

# Diuretics

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# 18

## I. OVERVIEW

Diuretics are drugs that increase the volume of urine excreted. Most diuretic agents are inhibitors of renal ion transporters that decrease the reabsorption of  $\text{Na}^+$  at different sites in the nephron. As a result,  $\text{Na}^+$  and other ions, such as  $\text{Cl}^-$ , enter the urine in greater than normal amounts along with water, which is carried passively to maintain osmotic equilibrium. Diuretics, thus, increase the volume of urine and often change its pH, as well as the ionic composition of the urine and blood. The diuretic effect of the different classes of diuretics varies considerably, with the increase in  $\text{Na}^+$  secretion varying from less than 2% for the weak potassium-sparing diuretics to over 20% for the potent loop diuretics. In addition to the ion transport inhibitors, other types of diuretics include osmotic diuretics, aldosterone antagonists, and carbonic anhydrase inhibitors. Diuretics are most commonly used for management of abnormal fluid retention (edema) or treatment of hypertension. In this chapter, the diuretic drugs (Figure 18.1) are discussed according to the frequency of their use.

## II. NORMAL REGULATION OF FLUID AND ELECTROLYTES BY THE KIDNEYS

Approximately 16% to 20% of the blood plasma entering the kidneys is filtered from the glomerular capillaries into Bowman's capsule. The filtrate, although normally free of proteins and blood cells, contains most of the low molecular weight plasma components in concentrations similar to that in the plasma. These include glucose, sodium bicarbonate, amino acids, and other organic solutes, as well as electrolytes, such as  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$ . The kidney regulates the ionic composition and volume of urine by active reabsorption or secretion of ions and/or passive reabsorption of water at five functional zones along the nephron: 1) the proximal convoluted tubule, 2) the descending loop of Henle, 3) the ascending loop of Henle, 4) the distal convoluted tubule, and 5) the collecting tubule and duct (Figure 18.2).

### A. Proximal convoluted tubule

In the proximal convoluted tubule located in the cortex of the kidney, almost all the glucose, bicarbonate, amino acids, and other metabolites are reabsorbed. Approximately two-thirds of the  $\text{Na}^+$  is also

### THIAZIDE DIURETICS

*Chlorothiazide* DIURIL, SODIUM DIURIL

*Chlorthalidone* THALITONE

*Hydrochlorothiazide* (HCTZ) MICROZIDE

*Indapamide*

*Metolazone* ZAROXOLYN

### LOOP DIURETICS

*Bumetanide*

*Ethacrynic acid* EDECRIN

*Furosemide* LASIX

*Torsemide* DEMADEx

### POTASSIUM-SPARING DIURETICS

*Amiloride* MIDAMOR

*Eplerenone* INSPRA

*Spirolactone* ALDACTONE

*Triamterene* DYRENIUM

### CARBONIC ANHYDRASE INHIBITORS

*Acetazolamide* DIAMOX

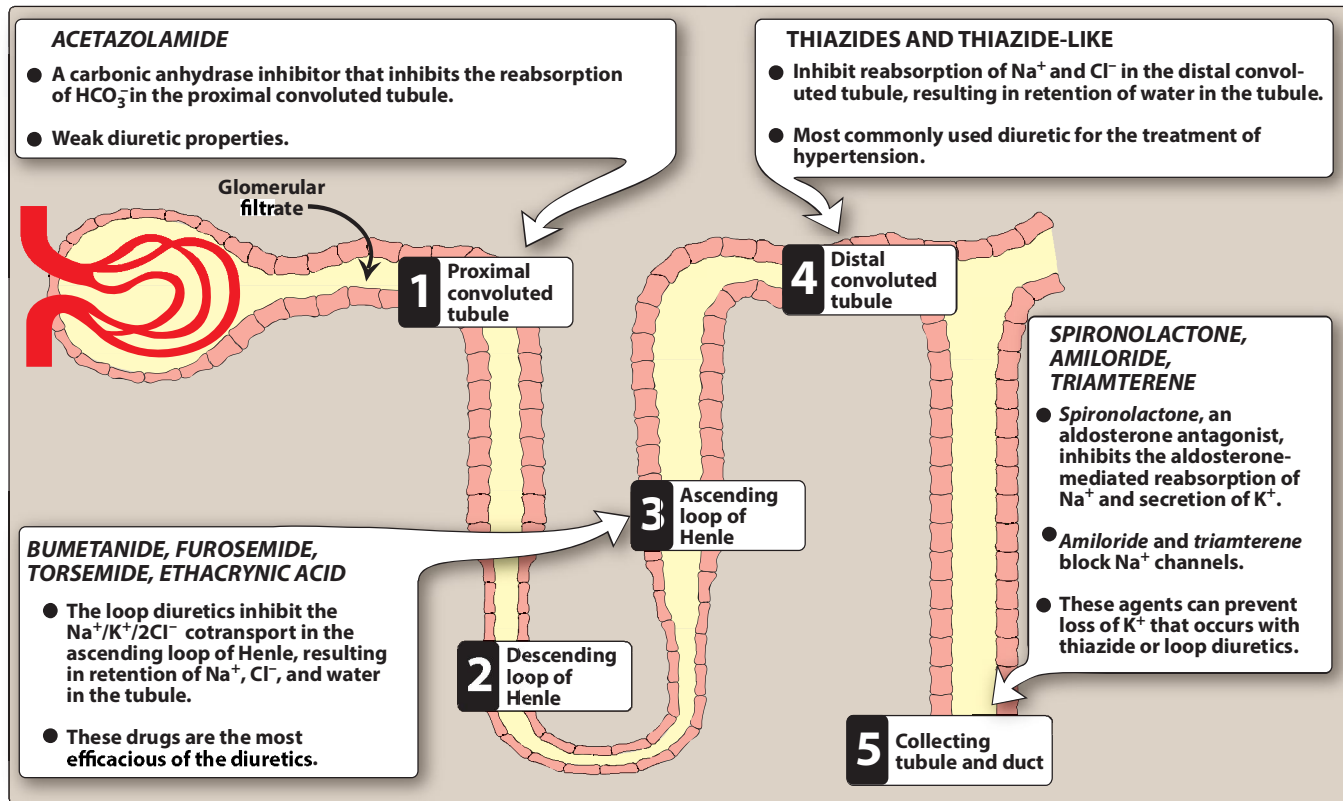
### OSMOTIC DIURETICS

*Mannitol* OSMITROL

*Urea*

**Figure 18.1**

Summary of diuretic drugs.



