoxzolamide – Methazolamide- Dichlorphenamide

**Acidifying Diuretics**

**Ammonium Chloride (NH₄Cl)**

*Dynamic:

1. NH₄Cl is absorbed orally, where in the liver, it is hydrolyzed to
   ➔ NH₃ + H⁺ + Cl⁻.
   a. Ammonia (NH₃) is metabolized in liver ➔ urea ➔ excreted in urine.
   b. H⁺ passes to the blood to neutralize HCO₃ producing metabolic acidosis.
   c. Cl⁻ passes to the blood producing hyperchloremia.
      Excess chloride load will be excreted in urine + Na⁺ + iso-osmotic water ➔
      very weak diuretic effect.
2. The kidney starts to synthesize NH₄ to correct acidosis.
   NH₄⁺ will be excreted in exchange for Na⁺ ➔ ↓ diuretic effect (self
   limiting diuretic)

*Uses:
2. Urine:
   a. Acidify the urine to help excretion of weak base drugs, e.g.: amphetamine
      & ephedrine.
   b. Diuretic with mercury (obsolete)
3. Respiration: Nauseant expectorant.

*Contraindication: In liver & kidney disease
**N.B: Self limiting diuretics:**
1. Carbonic anhydrase inhibitors (acetazolamide)
2. Acidifying diuretics (NH₄Cl)
They are self limiting as they cause acidosis → reabsorption of Na⁺ in exchange for H⁺

**Osmotic non- electrolyte Diuretics**

**Mechanism:**
1. Not active (inert) & Small molecular weight → freely filterable through glomeruli with minimal or no reabsorption.
2. They ↓ H₂O reabsorption from P.C.T & descending loop of Henle.

**Examples:**
A) *Mannitol:*  
   b. *Side effects:* Transient ↑ in extracellular volume → so, not given to patients with CHF
B) *Glucose & Urea: I.V*
C) *Glycerin & Isosorbid:* orally to ↓ I.O.P.

**Methyl- Xanthines**

**Mechanism as diuretic:**
2. Renal: ↓ NaCl reabsorption from the nephrone.

**Uses as diuretic:** I.V. *Aminophylline* is used in acute pulmonary edema.

**N.B:**
- Theophylline “Aminophylline” > Theobromine > Caffeine
- Tolerance occurs to the diuretic effect.

**N.B: Anti- Diuretics**

1. Anti diuretic hormone (A.D.H.).
2. A.D.H. releasers e.g.:  
   - Nicotine, Yohimbine, Barbiturates, Morphine.  
   - Chloropamide “oral hypoglycemic” & Carbamazepine “anti- epileptic” in pituitary Diabetes Insipidus.

3. Drugs producing renal V.C. e.g.:  
   Adrenaline, Noradrenaline & Dopamine (in large dose).

**N.B: A.D.H. antagonists:**
Useful in treatment of syndrome of inappropriate ADH secretion (SIADH).
1. Demeclocycline “Tetracycline antibiotic”.
2. Lithium carbonate “antimanic drug”.
3. Methoxyflurane “general inhaled anesthetic drug”