DIURETICS

NAFRIALDI

Departement of Pharmacology FKUI
Introduction

• Kidney: 1.3 million nephron each

• Glomeruli:
  – Receive 25% of cardiac output
  – Filtration rate: 100-120 ml/minute

• Tubules:
  – Reabsorption of 99% of glomerular filtrate → only ± 1 ml/min. excreted as urine
  – Secretion
Introduction

• Proximal tubules:
  – Reabsorption of 65% Na⁺
  – Permeable to water → isotonic urine

• Loop of Henle
  – Thick decending limb: most active water reabsorption
  – Thin ascending limb
  – Thick ascending limb:
    • Reabsorption of Na⁺,
    • Water impermeable → diluting segment

• Distal tubules:
  – Na⁺ reabsorption
Electrolyte Transport and Site of Action of Diuretics

Diagram showing the tubule transport systems and sites of action of diuretics. The diagram depicts various sections of the nephron, including the proximal convoluted tubule, proximal straight tubule, thin descending limb, thin ascending limb, and loop of Henle. The sites of action for different types of diuretics are indicated with corresponding labels and processes:

1. Acetazolamide
2. Osmotic agents (mannitol)
3. Loop agents (e.g., furosemide)
4. Thiazides
5. Aldosterone antagonists
6. ADH antagonists

The process involves the transport of various electrolytes and ions, such as Na^+, K^+, Ca^2+, Mg^2+, NaCl, and H_2O, across different segments of the nephron.
# Site and Mechanisms of Actions of Diuretics

<table>
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<tr>
<th>Diuretics</th>
<th>Site of Action</th>
<th>Mechanism</th>
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</table>
| Osmotic Diuretic                        | 1. Proximal tubules  
2. Loop of Henle  
3. Collecting duct | Inhibition of water and Na\(^+\) reabsorption                          |
| Carbonic Anhydrase Inhibitor (CA-I)     | Proximal tubules                                           | Inhibition of bicarbonate reabsorption                                  |
| Loop Diuretic                           | Loop of Henle \((thick ascending limb)\)            | Inhibition of Na\(^+\), K\(^+\), Cl\(^-\) cotransport                 |
| Thiazide                                | Early distal tubule                                      | Inhibition of Na\(^+\), Cl\(^-\) cotransport                           |
| Potassium sparing diuretics             | Late distal tubule  
Collecting duct                         | Inhibition of Na\(^+\) reabsorption and K\(^+\) secretion             |
Osmotic Diuretics

- **Mannitol**, urea, glycerine, isosorbide
- Properties of osmotic diuretics:
  - Freely filtrated by glomerulus
  - Negligible tubular reabsorption
  - Chemically inert
  - Usually non metabolized
Mechanism of Action

- OD is filtrated and increases osmotic pressure in tubular lumen
- Hence, increases excretion of water and electrolytes
- Almost all of electrolyte are excreted: Na\(^+\), K\(^+\), Ca\(^{++}\), Mg\(^{++}\), HCO\(_3\)^{-}, phosphate
Pharmacokinetics

- Mannitol and urea:
  - Not absorbed from GI tract → intravenous
- Glycerine and isosorbide:
  - Can be administered orally
- Metabolism:
  - Glycerine 80% metabolized
  - Mannitol 20%
  - Urea, isosorbide: not metabolized
- Excretion: renal
Indications

• Glaucoma (rare)
• Brain edema
  – mannitol and urea are given before and after brain surgery
• Disequilibrium syndrome after hemodialysis
• Prophylaxis of ATN (acute tubular necrosis) due to contrast media, surgery, and trauma.
Adverse Effects

- Initial increase of plasma volume → potentially dangerous in heart failure and lung edema
- Hypo Na+ → headache, nausea, vomitus
- Hypovolemia
- Hypersensitivity reaction
- Vein thrombosis, pain if extravasation (urea)
- Hyperglycemia, glycosuria (glycerine)
Contraindications

- Renal failure and anuria
- Lung edema
- Dehydration
- Intracranial hemorrhage, except before craniotomy
Carbonic Anhydrase Inhibitor
Acetazolamide, Dichlorphenamidine, Metazolamide

Mecanism of Actions

• Kidney:
  – Inhibition of Bicarbonate (HCO3-) reabsorption
  – Reduces Na-H-exchange → NaHCO$_3$ is excreted along w/ H2O

