Chapter 15. Diuretic Agents

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Diuretic Agents: Introduction

Abnormalities in fluid volume and electrolyte composition are common and important clinical problems. Drugs that block the transport functions of the renal tubules are valuable clinical tools in the treatment of these disorders. Although various agents that increase urine flow have been described since antiquity, it was not until 1957 that a practical and powerful diuretic agent (chlorothiazide) became available for widespread use. Technically, the term "diuresis" signifies an increase in urine volume, while "natriuresis" denotes an increase in renal sodium excretion. Because natriuretic drugs almost always also increase water excretion, they are usually called diuretics.

Many diuretic agents (loop diuretics, thiazides, amiloride, and triamterene) exert their effects on specific membrane transport proteins in renal tubular epithelial cells. Other diuretics exert osmotic effects that prevent water reabsorption (mannitol), inhibit enzymes (acetazolamide), or interfere with hormone receptors in renal epithelial cells (spironolactone).

Most diuretics act upon a single anatomic segment of the nephron (Figure 15–1). Because these segments have distinctive transport functions, the first section of this chapter is devoted to a review of those features of renal tubule physiology that are relevant to diuretic action. The second section is devoted to the basic pharmacology of diuretics, and the third section discusses the clinical applications of these drugs.

Figure 15–1.
Renal Tubule Transport Mechanisms

Proximal Tubule

Sodium bicarbonate, sodium chloride, glucose, amino acids, and other organic solutes are reabsorbed via specific transport systems in the early proximal tubule. Water is reabsorbed passively so as to maintain nearly constant osmolality of proximal tubular fluid. As tubule fluid is processed along the length of the proximal tubule, the luminal concentrations of the solutes decrease relative to the concentration of inulin, an experimental marker that is neither secreted nor absorbed by renal tubules (Figure 15–2). Approximately 85% of the filtered sodium bicarbonate, 40% of the sodium chloride, 60% of the water, and virtually all of the filtered organic solutes are reabsorbed in the proximal tubule.
Of the various solutes reabsorbed in the proximal tubule, the most relevant to diuretic action are sodium bicarbonate and sodium chloride. Of the currently available diuretics, only one group (carbonic anhydrase inhibitors, which block NaHCO₃ reabsorption) acts predominantly in the proximal tubule. In view of the large quantity of sodium chloride absorbed in the proximal tubule, a drug that specifically blocked reabsorption of this salt at this site might be a particularly powerful diuretic agent. No such drug is currently available.

Sodium bicarbonate reabsorption by the proximal tubule is initiated by the action of a Na⁺/H⁺ exchanger located in the luminal membrane of the proximal tubule epithelial cell (Figure 15–3). This transport system allows sodium to enter the cell from the tubular lumen in exchange for a proton from inside the cell. As in all portions of the nephron, Na⁺/K⁺ ATPase in the basolateral...
membrane pumps the reabsorbed \( \text{Na}^+ \) into the interstitium so as to maintain the normal intracellular concentration of this ion. Protons secreted into the lumen combine with bicarbonate to form carbonic acid, \( \text{H}_2\text{CO}_3 \). Carbonic acid is rapidly dehydrated to \( \text{CO}_2 \) and \( \text{H}_2\text{O} \) by carbonic anhydrase. \( \text{CO}_2 \) produced by dehydration of \( \text{H}_2\text{CO}_3 \) enters the proximal tubule cell by simple diffusion where it is then rehydrated back to \( \text{H}_2\text{CO}_3 \). After dissociation of \( \text{H}_2\text{CO}_3 \), the \( \text{H}^+ \) is available for transport by the \( \text{Na}^+/\text{H}^+ \) exchanger, and the bicarbonate is transported out of the cell by a basolateral membrane transporter (Figure 15–3). Bicarbonate reabsorption by the proximal tubule is thus dependent on carbonic anhydrase. This enzyme can be inhibited by acetazolamide and related agents.

![Figure 15–3.](image)

Apical membrane \( \text{Na}^+/\text{H}^+ \) exchange and bicarbonate reabsorption in the proximal convoluted tubule cell. \( \text{Na}^+/\text{K}^+ \) ATPase is present in the basolateral membrane to maintain intracellular sodium and potassium levels within the normal range. Because of rapid equilibration, concentrations of the solutes shown are approximately equal in the interstitial fluid and the blood. Carbonic anhydrase (CA) is found in other locations in addition to the brush border of the luminal membrane.

In the late proximal tubule, as bicarbonate and organic solutes have been largely removed from the tubular fluid, the residual luminal fluid contains predominantly \( \text{NaCl} \). Under these conditions, \( \text{Na}^+ \) reabsorption continues, but the protons secreted by the \( \text{Na}^+/\text{H}^+ \) exchanger can no longer bind to bicarbonate. Free \( \text{H}^+ \) causes luminal pH to fall, activating a still poorly defined \( \text{Cl}^-/\text{base} \) exchanger (Figure 15–3). The net effect of parallel \( \text{Na}^+/\text{H}^+ \) exchange and \( \text{Cl}^-/\text{base} \) exchange is \( \text{NaCl} \) reabsorption. As yet, there are no diuretic agents that are known to act on this conjoint process.

Because of the high water permeability of the proximal tubule, water is reabsorbed in direct proportion to salt reabsorption in this segment. Thus, luminal fluid osmolality and sodium concentration remain nearly constant along the length of the proximal tubule (Figure 15–2). An experimental impermeant solute like inulin will rise in concentration as water is reabsorbed (Figure 15–2). If large amounts of an impermeant solute such as mannitol are present in the tubular fluid,
water reabsorption will cause the concentration of the solute to rise to a point at which further water reabsorption is prevented. This is the mechanism by which osmotic diuretics act (see below).

Organic acid secretory systems are located in the middle third of the proximal tubule (S2 segment). These systems secrete a variety of organic acids (uric acid, nonsteroidal anti-inflammatory drugs NSAIDs, diuretics, antibiotics, etc) into the luminal fluid from the blood. These systems thus help deliver diuretics to the luminal side of the tubule, where most of them act. Organic base secretory systems (creatinine, choline, etc) are also present, in the early (S1) and middle (S2) segments of the proximal tubule.

Loop of Henle

At the boundary between the inner and outer stripes of the outer medulla, the thin limb of Henle's loop begins. Water is extracted from the thin descending limb of the loop of Henle by osmotic forces created in the hypertonic medullary interstitium. As in the proximal tubule, impermeant luminal solutes such as mannitol oppose water extraction.

The thick ascending limb of the loop of Henle actively reabsorbs NaCl from the lumen (about 35% of the filtered sodium), but unlike the proximal tubule and the thin limb, it is nearly impermeable to water. Salt reabsorption in the thick ascending limb therefore dilutes the tubular fluid, leading to its designation as a "diluting segment." Medullary portions of the thick ascending limb contribute to medullary hypertonicity and thereby also play an important role in concentration of urine.

The NaCl transport system in the luminal membrane of the thick ascending limb is a Na⁺/K⁺/2Cl⁻ cotransporter (Figure 15–4). This transporter is selectively blocked by diuretic agents known as "loop" diuretics (see below). Although the Na⁺/K⁺/2Cl⁻ transporter is itself electrically neutral (two cations and two anions are cotransported), the action of the transporter contributes to excess K⁺ accumulation within the cell. This results in back diffusion of K⁺ into the tubular lumen and development of a lumen-positive electrical potential. This electrical potential provides the driving force for reabsorption of cations—including Mg²⁺ and Ca²⁺—via the paracellular pathway (between the cells). Thus, inhibition of salt transport in the thick ascending limb by loop diuretics causes an increase in urinary excretion of divalent cations in addition to NaCl.

