

## Diuretics

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### I. Overview

#### 1. Definition:

Diuretic agents are drugs that increase renal excretion of water and solutes (mainly sodium salt).

#### 2. Purpose of diuretic therapy:

Major purposes of diuretic therapy are to decrease fluid volume of the body, and to adjust the water and electrolyte balance.

Diuretics are often used in the management of pathological conditions such as edema (e.g. in congestive heart failure and certain renal diseases) and hypertension.

#### 3. Commonly seen side effects:

The most common side effect associated with most diuretics is the distortion of water and electrolyte balance (such as hypokalemia, hyperkalemia, metabolic alkalosis, acidosis, and hyponatremia). Specific side effects of each diuretic are mainly determined by its mechanism of action and conditions of the patient.

#### 4. Mechanisms of action:

Most diuretics exert their effects by inhibiting tubular sodium and water reabsorption by epithelial cells lining the renal tubule system. Certain diuretics (such as carbonic anhydrase inhibitors, loop diuretics, thiazide-like diuretics and potassium-sparing diuretics) suppress sodium and water reabsorption by inhibiting the function of specific proteins that are responsible for (or participate in) the transportation of electrolytes across the epithelial membrane; osmotic diuretics inhibit water and sodium reabsorption by increasing intratubular osmotic pressure. Different types of diuretics may inhibit different transporters in different segments of the tubular system.

#### 5. Different types of diuretics

| Type                                   | Example                   | Site of action                         | Mechanism   |
|--|---------------------------|--|---|
| Carbonic anhydrase (CA) inhibitors     | acetazolamide             | Proximal tubule                        | inhibition of CA  |
| Osmotic                                | Mannitol                  | Loop of Henle (DTL)<br>Proximal tubule | Osmotic action  |
| Loop diuretics                         | furosemide                | Loop of Henle (TAL)                    | inhibition of Na <sup>+</sup> -K <sup>+</sup> -2Cl <sup>-</sup> symport |
| Thiazides                              | hydrochlorothiazide       | Distal convoluted tubule               | inhibition of Na <sup>+</sup> -Cl <sup>-</sup> symport                  |
| Potassium-sparing diuretics            |                           |  |   |
| (1) Na <sup>+</sup> channel inhibitors | triamterene,<br>amiloride | Cortical collecting tubule             | inhibition of Na <sup>+</sup> channel                                   |
| (2) aldosterone spironolactone         |                           | Cortical collecting tubule             | inhibition of   |

## II. Renal tubule transport mechanisms

### 1. Basic mechanisms for transmembrane transport of solutes

#### A Active transport

a. Primary active transport:  $\text{Na}^+\text{-K}^+$  ATPase (sodium pump) in the basolateral membrane of epithelial cells is the major driving force for the transport of solutes in kidney.

b. Secondary active transport: Secondary active transport utilizes energy available from the transmembrane  $\text{Na}^+$  gradient established by sodium pump to transport other solutes against their electrochemical gradient. Secondary active transport includes symport (co-transport) which transports sodium and other solutes in the same direction, and antiport (counter-transport) which exchanges movement of sodium for the counter movement of other solutes.

#### B Passive transport

- a. Convection.
- b. Simple diffusion.
- c. Channel-mediated diffusion.
- d. Carrier-mediated diffusion.

### 2. Characteristics of different segments of the renal tubule.

#### A Proximal tubule

Proximal tubule reabsorbs 40% of filtered salt and 60% filtered water.

Proximal tubule is the major site for sodium carbonate reabsorption (85%), which requires sodium-proton exchanger (antiport) and carbonic anhydrase. Inhibitors of carbonic anhydrase exert diuretic effects by inhibition of sodium carbonate transport.

The proximal tubule is the major site for the secretion of the organic acid and bases to the tubular lumen. This is the mechanism by which most diuretics reach their sites of action.

#### B Loop of Henle

Descending thin limb (DTL) of loop of Henle is highly permeable to water but non-permeable to sodium. Water is extracted from DTL by osmotic pressure from the hypertonic medullary interstitium.

Thick ascending limb (TAL) of loop of Henle actively reabsorbs  $\text{NaCl}$  and  $\text{KCl}$  via the  $\text{Na}^+\text{-K}^+\text{-2Cl}^-$  symport (35% of salt absorption). TAL is not permeable to water and thus is a urine-diluting segment. Active sodium reabsorption at TAL contributes to the hypertonicity in medullary interstitium.