**Figure 18.2**

Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.

reabsorbed. Chloride enters the lumen of the tubule in exchange for an anion, such as oxalate, as well as paracellularly through the lumen. Water follows passively from the lumen to the blood to maintain osmolar equality. If not for the extensive reabsorption of solutes and water in the proximal tubule, the mammalian organism would rapidly become dehydrated and fail to maintain normal osmolarity. The  $\text{Na}^+$  that is reabsorbed is pumped into the interstitium by  $\text{Na}^+/\text{K}^+$ -adenosine triphosphatase (ATPase) pump, thereby maintaining normal levels of  $\text{Na}^+$  and  $\text{K}^+$  in the cell. Carbonic anhydrase in the luminal membrane and cytoplasm of the proximal tubular cells modulates the reabsorption of bicarbonate.

The proximal tubule is the site of the organic acid and base secretory systems (Figure 18.3). The organic acid secretory system, located in the middle-third of the proximal tubule, secretes a variety of organic acids, such as uric acid, some antibiotics, and diuretics, from the bloodstream into the proximal tubular lumen. Most diuretic drugs are delivered to the tubular fluid via this system. The organic acid secretory system is saturable, and diuretic drugs in the bloodstream compete for transfer with endogenous organic acids such as uric acid. A number of other interactions can also occur. For example, *probenecid* interferes with *penicillin* secretion. The organic base secretory system, located in the upper and middle segments of the proximal tubule, is responsible for the secretion of creatinine and choline.

### B. Descending loop of Henle

The remaining filtrate, which is isotonic, next enters the descending limb of the loop of Henle and passes into the medulla of the kidney. The osmolarity increases along the descending portion of the loop of Henle because of the countercurrent mechanism that is responsible for water reabsorption. This results in a tubular fluid with a threefold increase in salt concentration. Osmotic diuretics exert part of their action in this region.

### C. Ascending loop of Henle

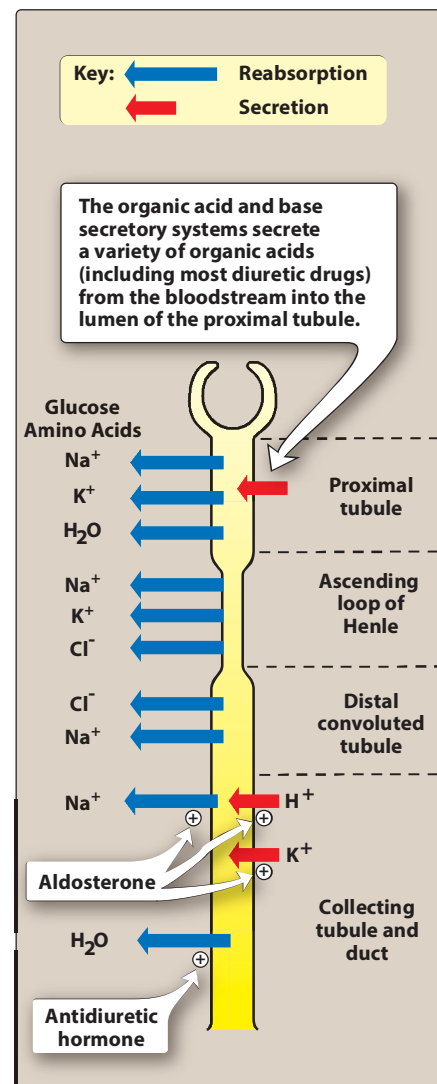
The cells of the ascending tubular epithelium are unique in being impermeable to water. Active reabsorption of  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$  is mediated by a  $\text{Na}^+/\text{K}^+/\text{2Cl}^-$  cotransporter. Both  $\text{Mg}^{2+}$  and  $\text{Ca}^{2+}$  enter the interstitial fluid via the paracellular pathway. The ascending loop is, thus, a diluting region of the nephron. Approximately 25% to 30% of the tubular sodium chloride returns to the interstitial fluid, thereby helping to maintain high osmolarity. Because the ascending loop of Henle is a major site for salt reabsorption, drugs affecting this site, such as loop diuretics (Figure 18.2), have the greatest diuretic effect.

### D. Distal convoluted tubule

The cells of the distal convoluted tubule are also impermeable to water. About 10% of the filtered sodium chloride is reabsorbed via a  $\text{Na}^+/\text{Cl}^-$  transporter that is sensitive to thiazide diuretics. Calcium reabsorption is mediated by passage through a channel and then transported by a  $\text{Na}^+/\text{Ca}^{2+}$ -exchanger into the interstitial fluid. The mechanism, thus, differs from that in the loop of Henle. Additionally,  $\text{Ca}^{2+}$  excretion is regulated by parathyroid hormone in this portion of the tubule.

### E. Collecting tubule and duct

The principal cells of the collecting tubule and duct are responsible for  $\text{Na}^+$ ,  $\text{K}^+$ , and water transport, whereas the intercalated cells affect  $\text{H}^+$  secretion. Sodium enters the principal cells through channels (epithelial sodium channels) that are inhibited by *amiloride* and *triamterene*. Once inside the cell,  $\text{Na}^+$  reabsorption relies on a  $\text{Na}^+/\text{K}^+$ -ATPase pump to be transported into the blood. Aldosterone receptors in the principal cells influence  $\text{Na}^+$  reabsorption and  $\text{K}^+$  secretion. Aldosterone increases the synthesis of  $\text{Na}^+$  channels and of the  $\text{Na}^+/\text{K}^+$ -ATPase pump, which when combined increase  $\text{Na}^+$  reabsorption. Antidiuretic hormone (ADH; vasopressin) receptors promote the reabsorption of water from the collecting tubules and ducts (Figure 18.3).



**Figure 18.3**

Sites of transport of solutes and water along the nephron.