Figure 15–4.
Ion transport pathways across the luminal and basolateral membranes of the thick ascending limb cell. The lumen positive electrical potential created by K⁺ back diffusion drives divalent cation reabsorption via the paracellular pathway.

Distal Convoluted Tubule

Only about 10% of the filtered NaCl is reabsorbed in the distal convoluted tubule. Like the thick ascending limb, this segment is relatively impermeable to water, and the NaCl reabsorption therefore further dilutes the tubular fluid. The mechanism of NaCl transport in the distal convoluted tubule is electrically neutral Na⁺ and Cl⁻ cotransport (Figure 15–5). This NaCl transporter is blocked by diuretics of the thiazide class.

Figure 15–5.

Ion transport pathways across the luminal and basolateral membranes of the distal convoluted tubule cell. As in all tubular cells, Na⁺/K⁺ ATPase is present in the basolateral membrane. (R, PTH receptor.)
Because K\(^+\) does not recycle across the apical membrane of the distal convoluted tubule as it does in the loop of Henle, there is no lumen-positive potential in this segment, and Ca\(^{2+}\) and Mg\(^{2+}\) are not driven out of the tubular lumen by electrical forces. However, Ca\(^{2+}\) is actively reabsorbed by the distal convoluted tubule epithelial cell via an apical Ca\(^{2+}\) channel and basolateral Na\(^+\)/Ca\(^{2+}\) exchanger (Figure 15–5). This process is regulated by parathyroid hormone. As will be seen below, the differences in the mechanism of Ca\(^{2+}\) transport in the distal convoluted tubule and in the loop of Henle have important implications for the effects of various diuretics on Ca\(^{2+}\) transport.

Collecting Tubule

The collecting tubule is responsible for only 2–5% of NaCl reabsorption by the kidney. Despite this small contribution, the collecting tubule plays an important role in renal physiology and in diuretic action. As the final site of NaCl reabsorption, the collecting tubule is responsible for volume regulation and for determining the final Na\(^+\) concentration of the urine. Furthermore, the collecting tubule is a site at which mineralocorticoids exert a significant influence. Lastly, the collecting tubule is the major site of potassium secretion by the kidney and the site at which virtually all diuretic-induced changes in potassium balance occur.

The mechanism of NaCl reabsorption in the collecting tubule is distinct from the mechanisms found in other tubule segments. The principal cells are the major sites of Na\(^+\), K\(^+\), and H\(_2\)O transport (Figure 15–6), and the intercalated cells are the primary sites of proton secretion. Unlike cells in other nephron segments, the principal cells do not contain cotransport systems for Na\(^+\) and other ions in their apical membranes. Rather, principal cell membranes exhibit separate ion channels for Na\(^+\) and K\(^+\). Since these channels exclude anions, transport of Na\(^+\) or K\(^+\) leads to a net movement of charge across the membrane. Because the driving force for Na\(^+\) entry into the principal cell greatly exceeds that for K\(^+\) exit, Na\(^+\) reabsorption predominates, and a 10–50 mV lumen-negative electrical potential develops. Na\(^+\) that enters the principal cell from the urine is then transported back to the blood via the basolateral Na\(^+\)/K\(^+\) ATPase (Figure 15–6). The lumen-negative electrical potential drives the transport of Cl\(^-\) back to the blood via the paracellular pathway and also pulls K\(^+\) out of the cell through the apical membrane K\(^+\) channel. Thus, there is an important relationship between Na\(^+\) delivery to the collecting tubule and the resulting secretion of K\(^+\). Diuretics that act upstream of the collecting tubule will increase Na\(^+\) delivery to this site and will enhance K\(^+\) secretion. If the Na\(^+\) is delivered with an anion which cannot be reabsorbed as readily as Cl\(^-\) (eg, bicarbonate), the lumen-negative potential is increased, and K\(^+\) secretion will be enhanced. This mechanism, combined with enhanced aldosterone secretion due to volume depletion, is the basis for most diuretic-induced K\(^+\) wasting.

Figure 15–6.
Ion and H₂O transport pathways across the luminal and basolateral membranes of collecting tubule and collecting duct cells. Inward diffusion of Na⁺ leaves a lumen-negative potential, which drives reabsorption of Cl⁻ and efflux of K⁺. (R, aldosterone or ADH receptor.)

Reabsorption of Na⁺ via the epithelial Na channel (ENaC) and its coupled secretion of K⁺ is regulated by aldosterone. This steroid hormone, through its actions on gene transcription, increases the activity of both apical membrane channels and the basolateral N⁺/K⁺ ATPase. This leads to an increase in the transepithelial electrical potential and a dramatic increase in both Na⁺ reabsorption and K⁺ secretion.

A key determinant of the final urine concentration is antidiuretic hormone (ADH; also called vasopressin). In the absence of ADH, the collecting tubule (and duct) is impermeable to water, and dilute urine is produced. However, membrane water permeability of principal cells can be increased by ADH-induced fusion of vesicles containing preformed water channels with the apical membranes (Figure 15–6). ADH secretion is regulated by serum osmolality and by volume status.

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Basic Pharmacology of Diuretic Agents

Carbonic Anhydrase Inhibitors

Carbonic anhydrase is present in many nephron sites, but the predominant location of this enzyme is the luminal membrane of the proximal tubule cells (Figure 15–3), where it catalyzes the dehydration of H₂CO₃, a critical step in the reabsorption of bicarbonate. By blocking carbonic
anhydrase, inhibitors block sodium bicarbonate reabsorption and cause diuresis.

The carbonic anhydrase inhibitors were the forerunners of modern diuretics. They are unsubstituted sulfonamide derivatives and were discovered when it was found that bacteriostatic sulfonamides caused an alkaline diuresis and hyperchloremic metabolic acidosis. With the development of newer agents, carbonic anhydrase inhibitors are now rarely used as diuretics, but they still have several specific applications that are discussed below. The prototypical carbonic anhydrase inhibitor is acetazolamide.

Pharmacokinetics

The carbonic anhydrase inhibitors are well absorbed after oral administration. An increase in urine pH from the bicarbonate diuresis is apparent within 30 minutes, maximal at 2 hours, and persists for 12 hours after a single dose. Excretion of the drug is by secretion in the proximal tubule S2 segment. Therefore, dosing must be reduced in renal insufficiency.

Pharmacodynamics

Inhibition of carbonic anhydrase activity profoundly depresses bicarbonate reabsorption in the proximal tubule. At its maximal safely administered dosage, 85% of the bicarbonate reabsorptive capacity of the superficial proximal tubule is inhibited. Some bicarbonate can still be absorbed at other nephron sites by carbonic anhydrase–independent mechanisms, and the overall effect of maximal acetazolamide dosage is about 45% inhibition of whole kidney bicarbonate reabsorption. Nevertheless, carbonic anhydrase inhibition causes significant bicarbonate losses and hyperchloremic metabolic acidosis. Because of this and the fact that HCO₃⁻ depletion leads to enhanced NaCl reabsorption by the remainder of the nephron, the diuretic efficacy of acetazolamide decreases significantly with use over several days.

The major clinical applications of acetazolamide involve carbonic anhydrase–dependent bicarbonate transport at sites other than the kidney. The ciliary body of the eye secretes bicarbonate from the blood into the aqueous humor. Likewise, formation of cerebrospinal fluid by the choroid plexus involves bicarbonate secretion into the cerebrospinal fluid. Although these processes remove bicarbonate from the blood (the direction opposite to that in the proximal tubule), they are significantly inhibited by carbonic anhydrase inhibitors, which in both cases dramatically alter the pH and quantity of fluid produced.