Loop diuretics inhibit the  $\text{Na}^+\text{-K}^+\text{-2Cl}^-$  symport.

$\text{Na}^+\text{-K}^+\text{-2Cl}^-$  symport and sodium pump together generate a positive lumen potential that drives the reabsorption of  $\text{Ca}^{++}$  and  $\text{Mg}^{++}$ .

#### C Distal convoluted tubule

Distal convoluted tubule absorbs about 10% of NaCl via  $\text{Na}^+\text{-Cl}^-$  symport, which is a different protein from the  $\text{Na}^+\text{-K}^+\text{-2Cl}^-$  symport.

Thiazides inhibit  $\text{Na}^+\text{-Cl}^-$  symport.

#### D. Collecting tubule

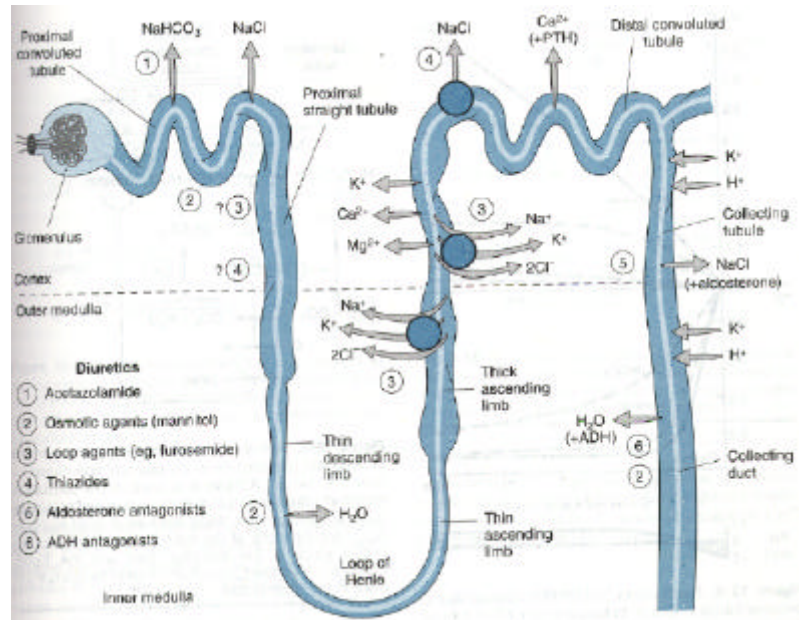
The collecting tubule is the final site for NaCl reabsorption (2-5% NaCl).

Sodium reabsorption in the collecting tubule is regulated by aldosterone. Aldosterone antagonists exert diuretic effect by inhibiting aldosterone receptor.

Sodium reabsorption in the collecting tubule is mediated by a sodium channel, which can be inhibited by amiloride and triamterene.

The collecting tubule is the major site for  $\text{K}^+$  secretion.  $\text{K}^+$  secretion is driven by a negative lumen potential established by  $\text{Na}^+$  reabsorption. Drugs that inhibit  $\text{Na}^+$  reabsorption in the collecting tubule thus also inhibit  $\text{K}^+$  secretion. These drugs are called  $\text{K}^+$ -sparing diuretics. Diuretics that act on upstream segments of the tubular system increase  $\text{Na}^+$  concentration in the tubular fluid, resulting in increased  $\text{Na}^+$  absorption in the collecting tubule. These diuretics may thus cause increased  $\text{K}^+$  secretion, and hypokalemia.

Water permeability in the collecting tubule is regulated by anti-diuretic hormone (ADH).



Tubule Transport system

### III. Pharmacology of diuretics

#### 1. Carbonic anhydrase (CA) inhibitors

##### A. Chemistry

Sulfonamide derivatives (See the table below).

Sulfonamide group ( $-\text{SO}_2\text{NH}_2$ ) is essential for activity.

