Pharmacology and Clinical Use of Diuretics

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Katie Herndon is not speaking on behalf of Pfizer, but solely as a medical professional with an expertise in pharmacotherapy.

Objectives

- Review the mechanism of action, pharmacokinetics, and pharmacodynamics of diuretics
- Contrast the pharmacology of different classes of diuretic agents
- Discuss the clinical use of diuretics

Diuretic Classes

- Thiazide Diuretics
  - Hydrochlorothiazide
  - Chlorothiazide
  - Methyclothiazide
- Thiazide-Like Diuretics
  - Chlorthalidone
  - Indapamide
  - Metolazone
- Loop Diuretics
  - Bumetanide
  - Furosemide
  - Ethacrynic acid
  - Torsemide
- Potassium-Sparing Diuretics
  - Amiloride
  - Triamterene
- Aldosterone Antagonists
  - Spironolactone
  - Eplerenone
- Carbonic Anhydrase Inhibitors
  - Acetazolamide

Sodium Reabsorption in the Renal Tubule
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• Na⁺ is reabsorbed by a two-step process:
  1. Na⁺ entrance into the cell via a Na⁺ transporter present in the luminal cell membrane
  2. Once Na⁺ enters the tubular cell, it is transferred across the basolateral membrane into the interstitium and blood by the Na⁺-K⁺-ATPase pump

• Cell interior is electrically negative in relation to the extracellular fluid

Principles of Diuretic Action

• Diuretics act by inhibiting sodium reabsorption in the renal tubules, thereby increasing urinary sodium, and consequently, water loss
• Agents differ with respect to the specific tubular ion transport systems they inhibit
  – Site of action within the nephron
  – Natriuretic efficacy
  – Pharmacological effects
  – Clinical indications

Sites of Diuretic Action in the Nephron

• Under physiological conditions of Na⁺ intake, FENa remains under 1%
• After formation of a plasma ultrafiltrate in the glomerulus, the tubular fluid enters the proximal convoluted tubule
• 65-70% of filtered Na⁺ is reabsorbed in the proximal tubule

Sodium Reabsorption in the Renal Tubule

• The electrochemical gradient is the force driving positively charged Na⁺ ions across the luminal membrane into the cell
• Na⁺ movement is facilitated by transporters on the luminal side of the tubular epithelial cell
• Transporter pathways differ between various segments of the nephron

Principles of Diuretic Action

• Site of action is located on the luminal surface of the tubule
• Extensively bound to serum albumin
• Transported into the proximal tubule lumen by active secretion
  – Organic acid secretory pathway: thiazides, loop diuretics, acetazolamide
  – Organic base secretory pathway: potassium-sparing diuretics
  – Exception: spironolactone and eplerenone enter renal tubules from plasma

Sites of Diuretic Action in the Nephron

• The net effect of carbonic anhydrase inhibitors is increased Na⁺, HCO₃⁻, K⁺, and water loss
• Diuresis is modest because Na⁺ remaining in the lumen is absorbed at distal segments
• Alkaline diuresis leading to metabolic acidosis
Sites of Diuretic Action in the Nephron

- Loop diuretics act at the thick ascending limb of the loop of Henle where ~25% of filtered Na+ is reabsorbed
- Loop diuretics bind to the Na+-K+-2Cl- co-transport protein, impairing the reabsorption of Na+, K+, and Cl-

Diuretic Tolerance

- Use of diuretics elicits both short and long-term adaptations intended to protect intravascular volume
- Short-term tolerance: Decreased response to the after the first dose of diuretic has been administered
  - Nephron is primed to avidly reabsorb sodium after drug levels decline below the diuretic threshold
  - Triggered by intravascular volume depletion
  - Renin-angiotensin system and sympathetic nervous system thought to contribute
  - Post-dose sodium retention significantly influenced by dietary sodium intake