Clinical Indications & Dosage

See Table 15–1.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Oral Dose (1–4 Times Daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>250 mg</td>
</tr>
<tr>
<td>Dichlorphenamide</td>
<td>50 mg</td>
</tr>
<tr>
<td>Methazolamide</td>
<td>50 mg</td>
</tr>
</tbody>
</table>
Glaucoma

The reduction of aqueous humor formation by carbonic anhydrase inhibitors decreases the intraocular pressure. This effect is valuable in the management of severe forms of glaucoma, making it the most common indication for use of carbonic anhydrase inhibitors. Topically active carbonic anhydrase inhibitors (dorzolamide, brinzolamide) are also available. These topical compounds reduce intraocular pressure, but plasma levels are undetectable. Thus, diuretic and systemic metabolic effects are eliminated.

Urinary Alkalinization

Uric acid, cystine, and some other weak acids are relatively insoluble in, and easily reabsorbed from, acidic urine. Renal excretion of these compounds can be enhanced by increasing urinary pH with carbonic anhydrase inhibitors. In the absence of continuous bicarbonate administration, these effects of acetazolamide are of relatively short duration (2–3 days). Prolonged therapy requires bicarbonate administration.

Metabolic Alkalosis

Metabolic alkalosis is generally treated by correction of abnormalities in total body K⁺, intravascular volume, or mineralocorticoid levels.

However, when the alkalosis is due to excessive use of diuretics in patients with severe heart failure, saline administration may be contraindicated. In these cases, acetazolamide can be useful in correcting the alkalosis as well as producing a small additional diuresis for the correction of heart failure. Acetazolamide has also been used to rapidly correct the metabolic alkalosis that may develop in the setting of respiratory acidosis.

Acute Mountain Sickness

Weakness, dizziness, insomnia, headache, and nausea can occur in mountain travelers who rapidly ascend above 3000 m. The symptoms are usually mild and last for a few days. In more serious cases, rapidly progressing pulmonary or cerebral edema can be life-threatening. By decreasing cerebrospinal fluid formation and by decreasing the pH of the cerebrospinal fluid and brain, acetazolamide can enhance performance status and diminish symptoms of mountain sickness.

Other Uses

Carbonic anhydrase inhibitors have been used as adjuvants for the treatment of epilepsy, in some forms of hypokalemic periodic paralysis, and to increase urinary phosphate excretion during severe hyperphosphatemia.

Toxicity

Hyperchloremic Metabolic Acidosis

Acidosis predictably results from chronic reduction of body bicarbonate stores by carbonic anhydrase inhibitors and limits the diuretic efficacy of these drugs to 2 or 3 days.

Renal Stones
Phosphaturia and hypercalciuria occur during the bicarbonaturic response to inhibitors of carbonic anhydrase. Renal excretion of solubilizing factors (eg, citrate) may also decline with chronic use. Calcium salts are relatively insoluble at alkaline pH, which means that the potential for renal stone formation from these salts is enhanced.

Renal Potassium Wasting

Potassium wasting can occur because NaHCO₃ presented to the collecting tubule increases the lumen-negative electrical potential in that segment and enhances K⁺ secretion. This effect can be counteracted by simultaneous administration of KCl.

Other Toxicities

Drowsiness and paresthesias are common following large doses. Carbonic anhydrase inhibitors may accumulate in patients with renal failure, leading to nervous system toxicity. Hypersensitivity reactions (fever, rashes, bone marrow suppression, and interstitial nephritis) may also occur.

Contraindications

Carbonic anhydrase inhibitor-induced alkalinization of the urine will decrease urinary excretion of NH₄⁺ and may contribute to the development of hyperammonemia and hepatic encephalopathy in patients with cirrhosis.

Loop Diuretics

Loop diuretics selectively inhibit NaCl reabsorption in the thick ascending limb of the loop of Henle. Due to the large NaCl absorptive capacity of this segment and the fact that diuresis is not limited by development of acidosis, as it is with the carbonic anhydrase inhibitors, these drugs are the most efficacious diuretic agents available.

Chemistry

The two prototypical drugs of this group are furosemide and ethacrynic acid. The structures of several loop diuretics are shown in Figure 15–7. Like the carbonic anhydrase inhibitors, furosemide, bumetanide, and torsemide are sulfonamide derivatives.
Some loop diuretics. The shaded methylene group on ethacrynic acid is reactive and may combine with free sulphydryl groups.

Ethacrynic acid—not a sulfonamide derivative—is a phenoxyacetic acid derivative containing an adjacent ketone and methylene group (Figure 15–7). The methylene group (shaded) forms an adduct with the free sulphydryl group of cysteine. The cysteine adduct appears to be an active form of the drug.

Organic mercurial diuretics also inhibit salt transport in the thick ascending limb but are no longer used because of their high toxicity.

Pharmacokinetics

The loop diuretics are rapidly absorbed. They are eliminated by tubular secretion as well as by glomerular filtration. Absorption of oral torsemide is more rapid (1 hour) than that of furosemide (2–3 hours) and is nearly as complete as with intravenous administration. Diuretic response is extremely rapid following intravenous injection. The duration of effect for furosemide is usually 2–3 hours and that of torsemide is 4–6 hours. Half-life depends on renal function. Since loop agents act on the luminal side of the tubule, their diuretic activity correlates with their secretion by the proximal tubule. Reduction in the secretion of loop diuretics may result from simultaneous administration of agents such as NSAIDs or probenecid, which compete for weak acid secretion in the proximal tubule. Metabolites of ethacrynic acid and furosemide have been identified, but it is not known if they have any diuretic activity. Torsemide has at least one active metabolite with a
half-life considerably longer than that of the parent compound.

Pharmacodynamics

These drugs inhibit the luminal Na⁺/K⁺/2Cl⁻ transporter in the thick ascending limb of Henle's loop. By inhibiting this transporter, the loop diuretics reduce the reabsorption of NaCl and also diminish the lumen-positive potential that derives from K⁺ recycling (Figure 15–4). This electrical potential normally drives divalent cation reabsorption in the loop, and by reducing this potential, loop diuretics cause an increase in Mg²⁺ and Ca²⁺ excretion. Prolonged use can cause significant hypomagnesemia in some patients. Since Ca²⁺ is actively reabsorbed in the distal convoluted tubule, loop diuretics do not generally cause hypocalcemia. However, in disorders that cause hypercalcemia, Ca²⁺ excretion can be greatly enhanced by combining loop agents with saline infusions.

Loop diuretics induce renal prostaglandin synthesis, and these prostaglandins participate in the renal actions of these drugs. NSAIDs (eg, indomethacin) can interfere with the actions of the loop diuretics by reducing prostaglandin synthesis in the kidney. This interference is minimal in otherwise normal subjects but may be significant in patients with nephrotic syndrome or hepatic cirrhosis.

In addition to their diuretic activity, loop agents appear to have direct effects on blood flow through several vascular beds. Furosemide increases renal blood flow. Furosemide and ethacrynic acid have also been shown to reduce pulmonary congestion and left ventricular filling pressures in heart failure before a measurable increase in urinary output occurs, and in anephric patients.

Clinical Indications & Dosage

The most important indications for the use of the loop diuretics include acute pulmonary edema, other edematous conditions, and acute hypercalcemia (Table 15–2). The use of loop diuretics in these conditions is discussed in Clinical Pharmacology. Other indications for loop diuretics include hyperkalemia, acute renal failure, and anion disease.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Oral Dose¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bumetanide</td>
<td>0.5–2 mg</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td>50–200 mg</td>
</tr>
<tr>
<td>Furosemide</td>
<td>20–80 mg</td>
</tr>
<tr>
<td>Torsemide</td>
<td>2.5–20 mg</td>
</tr>
</tbody>
</table>

¹ As single dose or in two divided doses.

