21 Diuretic Drugs

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DRUG LIST

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By selectively regulating solute or fluid reabsorption, the kidneys play the major role in maintaining the volume and composition of extracellular fluid. Many diseases, including congestive heart failure, hepatic cirrhosis, and Cushing's syndrome (glucocorticoid excess), are associated with or cause significant alterations in extracellular fluid balance. *Diuretics inhibit renal sodium transport and thereby interfere with the normal regulatory activity of the kidney.* In some instances, administration of a diuretic drug is the primary treatment indicated, while in others it is one of several drugs that are used as part of a treatment regimen. In either case, an ideal diuretic would be one that caused the excretion of "extra" urine with an electrolyte composition similar to that of normal plasma. No such diuretic exists. Thus, although diuretic therapy provides welcome relief from pulmonary congestion, ascites, edema, and hypertension, it also invites complications of organ hypoperfusion that may be accompanied by marked distortions of plasma composition.

This chapter includes an overview of the features of fluid balance and renal function that are essential to understanding diuretic action, a discussion of the uses of diuretics for treating abnormalities of fluid balance, and a detailed description of the various classes of diuretics. The practitioner who is armed with the knowledge of the mechanism of action of diuretic drugs and with appropriate recognition and respect for their potential side effects can use these compounds with a high degree of efficacy and safety.

BODY WATER AND ELECTROLYTE METABOLISM

Body fluids are partitioned between the intracellular fluids (ICF), which constitute two-thirds of total body water, and extracellular fluids (ECF), which constitute one-third of total body water. The ECF consists of plasma and interstitial fluid plus lymph. The ionic composition differs substantially between ECF and ICF (Table 21.1). Sodium is the primary cation in ECF, whereas potassium is the principal intracellular cation.

The concentrations and distribution of electrolytes are not fixed, because cell membranes are permeant to ions and to water. Movement of ions and water in and out of cells is determined by the balance of thermodynamic forces, which are normally close to equilibrium. Selective changes of ion concentrations cause movement of water in or out of cells to compensate for these alterations. The kidneys are a major site where changes in salt or water are sensed. The loss of fluids due to illness or disease may alter intracellular and extracellular electrolyte concentrations, with attendant changes in fluid movement in or out of cells. Changes of extracellular or intracellular ion concentrations, particularly for potassium, sodium, and calcium, can have profound effects on neuronal excitability and contractility of the heart and other muscles.

Glomerular Filtration

Urine formation begins with the ultrafiltration of blood at the glomerulus. None of the available diuretics exerts its effects by altering the rate of glomerular filtration. Some agents, discussed later, reduce the glomerular filtration rate (GFR). However, this generally is an undesired or adverse reaction. Furthermore, at reduced GFRs, the delivery of sodium to the loop of Henle and the distal convoluted tubule, where the most efficacious classes of diuretics act, may be sufficiently compromised to reduce the action of the drugs. *Understanding the process of filtration is important to understanding the pharmacokinetics of diuretic action because most of these agents exert their inhibitory effect by blocking the entry of sodium from the urine into the cell.* Therefore, these diuretics have to be present at sufficient concentrations within the tubular fluid to exert their inhibitory action on sodium transport. Most diuretics are variably bound to albumin and therefore are only partially filtered. They gain access to the tubular fluid by secretion into the proximal tubule (discussed later). In conditions of hemorrhage or liver disease resulting in hypoalbuminemia, the concentration of albumin is reduced and the fraction of bound diuretic is altered. Although this may suggest that more of the diuretic is unbound (or free) and filtered at the glomerulus, this does not occur. The decrease in Starling forces, which govern the rate of fluid filtration across the glomerular and other capillaries, now results in greater entry of fluid into the interstitial space.

Most estimates of diuretic binding to albumin assume that the protein itself is not altered as part of the disease process. In renal failure, however, the number of binding sites on the protein may change, which in turn affects the pharmacokinetics and dynamics of the response to an administered diuretic. Another setting associated with diminished effective diuretic concentrations occurs in *nephrotic syndrome*. In this disease, protein escaping from the glomerulus into the tubules binds the diuretic within the lumen. The bound drug is unavailable to exert its inhibitory effect on sodium transport.

