Diuretics

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- Loop diuretics
  1. Bumetanide (Bumid)
  2. Etacrynico acid (Edocrin)
  3. Furosemide (Lasix)
  4. Torsemide (Demadex)

- Thiazides and related compounds
  1. Bendroflumethiazide (Naturtin)
  2. Benzthiazide (Ena)
  3. Hydroflumethiazide (Diuarcin)
  4. Hydrochlorothiazide (refer to combinations)
  5. Indapamide (Fludex)
  6. Quinethazone (Hychromox)
  7. Chlorothiazide (Diuil)
  8. Chlorthalidone (Akudon)
  9. Methylothiazide (Enduron)
  10. Metolazone (Hykron)
  11. Polythiazide (Renage)
  12. Trichlormethiazide (Nequa)
Main functions of the kidney

- Excretion of waste products: urea, uric acid, creatinine etc.
- Regulation of electrolyte content and the volume of extracellular fluid.
- Acid-base balance.
- Role in erythropoiesis.

Renal blood flow = 1200 mL/min
   (20-25% of cardiac output)
Renal plasma flow = 660 mL/min
Glomerular filtration rate = 125 mL/min
### Electrolytes and kidney

<table>
<thead>
<tr>
<th></th>
<th>Filtered/day</th>
<th>Excreted/day</th>
<th>Reabsorbed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>20.000 mEq</td>
<td>110 mEq</td>
<td>99+</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>5000 mEq</td>
<td>2 mEq</td>
<td>99+</td>
</tr>
<tr>
<td>K⁺</td>
<td>700 mEq</td>
<td>50 mEq</td>
<td>93+</td>
</tr>
<tr>
<td>H₂O</td>
<td>170 L</td>
<td>1.5 L</td>
<td>99+</td>
</tr>
</tbody>
</table>

### The nephron

- The functional unit of the kidney is the nephron of which there are more than $1 \times 10^6$ in each kidney.
- The nephron consists of glomerulus, proximal convoluted tubule, loop of Henle, distal tubule and collecting duct.
Fig. 20.1  Simplified diagram of a juxtamedullary nephron and its blood supply. The tubules and the blood vessels are shown separately for clarity. In the kidney the peritubular capillary network surrounds the convoluted tubules, and the distal convoluted tubule passes close to the glomerulus, between the afferent and efferent arterioles. (This last is shown in more detail in Fig. 20.2.)
**Diuretic agents**

- **Diuresis**: An increase in urine volume
- **Natriuresis**: An increase in renal sodium excretion.
- Diuretic agents can have a direct action on the cells of the nephron or indirectly modify the content of the filtrate.
Classification of diuretic agents

A. Direct acting agents
- Loop diuretics
- Thiazides and related drugs
- Potassium-sparing diuretics (triamterene, and amiloride)
- Aldosterone antagonists (spironolactone)

B. Indirect acting agents
- Osmotic diuretics (mannitol, urea)

C. Obsolete or near obsolete diuretics
- Carbonic anhydrase inhibitors (acetazolamide)
- Methylxanthines (aminophylline)
- Organic mercurial compounds (mersanyl)
**Loop or high-ceiling diuretics**

(bumetanide, furosemide, torsemide, ethacrynic acid)

- These drugs have the highest efficacy in mobilizing Na\(^+\) and Cl\(^-\) from the body. They inhibit the Na\(^+\)/K\(^+\)/2Cl\(^-\) cotransport of the luminal membrane in the ascending limb of the loop of Henle.
- As this part accounts for the reabsorption of 25-30% of filtered NaCl and downstream sites are not able to compensate for this increased Na\(^+\) load.
- They act promptly even in patients who have poor renal function.
- They increase urinary secretion of Na\(^+\), K\(^+\) and Ca\(^{2+}\) as well as Mg\(^{2+}\) and H\(^+\).
- They decrease renal vascular resistance and increase renal blood flow.

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![Diagram showing ion transport in the cells of the thick ascending limb of Henle's loop](image)
Loop or high-ceiling diuretics II

Pharmacokinetics
• They can be administered orally or parenterally. Their duration of action is relatively brief (1-4 hours)

Therapeutic Uses
• Reducing the acute pulmonary edema of congestive heart failure.
• Hyperkalemia, hypercalcemia
• Acute renal failure
• Anion overdose

Loop or high-ceiling diuretics III

Adverse Effects
• Ethacrynic acid shows greater side effects than the others and is not widely used.
• Hypokalemic metabolic alkalosis
• Ototoxicity
• Hypomagnesemia
• Hypotension
• Cardiac arrhythmias
Thiazides and related drugs I