• Eye:
  – Inhibits formation of aqueous humor → decreases intra ocular pressure

• CNS: anti convulsive effects
  – due to pH decrease
  – direct effect
Mechanism of Action of CA-I
Indications of CA-I

- Glaucoma
- Epilepsi: limited usage
- Acute mountain sickness
- Familial periodic paralysis
- Urinary alkalination: preventing uric acid and cystine stones
- Metabolic alkalosis
Adverse Effects and Contraindications

• Metabolic acidosis
• Renal stones (Phosphate and Calcium stone)
• Renal potassium wasting (NaHCO$_3^-$ enhances K+ secretion)
• Drowsiness, paresthesia, disorientation

Contraindication
  – Liver cirrhosis (CA-I inhibits conversion of NH3 to NH4) $\rightarrow$ NH3 increased
  – Renal failure (↑ risk of metabolic acidosis)
Preparations

• Acetazolamide (Diamox®):
  – Tablet 125 and 250 mg
  – Doses: 250-1000 mg/day

• Dichlorphenamide: tablet 50 mg (1-4 times daily)

• Metazolamide: tablet 25 and 50 mg (1-4 times daily)
Thiazides

- Hydrochlorothiazide (HCT), Chlorothiazide, Bendroflumethiazide, Clortalidone, Metolazone, Indapamide

**Mechanism of Actions**

- Thiazides are secreted by proximal tubules but works in distal convoluted tubules
- Inhibit Na\(^+\)-Cl\(^-\) symporter from the lumen to tubular cells → increase Na\(^+\), Cl\(^-\) excretion (and water)
- Some thiazides have weak CA-I effect
Mechanism of Action of Thiazide
Thiazides
Effects on Electrolytes

- Increases Na\(^+\) and Cl\(^-\) excretion
- \(K^+\) excretion also increase associated w/ increased Na\(^+\) in distal tubules.
- Inhibits uric acid secretion → hyper uricemia and gout
- Decreases Ca\(^{2+}\) excretion (unknown mechanism)
  → tends to increase plasma Ca\(^{++}\)
  → Delays osteoporotic process
- Increases Mg\(^{2+}\) excretion
## Pharmacokinetics

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Potency</th>
<th>$T^{1/2}$ (h)</th>
<th>Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendroflumethiazide</td>
<td>10</td>
<td>3-3.9</td>
<td>30% renal 70% metabolism</td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>0.1</td>
<td>1.5</td>
<td>renal</td>
</tr>
<tr>
<td>HCT</td>
<td>1</td>
<td>2.5</td>
<td>renal</td>
</tr>
<tr>
<td>Polithiazide</td>
<td>25</td>
<td>2.5</td>
<td>2.5 % renal 75% unknown</td>
</tr>
<tr>
<td>Clortalidon</td>
<td>1</td>
<td>47</td>
<td>65% renal 10% bile 25% unknown</td>
</tr>
<tr>
<td>Indapamid</td>
<td>20</td>
<td>14</td>
<td>metabolism</td>
</tr>
</tbody>
</table>
Adverse Effects

- Hypo K+ $\Rightarrow$ Increased risk of digitalis toxicity
- Hypo Na+, Hypo Mg++
- Hyper uricemia $\Rightarrow$ caution in gout arthritis
- Hyperglycemia and hypercholesterolemia $\Rightarrow$ not favorable for DM and dyslipidemia (although not contraindicated)
- (Indapamid has less effects on lipid and uric acid)
- Hypercalcemia (long-term) $\Rightarrow$ good for elderly
- Sexual dysfunction
Interactions

- Increases the risk of arrhythmia when combined w/ digitalis, quinidine and other anti arrhythmias
- Reduces efficacy of anticoagulant and uricosuric
- NSAID reduce the efficacy of thiazide
- Reduces the efficacy oral antidiabetics
Indications of Thiazides

• Hypertension (single drug or in combination)
• Chronic, mild- heart failure
• Edema (loop diuretic is preferable)
• Diabetes insipidus (mainly nephrogenic)
• Prevention of Ca^{++} excretion in osteoporosis and calcium nephrolithiasis
Loop Diuretics