## III. THIAZIDES AND RELATED AGENTS

The thiazides are the most widely used diuretics. They are sulfonamide derivatives. All thiazides affect the distal convoluted tubule, and all have equal maximum diuretic effects, differing only in potency. Thiazides are sometimes called “low ceiling diuretics,” because increasing the dose above normal therapeutic doses does not promote further diuretic response.

## A. Thiazides

*Chlorothiazide* [klor-oh-THYE-ah-zide] was the first orally active diuretic that was capable of affecting the severe edema often seen in hepatic cirrhosis and heart failure with minimal side effects. Its properties are representative of the thiazide group, although *hydrochlorothiazide* [hi-dro-klor-oh-THYE-ah-zide] and *chlorthalidone* are now used more commonly. *Hydrochlorothiazide* is more potent, so the required dose is considerably lower than that of *chlorothiazide*, but the efficacy is comparable to that of the parent drug. In all other aspects, *hydrochlorothiazide* resembles *chlorothiazide*. [Note: *Chlorthalidone*, *indapamide*, and *metolazone* are referred to as thiazide-like diuretics, because they contain the sulfonamide residue in their chemical structures, and their mechanism of action is similar. However, they are not truly thiazides.]

**1. Mechanism of action:** The thiazide and thiazide-like diuretics act mainly in the cortical region of the ascending loop of Henle and the distal convoluted tubule to decrease the reabsorption of  $\text{Na}^+$ , apparently by inhibition of a  $\text{Na}^+/\text{Cl}^-$  cotransporter on the luminal membrane of the tubules (Figure 18.2). They have a lesser effect in the proximal tubule. As a result, these drugs increase the concentration of  $\text{Na}^+$  and  $\text{Cl}^-$  in the tubular fluid. [Note: Because the site of action of the thiazide derivatives is on the luminal membrane, these drugs must be excreted into the tubular lumen to be effective. Therefore, with decreased renal function, thiazide diuretics lose efficacy.] The efficacy of these agents may be diminished with concomitant use of NSAIDs, such as *indomethacin*, which inhibit production of renal prostaglandins, thereby reducing renal blood flow.

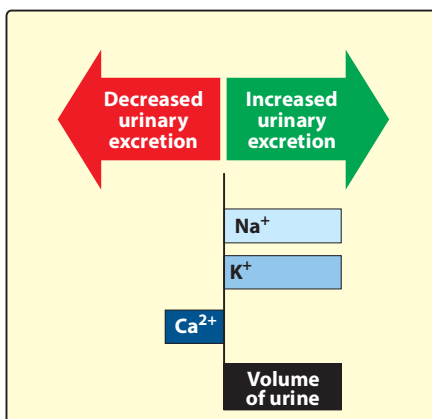
### 2. Actions:

**a. Increased excretion of  $\text{Na}^+$  and  $\text{Cl}^-$ :** Thiazide and thiazide-like diuretics cause diuresis with increased  $\text{Na}^+$  and  $\text{Cl}^-$  excretion, which can result in the excretion of very hyperosmolar (concentrated) urine. This latter effect is unique, as the other diuretic classes are unlikely to produce a hyperosmolar urine. The diuretic action is not affected by the acid–base status of the body, and *hydrochlorothiazide* does not change the acid–base status of the blood. Figure 18.4 outlines relative changes in the ionic composition of the urine with thiazide and thiazide-like diuretics.

**b. Loss of  $\text{K}^+$ :** Because thiazides increase  $\text{Na}^+$  in the filtrate arriving at the distal tubule, more  $\text{K}^+$  is also exchanged for  $\text{Na}^+$ , resulting in a continual loss of  $\text{K}^+$  from the body with prolonged use of these drugs. Thus, serum  $\text{K}^+$  should be measured periodically (more frequently at the beginning of therapy) to monitor for the development of hypokalemia.

**c. Loss of  $\text{Mg}^{2+}$ :** Magnesium deficiency requiring supplementation can occur with chronic use of thiazide diuretics, particularly in elderly patients. The mechanism for the magnesuria is not understood.

**d. Decreased urinary calcium excretion:** Thiazide and thiazide-like diuretics decrease the  $\text{Ca}^{2+}$  content of urine by promoting



**Figure 18.4**

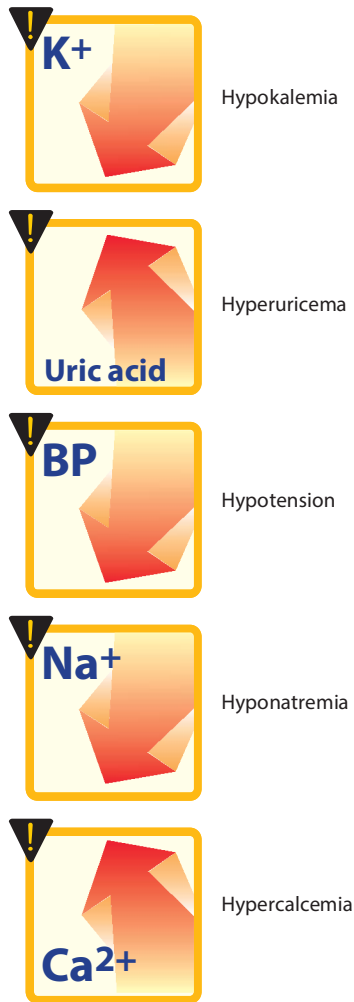
Relative changes in the composition of urine induced by thiazides and thiazide-like diuretics.

the reabsorption of  $\text{Ca}^{2+}$  in the distal convoluted tubule where parathyroid hormone regulates reabsorption. This effect contrasts with the loop diuretics, which increase the  $\text{Ca}^{2+}$  concentration in the urine. [Note: Epidemiologic evidence suggests that use of thiazides preserves bone mineral density at the hip and spine and may reduce the risk of fractures.]

- e. **Reduced peripheral vascular resistance:** An initial reduction in blood pressure results from a decrease in blood volume and, therefore, a decrease in cardiac output. With continued therapy, volume recovery occurs. However, there are continued antihypertensive effects, resulting from reduced peripheral vascular resistance caused by relaxation of arteriolar smooth muscle. How these agents induce vasodilation is unknown.

