Renal Pharmacology - Diuretics

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Renal Anatomy

- Nephron: structural unit of kidney
- Glomerulus: site of ultrafiltration
- Tubular system: contains highly specialized cells that contain ion transport systems and possess water permeable properties.
- Hormonal control: by antidiuretic hormone (ADH, Post. Pit.) and aldosterone (adrenal cortex).

Renal function - Recycle, Recycle, Recycle

Filtration, Reabsorption & Excretion

GFR: 180 L/day (125 ml/min)
Urine output: 1-1.5 L/day
Filtered Na+: 25,200 mEq/d
Na+ excreted: 100 -150 mEq/d

Diuretics drugs increase the daily urine output/excretion of Na+ by inhibiting the re-absorption of ions (Na+ or Cl-). 

Glomeruli

About 1 million nephrons / kidney
Electron micrographs

Surface view
Cross-section

% Reabsorbed

<table>
<thead>
<tr>
<th>Substance</th>
<th>Filtered</th>
<th>Reabsorbed</th>
<th>Excreted</th>
<th>% Reabsorbed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na (mEq)</td>
<td>26,000</td>
<td>25,850</td>
<td>150</td>
<td>99.4</td>
</tr>
<tr>
<td>Na (mEq)</td>
<td>18,000</td>
<td>17,850</td>
<td>150</td>
<td>99.2</td>
</tr>
<tr>
<td>HCO₃ (mEq)</td>
<td>4,900</td>
<td>4,900</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Urea (mM)</td>
<td>870</td>
<td>460</td>
<td>410</td>
<td>53</td>
</tr>
<tr>
<td>Glucose (mM)</td>
<td>800</td>
<td>800</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Water (L)</td>
<td>180</td>
<td>179,000</td>
<td>1,000</td>
<td>99.4</td>
</tr>
<tr>
<td>K⁺ (mEq)</td>
<td>900</td>
<td>900</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

*While all filtered K⁺ is reabsorbed, some is secreted in the distal tubule in exchange for Na⁺.
### Therapeutic uses of diuretics

- **Congestive heart failure:** Thiazide
- **Hypertension:** Thiazide, K+ sparing, Loop
- **Kidney disease:** Osmotic
- **Nephrolithiasis (kidney stones):** CA inhibitors
- **Hepatic cirrhosis:** Thiazide, Loop
- **Hypercalcemia:** Loop
- **Idiopathic edema:** Loop
- **Diabetes insipidus:** Thiazide
- **Increase drug elimination:** CA inhibitors, Osmotic
- **Reduce intracranial pressure:** Osmotic, CA inhibitors
- **Reduce intraocular pressure:** Osmotic, CA inhibitors
- **Altitude sickness:** CA inhibitors

### Glomerular Filtration in Bowman's Capsule

- **Glomerular filtration:** production of an ultrafiltrate of the plasma
- **Glomerular filtration:** dependent on Effective Filtration Pressure (EFP)

\[
EFP = 55 - (25 + 10) = 20 \text{ mmHg}
\]

**Note:** During hypotension, glomerular filtration may cease, and urine output may stop. This retains vascular volume and may preserve BP.

### Proximal Tubule

- **Active Na reabsorption (60% of filtered load) by Na+/H+ antiporter**
- **85% of filtered bicarbonate (HCO}_3^-\) is reabsorbed**
- **60% of filtered water (passive water reabsorption of iso-osmotic urine 300 mOsmol)**

<table>
<thead>
<tr>
<th>Element</th>
<th>%Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>40</td>
</tr>
<tr>
<td>Na+</td>
<td>40</td>
</tr>
</tbody>
</table>

**Note:** Water is NEVER actively pumped anywhere in a nephron.

### Proximal tubular - Osmotic diuretics

Freely filtered through glomerulus; increase the osmolality of the tubular fluid → hinder water reabsorption in the proximal tubule (major site), the descending loop of Henle, and the collecting tubules.

**A. Mannitol (Osmotrol®)**
- Given i.v., 90% recovered unchanged in urine after 24 hr
- Promote diuresis during acute renal failure
- Reduction of intracranial pressure of cerebral edema
- Promote excretion of toxic substances

**B. Urea (Ureaphil®)**
- 30% solution i.v. to reduce intracranial pressure

### Action of Mannitol

- **- Mannitol**
- **+ Mannitol**
Proximal tubular – Carbonic Anhydrase Inhibitors
- Not commonly used (weak action)
- Inhibit carbonic anhydrase that converts \( \text{HCO}_3^- \) into \( \text{H}_2\text{O} \) and \( \text{CO}_2 \), and back
- Net effect: ↓water, \( \text{Na}^+ \) and \( \text{HCO}_3^- \) in proximal tubule.

Acetazolamide (Diamox®), Dichlorphenamide (Daranide®); Methazolamide (various)
- Glaucoma: reduce aqueous humor formation
- Nausea and vomiting associated with acute mountain sickness
- Epilepsy: adjunctive agent; retards abnormal, excessive discharge of CNS neurons
- Reversal of metabolic alkalosis
- Potential adverse effect: Metabolic acidosis

Carbonic Anhydrase Inhibitors

Loop of Henle
Descending loop of Henle
- No active pumps
- Water leaves tubule by osmosis
- \( \text{Na}^+ \) and urea concentrations outside the tubule (medullary interstitium) increase from 400 to 1200 mOsmol from the top to the bottom of the loop, respectively.
- As the fluid in the lumen of the tubule moves down the tubule, the fluid osmolarity increases in a concomitant fashion (i.e., 400 to 1200 mOsmol).