## Inhibitors of Carbonic Anhydrase

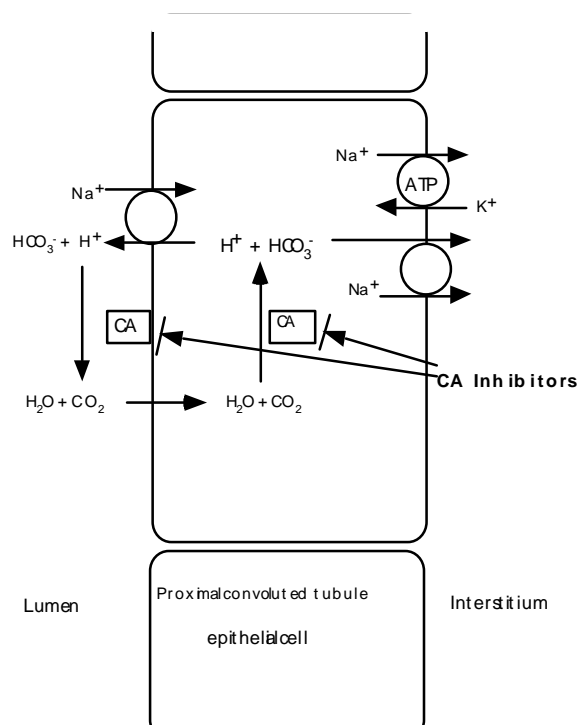
|                   | STRUCTURE | RELATIVE POTENCY | ORAL ABSORPTION | $t_{1/2}$ | ROUTE OF ELIMINATION |
|-------------------|-----------|------------------|-----------------|-----------|----------------------|
| Acetazolamide     |           | 1                | Nearly complete | 6-9 h     | R                    |
| Dichlorophenamide |           | 30               | ID              | ID        | ID                   |
| Methazolamide     |           | >1<br><10        | Nearly complete | ~14 h     | 25%R, 75%M           |

## B. Mechanism of action

This class of diuretics inhibits carbonic anhydrase in the membrane and cytoplasm of the epithelial cells. The primary site of action is in proximal tubules.

In the proximal tubule,  $\text{Na}^+$ - $\text{H}^+$  antiport in the apical membrane of epithelial cells transports  $\text{H}^+$  into tubular lumen in exchange for  $\text{Na}^+$  movement into the cytoplasm.  $\text{Na}^+$  in the cytoplasm is pumped out to the interstitium by sodium pump.  $\text{H}^+$  in the lumen reacts with  $\text{HCO}_3^-$  to form  $\text{H}_2\text{CO}_3$ .  $\text{H}_2\text{CO}_3$  is dehydrated to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . This reaction is catalyzed by carbonic anhydrase in the luminal membrane. Both  $\text{CO}_2$  and  $\text{H}_2\text{O}$  can permeate into cells, and rehydrate to form  $\text{H}_2\text{CO}_3$ . The rehydration is catalyzed by the cytoplasmic carbonic anhydrase.  $\text{H}_2\text{CO}_3$  dissociates to form  $\text{H}^+$  which is secreted into lumen, and  $\text{HCO}_3^-$  which is transported into interstitium. Inhibition of anhydrase thus inhibits  $\text{HCO}_3^-$  reabsorption. Accumulation of  $\text{HCO}_3^-$  in the tubular lumen subsequently inhibits  $\text{Na}^+$ - $\text{H}^+$  exchange and  $\text{Na}^+$  reabsorption.

The increase in sodium concentration in the tubular fluid may be compensated partially by increased  $\text{NaCl}$  reabsorption in later segments of the tubule. Thus, the diuretic effect of the carbonic anhydrase inhibitors is mild.



## C. Clinical indications

- (i) Glaucoma
- (ii) Treatment of cystinuria, and enhance excretion of uric acid and other organic acids.
- (iii) Metabolic alkalosis

(iv) Acute mountain sickness

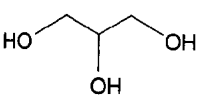
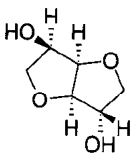
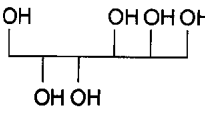
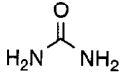
D. Major side effects and toxicity

- (i) Electrolyte imbalance: Hyperchloremic metabolic acidosis is the most common side effect.
- (ii) Renal stones
- (iii) Central nerve system effects: drowsiness and paresthesias.
- (iv) Allergic reactions to sulfonamides such as rash, fever, and interstitial nephritis.