### 3. Therapeutic uses:

- a. **Hypertension:** Clinically, the thiazides are a mainstay of anti-hypertensive medication, because they are inexpensive, convenient to administer, and well tolerated. They are effective in reducing blood pressure in the majority of patients with mild to moderate essential hypertension. Blood pressure can be maintained with a daily dose of thiazide, which causes lower peripheral resistance without having a major diuretic effect. Some patients can be continued for years on thiazides alone; however, many patients require additional medication for blood pressure control (see Chapter 17), such as adrenergic blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. [Note: The antihypertensive actions of angiotensin-converting enzyme inhibitors are enhanced when given in combination with the thiazides.]
  - b. **Heart failure:** Loop diuretics (not thiazides) are the diuretics of choice in reducing extracellular volume in heart failure. However, thiazide diuretics may be added if additional diuresis is needed. When given in combination, thiazides should be administered 30 minutes prior to loop diuretics in order to allow the thiazide time to reach the site of action and produce effect.
  - c. **Hypercalciuria:** The thiazides can be useful in treating idiopathic hypercalciuria, because they inhibit urinary  $\text{Ca}^{2+}$  excretion. This is particularly beneficial for patients with calcium oxalate stones in the urinary tract.
  - d. **Diabetes insipidus:** Thiazides have the unique ability to produce a hyperosmolar urine. Thiazides can substitute for ADH in the treatment of nephrogenic diabetes insipidus. The urine volume of such individuals may drop from 11 L/d to about 3 L/d when treated with the drug.
4. **Pharmacokinetics:** The drugs are effective orally. Most thiazides take 1 to 3 weeks to produce a stable reduction in blood pressure, and they exhibit a prolonged half-life. All thiazides are secreted by the organic acid secretory system of the kidney (Figure 18.3).



**Figure 18.5**

Summary of some adverse effects commonly observed with thiazides and thiazide-like diuretics. BP = blood pressure.

**5. Adverse effects:** These mainly involve problems in fluid and electrolyte balance.

- a. Potassium depletion:** Hypokalemia is the most frequent problem with the thiazide diuretics, and it can predispose patients who are taking *digoxin* to ventricular arrhythmias (Figure 18.5). Often,  $K^+$  can be supplemented by dietary measures such as increasing the consumption of citrus fruits, bananas, and prunes. In some cases,  $K^+$  supplementation may be necessary. Thiazides decrease the intravascular volume, resulting in activation of the renin–angiotensin–aldosterone system. Increased aldosterone contributes significantly to urinary  $K^+$  losses. Under these circumstances, the  $K^+$  deficiency can be overcome by administering *spironolactone*, which interferes with aldosterone action, or by administering *triamterene* or *amiloride*, which act to retain  $K^+$ . Low-sodium diets blunt the potassium depletion caused by thiazide diuretics.
- b. Hyponatremia:** Hyponatremia may develop due to elevation of ADH as a result of hypovolemia, as well as diminished diluting capacity of the kidney and increased thirst. Limiting water intake and lowering the diuretic dose can prevent hyponatremia.
- c. Hyperuricemia:** Thiazides increase serum uric acid by decreasing the amount of acid excreted by the organic acid secretory system. Being insoluble, uric acid deposits in the joints and may precipitate a gouty attack in predisposed individuals. Therefore, thiazides should be used with caution in patients with gout or high levels of uric acid.
- d. Volume depletion:** This can cause orthostatic hypotension or light-headedness.
- e. Hypercalcemia:** The thiazides inhibit the secretion of  $Ca^{2+}$ , sometimes leading to hypercalcemia (elevated levels of  $Ca^{2+}$  in the blood).
- f. Hyperglycemia:** Therapy with thiazides can lead to glucose intolerance, possibly due to impaired release of insulin and tissue uptake of glucose. New-onset diabetes has been reported more often with thiazides than with other antihypertensive agents. Patients with diabetes who are taking thiazides should monitor glucose to assess the need for an adjustment in diabetes therapy.

## B. Thiazide-like diuretics

These compounds lack the thiazide structure, but, like the thiazides, they have the unsubstituted sulfonamide group and, therefore, share their mechanism of action. The therapeutic uses and adverse effect profiles are similar to those of the thiazides.

- 1. Chlorthalidone:** *Chlorthalidone* [klor-THAL-i-done] is a nonthiazide derivative that behaves pharmacologically like *hydrochlorothiazide*. It has a long duration of action and, therefore, is often used once daily to treat hypertension.



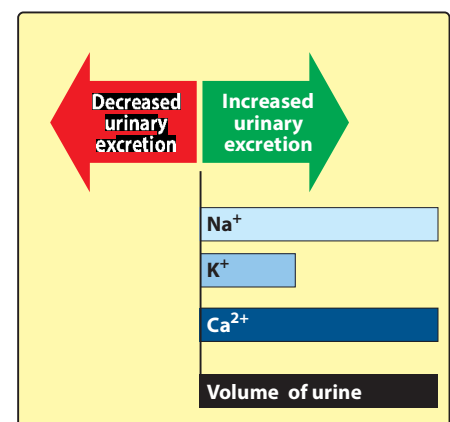
- 2. Metolazone:** *Metolazone* [me-TOL-ah-zone] is more potent than the thiazides and, unlike the thiazides, causes  $\text{Na}^+$  excretion even in advanced renal failure.
- 3. Indapamide:** *Indapamide* [in-DAP-a-mide] is a lipid-soluble, nonthiazide diuretic that has a long duration of action. At low doses, it shows significant antihypertensive action with minimal diuretic effects. *Indapamide* is metabolized and excreted by the gastrointestinal tract and the kidneys. Thus, it is less likely to accumulate in patients with renal failure and may be useful in their treatment.

## IV. LOOP OR HIGH-CEILING DIURETICS

*Bumetanide* [byoo-MET-ah-nide], *furosemide* [fur-OH-se-mide], *torse-mide* [TOR-se-mide], and *ethacrynic acid* [eth-a-KRIN-ik] have their major diuretic action on the ascending limb of the loop of Henle (Figure 18.2). Of all the diuretics, these drugs have the highest efficacy in mobilizing  $\text{Na}^+$  and  $\text{Cl}^-$  from the body. They produce copious amounts of urine. *Furosemide* is the most commonly used of these drugs. *Bumetanide* and *torse-mide* are much more potent than *furosemide*, and the use of these agents is increasing. *Ethacrynic acid* is used infrequently due to its adverse effect profile.