TABLE 21.1 Approximate Electrolyte Content of Body Fluids

Ions	Extracellular Fluid (mEq/L)	Intracellular Fluid (mEq/L)
Cations		
Sodium	140.0	10
Potassium	4.5	125
Magnesium	1.7	40
Anions		
Bicarbonate	25.0	10
Chloride	100.0	25
Phosphate	3.0	150
Protein	15.0	40

Tubular Reabsorption and Secretion

Two additional processes that participate in urine formation are reabsorption and secretion. Reabsorption defines movement of solute or water from the tubule lumen to the blood, whereas secretion denotes transport from the blood to the tubule lumen. For many solutes, such as organic acids, transport proceeds in both directions. Net transport is determined by the dominant flux. As described later, the tubular secretion of some diuretics is critical for their action. The nephron sites where ions and organic solutes are transported are spatially separated. Figure 21.1 illustrates the various nephron segments, the primary sites of solute transport, and the magnitude of sodium reabsorption. In some instances, as with sodium, several transport mechanisms mediate its reabsorption. Importantly, each mechanism is spatially separated within different nephron segments. This is important in understanding diuretic action, which is specific to particular sodium transport mechanisms. Furthermore, some common side effects caused by diuretics, such as potassium wasting, develop as a direct consequence of the mechanism and the particular location of diuretic action at sites upstream from

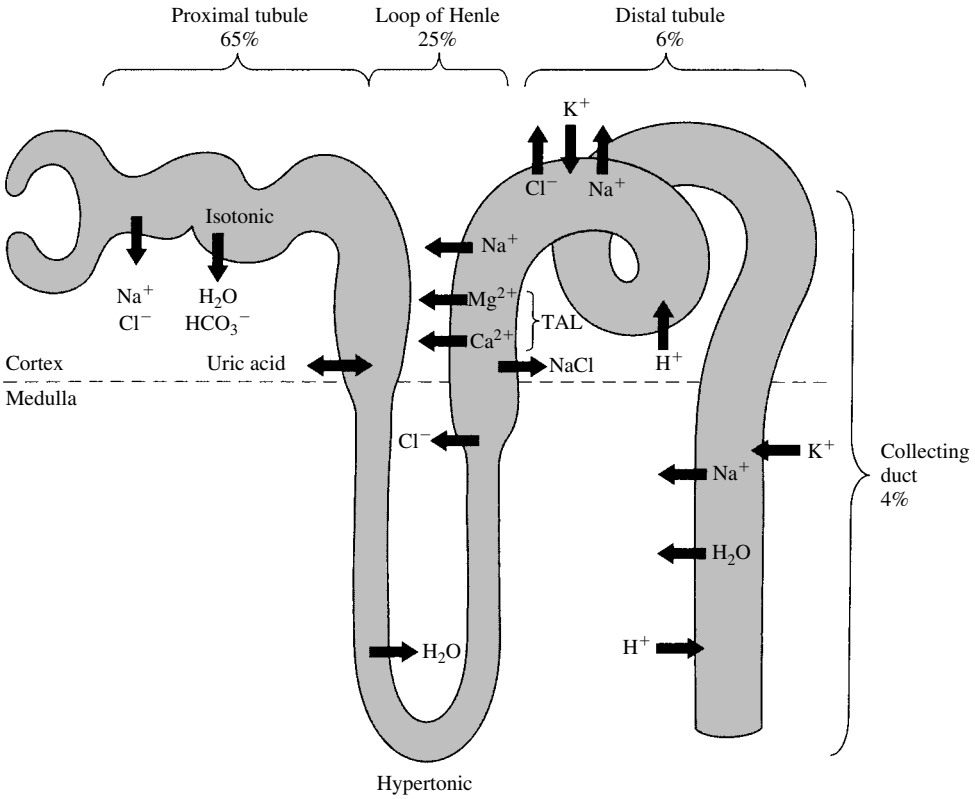

FIGURE 21.1
A nephron, showing the major sites and percentage (in braces) of sodium absorption along with other features of solute transport. The filtered load = GFR (180 L/day) ×plasma Na^+ (140 mEq/L) or 25,200 mEq/day. About 1% of this amount is excreted in voided urine. Sites where tubular fluid is isosmotic, hypertonic, or hypotonic relative to plasma are shown. PCT, proximal convoluted tubule; LH, loop of Henle; DCT, distal convoluted tubule; CCD, cortical collecting duct; TAL, thick ascending loop.

the distal nephron. The emphasis of the following sections is on the tubular transport properties that affect or are influenced by diuretics.