(chlorothiazide, hydrochlorothiazide, chlorthalidone...)
- They are the most widely used of the diuretic drugs.
- All effect on the distal tubule and all have equal maximum diuretic effect (5-10% of filtered Na\(^+\) is excreted).
- Thiazide derivatives act mainly in the distal tubule to decrease the reabsorption of Na\(^+\)/Cl\(^-\) cotransporter on the luminal membrane.
- They increase the concentration of Na\(^+\) and Cl\(^-\) but decrease the concentration of Ca\(^{2+}\) in the tubular fluid.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Oral Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bumetanide</td>
<td>0.5–2 mg</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td>50–200 mg</td>
</tr>
<tr>
<td>Furosemide</td>
<td>20–80 mg</td>
</tr>
<tr>
<td>Torsemide</td>
<td>2.5–20 mg</td>
</tr>
</tbody>
</table>

\(^1\)As single dose or in two divided doses.
Thiazides and related drugs II

- The acid-base balance is not usually affected.
- These drugs must be excreted into the tubular lumen to be effective.
- They reduce peripheral vascular resistance, by relaxation of arteriolar smooth muscle. This usually occurs prior to the diuretic effect.
- Their efficacy is reduced in renal failure (if GFR < 50 ml/min.)
**Thiazides and related drugs III**

**Therapeutic Uses**
- Hypertension
- Congestive heart failure
- Renal impairment
- Hypercalcuria (for preventing nephrolithiasis)
- Diabetes incipitus (nephrogenic)

**Thiazides have unique ability to produce a hyperosmolar urine.**

**Thiazides and related drugs IV**

**Pharmacokinetics**
- They are orally effective.
- Usually it takes 1-3 weeks to produce a stable reduction in blood pressure.
- They have long biological half-life.

**Adverse Effects**
- Potassium depletion
- Hyperuricemia
- Volume depletion
- Hypercalcemia
- Hyperglycemia
- Hyperlipidemia
**Thiazide analogues**

- **Metolazone**: It is more potent and causes Na⁺ excretion in advanced renal failure.
- **Indapamide**: It has minimal diuretic effects, but has significant antihypertensive action.

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**Table 15–3. Thiazides and related diuretics: Dosages.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Oral Dose</th>
<th>Frequency of Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendroflumethiazide</td>
<td>2.5–10 mg</td>
<td>As single dose</td>
</tr>
<tr>
<td>Benzthiazide</td>
<td>25–100 mg</td>
<td>In two divided doses</td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>0.5–1 g</td>
<td>In two divided doses</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>50–100 mg</td>
<td>As single dose</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>25–100 mg</td>
<td>As single dose</td>
</tr>
<tr>
<td>Hydroflumethiazide</td>
<td>25–100 mg</td>
<td>In two divided doses</td>
</tr>
<tr>
<td>Indapamide</td>
<td>2.5–10 mg</td>
<td>As single dose</td>
</tr>
<tr>
<td>Methyclothiazide</td>
<td>2.5–10 mg</td>
<td>As single dose</td>
</tr>
<tr>
<td>Metolazine</td>
<td>2.5–10 mg</td>
<td>As single dose</td>
</tr>
<tr>
<td>Polythiazide</td>
<td>1–4 mg</td>
<td>As single dose</td>
</tr>
<tr>
<td>Quinethazone</td>
<td>50–100 mg</td>
<td>As single dose</td>
</tr>
<tr>
<td>Trichlormethiazide</td>
<td>2–8 mg</td>
<td>As single dose</td>
</tr>
</tbody>
</table>

1 Not a thiazide but a sulfonamide qualitatively similar to the thiazides.
Potassium-sparing diuretics and aldosterone antagonists

(spironolactone, amiloride, triamterene)
- These agents act in the collecting tubule, and inhibit Na⁺ reabsorption, K⁺ secretion, and H⁺ secretion.
- At that part 5% of filtered Na⁺ may be excreted)
Aldosterone antagonists I

Spironolactone
• It is a synthetic aldosterone antagonist that competes with aldosterone for intracellular cytoplasmic receptor sites.
• Spironolactone-receptor complex is inactive, and thus it prevents the production of proteins that are normally synthesized in response to aldosterone. These mediator proteins normally stimulate Na⁺-K⁺ exchange sites of the collecting tubule.
• In most edematous states blood levels of aldosterone are high, that results in Na⁺ retention.
• In cases in which there are no circulating levels of aldosterone (e.g. Addison’s disease) no diuretic effect of the drug occurs.

Aldosterone antagonists II

Therapeutic uses
• Diuretic (low efficacy, but used together with a loop diuretic or a thiazide to prevent K⁺ excretion)
• Treatment of heart failure
• Secondary hyperaldosteronism

Pharmacokinetics
• Completely absorbed orally. Rapidly converted to an active metabolite (canrenone); its action is largely due to the effect of canrenone.
**Aldosterone antagonists III**

**Adverse effects**
- Hyperkalemia
- Hyperchloremic metabolic acidosis
- Gynecomastia

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**Potassium-sparing diuretics I**

**Triamterene and amiloride**
- Both block Na\(^+\) transport channels resulting in a decrease in Na\(^+\)-K\(^+\) exchange.
- They have K\(^+\)-sparing diuretic actions similar to that of spironolactone.
- The ability of these drugs does not depend upon the presence of aldosterone.
- They are frequently used in combination with other diuretic agents, usually for their potassium sparing properties.
Potassium-sparing diuretics II

Adverse effects
- Leg cramps
- Possibility of increased BUN, uric acid
- K⁺ retention
- Kidney stones (for triamterene)
- Acute renal failure (for triamterene and NSAIDs combination)
**Osmotic diuretics I**

- A number of simple, hydrophilic chemical substances that are filtered through the glomerulus such as mannitol and urea result in some degree of diuresis.
- This is due to their ability to carry water with them into the tubular fluid.
- Osmotic diuretics are used to effect increased water excretion rather than Na+ excretion.
- They are used to maintain urine flow following acute toxic ingestion of substances capable of producing acute renal failure.
- They are a mainstay of treatment for patients with increased intracranial or intraocular pressure or acute renal failure due to shock, drug toxicities and trauma.