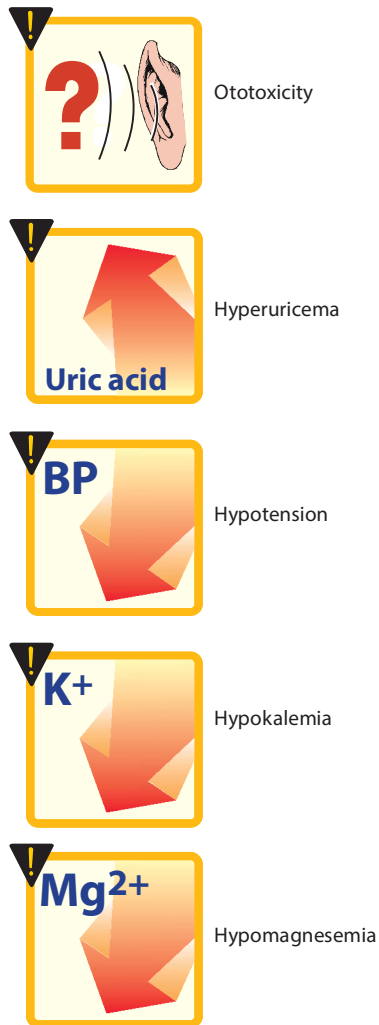
### A. Bumetanide, furosemide, torsemide, and ethacrynic acid

- 1. Mechanism of action:** Loop diuretics inhibit the cotransport of  $\text{Na}^+/\text{K}^+/2\text{Cl}^-$  in the luminal membrane in the ascending limb of the loop of Henle. Therefore, reabsorption of these ions is decreased. These agents have the greatest diuretic effect of all the diuretic drugs, since the ascending limb accounts for reabsorption of 25% to 30% of filtered  $\text{NaCl}$ , and downstream sites are unable to compensate for the increased  $\text{Na}^+$  load.
- 2. Actions:** Loop diuretics act promptly, even in patients with poor renal function or lack of response to other diuretics. Changes in the composition of the urine induced by loop diuretics are shown in Figure 18.6. [Note: Unlike thiazides, loop diuretics increase the  $\text{Ca}^{2+}$  content of urine. In patients with normal serum  $\text{Ca}^{2+}$  concentrations, hypocalcemia does not result, because  $\text{Ca}^{2+}$  is reabsorbed in the distal convoluted tubule.] The loop diuretics may increase renal blood flow, possibly by enhancing prostaglandin synthesis. NSAIDs inhibit renal prostaglandin synthesis and can reduce the diuretic action of loop diuretics.
- 3. Therapeutic uses:** The loop diuretics are the drugs of choice for reducing acute pulmonary edema and acute/chronic peripheral edema caused from heart failure or renal impairment. Because of their rapid onset of action, particularly when given intravenously, the drugs are useful in emergency situations such as acute pulmonary edema. Loop diuretics (along with hydration) are also useful in treating hypercalcemia, because they stimulate tubular  $\text{Ca}^{2+}$  excretion. They also are useful in the treatment of hyperkalemia.



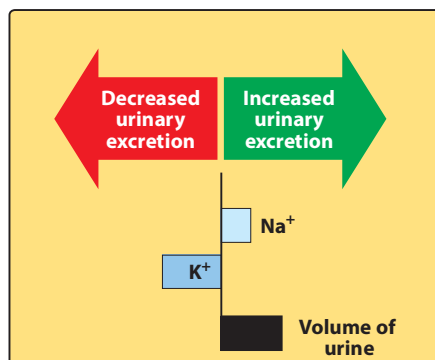
**Figure 18.6**

Relative changes in the composition of urine induced by loop diuretics.



**Figure 18.7**

Summary of some adverse effects commonly observed with loop diuretics. BP = blood pressure.



**Figure 18.8**

Relative changes in the composition of urine induced by potassium-sparing diuretics.

**4. Pharmacokinetics:** Loop diuretics are administered orally or parenterally. Their duration of action is relatively brief (2 to 4 hours), allowing patients to predict the window of diuresis. They are secreted into urine.

**5. Adverse effects:** Figure 18.7 summarizes the adverse effects of the loop diuretics.

**a. Ototoxicity:** Reversible or permanent hearing loss may occur with loop diuretics, particularly when used in conjunction with other ototoxic drugs (for example, aminoglycoside antibiotics). *Ethacrynic acid* is the most likely to cause deafness. Although less common, vestibular function may also be affected, inducing vertigo.

**b. Hyperuricemia:** *Furosemide* and *ethacrynic acid* compete with uric acid for the renal secretory systems, thus blocking its secretion and, in turn, causing or exacerbating gouty attacks.

**c. Acute hypovolemia:** Loop diuretics can cause a severe and rapid reduction in blood volume, with the possibility of hypotension, shock, and cardiac arrhythmias.

**d. Potassium depletion:** The heavy load of  $\text{Na}^+$  presented to the collecting tubule results in increased exchange of tubular  $\text{Na}^+$  for  $\text{K}^+$ , leading to the possibility of hypokalemia. The loss of  $\text{K}^+$  from cells in exchange for  $\text{H}^+$  leads to hypokalemic alkalosis. Use of potassium-sparing diuretics or supplementation with  $\text{K}^+$  can prevent the development of hypokalemia.

**e. Hypomagnesemia:** Chronic use of loop diuretics combined with low dietary intake of  $\text{Mg}^{2+}$  can lead to hypomagnesemia, particularly in the elderly. This can be corrected by oral supplementation.

## V. POTASSIUM-SPARING DIURETICS

Potassium-sparing diuretics act in the collecting tubule to inhibit  $\text{Na}^+$  reabsorption and  $\text{K}^+$  excretion (Figure 18.8). The major use of potassium-sparing agents is in the treatment of hypertension (most often in combination with a thiazide) and in heart failure (aldosterone antagonists). It is extremely important that potassium levels are closely monitored in patients treated with potassium-sparing diuretics. These drugs should be avoided in patients with renal dysfunction because of the increased risk of hyperkalemia. Within this class, there are drugs with two distinct mechanisms of action: aldosterone antagonists and sodium channel blockers.