Hyperkalemia

In mild hyperkalemia—or after acute management of severe hyperkalemia by other measures—loop diuretics can significantly enhance urinary excretion of K⁺. This response is enhanced by
simultaneous NaCl and water administration.

Acute Renal Failure

Loop agents can increase the rate of urine flow and enhance K⁺ excretion in acute renal failure. However, they do not seem to shorten the duration of renal failure. If a large pigment load has precipitated acute renal failure or threatens to do so, loop agents may help flush out intratubular casts and ameliorate intratubular obstruction. On the other hand, loop agents can theoretically worsen cast formation in myeloma and light chain nephropathy.

Anion Overdose

Loop diuretics are useful in treating toxic ingestions of bromide, fluoride, and iodide, which are reabsorbed in the thick ascending limb. Saline solution must be administered to replace urinary losses of Na⁺ and to provide Cl⁻, so as to avoid extracellular fluid volume depletion.

Toxicity

Hypokalemic Metabolic Alkalosis

Loop diuretics increase delivery of salt and water to the collecting duct and thus enhance the renal secretion of K⁺ and H⁺, causing hypokalemic metabolic alkalosis. This toxicity is a function of the magnitude of the diuretic effect and can be reversed by K⁺ replacement and correction of hypovolemia.

Ototoxicity

Loop diuretics can cause dose-related hearing loss that is usually reversible. It is most common in patients who have diminished renal function or who are also receiving other ototoxic agents such as aminoglycoside antibiotics.

Hyperuricemia

Loop diuretics can cause hyperuricemia and precipitate attacks of gout. This is caused by hypovolemia-associated enhancement of uric acid reabsorption in the proximal tubule. It may be avoided by using lower doses.

Hypomagnesemia

Magnesium depletion is a predictable consequence of the chronic use of loop agents and occurs most often in patients with dietary magnesium deficiency. It can be reversed by administration of oral magnesium preparations.

Allergic Reactions

Skin rash, eosinophilia and, less often, interstitial nephritis are occasional side effects of furosemide, bumetanide, and torsemide therapy. These usually resolve rapidly after drug withdrawal. Allergic reactions are much less common with ethacrynic acid.

Other Toxicities
Even more than other diuretics, loop agents can cause severe dehydration. Hyponatremia is less common than with the thiazides (see below), but patients who increase water intake in response to hypovolemia-induced thirst can become severely hyponatremic with loop agents. Loop agents are known for their calciuric effect, but hypercalcemia can occur in patients who have another—previously occult—cause for hypercalcemia, such as an oat cell carcinoma of the lung if they become severely volume-depleted.

Contraindications

Furosemide, bumetanide, and torsemide may demonstrate cross-reactivity in patients who are sensitive to other sulfonamides. Overzealous use of any diuretic is dangerous in hepatic cirrhosis, borderline renal failure, or heart failure (see below).

Thiazides

The thiazide diuretics emerged from efforts to synthesize more potent carbonic anhydrase inhibitors. It subsequently became clear that the thiazides inhibit NaCl transport predominantly in the distal convoluted tubule. However, some members of this group retain significant carbonic anhydrase inhibitory activity. The prototypical thiazide is hydrochlorothiazide.

Chemistry & Pharmacokinetics

Similar to the carbonic anhydrase inhibitors, all of the thiazides have an unsubstituted sulfonamide group (Figure 15–8).

Figure 15–8.
Hydrochlorothiazide and related agents.

All of the thiazides can be administered orally, but there are differences in their metabolism. Chlorothiazide, the parent of the group, is not very lipid-soluble and must be given in relatively large doses. It is the only thiazide available for parenteral administration. Chlorthalidone is slowly absorbed and has a longer duration of action. Although indapamide is excreted primarily by the biliary system, enough of the active form is cleared by the kidney to exert its diuretic effect in the distal convoluted tubule.

All of the thiazides are secreted by the organic acid secretory system in the proximal tubule and compete with the secretion of uric acid by that system. As a result, uric acid secretion may be reduced, with an elevation in serum uric acid level.

Pharmacodynamics

Thiazides inhibit NaCl reabsorption from the luminal side of epithelial cells in the distal convoluted tubule by blocking the Na⁺/Cl⁻ transporter. In contrast to the situation in the loop of Henle, where loop diuretics inhibit Ca²⁺ reabsorption, thiazides actually enhance Ca²⁺ reabsorption in the distal convoluted tubule. This enhancement has been postulated to result from a lowering of intracellular Na⁺ upon blockade of Na⁺ entry by thiazides. The lower cell Na⁺ would enhance Na⁺/Ca²⁺ exchange in the basolateral membrane (Figure 15–5), increasing overall reabsorption of Ca²⁺. While thiazides rarely cause hypercalcemia as the result of this enhanced reabsorption, they can unmask
hypercalcemia due to other causes (e.g., hyperparathyroidism, carcinoma, sarcoidosis). Thiazides are useful in the treatment of kidney stones caused by hypercalciuria.

The action of thiazides depends in part on renal prostaglandin production. As described above for the loop diuretics, the actions of thiazides can also be inhibited by NSAIDs under certain conditions.

Clinical Indications & Dosage

The major indications for thiazide diuretics are (1) hypertension, (2) heart failure, (3) nephrolithiasis due to idiopathic hypercalciuria, and (4) nephrogenic diabetes insipidus (Table 15–3). Use of the thiazides in each of these conditions is described below in the section on clinical pharmacology.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Oral Dose</th>
<th>Frequency of Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendroflumethiazide</td>
<td>2.5–10 mg</td>
<td>As single dose</td>
</tr>
<tr>
<td>Benzthiazide</td>
<td>25–100 mg</td>
<td>In two divided doses</td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>0.5–1 g</td>
<td>In two divided doses</td>
</tr>
<tr>
<td>Chlorthalidon</td>
<td>50–100 mg</td>
<td>As single dose</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>25–100 mg</td>
<td>As single dose</td>
</tr>
<tr>
<td>Hydroflumethiazide</td>
<td>25–100 mg</td>
<td>In two divided doses</td>
</tr>
<tr>
<td>Indapamide</td>
<td>2.5–10 mg</td>
<td>As single dose</td>
</tr>
<tr>
<td>Methyclothiazide</td>
<td>2.5–10 mg</td>
<td>As single dose</td>
</tr>
<tr>
<td>Metolazone</td>
<td>2.5–10 mg</td>
<td>As single dose</td>
</tr>
<tr>
<td>Polythiazide</td>
<td>1–4 mg</td>
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</tr>
<tr>
<td>Quinethazone</td>
<td>50–100 mg</td>
<td>As single dose</td>
</tr>
<tr>
<td>Trichlormethiazide</td>
<td>2–8 mg</td>
<td>As single dose</td>
</tr>
</tbody>
</table>

\[^1\] Not a thiazide but a sulfonamide qualitatively similar to the thiazides.

Toxicity

Hypokalemic Metabolic Alkalosis and Hyperuricemia

These toxicities are similar to those observed with loop diuretics (see above).

Impaired Carbohydrate Tolerance
Hyperglycemia may occur in patients who are overtly diabetic or who have even mildly abnormal glucose tolerance tests. The effect is due both to impaired pancreatic release of insulin and to diminished tissue utilization of glucose. Hyperglycemia may be partially reversible with correction of hypokalemia.