**Osmotic diuretics II**

**Adverse Effects**

- Extracellular volume expansion (because they extract fluid from the intracellular compartment)
- Dehidratation and hypernatremia
Investigational drugs

- A variety of medical conditions e.g. tumors that secrete ADH-like peptides cause water retention as the result of ADH excess. Specific ADH-antagonists are available for investigational purposes (V₂ receptor blockers)
- Adenosine A₁ receptor blockers (such as FK 453) induce natriuresis with minimal effects on K⁺ excretion.
- Recently the water channels of the proximal tubule and of the collecting duct were cloned (aquaporin-CHIP and aquaporin-CD respectively).
- Inhibitors are not present yet but;
  - Inhibitors of aquaporin-CHIP may be useful natriuretic agents.
  - Inhibitors of aquaporin-CD may be highly efficacious “aquauretic” diuretics.

Carbonic anhydrase inhibitors I

- Acetazolamide inhibits the enzyme carbonic anhydrase in the proximal tubular epithelial cells. However, it is more often used for other pharmacologic actions rather than its diuretic effect, because it is less efficacious than thiazides or loop diuretics.
- Carbonic anhydrase inhibition results in decreased ability to exchange Na⁺ for H⁺. This causes a mild diuresis. HCO₃⁻ is retained in the lumen with marked elevation of urinary pH.
**Carbonic anhydrase inhibitors II**

**Therapeutic uses**
- Treatment of glaucoma (acetazolamide decreases production of aqueus humor)
- Epilepsy
- Mountain sickness
- Urinary alkalinisation
- Metabolic alkalosis
Carbonic anhydrase inhibitors III

Adverse Effects

- Metabolic acidosis
- K⁺ depletion
- Renal stone formation
- Drowsiness, paresthesia

Table 15–5. Changes in urinary electrolyte patterns in response to diuretic drugs.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Urinary Electrolyte Patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NaCl</td>
</tr>
<tr>
<td>Carbonic anhydrase inhibitors</td>
<td>+</td>
</tr>
<tr>
<td>Loop agents</td>
<td>+++</td>
</tr>
<tr>
<td>Thiazides</td>
<td>++</td>
</tr>
<tr>
<td>Loop agents plus thiazides</td>
<td>++++</td>
</tr>
<tr>
<td>K⁺-sparing agents</td>
<td>+</td>
</tr>
</tbody>
</table>

+, increase; −, decrease.
Tablo 14.2: Düüretiklerin idrar elektrolit düzeyleri ve idrar miktarını değiştirmeleri.

<table>
<thead>
<tr>
<th>Idrar elektrolitleri</th>
<th>İdrar miktarı</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>NaHCO₃</td>
</tr>
<tr>
<td>Karbonik anhidraz inhibitörleri</td>
<td>+</td>
</tr>
<tr>
<td>Loop diüretikleri</td>
<td>++++</td>
</tr>
<tr>
<td>Tiaziliter</td>
<td>++</td>
</tr>
<tr>
<td>Loop diüretikleri + tiaziliter</td>
<td>++++</td>
</tr>
<tr>
<td>K⁺ koruyucu diüretikler</td>
<td>+</td>
</tr>
<tr>
<td>+ artına, – azalma</td>
<td></td>
</tr>
</tbody>
</table>

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Tablo 14.2 Düüretiklerin idrar elektrolit düzeyleri ve idrar miktarını değiştirmeleri.

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</tr>
<tr>
<td>Loop diüretikleri</td>
<td>++++</td>
</tr>
<tr>
<td>Tiaziliter</td>
<td>++</td>
</tr>
<tr>
<td>Loop diüretikleri + tiaziliter</td>
<td>++++</td>
</tr>
<tr>
<td>K⁺ koruyucu diüretikler</td>
<td>+</td>
</tr>
<tr>
<td>+ artına, – azalma</td>
<td></td>
</tr>
</tbody>
</table>
Drugs which alter the pH of the urine

Agents which increase the urinary pH
- Sodium or potassium citrate, lactate or acetate.
- These are metabolized and the cations are excreted with $\text{HCO}_3^-$ to give an alkaline urine

Agents which decrease the urinary pH
- Ammonium chloride
- Ammonia is metabolized to urea in the liver leaving chloride and hydrogen ion.
Happy New Year...