Pharmacology of Drugs Acting on Renal System

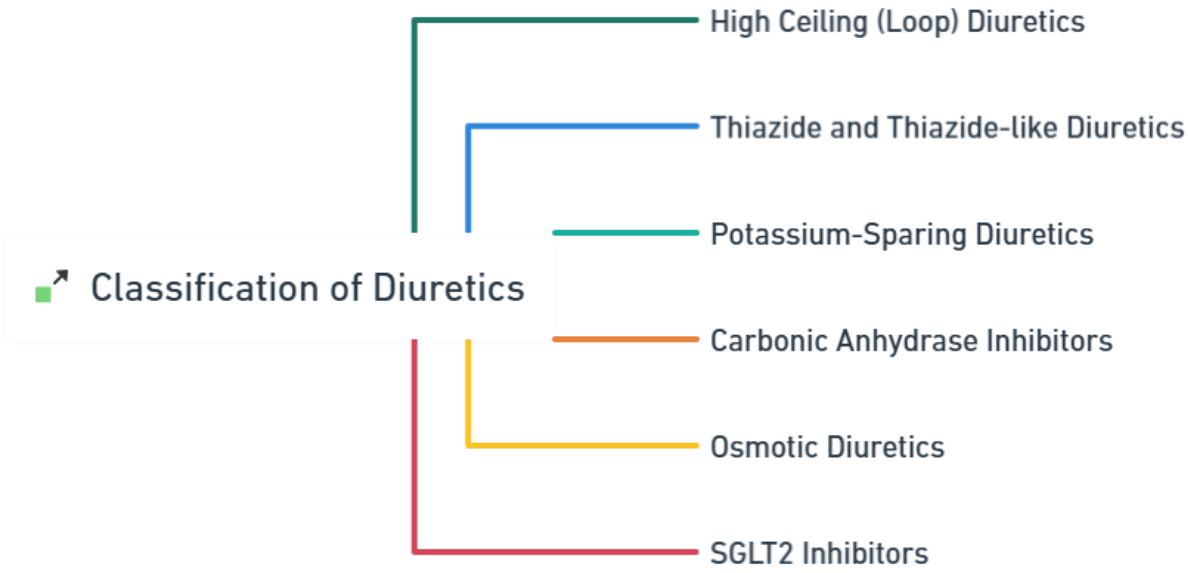
Diuretics

Introduction

- Diuretics are a class of drugs that increase the excretion of water and electrolytes (mainly sodium and chloride) by the kidneys.
- They act by interfering with the reabsorption of sodium at different segments of the nephron, leading to increased urine output (diuresis).
- They are primarily used to manage conditions such as hypertension, edema, heart failure, renal disorders, and cirrhosis.

Classification Of Diuretics

Diuretics are classified based on their site and mechanism of action in the nephron:



A. High Ceiling (Loop) Diuretics

- **Examples**: Furosemide, Bumetanide, Torsemide, Ethacrynic acid
- **Site of Action**: Thick ascending limb of the loop of Henle

B. Thiazide and Thiazide-like Diuretics

- **Examples**: Hydrochlorothiazide, Chlorthalidone, Indapamide, Metolazone
- **Site of Action**: Distal convoluted tubule

C. Potassium-Sparing Diuretics

- **Subtypes**:
  - **Aldosterone antagonists**: Spironolactone, Eplerenone
  - **Epithelial Na+ channel inhibitors**: Amiloride, Triamterene
- **Site of Action**: Collecting ducts

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D. Carbonic Anhydrase Inhibitors

- **Examples**: Acetazolamide, Methazolamide
- **Site of Action**: Proximal convoluted tubule

E. Osmotic Diuretics

- **Examples**: Mannitol, Urea, Glycerol
- **Site of Action**: Entire nephron, primarily proximal tubule and loop of Henle

F. SGLT2 Inhibitors (Glucose-induced osmotic diuresis)

- **Examples**: Canagliflozin, Dapagliflozin, Empagliflozin
- **Site of Action**: Proximal tubule

Mechanism Of Action

Each class of diuretics has a unique mechanism:

A. Loop Diuretics

- Inhibit the $Na^+/K^+/2Cl^-$ cotransporter in the thick ascending limb of the loop of Henle.
- This leads to:
  - Decreased reabsorption of Na^+, K^+, and Cl^-
  - Increased excretion of Ca^{2+} and Mg^{2+}
  - Reduced medullary hypertonicity → reduced water reabsorption

B. Thiazide Diuretics

- Inhibit Na^+/Cl^- symporter in the distal convoluted tubule.
- Promotes excretion of Na^+ and Cl^-, but increases Ca^{2+} reabsorption (opposite of loop diuretics).