Proximal Tubule

The majority (two-thirds) of filtered Na^+ is reabsorbed by proximal tubules. A number of transport mechanisms, including Na^+–H^+ exchange, Na^+–phosphate cotransport, Na^+–glucose, Na^+–lactate, and Na^+–amino acid cotransport, participate in Na^+ reabsorption. *Na^+–H^+ exchange is the primary mechanism of Na^+ transport in the proximal tubules* (Fig. 21.2). Na^+ and HCO_3^- enter the proximal tubule after being filtered at the glomerulus. Na^+ diffusion from the lumen into the cell is coupled to the extrusion of a hydrogen ion into the lumen. In the lumen, the H^+ combines with HCO_3^- to form carbonic acid (H_2CO_3), which in the presence of the zinc metalloenzyme *carbonic anhydrase* is rapidly converted to H_2O and CO_2. The CO_2 generated in this reaction readily diffuses into proximal tubule cells, and the process reverses. That is, the CO_2 that was generated combines with intracellular water and in the presence of cytoplasmic carbonic anhydrase forms carbonic acid. The carbonic acid in turn is dehydrated to HCO_3^- and H^+. The HCO_3^- is transported across the basolateral membranes into the blood, while the H^+ becomes available for another cycle of Na^+–H^+ exchange. The net result of this process is the reabsorption of Na^+ and HCO_3^-. *Carbonic anhydrase plays a pivotal role both in the cytoplasm and in the lumen in mediating Na^+–H^+ exchange and thus in some 40% of total proximal Na^+ and H_2O absorption.* If this enzyme is inhibited, Na^+ absorption is slowed because of the accumulation of H_2CO_3 in the lumen and the lack of H^+ within the cell that can be exchanged for Na^+. Similarly, HCO_3^- reabsorption is reduced with a concomitant increase of HCO_3^- excretion.

Several additional noteworthy features of proximal Na^+ transport are relevant to diuretic action. First, since several transport proteins mediate proximal Na^+ reabsorption, no single diuretic would be expected to inhibit all these processes. Consequently, inhibition of any one mechanism leaves the others unaffected and able to

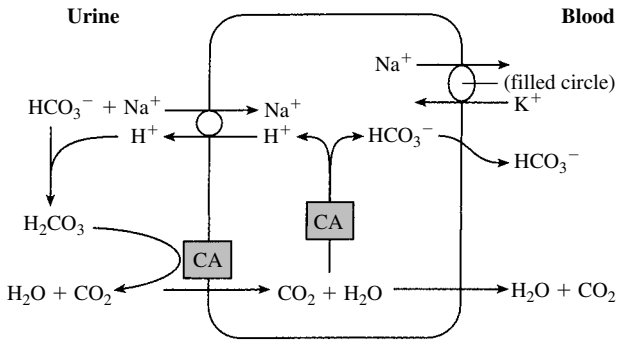

FIGURE 21.2
Carbonic anhydrase-mediated Na^+/H^+ exchange in proximal convoluted tubule. Na^+/H^+ exchange across apical cell membranes is shown by the open circle. Carbonic anhydrase (CA) is present in a membrane-bound form in the apical membrane and a soluble form within the cytoplasm. The Na^+/K^+-ATPase is shown by the filled circle at the basolateral membrane.

continue to absorb the remaining Na^+. Second, Na^+ that escapes proximal tubular transport is delivered to more distal nephron segments, where compensatory reabsorption reduces the impact of diminished upstream Na^+ recovery. *Hence, although most Na^+ is reabsorbed by proximal tubules, diuretics inhibiting its transport in this nephron segment have only a modest effect in reducing overall Na^+ reabsorption.*

Most of the K^+ that is filtered at the glomerulus is reabsorbed by proximal tubules. K^+ appearing in the voided urine was secreted by distal and terminal nephron segments (discussed later).

Another significant feature of the proximal tubule is that it is the site of organic acid transport. This is important in understanding both the pharmacokinetics of many of the diuretics, most of which are weak organic acids, and also certain of the side effects induced by these drugs. For instance, uric acid, which is the end product of purine metabolism in humans, is both reabsorbed and secreted by the organic acid transport pathway (see Chapter 37).

An important functional characteristic of the proximal tubule is that fluid reabsorption is isosmotic; that is, proximal reabsorbed tubular fluid has the same osmotic concentration as plasma. Solute and water are transported in the same proportions as in the plasma because of the high water permeability of the proximal tubule. Thus, the total solute concentration of the fluid in the proximal convoluted tubule does not change as the fluid moves toward the descending loop of Henle. The corollary of this high water permeability is that *unabsorbable or poorly permeable solutes in the luminal fluid retard fluid absorption by proximal tubules.* This is an important consideration for understanding the actions of osmotic diuretics.