## 2. Osmotic diuretics

### A. Chemistry

#### Osmotic Diuretics

|            | STRUCTURE   | ORAL ABSORPTION | $t_{1/2}$   | ROUTE OF ELIMINATION |
|------------|---|-----------------|-------------|----------------------|
| Glycerin   |  | Orally active   | 0.5–0.75 h  | M                    |
| Isosorbide |  | Orally active   | 5–9.5 h     | R                    |
| Mannitol   |  | Negligible      | 0.25–1.7 h* | R                    |
| Urea       |  | Negligible      | ID          | R                    |

R, renal excretion; M metabolism; ID, insufficient data.

**B. Mechanism of action**

Osmotic diuretics are substances to which the tubule epithelial cell membrane has limited permeability. When administered (often in a large dosage), osmotic diuretics significantly increase the osmolarity of plasma and tubular fluid. The osmotic force thus generated prevents water reabsorption, and also extracts water from the intracellular compartment, expands extracellular fluid volume and increases renal blood flow resulting in reduced medulla tonicity. The primary sites of action for osmotic diuretics are the Loop of Henle and the proximal tubule where the membrane is most permeable to water.

**C. Clinical indications**

- (i) To increase urine volume in some patients with acute renal failure caused by ischemia, nephrotoxins, hemoglobinuria and myoglobinuria (test for responsiveness).
- (ii) Reduction of intracranial pressure before and after neurosurgery and in neurological conditions.
- (iii) Reduction of intraocular pressure before ophthalmologic procedures and during acute attack of glaucoma.

**D. Major side effect and toxicity**

- (i) Water and electrolyte imbalance: excessive loss of more water relative to sodium may cause dehydration and hypernatremia.
- (ii) Expansion of extracellular fluid volume may result in hyponatremia causing central nerve system symptoms such as nausea, headache, and vomiting. In patients with congestive heart failure, expansion of extracellular volume may produce pulmonary edema.

**3. Loop diuretics****A. Chemistry**

Two major classes of loop diuretics: 1) sulfonamide derivatives such as furosemide, bumetanide and torsemide; and 2) non-sulfonamide loop diuretic such as ethacrynic acid.

**Inhibitors of Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> Symport (Loop Diuretics; High-Ceiling Diuretics)**

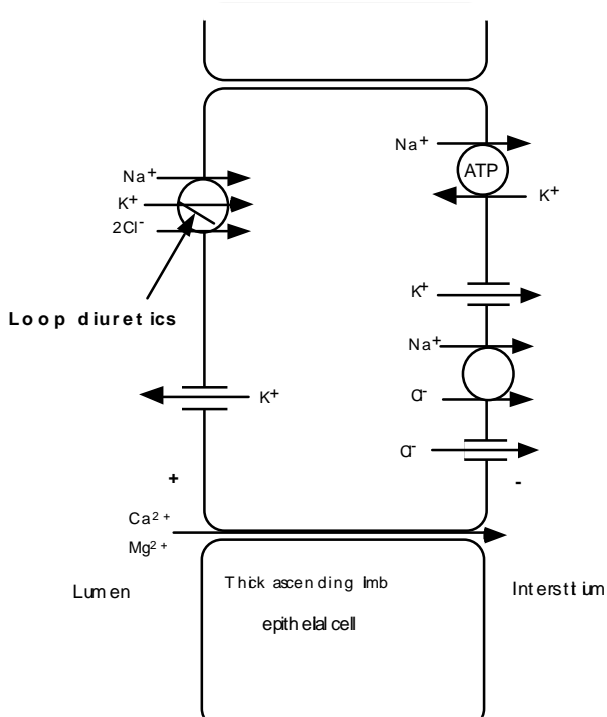
| DRUG            | STRUCTURE | RELATIVE POTENCY | ORAL ABSORPTION | t <sub>1/2</sub> |
|-----------------|-----------|------------------|-----------------|------------------|
| Furosemide      |           | 1                | 11-90%          | 0.3-3.4          |
| Bumetanide      |           | 40               | 59-89%          | 0.3-1.5          |
| Ethacrynic acid |           | 0.7              | Nearly complete | 0.5-1 h          |
| Torsemide       |           | 3                | 79-91%          | 0.8-6.0          |

**B. Mechanism of action**

Loop diuretics inhibit reabsorption of NaCl and KCl by inhibiting the Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> symport in the luminal membrane of the thick ascending limb (TAL) of loop of Henle. As TAL is responsible for the reabsorption of 35% of filtered sodium, and there are no significant downstream compensatory reabsorption mechanisms, loop diuretics are highly efficacious and are thus called high ceiling diuretics.