Hyperlipidemia

Thiazides cause a 5–15% increase in serum cholesterol and increased low-density lipoproteins (LDL). These levels may return toward baseline after prolonged use.

Hyponatremia

Hyponatremia is an important adverse effect of thiazide diuretics. It is due to a combination of hypovolemia-induced elevation of ADH, reduction in the diluting capacity of the kidney, and increased thirst. It can be prevented by reducing the dose of the drug or limiting water intake.

Allergic Reactions

The thiazides are sulfonamides and share cross-reactivity with other members of this chemical group. Photosensitivity or generalized dermatitis occurs rarely. Serious allergic reactions are extremely rare but do include hemolytic anemia, thrombocytopenia, and acute necrotizing pancreatitis.

Other Toxicities

Weakness, fatigability, and paresthesias similar to those of carbonic anhydrase inhibitors may occur. Impotence has been reported but is probably related to volume depletion.

Contraindications

Excessive use of any diuretic is dangerous in hepatic cirrhosis, borderline renal failure, or heart failure (see below).

Potassium-Sparing Diuretics

These diuretics antagonize the effects of aldosterone at the late distal tubule and cortical collecting tubule. Inhibition may occur by direct pharmacologic antagonism of mineralocorticoid receptors (spironolactone, eplerenone) or by inhibition of Na⁺ influx through ion channels in the luminal membrane (amiloride, triamterene).

Chemistry & Pharmacokinetics

Spironolactone is a synthetic steroid that acts as a competitive antagonist to aldosterone. Its onset and duration of action are determined by the kinetics of the aldosterone response in the target tissue. Substantial inactivation of spironolactone occurs in the liver. Overall, spironolactone has a rather slow onset of action, requiring several days before full therapeutic effect is achieved. Eplerenone, a new spironolactone analog with greater selectivity for the aldosterone receptor, has recently been approved for the treatment of hypertension.

Amiloride is excreted unchanged in the urine. Triamterene is metabolized in the liver, but renal excretion is a major route of elimination for the active form and the metabolites. Because
triamterene is extensively metabolized, it has a shorter half-life and must be given more frequently than amiloride. The structures of spironolactone, triamterene, and amiloride are shown in Figure 15–9.

Figure 15–9.

Pharmacodynamics

Potassium-sparing diuretics reduce Na\(^+\) absorption in the collecting tubules and ducts. Na\(^+\) absorption (and K\(^-\) secretion) at this site is regulated by aldosterone, as described above. Aldosterone antagonists interfere with this process. Similar effects are observed with respect to H\(^+\) handling by the intercalated cells of the collecting tubule, in part explaining the metabolic acidosis seen with aldosterone antagonists.

Spironolactone and eplerenone bind to aldosterone receptors and may also reduce the intracellular formation of active metabolites of aldosterone. Triamterene and amiloride do not block the aldosterone receptor but instead directly interfere with Na\(^+\) entry through the sodium-selective (ENaC) ion channels in the apical membrane of the collecting tubule. Since K\(^-\) secretion is coupled
with Na⁺ entry in this segment, these agents are also effective potassium-sparing diuretics.

The actions of triamterene and spironolactone depend on renal prostaglandin production. As described above for loop diuretics and thiazides, the actions of triamterene and spironolactone can also be inhibited by NSAIDs under certain conditions.

Clinical Indications & Dosage

These agents are most useful in states of mineralocorticoid excess, due either to primary hypersecretion (Conn's syndrome, ectopic ACTH production) or to secondary aldosteronism (from heart failure, hepatic cirrhosis, nephrotic syndrome, and other conditions associated with diminished effective intravascular volume) (Table 15–4). Use of other diuretics, like thiazides or loop agents, can cause or exacerbate volume contraction and thus intensify secondary aldosteronism. In the setting of enhanced mineralocorticoid secretion and continuing delivery of Na⁺ to distal nephron sites, renal K⁺ wasting occurs. Potassium-sparing diuretics of either type may be used in this setting to blunt the K⁺ secretory response.

Table 15–4. Potassium-Sparing Diuretics and Combination Preparations.

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Potassium-Sparing Agent</th>
<th>Hydrochlorothiazide</th>
<th>Frequency of Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldactazide</td>
<td>Spironolactone 25 mg</td>
<td>25 mg</td>
<td>1–4 times daily</td>
</tr>
<tr>
<td>Aldactone</td>
<td>Spironolactone 25 mg</td>
<td>. . .</td>
<td>1–4 times daily</td>
</tr>
<tr>
<td>Dyazide</td>
<td>Triamterene 50 mg</td>
<td>25 mg</td>
<td>1–4 times daily</td>
</tr>
<tr>
<td>Dyrenium</td>
<td>Triamterene 50 mg</td>
<td>. . .</td>
<td>1–3 times daily</td>
</tr>
<tr>
<td>Inspra</td>
<td>Eplerenone 25, 50 mg</td>
<td>. . .</td>
<td>Once or twice daily</td>
</tr>
<tr>
<td>Maxzide</td>
<td>Triamterene 75 mg</td>
<td>50 mg</td>
<td>Once daily</td>
</tr>
<tr>
<td>Maxzide-25</td>
<td>Triamterene 27.5 mg</td>
<td>25 mg</td>
<td>Once daily</td>
</tr>
<tr>
<td>Midamor</td>
<td>Amiloride 5 mg</td>
<td>. . .</td>
<td>Once daily</td>
</tr>
<tr>
<td>Moduretic</td>
<td>Amiloride 5 mg</td>
<td>50 mg</td>
<td>Once or twice daily</td>
</tr>
</tbody>
</table>

Eplerenone is currently approved for use only in hypertension.

Toxicity

Hyperkalemia

Unlike other diuretics, these agents can cause mild, moderate, or even life-threatening hyperkalemia. The risk of this complication is greatly increased in the presence of renal disease or of other drugs that reduce renin (β-blockers, NSAIDs) or angiotensin II activity (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor inhibitors). Since most other diuretic agents lead to K⁺ losses, hyperkalemia is more common when aldosterone antagonists are used as the sole diuretic agent, especially in patients with renal insufficiency. With fixed-dosage combinations of potassium-sparing and thiazide diuretics, the thiazide-induced hypokalemia and metabolic alkalosis are ameliorated by the aldosterone antagonist. However, owing to variations in
the bioavailability of the components of fixed-dosage forms, the thiazide-associated adverse effects may predominate. Therefore, it is generally preferable to adjust the doses of the two drugs separately.

Hyperchloremic Metabolic Acidosis

By inhibiting H⁺ secretion in parallel with K⁺ secretion, the potassium-sparing diuretics can cause acidosis similar to that seen with type IV renal tubular acidosis.

Gynecomastia

Synthetic steroids may cause endocrine abnormalities by effects on other steroid receptors. Gynecomastia, impotence, and benign prostatic hyperplasia have all been reported with spironolactone. Such effects have not been reported with eplerenone.

Acute Renal Failure

The combination of triamterene with indomethacin has been reported to cause acute renal failure. This has not been reported with other potassium-sparing agents.

Kidney Stones

Triamterene is poorly soluble and may precipitate in the urine, causing kidney stones.

Contraindications

These agents can cause severe, even fatal hyperkalemia in susceptible patients. Oral K⁺ administration should be discontinued if aldosterone antagonists are administered. Patients with chronic renal insufficiency are especially vulnerable and should rarely be treated with aldosterone antagonists. Concomitant use of other agents that blunt the renin-angiotensin system (β-blockers or ACE inhibitors) increases the likelihood of hyperkalemia. Patients with liver disease may have impaired metabolism of triamterene and spironolactone, and dosing must be carefully adjusted. Strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole) can markedly increase blood levels of eplerenone.