C. Potassium-Sparing Diuretics

- Aldosterone antagonists block aldosterone receptors, preventing the synthesis of Na^+ channels and Na^+/K^+ ATPase → Na^+ excretion and K^+ retention.
- ENaC inhibitors (e.g., amiloride) directly inhibit epithelial sodium channels in the collecting duct.

D. Carbonic Anhydrase Inhibitors

- Inhibit carbonic anhydrase in the proximal tubule.
- Decreased reabsorption of bicarbonate → increased urinary loss of HCO_3^-, Na^+, and water.

E. Osmotic Diuretics

- Increase the osmolarity of the tubular fluid → draw water into the tubule lumen.

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- Work passively by osmosis, without inhibiting any transporter.

F. SGLT2 Inhibitors

- Inhibit sodium-glucose co-transport in the proximal tubule → glucosuria-induced osmotic diuresis.

Pharmacokinetics

Varies by class and individual drug:

A. Loop Diuretics:

- **Absorption**: Well absorbed orally; IV forms available (e.g., furosemide)
- **Onset**: Fast (30–60 min oral, 5 min IV)
- **Duration**: Short (6–8 hrs)
- **Excretion**: Renal

B. Thiazides:

- **Absorption**: Good oral bioavailability
- **Onset**: 2–4 hrs
- **Duration**: 12–24 hrs
- **Excretion**: Renal

C. Potassium-Sparing Diuretics:

- **Spironolactone**: Prodrug, metabolized in liver; delayed onset (up to 72 hrs)
- **Amiloride/Triamterene**: Rapid onset; renal excretion

D. Carbonic Anhydrase Inhibitors:

- **Absorption**: Oral or IV
- **Onset**: 30 min (oral)
- **Duration**: 8–12 hrs
- **Excretion**: Renal

E. Osmotic Diuretics:

- **Route**: IV only (oral causes diarrhea)
- **Onset**: Rapid
- **Excretion**: Filtered at glomerulus, not reabsorbed

Pharmacodynamics

- **Dose-dependent natriuresis**: More drug → more Na^+ loss
- Loop diuretics have the most potent diuretic effect (high-ceiling), others have moderate (thiazides) or mild effects (K^+-sparing).

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- All lead to reduction in plasma volume, blood pressure, and extracellular fluid volume.

Adverse Effects

Loop Diuretics:

- Hypokalemia
- Hyponatremia
- Hypomagnesemia
- Ototoxicity (dose-dependent)
- Dehydration, hypotension
- Hyperuricemia (→ gout)

Thiazides:

- Hypokalemia, hyponatremia
- Hypercalcemia
- Hyperuricemia
- Hyperglycemia
- Hyperlipidemia

Potassium-Sparing Diuretics:

- Hyperkalemia
- Spironolactone: Gynecomastia, menstrual irregularities

Carbonic Anhydrase Inhibitors:

- Metabolic acidosis
- Hypokalemia
- Renal stones
- Drowsiness, paresthesia

Osmotic Diuretics:

- Transient volume expansion → pulmonary edema, heart failure
- Electrolyte imbalance

Contraindications

Loop and Thiazides:

- Anuria
- Severe electrolyte imbalance
- Hypotension or dehydration

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Potassium-Sparing:

- Hyperkalemia
- Renal failure

Carbonic Anhydrase Inhibitors:

- Hepatic cirrhosis (risk of hyperammonemia)
- Sulfa allergy

Osmotic Diuretics:

- Active cranial bleeding
- Severe dehydration
- Anuria

Therapeutic Uses

Loop Diuretics:

- Acute pulmonary edema
- Congestive heart failure (CHF)
- Hypertension (if thiazides not effective)
- Hypercalcemia
- Renal failure

Thiazides:

- Hypertension (first-line)
- CHF (mild edema)
- Nephrolithiasis (↓ Ca^{2+} excretion)
- Nephrogenic diabetes insipidus

Potassium-Sparing:

- Used with other diuretics to prevent hypokalemia
- Hyperaldosteronism (primary or secondary)
- CHF (spironolactone improves survival)

Carbonic Anhydrase Inhibitors:

- Glaucoma
- Altitude sickness
- Epilepsy
- Alkalosis

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