As the Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> symport and sodium pump together generate a positive lumen potential that drives the reabsorption of Ca<sup>++</sup> and Mg<sup>++</sup>, inhibitors of the Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> symport also inhibit reabsorption of Ca<sup>++</sup> and Mg<sup>++</sup>.

By unknown mechanisms (possibly prostaglandin-mediated), loop diuretics also have direct effects on vasculature including increase in renal blood flow, and increase in systemic venous capacitance.



(iii) Hyperuricemia

#### 4. Thiazides

##### A. Chemistry

Thiazides are also called benzothiadiazides. Thiazides are sulfonamide derivatives.

##### B. Mechanism of action

Thiazides inhibit a  $\text{Na}^+\text{-Cl}^-$  symport in the luminal membrane of the epithelial cells in the distal convoluted tubule. Thus, Thiazides inhibit  $\text{NaCl}$  reabsorption in the distal convoluted tubule, and may have a small effect on the  $\text{NaCl}$  reabsorption in the proximal tubule.

Thiazides enhance  $\text{Ca}^{++}$  reabsorption in the distal convoluted tubule by inhibiting  $\text{Na}^+$  entry and thus enhancing the activity of  $\text{Na}^+\text{-Ca}^{++}$  exchanger in the basolateral membrane of epithelial cells.

##### C. Major clinical indications

- (i) Hypertension.
- (ii) Edema associated with congestive heart failure, hepatic cirrhosis and renal diseases.
- (iii) Nephrolithiasis due to hypercalciuria
- (iv) Nephrogenic diabetes insipidus.

##### D. Major side effects and toxicity

- (i) Water and electrolyte imbalance is the major side effect.

##### C. Major Clinical indications

- (i) Acute pulmonary edema
- (ii) Chronic congestive heart failure when diminution of extracellular fluid volume is desirable to reduce venous and pulmonary edema.
- (iii) Treatment of hypertension when patients do not respond satisfactorily to thiazide diuretics and anti-hypertensive drugs.
- (iv) Hypercalcemia
- (v) Treatment of hyperkalemia in combination with isotonic  $\text{NaCl}$  administration.
- (vi) Used in acute renal failure to increase the urine flow and  $\text{K}^+$  secretion.
- (vii) Treatment of toxic ingestions of bromide, fluoride and iodide (with simultaneous saline administration).

##### D. Major side effects and toxicity

- (i) Hypokalemic metabolic alkalosis
- (ii) Ototoxicity
- (iv) Hypomagnesemia
- (v) Allergic reactions

Hypokalemic metabolic alkalosis, and hyperuricemia. Also may cause extracellular volume depletion, hypotension, hypochloremia, and hypomagnesemia. These effects are similar to that caused by loop diuretics.

Hypercalcemia.

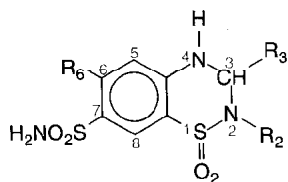
Hyponatremia is more common with thiazides than with loop diuretics.

(ii) Thiazides may impair glucose tolerance and hyperglycemia. Hyperglycemia can be reduced when  $K^+$  is administered together with thiazides, suggesting that hyperglycemia may be related to hypokalemia.

(iii) Thiazides may cause hyperlipidemia. Plasma LDL, cholesterol and triglycerides are increased.