Agents That Alter Water Excretion

Osmotic Diuretics

The proximal tubule and descending limb of Henle's loop are freely permeable to water. An osmotic agent that is not reabsorbed causes water to be retained in these segments and promotes a water diuresis. Such agents can be used to reduce increased intracranial pressure and to promote prompt removal of renal toxins. The prototypic osmotic diuretic is mannitol.

Pharmacokinetics

Osmotic diuretics are poorly absorbed, which means that they must be given parenterally. If administered orally, mannitol causes osmotic diarrhea. Mannitol is not metabolized and is excreted primarily by glomerular filtration within 30–60 minutes, without any important tubular reabsorption or secretion.
Pharmacodynamics

Osmotic diuretics have their major effect in those segments of the nephron that are freely permeable to water: the proximal tubule and the descending limb of the loop of Henle. They also oppose the action of ADH in the collecting tubule. The presence of a nonreabsorbable solute such as mannitol prevents the normal absorption of water by interposing a countervailing osmotic force. As a result, urine volume increases. The increase in urine flow rate decreases the contact time between fluid and the tubular epithelium, thus reducing Na⁺ reabsorption. However, the resulting natriuresis is of lesser magnitude than the water diuresis, leading eventually to hypernatremia.

Clinical Indications & Dosage

to Increase Urine Volume

Osmotic diuretics are used to increase water excretion in preference to sodium excretion. This effect can be useful when avid Na⁺ retention limits the response to conventional agents. It can be used to maintain urine volume and to prevent anuria that might otherwise result from presentation of large pigment loads to the kidney (eg, from hemolysis or rhabdomyolysis). Some oliguric patients do not respond to an osmotic diuretic. Therefore, a test dose of mannitol (12.5 g intravenously) should be given prior to starting a continuous infusion. Mannitol should not be continued unless there is an increase in urine flow rate to more than 50 mL/h during the 3 hours following the test dose. Mannitol (12.5–25 g) can be repeated every 1–2 hours to maintain urine flow rate greater than 100 mL/h. Prolonged use of mannitol is not advised.

Reduction of Intracranial and Intraocular Pressure

Osmotic diuretics alter Starling forces so that water leaves cells and reduces intracellular volume. This effect is used to reduce intracranial pressure in neurologic conditions and to reduce intraocular pressure before ophthalmologic procedures. A dose of 1–2 g/kg mannitol is administered intravenously. Intracranial pressure, which must be monitored, should fall in 60–90 minutes.

Toxicity

Extracellular Volume Expansion

Mannitol is rapidly distributed in the extracellular compartment and extracts water from cells. Prior to the diuresis, this leads to expansion of the extracellular volume and hyponatremia. This effect can complicate heart failure and may produce florid pulmonary edema. Headache, nausea, and vomiting are commonly observed in patients treated with osmotic diuretics.

Dehydration and Hypernatremia

Excessive use of mannitol without adequate water replacement can ultimately lead to severe dehydration, free water losses, and hypernatremia. These complications can be avoided by careful attention to serum ion composition and fluid balance.

Antidiuretic hormone (ADH) Agonists

Vasopressin and desmopressin are used in the treatment of pituitary diabetes insipidus. They are discussed in Chapter 37: Hypothalamic & Pituitary Hormones.
Antidiuretic Hormone (ADH) Antagonists

A variety of medical conditions cause water retention as the result of ADH excess. Unfortunately, specific ADH antagonists are available only for investigational purposes. Two nonselective agents, lithium and demeclocycline (a tetracycline derivative), are of limited use in some situations.

Pharmacokinetics

Both lithium and demeclocycline are orally active. Lithium is excreted by the kidney, and demeclocycline is metabolized in the liver.

Pharmacodynamics

ADH antagonists inhibit the effects of ADH in the collecting tubule. Both lithium and demeclocycline appear to reduce the formation of cyclic adenosine monophosphate (cAMP) in response to ADH and also to interfere with the actions of cAMP in the collecting tubule cells.

Clinical Indications & Dosage

Syndrome of Inappropriate ADH Secretion (SIADH)

ADH antagonists are used to manage SIADH when water restriction has failed to correct the abnormality. This generally occurs in the outpatient setting, where water restriction cannot be enforced, or in the hospital when large quantities of intravenous fluid are administered with drugs. Lithium carbonate has been used to treat this syndrome, but the response is unpredictable. Serum levels of lithium must be monitored closely, as serum concentrations greater than 1 mmol/L are toxic. Demeclocycline, in dosages of 600–1200 mg/d, yields a more predictable result and is less toxic. Appropriate plasma levels (2 μg/mL) should be maintained by monitoring.

Other Causes of Elevated Antidiuretic Hormone (ADH)

ADH is also elevated in response to diminished effective circulating blood volume. When treatment by volume replacement is not possible, as in heart failure or liver disease, hyponatremia may result. As for SIADH, water restriction is the treatment of choice, but if it is not successful, demeclocycline may be used.

Toxicity

Nephrogenic Diabetes Insipidus

If serum Na⁺ is not monitored closely, ADH antagonists can cause severe hypernatremia and nephrogenic diabetes insipidus. If lithium is being used for an affective disorder, nephrogenic diabetes insipidus can be treated with a thiazide diuretic or amiloride (see below).

Renal Failure

Both lithium and demeclocycline have been reported to cause acute renal failure. Long-term lithium therapy may also cause chronic interstitial nephritis.

Other
Adverse effects associated with lithium therapy include tremulousness, mental obtundation, cardiotoxicity, thyroid dysfunction, and leukocytosis (see Chapter 29: Antipsychotic Agents & Lithium). Demeclocycline should be avoided in patients with liver disease (see Chapter 44: Chloramphenicol, Tetracyclines, Macrolides, Clindamycin, & Streptogramins) and in children younger than 12 years.

Diuretic Combinations

Loop Agents & Thiazides

Some patients are refractory to the usual dose of loop diuretics or become refractory after an initial response. Since these agents have a short half-life, refractoriness may be due to an excessively long interval between doses. Renal Na⁺ retention is enhanced during the time period when the drug is no longer active. After the dosing interval for loop agents is minimized or the dose is maximized, the use of two drugs acting at different nephron sites may exhibit synergy. Loop agents and thiazides in combination will often produce diuresis when neither agent acting alone is even minimally effective. There are several reasons for this phenomenon. First, salt and water reabsorption in either the thick ascending limb or the distal convoluted tubule can increase when the other is blocked. Inhibition of both can therefore produce more than an additive diuretic response. Second, thiazide diuretics may produce a mild natriuresis in the proximal tubule that is usually masked by increased reabsorption in the thick ascending limb. The combination of loop diuretics and thiazides will therefore blunt Na⁺ reabsorption, to some extent, from all three segments.

Metolazone is the usual choice of thiazide-like drug in patients refractory to loop agents alone, but it is likely that other thiazides would be as effective as metolazone. Moreover, metolazone is available only in an oral preparation, while chlorothiazide can be given parenterally.

The combination of loop diuretics and thiazides can mobilize large amounts of fluid, even in patients who have not responded to single agents. Therefore, close hemodynamic monitoring is essential. Routine outpatient use is not recommended. Furthermore, K⁺-wasting is extremely common and may require parenteral K⁺ administration with careful monitoring of fluid and electrolyte status.