Sites of Diuretic Action in the Nephron

- Thiazides act mainly at the distal convoluted tubule where ~5-10% of the filtered Na+ load is reabsorbed
- Thiazides inhibit Na+ and Cl- reabsorption by inhibiting the electroneutral Na+-Cl- symport

Loop Diuretics

- Most potent diuretic class with maximally effective doses causing excretion of 20-25% of filtered Na+
- Primary role is edematous disorders (heart failure, cirrhosis, nephrotic syndrome), blood pressure and volume control in chronic kidney disease
- No evidence of a significant difference in potency if administered in equipotent doses
- Not recommended for treatment of uncomplicated hypertension due to short duration of action
- In normal patients, 40 mg IV furosemide (or equivalent dose of other loop) elicits a maximal response: 200 to 250 mEq of sodium in 3 to 4 L of urine over 3 to 4 hours

K+-sparing diuretics (amiloride and triamterene) act primarily at the cortical part of the collecting duct where only ~2% of Na+ is reabsorbed
- Na+ movement creates an electrical gradient that drives K+ from the epithelial cell to the lumen
- K+-sparing diuretics inhibit the epithelial Na+ channel of the collecting duct

Long-term tolerance: Gradual return of sodium-chloride balance to an electroneutral level
- Loop diuretics cause sodium to flood more distal nephron sites
- Over time, increased exposure to sodium causes hypertrophy of distal nephron segments with concomitant increases in the reabsorption of sodium
- Persistent volume removal appears to trigger long-term activation of the renin-angiotension-aldosterone system
- Up-regulation of sodium transporters downstream from the primary site of diuretic action
Loop Diuretics

- Amount of loop diuretic absorbed is normal in patients with edema, although absorption is slower than normal
- Variability of absorption is likely more important than absolute bioavailability
- 40 mg IV furosemide = 20 mg torsemide = 1 mg bumetanide

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability</th>
<th>$t_{1/2}$</th>
<th>Route of Elimination</th>
<th>N/PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>55% (Highly variable)</td>
<td>1.5-2 hr</td>
<td>Renal</td>
<td>1:2</td>
</tr>
<tr>
<td>Torsemide</td>
<td>80-100%</td>
<td>1 hr</td>
<td>Liver</td>
<td>1:1</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>80-100%</td>
<td>3-4 hr</td>
<td>Liver</td>
<td>1:1</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td>---100%</td>
<td>1 hr</td>
<td>Liver</td>
<td>1:1</td>
</tr>
</tbody>
</table>

Pharmacodynamics of a Loop Diuretic

Conditions of Diminished Response to Loop Diuretics: Renal Insufficiency

- Loop diuretics are diuretics of choice
- Pharmacodynamics are not altered; residual nephrons retain their responsiveness to the diuretic
- FeNa is similar to healthy subjects, but absolute Na+ excretion is lower due to the decrease in the filtered Na+ load

Conditions of Diminished Response to Loop Diuretics: Heart Failure

- Access of diuretics to site of action is normal
- Slower po absorption. Use IV for immediate response
- Patients with NYHA Class II and III HF have 1/4 to 1/3 the natriuretic response to maximally effective doses of loop diuretics
- Diuretic resistance results from an interaction between the pathophysiology of Na+ retention in HF and the renal response to diuretic therapy

- Strategies:
  - Larger doses should be administered to attain effective drug amounts at the site of action
  - Administer effective doses several times per day
  - Add an oral thiazide diuretic
  - Continuous intravenous infusion of diuretic
Conditions of Diminished Response to Loop Diuretics

- **Nephrotic Syndrome**
  - Mechanism of diminished response to diuretics is unknown
  - Hypoalbuminemia and albuminuria may have a PK effect
  - Strategies:
    - 2-3 times higher dose to attain normal amounts of unbound diuretic in urine
    - Administer effective doses several times per day
    - Add an oral thiazide diuretic

- **Cirrhosis**
  - Mainstay of diuretic therapy is spironolactone
  - Mechanism of diminished response to loop diuretics is unknown
  - Add a thiazide or loop to spironolactone if needed