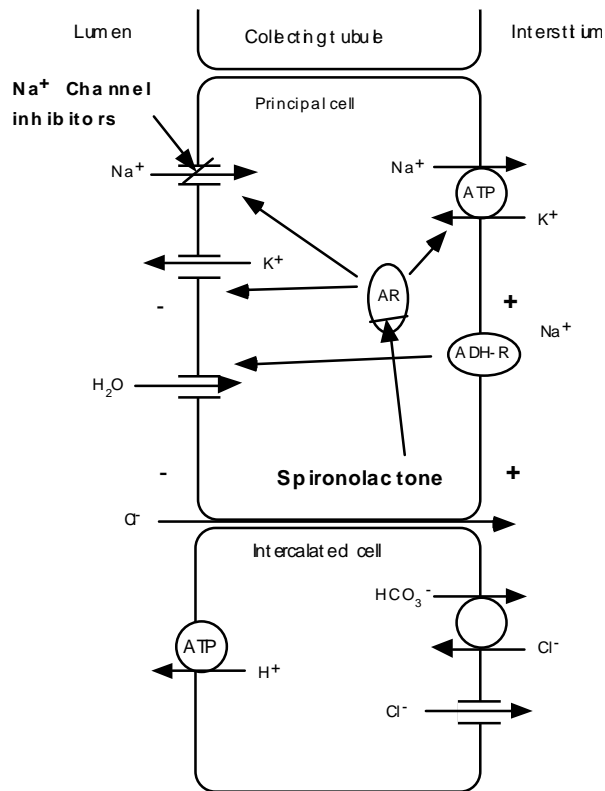
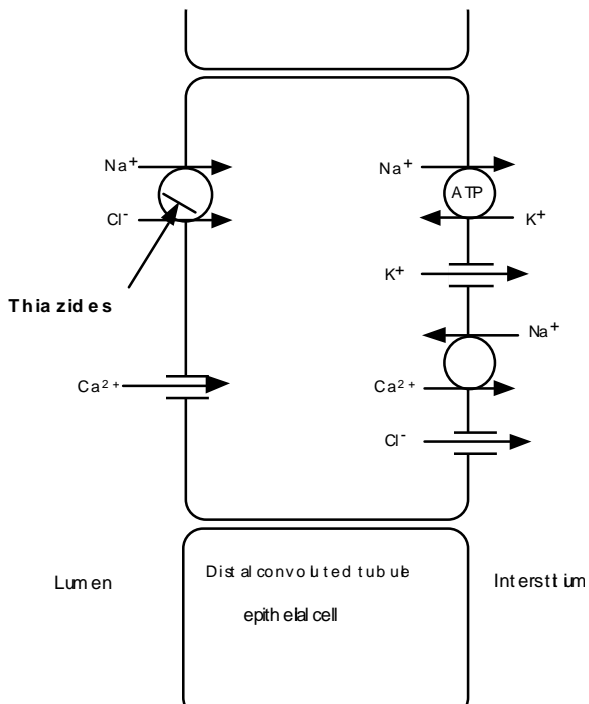
(iv) Allergic reactions to sulfonamides

(v) CNS symptoms and impotence can be seen but not common.

Inhibitors of Na<sup>+</sup>-Cl<sup>-</sup> Sympor

| Drug                | STRUCTURE   | RELATIVE POTENCY | ORAL ABSORPTION | <i>t</i> <sub>1/2</sub> | ROUTE OF ELIMINATION |
|---------------------|---|------------------|-----------------|-------------------------|----------------------|
| Bendroflumethiazide | $R_2 = H, R_3 = CH_2$ -, $R_6 = CF_3$                           | 10               | Nearly complete | 3–3.9 h                 | 30% R, 70% M         |
| Chlorothiazide      | $R_2 = H, R_3 = H, R_6 = Cl$<br>(Unsaturated between C3 and N4) | 0.1              | 10–21%          | 1.5 h                   | R                    |
| Hydrochlorothiazide | $R_2 = H, R_3 = H, R_6 = Cl$                                    | 1                | 65–75%          | 2.5 h                   | R                    |
| Chlothaldione       |   | 1                | 60–70%          | 44 h                    | 65% R, 10% B, 25% U  |
| Indapamide          |   | 20               | Nearly complete | 10–22 hr                | M                    |
| Metolazone          |   | 10               | ~65%            | 4–5 h                   | 80% R, 10% B, 10% M  |
| Quinethazone        |   | 1                | ID              | ID                      | ID                   |

R, renal excretion of intact drug; M, metabolism; B, excretion of intact drug into bile; U, unknown pathway of elimination;  
ID, insufficient data



**5. Potassium-sparing diuretics**

**(1) Na<sup>+</sup> channel inhibitors**

**A. Chemistry**

Amiloride and triamterene are the only two drugs in this class.