Potassium-Sparing Diuretics & Loop Agents or Thiazides

Hypokalemia eventually develops in many patients who are placed on loop diuretics or thiazides. This can often be managed with dietary NaCl restriction. When hypokalemia cannot be managed in this way, or with dietary KCl supplements, the addition of a potassium-sparing diuretic can significantly lower potassium excretion. While this approach is generally safe, it should be avoided in patients with renal insufficiency in whom life-threatening hyperkalemia can develop in response to potassium-sparing diuretics.

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Clinical Pharmacology of Diuretic Agents

This section discusses the clinical use of diuretic agents in edematous and nonedematous states. The effects of these agents on urinary electrolyte excretion are shown in Table 15–5.
Edematous States

The most common reason for diuretic use is for reduction of peripheral or pulmonary edema that has accumulated as a result of cardiac, renal, or vascular diseases, or abnormalities in the blood oncotic pressure. Salt and water retention with edema formation often occurs when diminished blood delivery to the kidney is sensed as insufficient "effective" arterial blood volume. Judicious use of diuretics can mobilize interstitial edema fluid without significant reductions in plasma volume. However, excessive diuretic therapy in this setting may lead to further compromise of the effective arterial blood volume with reduction in perfusion of vital organs. Therefore, the use of diuretics to mobilize edema requires careful monitoring of the patient's hemodynamic status and an understanding of the pathophysiology of the underlying condition.

Heart Failure

When cardiac output is reduced by disease, the resultant changes in blood pressure and blood flow to the kidney are sensed as hypovolemia and thus induce renal retention of salt and water. This physiologic response initially expands the intravascular volume and venous return to the heart and may partially restore the cardiac output toward normal (see Chapter 13: Drugs Used in Heart Failure).

If the underlying disease causes cardiac function to deteriorate despite expansion of plasma volume, the kidney continues to retain salt and water, which then leaks from the vasculature and becomes interstitial or pulmonary edema. At this point, diuretic use becomes necessary to reduce the accumulation of edema, particularly that which is in the lungs. Reduction of pulmonary vascular congestion with diuretics may actually improve oxygenation and thereby improve myocardial function. Edema associated with heart failure is generally managed with loop diuretics. In some instances, salt and water retention may become so severe that a combination of thiazides and loop diuretics is necessary.

In treating the heart failure patient with diuretics, it must always be remembered that cardiac output in these patients is being maintained in part by high filling pressures and that excessive use of diuretics may diminish venous return and thereby impair cardiac output. This issue is especially
critical in right ventricular failure. Systemic rather than pulmonary vascular congestion is the hallmark of this disorder. Diuretic-induced volume contraction will predictably reduce venous return and can severely compromise cardiac output if left ventricular filling pressure is reduced below 15 mm Hg.

Diuretic-induced metabolic alkalosis is another adverse effect that may further compromise cardiac function. While this effect is generally treated with replacement of potassium and restoration of intravascular volume with saline, severe heart failure may preclude the use of saline even in patients who have received too much diuretic. In these cases, adjunctive use of acetazolamide can help correct the alkalosis.

Another serious toxicity of diuretic use, particularly in the cardiac patient, is hypokalemia. Hypokalemia can exacerbate underlying cardiac arrhythmias and contribute to digitalis toxicity. This can often be avoided by having the patient reduce sodium intake, thus decreasing sodium delivery to the K⁺-secreting collecting tubule. Patients who are noncompliant with a low sodium diet must take oral KCl supplements or a potassium-sparing diuretic or must stop using the thiazide diuretic.

Finally, it should be kept in mind that diuretics can never correct the underlying cardiac disease. Drugs that improve myocardial contractility or reduce peripheral vascular resistance are more direct approaches to the basic problem.

Kidney Disease

A variety of renal diseases may interfere with the kidney's critical role in volume homeostasis. Although renal disorders will occasionally cause salt wasting, most kidney diseases cause retention of salt and water. When loss of renal function is severe, diuretic agents are of little benefit, because there is insufficient glomerular filtration to sustain a natriuretic response. However, a large number of patients with milder degrees of renal insufficiency can be treated with diuretics when they retain sodium.

Many primary and secondary glomerular diseases, such as those associated with diabetes mellitus or systemic lupus erythematosus, exhibit renal retention of salt and water. The cause of this sodium retention is not precisely known, but it probably involves disordered regulation of the renal microcirculation and tubular function through release of vasoconstrictors, prostaglandins, cytokines, and other mediators. When edema or hypertension develops in these patients, diuretic therapy can be very effective. If heart failure is also present, see the warnings mentioned above.

Certain forms of renal disease, particularly diabetic nephropathy, are frequently associated with development of hyperkalemia at a relatively early stage of renal failure. In these cases, a thiazide or loop diuretic will enhance K⁺ excretion by increasing delivery of salt to the K⁺-secreting collecting tubule.

Patients with renal diseases leading to the nephrotic syndrome often present complex problems in volume management. These patients may have reduced plasma volume in conjunction with reduced plasma oncotic pressures, especially those with "minimal change" nephropathy. In these patients, diuretic use may cause further reductions in plasma volume that can impair glomerular filtration rate and may lead to orthostatic hypotension. However, most other causes of nephrotic syndrome are associated with a primary retention of salt and water by the kidney, leading to expanded plasma volume and hypertension despite the low plasma oncotic pressure. In these cases, diuretic therapy may be beneficial in controlling the volume-dependent component of hypertension. In choosing a
diuretic for the patient with kidney disease, there are a number of important limitations. Acetazolamide and potassium-sparing diuretics must usually be avoided because of their tendency to exacerbate acidosis and hyperkalemia, respectively. Thiazide diuretics are generally ineffective when glomerular filtration rate falls below 30 mL/min. Thus, loop diuretics are often the best choice in treating edema associated with kidney failure. Lastly, excessive use of diuretics will cause renal function to decline in all patients, but the consequences are more serious in those with underlying renal disease.

Hepatic Cirrhosis

Liver disease is often associated with edema and ascites in conjunction with elevated portal hydrostatic pressures and reduced plasma oncotic pressures. The mechanisms for retention of sodium by the kidney are complex. They probably involve a combination of factors, including diminished renal perfusion resulting from systemic vascular alterations, diminished plasma volume as the result of ascites formation, and diminished oncotic pressure from hypoalbuminemia. In addition, there may be primary sodium retention by the kidney. Plasma aldosterone levels are usually high in response to the reduction in effective circulating volume.

When ascites and edema become severe, diuretic therapy can be useful in initiating and maintaining diuresis. Cirrhotic patients are often resistant to loop diuretics, in part because of a decrease in secretion of the drug into the tubular fluid and in part because of high aldosterone levels leading to enhanced collecting duct salt reabsorption. In contrast, cirrhotic edema is unusually responsive to spironolactone. The combination of loop diuretics and spironolactone may be useful in some patients. However, even more than in heart failure, overly aggressive use of diuretics in this setting can be disastrous. Vigorous diuretic therapy can cause marked depletion of intravascular volume, hypokalemia, and metabolic alkalosis. Hepatorenal syndrome and hepatic encephalopathy are the unfortunate consequences of excessive diuretic use in the cirrhotic patient.

Idiopathic Edema

Despite intensive study, the pathophysiology of this disorder (fluctuating salt retention and edema) remains obscure. Some studies suggest that intermittent diuretic use may actually contribute to the syndrome. Therefore, idiopathic edema should be managed with mild salt restriction alone if possible.

Nondematosus States

Hypertension

The diuretic and mild vasodilator actions of the thiazides are useful in treating virtually all patients with essential hypertension, and may be completely sufficient in two thirds. Moderate restriction of dietary Na⁺ intake (60–100 meq/d) has been shown to potentiate the effects of diuretics in essential hypertension and to lessen renal K⁺ wasting.