Thick ascending loop of Henle
- Active \( \text{Na}^+ \) reabsorption (25% of filtered load) by \( \text{Na}^+ / \text{K}^+ / 2\text{Cl}^- \) co-transporter
- \( \text{Na}^+ \) reabsorption leads to dilution of the tubular fluid
- \( \text{Ca}^{++} \) and \( \text{Mg}^{++} \) are reabsorbed via a paracellular pathway

Distal Convoluted Tubule
- Active \( \text{Na}^+ \) reabsorption (10% of filtered load) by \( \text{Na}^+/\text{Cl}^- \) co-transporter
- Relatively impermeable to water, therefore \( \text{Na}^+ \) reabsorption further dilutes the tubular fluid.
- \( \text{Ca}^{++} \) is reabsorbed by an apical \( \text{Ca}^{++} \) channel and a basolateral \( \text{Na}^+/\text{Ca}^{++} \) exchanger

Distal Convoluted Tubule
- Administration: per os, i.v., i.m.

Indications
- Edema with hepatic cirrhosis, renal disease
- Edema associated with congestive heart failure
- Asthenes due to malignancy, lymphedema, idiopathic edema
- Hypertension (oral forms)
- Acute hypercalcemia

Adverse effects
- Excessive diuresis—dehydration, depletion of \( \text{Ca}^{++}, \text{Mg}^{++}, \text{K}^+ \), decreased blood volume (orthostasis, shock)
- Transient/reversible ototoxicity (i.e. hearing loss)
**Thiazide Diuretics**

Inhibition of the Na⁺-Cl⁻ cotransporter system

Thiazides: moderately effective since 85% of the filtered load of Na⁺ has been reabsorbed in earlier parts of the nephron.

Chlorothiazide (Diuril®), (12 other types available)
- **Hypertension**
  - Adjunctive therapy for edema of various types, including CHF
  - Prevention of kidney stones due to hypercalciuria (nephrolithiasis); thiazides have a direct effect to increase Ca++ reabsorption

**Adverse effects**
- Hypokalemia - increased delivery of Na⁺ to distal tubule reduces reabsorption of K⁺ (potassium supplements added to tmt)
- Hypercalcemia - due to increased Ca++ reabsorption.
- Hyperuricemia - long term reduces uric acid secretion (gout)

Birkenhager: J Hyperten. 1990, 8 (Suppl 2) S3 -S7.

**Collecting Tubule**

- Site of active Na⁺ reabsorption (2-5% of filtered load)
- Final site for determining Na⁺ concentration of the urine
- Site of K⁺ release into the tubular lumen through K⁺ channels

**Aldosterone:**
- Increases activity of membrane Na⁺ and K⁺ channels, and Na⁺/K⁺ ATPase pump
  - Na⁺ reabsorption and K⁺ excretion

**Antidiuretic hormone (ADH):**
- Absence of ADH tubule impermeable to water reabsorption
  - Diabetes Insipidus results in the production of as much as 20L/d of dilute urine
    - Central - inadequate ADH release from posterior pit.
    - Nephrogenic - absence of tubular response to ADH

**Intercalated Cells**: site for proton secretion into urine

**Diabetes Insipidus**

**Potassium Sparing Diuretics**

**Spironolactone (Aldactone®)**
- Competitive receptor antagonist of aldosterone
  - Inhibition of Na⁺ and K⁺ channels (decreased K⁺ excretion)
  - Seldom used alone (low potency), used in combination with K⁺ depleting agents; esp. in antihypertensive therapy.

**Adverse effects:**
- Hyperkalemia
- Estrogen-like effects (steroidal structure)
- Carcinogenic in rats

**Triamterene (Dyrenium®) (Amiloride (Midamor®))**
- Inhibition of Na⁺ and K⁺ channels (decreased K⁺ excretion)
- Seldom used alone (low potency), valuable in combination with K⁺ depleting agents, esp. in antihypertensive therapy.
- Adverse effects: hyperkalemia and photosensitivity
Sites of Diuretic Action

NaCl  NaHCO₃

Plasma

Diuretics

screated

NaK-2Cl

diuretics

ADH antagonists (L-arginine, doxazosin)

H₂O

NaK-2Cl

Na+-K+-2Cl⁻

Diuretics

screated

NaCl

Ca Inhibitors

Proximal tubule

Loop Diuretics

Loop of Henle

Thiazides: distal tubule

Hydrocortisone

Plasma Na 145 mEq/L

Filtered Load 26,100 mEq/day

GFR 180 L/day

Thick Ascending Limb

Urine Na 100 mEq/L

Na Excretion 155 mEq/day

Volume 1.5 L/day

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- Reduce intraocular pressure: Osmotic, CA inhibitors
- Altitude sickness: CA inhibitors

Summary

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