### A. Aldosterone antagonists: spironolactone and eplerenone

**1. Mechanism of action:** *Spironolactone* [spear-oh-no-LAK-tone] is a synthetic steroid that antagonizes aldosterone at intracellular cytoplasmic receptor sites rendering the spironolactone–receptor complex inactive. It prevents translocation of the receptor complex into the nucleus of the target cell, ultimately resulting in a failure to produce mediator proteins that normally stimulate the

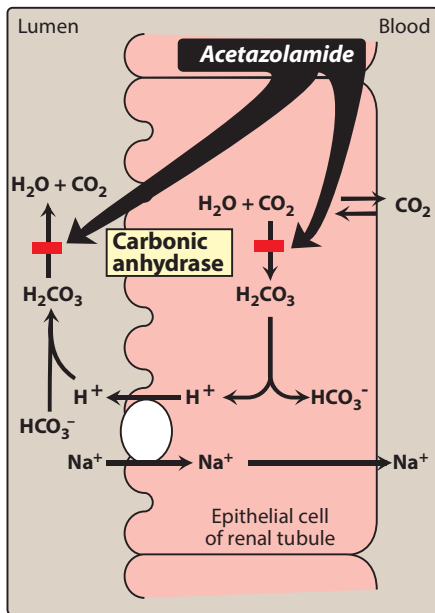


Na<sup>+</sup>/K<sup>+</sup>-exchange sites of the collecting tubule. Thus, a lack of mediator proteins prevents Na<sup>+</sup> reabsorption and, therefore, K<sup>+</sup> and H<sup>+</sup> secretion. *Eplerenone* [eh-PLUH-reh-none] is another aldosterone receptor antagonist, which has actions comparable to those of *spironolactone*, although it may have less endocrine effects than *spironolactone*.

**2. Actions:** In most edematous states, blood levels of aldosterone are high, causing retention of Na<sup>+</sup>. *Spironolactone* antagonizes the activity of aldosterone, resulting in retention of K<sup>+</sup> and excretion of Na<sup>+</sup> (Figure 18.8). Similar to thiazides and loop diuretics, the effect of these agents may be diminished by administration of NSAIDs.

**3. Therapeutic uses:**

- a. Diuretic:** Although the aldosterone antagonists have a low efficacy in mobilizing Na<sup>+</sup> from the body in comparison with the other diuretics, they have the useful property of causing the retention of K<sup>+</sup>. These agents are often given in conjunction with thiazide or loop diuretics to prevent K<sup>+</sup> excretion that would otherwise occur with these drugs. Since these drugs work by a mechanism in the later parts of the kidney, these agents can potentiate the effects of more proximally acting agents. *Spironolactone* is the diuretic of choice in patients with hepatic cirrhosis, as edema in these patients is caused by secondary hyperaldosteronism.
- b. Secondary hyperaldosteronism:** *Spironolactone* is particularly effective in clinical situations associated with secondary hyperaldosteronism, such as hepatic cirrhosis and nephrotic syndrome. In contrast, in patients who have no significant circulating levels of aldosterone, such as in Addison disease (primary adrenal insufficiency), there is no diuretic effect with the use of this drug.
- c. Heart failure:** Aldosterone antagonists prevent remodeling that occurs as compensation for the progressive failure of the heart. Use of these agents has been shown to decrease mortality associated with heart failure, particularly in those with reduced ejection fraction.
- d. Resistant hypertension:** Resistant hypertension, defined by the use of three or more medications without reaching the blood pressure goal, often responds well to aldosterone antagonists. This effect can be seen in those with or without elevated aldosterone levels.
- e. Ascites:** Accumulation of fluid in the abdominal cavity (ascites) is a common complication of hepatic cirrhosis. *Spironolactone* is effective in this condition.
- f. Polycystic ovary syndrome:** *Spironolactone* is often used off-label for the treatment of polycystic ovary syndrome. It blocks androgen receptors and inhibits steroid synthesis at high doses, thereby helping to offset increased androgen levels seen in this disorder.



**Figure 18.9**

Role of carbonic anhydrase in sodium retention by epithelial cells of the renal tubule.

**4. Pharmacokinetics:** Both *spironolactone* and *eplerenone* are absorbed after oral administration and are significantly bound to plasma proteins. *Spironolactone* is extensively metabolized and converted to several active metabolites. The metabolites, along with the parent drug, are thought to be responsible for the therapeutic effects. *Spironolactone* is a potent inhibitor of P-glycoprotein, and *eplerenone* is metabolized by cytochrome P450 3A4.

**5. Adverse effects:** *Spironolactone* can cause gastric upset. Because it chemically resembles some of the sex steroids, *spironolactone* may induce gynecomastia in male patients and menstrual irregularities in female patients. Hyperkalemia, nausea, lethargy, and mental confusion can occur. At low doses, *spironolactone* can be used chronically with few side effects. Potassium-sparing diuretics should be used with caution with other medications that can induce hyperkalemia, such as angiotensin-converting enzyme inhibitors and potassium supplements.

### B. Triamterene and amiloride

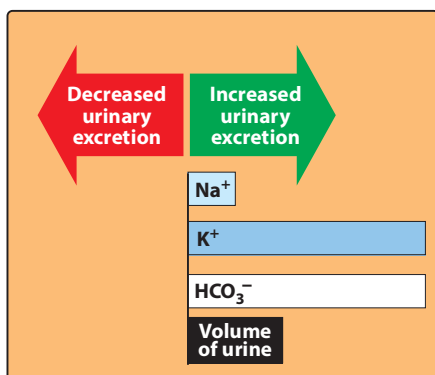
*Triamterene* [trye-AM-ter-een] and *amiloride* [a-MIL-oh-ride] block  $\text{Na}^+$  transport channels, resulting in a decrease in  $\text{Na}^+/\text{K}^+$  exchange. Although they have a  $\text{K}^+$ -sparing diuretic action similar to that of the aldosterone antagonists, their ability to block the  $\text{Na}^+/\text{K}^+$ -exchange site in the collecting tubule does not depend on the presence of aldosterone. Like the aldosterone antagonists, these agents are not very efficacious diuretics. Both *triamterene* and *amiloride* are commonly used in combination with other diuretics, usually for their potassium-sparing properties. Much like the aldosterone antagonists, they prevent the loss of  $\text{K}^+$  that occurs with thiazide and loop diuretics. The side effects of *triamterene* include increased uric acid, renal stones, and  $\text{K}^+$  retention.