A recent very large study (over 30,000 participants) has shown that inexpensive diuretics are similar or superior in outcomes to ACE inhibitor or calcium channel blocker therapy (ALLHAT, 2002). This important result reinforces the importance of thiazide therapy in hypertension.

Diuretics also play an important role in patients who require multiple drugs to control blood pressure. Diuretics enhance the efficacy of many agents, particularly the ACE inhibitors. Patients being treated with powerful vasodilators such as hydralazine or minoxidil usually require diuretics
simultaneously because the vasodilators cause significant salt and water retention.

Nephrolithiasis

Approximately two thirds of all renal stones contain calcium phosphate or calcium oxalate. Many patients with such stones exhibit a renal defect in calcium reabsorption that causes hypercalciuria. This can be treated with thiazide diuretics, which enhance calcium reabsorption in the distal convoluted tubule and thus reduce the urinary calcium concentration. Salt intake must be reduced in this setting, as excess dietary NaCl will overwhelm the hypocalciuric effect of thiazides. Calcium stones may also be caused by increased intestinal absorption of calcium, or they may be idiopathic. In these situations, thiazides are also effective, but should be used as adjunctive therapy with decreased calcium intake and other measures.

Hypercalcemia

Hypercalcemia can be a medical emergency. Since the loop of Henle is an important site of calcium reabsorption, loop diuretics can be quite effective in promoting calcium diuresis. However, loop diuretics alone can cause marked volume contraction. If this occurs, loop diuretics are ineffective (and potentially counterproductive) because calcium reabsorption in the proximal tubule is enhanced. Thus, saline must be administered simultaneously with loop diuretics if an effective calcium diuresis is to be achieved. The usual approach is to infuse normal saline and furosemide (80–120 mg) intravenously. Once the diuresis begins, the rate of saline infusion can be matched with the urine flow rate to avoid volume depletion. Potassium may be added to the saline infusion as needed.

Diabetes Insipidus

Thiazide diuretics can reduce polyuria and polydipsia in patients who are not responsive to ADH. This seemingly paradoxical beneficial effect is mediated through plasma volume reduction, with an associated fall in glomerular filtration rate, enhanced proximal reabsorption of NaCl and water, and decreased delivery of fluid to the diluting segments. Thus, the maximum volume of dilute urine that can be produced is lowered and thiazides can significantly reduce urine flow in the polyuric patient. Dietary sodium restriction can potentiate the beneficial effects of thiazides on urine volume in this setting. Lithium, used in the treatment of manic-depressive disorder, is a common cause of drug-induced diabetes insipidus, and thiazide diuretics have been found to be helpful in treating it. Serum lithium levels must be carefully monitored in this situation, since diuretics may reduce renal clearance of lithium and raise plasma lithium levels into the toxic range (see Chapter 29: Antipsychotic Agents & Lithium). Lithium polyuria can also be partially reversed by amiloride, which appears to block lithium entry into collecting duct cells, much as it blocks Na⁺ entry.

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Preparations Available

**Acetazolamide** (generic, Diamox)

Oral: 125, 250 mg tablets

Oral sustained-release: 500 mg capsules
Parenteral: 500 mg powder for injection

**Amiloride** (generic, Midamor, combination drugs)
Oral: 5 mg tablets

**Bendroflumethiazide** (Naturetin)
Oral: 5, 10 mg tablets

**Benzthiazide** (Exna, combination drugs)
Oral: 50 mg tablets

**Brinzolamide** (Azopt)
Ophthalmic: 1% suspension

**Bumetanide** (generic, Bumex)
Oral: 0.5, 1, 2 mg tablets
Parenteral: 0.5 mg/2 mL ampule for IV or IM injection

**Chlorothiazide** (generic, Diuril, others)
Oral: 250, 500 mg tablets; 250 mg/5 mL oral suspension
Parenteral: 500 mg for injection

**Chlorthalidone** (generic, Thalitone, combination drugs)
Oral: 15, 25, 50, 100 mg tablets

**Demeclocycline** (Declomycin)
Oral: 150 mg tablets and capsules; 300 mg tablets

**Dichlorphenamide** (Daranide)
Oral: 50 mg tablets

**Dorzolamide** (Trusopt)
Ophthalmic: 2% solution

**Eplerenone** (Inspra)
Oral: 25, 50, 100 mg tablets
Ethacrynic acid (Edecrin)
Oral: 25, 50 mg tablets
Parenteral: 50 mg IV injection

Furosemide (generic, Lasix, others)
Oral: 20, 40, 80 mg tablets; 8 mg/mL solutions
Parenteral: 10 mg/mL for IM or IV injection

Hydrochlorothiazide (generic, Microzide, Hydro-DIURIL, combination drugs)
Oral: 12.5 mg capsules; 25, 50, 100 mg tablets; 10 mg/mL solution

Hydroflumethiazide (generic, Diucardin)
Oral: 50 mg tablets

Indapamide (generic, Lozol)
Oral: 1.25, 2.5 mg tablets

Mannitol (generic, Osmolrol)
Parenteral: 5, 10, 15, 20, 25% for injection

Methazolamide (generic, Neptazane)
Oral: 25, 50 mg tablets

Methyclothiazide (generic, Aquatensen)
Oral: 2.5, 5 mg tablets

Metolazone (Mykrox, Zaroxolyn) (Note: Bio-
Availability of Mykrox is greater than that of Zaroxolyn.)
Oral: 0.5 (Mykrox); 2.5, 5, 10 mg (Zaroxolyn) tablets

Polythiazide (Renese)
Oral: 1, 2, 4 mg tablets

Quinethazone (Hydromox)
Oral: 50 mg tablets
Spironolactone (generic, Aldactone)
Oral: 25, 50, 100 mg tablets

Torsemide (Demadex)
Oral: 5, 10, 20, 100 mg tablets
Parenteral: 10 mg/mL for injection

Triamterene (Dyrenium)
Oral: 50, 100 mg capsules

Trichlormethiazide (generic, Diurese, others)
Oral: 2, 4 mg tablets

Section IV. Drugs with Important Actions on Smooth Muscle

Histamine, Serotonin, & the Ergot Alkaloids: Introduction

Histamine and serotonin (5-hydroxytryptamine) are biologically active amines that are found in many tissues, have complex physiologic and pathologic effects through multiple receptor subtypes, and are often released locally. Together with endogenous peptides (see Chapter 17: Vasoactive Peptides), prostaglandins and leukotrienes (see Chapter 18: The Eicosanoids: Prostaglandins, Thromboxanes, Leukotrienes, & Related Compounds), and cytokines (see Chapter 56: Immunopharmacology), they are sometimes called autacoids (Gk "self-remedy") or local hormones in recognition of these properties.

Because of their broad and largely undesirable effects, neither histamine nor serotonin has any clinical application in the treatment of disease. However, compounds that selectively activate certain receptor subtypes or selectively antagonize the actions of these amines are of considerable clinical usefulness. This chapter therefore emphasizes the basic pharmacology of the agonist amines and the clinical pharmacology of the more selective agonist and antagonist drugs. The ergot alkaloids, compounds with partial agonist activity at serotonin and several other receptors, are discussed at the end of the chapter.

Histamine

Histamine was synthesized in 1907 and later isolated from mammalian tissues. Early hypotheses concerning the possible physiologic roles of tissue histamine were based on similarities between histamine's actions and the symptoms of anaphylactic shock and tissue injury. Marked species variation is observed, but in humans histamine is an important mediator of immediate allergic and