Thiazide Diuretics

- Mainstay in the treatment of hypertension
  - Most have half-lives permitting once-daily dosing
  - Reductions in systolic and diastolic blood pressures of 10 to 15 mm Hg and 5 to 10 mm Hg, respectively
  - Combined effectively with most antihypertensive classes, often producing an additive decrease in blood pressure
  - Multiple studies demonstrating reductions in cardiovascular morbidity and mortality
  - Generally considered ineffective with CrCl <30 ml/min (exception is metolazone)
  - Shallow dose-response curve
  - Lower doses typically prescribed today (12.5 to 25 mg of HCTZ)

Hemodynamic Effects of Thiazide Diuretics

- Long-term blood pressure lowering due to a reduction in systemic vascular resistance (exact mechanism unclear)

Adverse Effects of Diuretics

- Hypotension and Orthostasis
- Volume Depletion
- Electrolyte Disorders
  - Hypokalemia
  - Hypomagnesemia
  - Hyponatremia
  - Hyperkalemia (loop diuretics)
  - Hypercalcemia (thiazides)
- Hyperuricemia
- Hyperglycemia, glucose intolerance
- Dyslipidemia
- Photosensitivity and skin reactions
- Ototoxicity
- Interstitial nephritis

Thiazide Diuretics

| Table 1. Pharmacokinetic characteristics of the thiazide diuretics approved for use in the United States.  
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td><strong>Relative Volume of Distribution</strong></td>
<td><strong>Maximal Plasma Level</strong></td>
<td><strong>Mean Blood Pressure</strong></td>
<td><strong>Steady-State Half-Life</strong></td>
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<td>-----------------</td>
</tr>
<tr>
<td>HCTZ</td>
<td>0.15-0.25</td>
<td>0.75</td>
<td>10-15</td>
<td>24-36</td>
</tr>
<tr>
<td>Metolazone</td>
<td>0.6</td>
<td>2.5</td>
<td>10-15</td>
<td>24-36</td>
</tr>
<tr>
<td>Indapamide</td>
<td>0.3</td>
<td>1.0-1.5</td>
<td>10-15</td>
<td>24-36</td>
</tr>
<tr>
<td>Aldactone</td>
<td>0.25</td>
<td>0.75</td>
<td>10-15</td>
<td>24-36</td>
</tr>
<tr>
<td>Thiazides</td>
<td>0.65</td>
<td>3-11</td>
<td>10-15</td>
<td>24-36</td>
</tr>
<tr>
<td>Metolazone</td>
<td>0.35</td>
<td>1.0-1.5</td>
<td>10-15</td>
<td>24-36</td>
</tr>
</tbody>
</table>

- All the diuretics listed are approved for use in the United States. The term "thiazide-like drugs" is used to group thiazides on the basis of their having a similar mode of action in the kidney. The thiazide-like drugs include the thiazides and the thiazide-like diuretics.
- The half-lives of these drugs are similar, but they may be more effective in reducing blood pressure.
- The diuretics listed above are generally effective in reducing blood pressure.
- They are useful in the treatment of hypertension and in the management of edema in patients with heart failure.

Treatment and Prevention of Diuretic-Induced Hypokalemia

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<table>
<thead>
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<tbody>
<tr>
<td><strong>Use low doses of the diuretic</strong></td>
<td><strong>Moderate Na⁺ restriction (70-100 mEq/24 h)</strong></td>
</tr>
<tr>
<td><strong>Correct magnesium deficit if present</strong></td>
<td><strong>Oral K⁺ supplements (20-40 mEq/24 h)</strong></td>
</tr>
<tr>
<td><strong>Combined therapy with an angiotensin-converting enzyme inhibitor, an angiotensin II-receptor antagonist, or a direct renin inhibitor</strong></td>
<td><strong>Combined therapy with a K⁺-sparking diuretic</strong></td>
</tr>
</tbody>
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