## VI. CARBONIC ANHYDRASE INHIBITOR

*Acetazolamide* [ah-set-a-ZOLE-a-mide] and other carbonic anhydrase inhibitors are more often used for their other pharmacologic actions than for their diuretic effect, because they are much less efficacious than the thiazide or loop diuretics.

### A. Acetazolamide

**1. Mechanism of action:** *Acetazolamide* inhibits carbonic anhydrase located intracellularly (cytoplasm) and on the apical membrane of the proximal tubular epithelium (Figure 18.9). [Note: Carbonic anhydrase catalyzes the reaction of  $\text{CO}_2$  and  $\text{H}_2\text{O}$ , leading to  $\text{H}_2\text{CO}_3$ , which spontaneously ionizes to  $\text{H}^+$  and  $\text{HCO}_3^-$  (bicarbonate).] The decreased ability to exchange  $\text{Na}^+$  for  $\text{H}^+$  in the presence of *acetazolamide* results in a mild diuresis. Additionally,  $\text{HCO}_3^-$  is retained in the lumen, with marked elevation in urinary pH. The loss of  $\text{HCO}_3^-$  causes a hyperchloremic metabolic acidosis and decreased diuretic efficacy following several days of therapy. Changes in the composition



**Figure 18.10**

Relative changes in the composition of urine induced by *acetazolamide*.

of urinary electrolytes induced by *acetazolamide* are summarized in Figure 18.10. Phosphate excretion is increased by an unknown mechanism.

## 2. Therapeutic uses:

**a. Glaucoma:** *Acetazolamide* decreases the production of aqueous humor and reduces intraocular pressure in patients with chronic open-angle glaucoma, probably by blocking carbonic anhydrase in the ciliary body of the eye. Topical carbonic anhydrase inhibitors, such as *dorzolamide* and *brinzolamide*, have the advantage of not causing systemic effects.

**b. Mountain sickness:** *Acetazolamide* can be used in the prophylaxis of acute mountain sickness. *Acetazolamide* prevents weakness, breathlessness, dizziness, nausea, and cerebral as well as pulmonary edema characteristic of the syndrome.

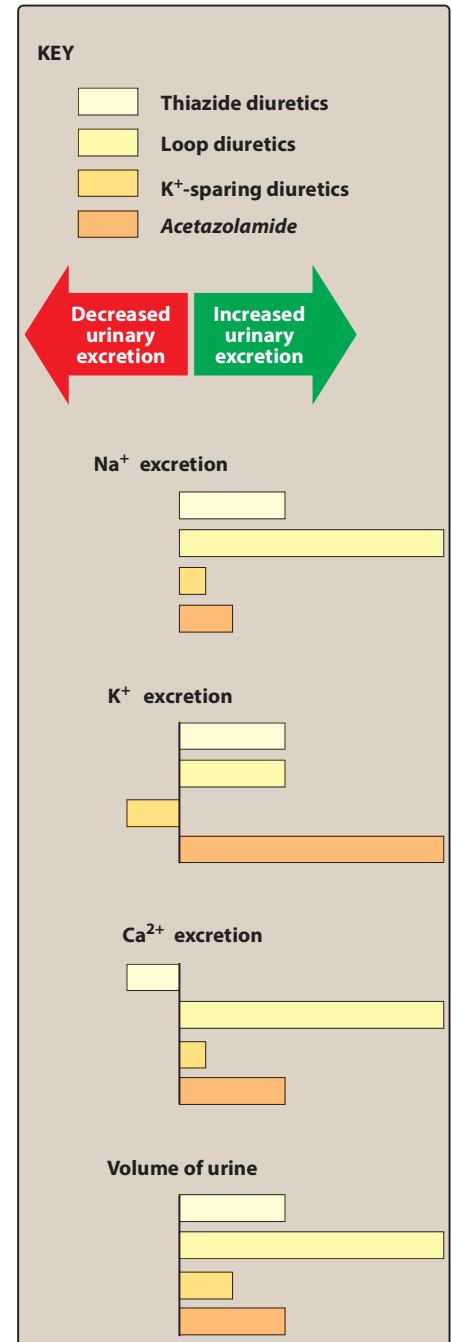
**3. Pharmacokinetics:** *Acetazolamide* can be administered orally or intravenously. It is approximately 90% protein bound and eliminated renally by both active tubular secretion and passive reabsorption.

**4. Adverse effects:** Metabolic acidosis (mild), potassium depletion, renal stone formation, drowsiness, and paresthesia may occur. The drug should be avoided in patients with hepatic cirrhosis, because it could lead to a decreased excretion of  $\text{NH}_4^+$ .

## VII. OSMOTIC DIURETICS

A number of simple, hydrophilic chemical substances that are filtered through the glomerulus, such as *mannitol* [MAN-i-to!] and *urea* [yu-REE-ah], result in some degree of diuresis. Filtered substances that undergo little or no reabsorption will cause an increase in urinary output. The presence of these substances results in a higher osmolarity of the tubular fluid and prevents further water reabsorption, resulting in osmotic diuresis. Only a small amount of additional salt may also be excreted. Because osmotic diuretics are used to increase water excretion rather than  $\text{Na}^+$  excretion, they are not useful for treating conditions in which  $\text{Na}^+$  retention occurs. They are used to maintain urine flow following acute toxic ingestion of substances capable of producing acute renal failure. Osmotic diuretics are a mainstay of treatment for patients with increased intracranial pressure or acute renal failure due to shock, drug toxicities, and trauma. Maintaining urine flow preserves long-term kidney function and may save the patient from dialysis. [Note: *Mannitol* is not absorbed when given orally and should be given intravenously.] Adverse effects include extracellular water expansion and dehydration, as well as hypo- or hypernatremia. The expansion of extracellular water results because the presence of *mannitol* in the extracellular fluid extracts water from the cells and causes hyponatremia until diuresis occurs.