**Sodium Channel Inhibitors**

|             | STRUCTURE                                 | RELATIVE POTENCY | ORAL ABSORPTION | <i>t</i> <sub>1/2</sub> | ROUTE OF ELIMINATION |
|-------------|---|------------------|-----------------|-------------------------|----------------------|
| Amiloride   | <chem>NC(=O)Nc1nc(Cl)c(N)nc1=O</chem>     | 1                | 15–25%          | 21 h                    | R                    |
| Triamterene | <chem>Nc1nc2c(nc1N)nc(N)c2c3ccccc3</chem> | 0.1              | 30–70%          | 4.2 h                   | M                    |

Retention of intact drug; M, metabolism; however, triamterene is transformed into an active metabolite that is excreted in the urine.

**B. Mechanism of action**

Amiloride and triamterene inhibit the sodium channel in the luminal membrane of the collecting tubule and collecting duct. This sodium channel is critical for Na<sup>+</sup> entry into cells down

the electrochemical gradient created by sodium pump in the basolateral membrane, which pumps  $\text{Na}^+$  into interstitium. This selective transepithelial transport of  $\text{Na}^+$  establishes a luminal negative transepithelial potential which in turn drives secretion of  $\text{K}^+$  into the tubule fluid. The luminal negative potential also facilitates  $\text{H}^+$  secretion via the proton pump in the intercalated epithelial cells in collecting tubule and collecting duct. Inhibition of the sodium channel thus not only inhibits  $\text{Na}^+$  reabsorption but also inhibits secretion of  $\text{K}^+$  and  $\text{H}^+$ , resulting in conservation of  $\text{K}^+$  and  $\text{H}^+$ .

C. Major clinical indications

- (i)  $\text{Na}^+$  channel inhibitors are mainly used in combination with other classes of diuretics such as loop diuretics and thiazides in order to enhance  $\text{Na}^+$  excretion and to counteract  $\text{K}^+$  wasting induced by these diuretics.
- (ii) Pseudo-hyperaldosteronism (Liddle's syndrome).
- (iii) Amiloride is used to treat Lithium-induced nephrogenic diabetes insipidus by blocking  $\text{Li}^+$  transport into tubular epithelial cells.
- (iv) Amiloride also inhibits  $\text{Na}^+$  channel in airway epithelial cells, and is used to improve mucociliary clearance in patients with cystic fibrosis.

D. Major side effects and toxicity

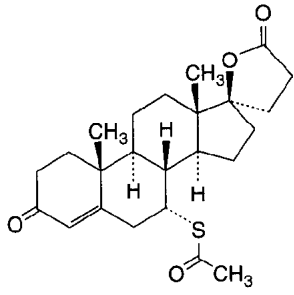
- (i) The major side effect is hyperkalemia.
- (ii) CNS symptoms such as nausea, vomiting, headache.
- (iii) Triamterene may reduce glucose tolerance.
- (iv) Triamterene may induce interstitial nephritis and renal stone.

**(2) Aldosterone antagonists**

A. Chemistry

Spironolactone is the only available aldosterone antagonist in US. A metabolite of spironolactone, canrenone, is also active and has a half-life of about 16 hours.

Aldosterone Antagonist, Spironolactone

| STRUCTURE   | ORAL ABSORPTION | $t_{1/2}$ | ROUTE OF ELIMINATION |
|---|-----------------|-----------|----------------------|
|  | 60–70%          | 1.6 h     | M                    |

B. Mechanism of action

Aldosterone, by binding to its receptor in the cytoplasm of epithelial cells in collecting tubule and duct, increases expression and function of  $\text{Na}^+$  channel and sodium pump, and thus enhances sodium reabsorption (see "  $\text{Na}^+$  channel inhibitors" above). Spironolactone competitively inhibits the binding of aldosterone to its receptor and abolishes its biological effects.

C. Major clinical indications

- (i) Used in combination with loop diuretics and thiazides in treatment of edema and hypertension. Spironolactone enhances  $\text{Na}^+$  excretion and reduces  $\text{K}^+$  wasting.
- (ii) Treatment of primary hyperaldosteronism (such as adrenal adenomas).
- (iii) Treatment of edema associated with secondary hyperaldosteronism (such as cardiac failure, hepatic cirrhosis and nephrotic syndrome). Spironolactone is the diuretic of choice in patients with hepatic cirrhosis.

D. Major side effects and toxicity

- (i) Hyperkalemia
- (ii) Metabolic acidosis in cirrhotic patients
- (iii) Due to its steroid structure, Spironolactone may cause gynecomastia, impotence, and hirsutism.
- (iv) CNS symptoms.