• Furosemide, torasemide, bumetanide, ethacrynic acid
• Site of action: thick ascending limb of Ansa Henle
• Mechanism:
  – Loop diuretics should be excreted into the lumen
  – Inhibits Na\(^+\), K\(^+\), 2Cl\(^-\) symporter → significantly increases the excretion of Na\(^+\), K\(^+\), Cl\(^-\)
  – Osmotic gradient for water reabsorption is also decreased → increasing water excretion
  – Ca\(^{2+}\) and Mg\(^{2+}\) are excreted as well.
Mechanism of Action of Loop Diuretic
Interactions

• Concomitant use w/ aminoglycoside or cisplatin increases the risk of nephrotoxicity and ototoxicity
• NSAID reduces the effects of diuretics
• Probenecid reduces the effects of diuretics by inhibiting its secretion into the lumen.
• Increases the risk of arrhythmia when combined w/ digitalis, quinidine and other anti arrhythmias
Indications

- Congestive heart failure (first line drug)
- Acute pulmonary edema
- Edema due to renal failure, nephrotic syndrome, ascites
- Hypercalsemia
- Severe hypertension
- Force diuresis during drug/chemical intoxication (drug that excreted through the kidney in active form)
Potassium Sparing Diuretics

1. **Na\(^+\) channel inhibitor (Amiloride, triamterene)**
   - Inhibit Na\(^+\) reabsorption → Na\(^+\) excretion
   - Reduced K\(^+\) secretion → K\(^+\) retention

1. **Aldosterone antagonist (Spironolactone, eplerenone)**
   - Aldosterone induces the expression of Na/K-ATPase and Na\(^+\) channel
   - Spironolactone and eplerenone blocks aldosterone receptor → reduces Na\(^+\) reabsorption and K\(^+\) secretion
1. Na+ Channel Inhibitors
• Potassium sparing diuretic has a weak diuretic action
• Usually used in combination w/ other diuretic:
  – Potentiation of diuretic and anti hypertensive effects
  – Prevents hypokalemia
• Spironolactone is metabolized to its active metabolite, canrenone.
• Longterm use of spironolactone can prevent myocardial hypertrophy and myocardial fibrosis
Adverse Effects

• Hyperkalemia
• Anti androgenic effect (gynecomastia, decrease of libido, impotency, menstrual disturbance): spironolakton
• Megaloblastic anemia : Triamteren (folate antagonist)
INDICATIONS

• Antihypertension:
  – In combination w/ other anti hypertensives
  – To increase the effect and to prevent hypokalemia

CONTRAINDICATIONS/PRECAUTIONS

• Conditions that prone to hyperkalemia:
  – Renal failure
  – Under treatment w/ ACE-inhibition, ARB, NSAID, K⁺ supplementation
Antidiuretic Hormone

- Vasopresin
- Arginin vasopresin (AVP)
- Desmopresin (DDAVP, 1-deamino-8D-arginine vasopresin) (synthetic)
- Secreted by posterior hypophysis
- Secretion increase in response to:
  - ↑ Plasma osmolarity (dehydration)
    - Hypovolemia, hypotension (bleeding, dehydration)
- Regulation
  - Osmoreceptor in the CNS (threshold of secretion 280 mOsm)
  - Volume receptor in left atrium and aortic arc
Mechanism of Action

• Works in ascending limb of Henle’s loop and collecting ducts

• 2 kind of receptors:
  – V1: vascular smooth muscle → vasoconstriction
  – V2: kidney → increase water permeability of tubular epithelium → water reabsorption
Indications

• Neurogenic Diabetes Insipidus (central type) (not for nephrogenic DI)
• DI due to head trauma or brain surgery
• Gastrintestinal bleeding due to portal hypertension (by reducing mesenteric blood flow)
• Von Willebrand disease (DDAVP stimulate secretion of vWF in endothelial cells)
Adverse Effects

• Hypertension
• Abdominal colic due to increased peristalsis
• Coronary vasoconstriction → angina pectoris

Preparation:
  – Pitressin for injection
  – Vasopresin tanat for IM injection
  – Intranasal powder
  – Lipresin (lisine-vasopresin) nasal spray
  – Desmopresin acetate (DDAVP): nasal drop
Kinetics

- Not to be administered orally (rapid degradation by trypsin)
- Administration: im, iv, sc, intranasal
- Half-life of ADH: 17-35 minutes
- Desmopresin (DDAVP): long half-life → effective until 48-96 h after intranasal administration.
Next section: Antihypertension