Figure 18.11 summarizes the relative changes in urinary composition induced by diuretic drugs.



**Figure 18.11**

Summary of relative changes in urinary composition induced by diuretic drugs.

## Study Questions

Choose the ONE best answer.

- 18.1 An elderly patient with a history of heart disease is brought to the emergency room with difficulty breathing. Examination reveals that she has pulmonary edema. Which treatment is indicated?
- Acetazolamide.
  - Chlorthalidone.
  - Furosemide.
  - Hydrochlorothiazide.
  - Spironolactone.
- 18.2 A group of college students is planning a mountain climbing trip to the Andes. Which would be appropriate for them to take to prevent mountain sickness?
- A thiazide diuretic such as hydrochlorothiazide.
  - An anticholinergic such as atropine.
  - A carbonic anhydrase inhibitor such as acetazolamide.
  - A loop diuretic such as furosemide.
  - A  $\beta$ -blocker such as metoprolol.
- 18.3 An alcoholic male has developed hepatic cirrhosis. To control the ascites and edema, which should be prescribed?
- Acetazolamide.
  - Chlorthalidone.
  - Furosemide.
  - Hydrochlorothiazide.
  - Spironolactone.
- 18.4 A 55-year-old male with kidney stones has been placed on a diuretic to decrease calcium excretion. However, after a few weeks, he develops an attack of gout. Which diuretic was he taking?
- Furosemide.
  - Hydrochlorothiazide.
  - Spironolactone.
  - Triamterene.
  - Urea.
- 18.5 A 75-year-old woman with hypertension is being treated with a thiazide. Her blood pressure responds well and reads at 120/76 mm Hg. After several months on the medication, she complains of being tired and weak. An analysis of the blood indicates low values for which of the following?
- Calcium.
  - Glucose.
  - Potassium.
  - Sodium.
  - Uric acid.

Correct answer = C. This is a potentially fatal situation. It is important to administer a diuretic that will reduce fluid accumulation in the lungs and, thus, improve oxygenation and heart function. The loop diuretics are most effective in removing large fluid volumes from the body and are the treatment of choice in this situation. In this situation, furosemide should be administered intravenously. The other choices are inappropriate.

Correct answer = C. Acetazolamide is used prophylactically for several days before an ascent above 10,000 feet. This treatment prevents the cerebral and pulmonary problems associated with the syndrome as well as other difficulties, such as nausea.

Correct answer = E. Spironolactone is very effective in the treatment of hepatic edema. These patients are frequently resistant to the diuretic action of loop diuretics, although a combination with spironolactone may be beneficial. The other agents are not indicated.

Correct answer = B. Hydrochlorothiazide is effective in increasing calcium reabsorption, thus decreasing the amount of calcium excreted, and decreasing the formation of kidney stones that contain calcium phosphate or calcium oxalate. However, hydrochlorothiazide can also inhibit the excretion of uric acid and cause its accumulation, leading to an attack of gout in some individuals. Furosemide increases the excretion of calcium, whereas the  $K^+$ -sparing osmotic diuretics, spironolactone and triamterene, and urea do not have an effect.

Correct answer = C. Hypokalemia is a common adverse effect of the thiazides and causes fatigue and lethargy in the patient. Supplementation with potassium chloride or foods high in  $K^+$  corrects the problem. Alternatively, a potassium-sparing diuretic, such as spironolactone, may be added. Calcium, uric acid, and glucose are usually elevated by thiazide diuretics. Sodium loss would not weaken the patient.

18.6 Which is contraindicated in a patient with hyperkalemia?

- A. Acetazolamide.
- B. Chlorthalidone.
- C. Chlorothiazide.
- D. Ethacrynic acid.
- E. Spironolactone.

Correct answer = E. Spironolactone acts in the collecting tubule to inhibit  $\text{Na}^+$  reabsorption and  $\text{K}^+$  excretion. It is extremely important that patients who are treated with any potassium-sparing diuretic be closely monitored for potassium levels. Exogenous potassium supplementation is usually discontinued when potassium-sparing diuretic therapy is instituted and spironolactone is contraindicated in patients with hyperkalemia. The other drugs promote the excretion of potassium.

18.7 Which of the following should be avoided in a patient with a history of severe anaphylactic reaction to sulfa medications?

- A. Amiloride.
- B. Hydrochlorothiazide.
- C. Mannitol.
- D. Spironolactone.
- E. Triamterene.

Correct answer = B. Hydrochlorothiazide, like many thiazide and thiazide-like diuretics, contains a sulfa moiety within its chemical structure. It is important to avoid use in those individuals with severe hypersensitivity to sulfa medications. It may be used with caution, however, in those with only minor reaction to sulfa medications.

18.8 A male patient is placed on a new medication and notes that his breasts have become enlarged and tender to the touch. Which medication is he most likely taking?

- A. Chlorthalidone.
- B. Furosemide.
- C. Hydrochlorothiazide.
- D. Spironolactone.
- E. Triamterene.

Correct answer = D. An adverse drug reaction to spironolactone is gynecomastia due to its effects on androgens and progesterone in the body. Eplerenone may be a suitable alternative if the patient is in need of an aldosterone antagonist but has a history of gynecomastia.

18.9 A patient presents to the emergency department with an extreme headache. After a thorough workup, the attending physician concludes that the pain is due to increased intracranial pressure. Which diuretic would work best to reduce this pressure?

- A. Acetazolamide.
- B. Indapamide.
- C. Furosemide.
- D. Hydrochlorothiazide.
- E. Mannitol.

Correct answer = E. Osmotic diuretics, such as mannitol, are a mainstay of treatment for patients with increased intracranial pressure or acute renal failure due to shock, drug toxicities, and trauma.

18.10 Which diuretic has been shown to improve blood pressure in resistant hypertension or those already treated with three blood pressure medications including a thiazide or thiazide-like diuretic?

- A. Chlorthalidone.
- B. Indapamide.
- C. Furosemide.
- D. Mannitol.
- E. Spironolactone.

Correct answer = E. Resistant hypertension, defined by the use of three or more medications without reaching the blood pressure goal, often responds well to aldosterone antagonists. This effect can be seen in those with or without elevated aldosterone levels.