Loop of Henle

Descending Thin Limb

The descending thin limb of Henle's loop begins at the end of the proximal straight tubule and continues past the hairpin bend in Henle's loop to the start of the thick ascending limb. *Descending thin limbs are virtually devoid of Na^+–K^+–ATPase and therefore do not participate in active sodium reabsorption.* Moreover, the descending thin limb is highly impermeable to sodium and urea. Although the descending thin limb is not a site of diuretic action per se, its permeability contributes importantly to the action of osmotic agents because of its high water permeability. The presence of unabsorbable solute in the lumen retards water absorption and thereby contributes to the osmotic diuresis. Furthermore, drugs and other compounds in the tubular fluid are concentrated as a result of the removal of water as the descending thin limb of long-looped nephrons passes through the hypertonic renal medulla. The elevation of drug concentrations for agents working at downstream segments may aid in raising the drug concentrations to the levels necessary for diuretic action. These elevated concentrations would not be achieved in the systemic circulation. The selective increase in the concentration of these drugs within the tubular fluid may account for the relatively selective action of these compounds on the kidney, even though the same sodium transport proteins are present in other tissues.

Thick Ascending Limb

The thick ascending limb is a major site of salt absorption and a principal locus of action of an important group of diuretics. Approximately 25% of the filtered sodium is reabsorbed by the thick ascending limb of Henle's loop. Sodium transport in this nephron segment is mediated by Na^+–K^+–$2Cl^-$ cotransport (Fig. 21.3). This transporter is present only on the apical, or urine, side of the tubule cells. Although K^+ is taken up by the transporter, little net K^+ reabsorption occurs in the thick ascending limb because much of the absorbed K^+

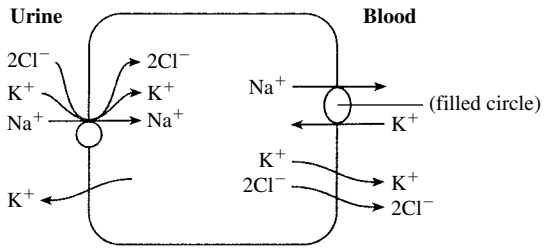

FIGURE 21.3
Na^+-K^+-$2Cl^-$ cotransport in thick ascending limbs. This transport protein is shown by the open circle on the apical cell membrane. Although K^+ enters the cell on the cotransporter, little net K^+ reabsorption occurs because much of the K^+ is recycled back to the urine from the cell.

is recycled across the apical cell membrane back into the urine. The recirculation of K^+ is important to the generation of the electropositive voltage within the lumen, which serves as a driving force for passive transport of Na^+, Ca^{++}, and Mg^{++} through the tight junctions joining adjacent cells. Hence, *although K^+ is transported by the Na^+–K^+–2Cl cotransporter, the primary solute absorbed into the blood is NaCl.*

Sodium reabsorption in thick ascending limbs depends on the amount, or load, of salt delivered from upstream segments. *The amount of sodium reabsorbed by the thick ascending limb increases as more is delivered.* In situations such as severe volume contraction, when abnormally large amounts of sodium are reabsorbed by proximal tubules, little sodium reaches the thick ascending limb. In this setting the diuretic action of agents that block Na^+–K^+–$2Cl^-$ cotransport is impaired. This is attributable to the reduction of sodium in the tubular fluid of the thick ascending limb.

The reabsorption of NaCl by the thick ascending limb is not accompanied by water because of the low hydraulic permeability of this nephron segment. Consequently, *the tubular fluid becomes dilute as it passes through the thick ascending limbs.* This process contributes to normal urinary dilution. Moreover, when Na^+ transport in thick ascending limbs is inhibited, urinary dilution will diminish.

The thick ascending limb is also an important site for the reabsorption of Ca^{++} and Mg^{++}. These cations are mostly passively reabsorbed through the paracellular pathway between adjacent cells. The driving force for their transport is the transepithelial voltage, which is established by the rate of Na^+ reabsorption. Thus, changes in voltage cause proportionate changes in the rate and magnitude of Ca^{++} and Mg^{++} reabsorption.

Distal Convoluted Tubule

Sodium reabsorption continues in the distal convoluted tubule, which accounts for some 6 to 8% of the transport of sodium. The entry of Na^+ across the apical cell membrane is mediated by Na^+–Cl^- cotransport (Fig. 21.4). This protein is a distinct gene product that differs from the Na^+–K^+–2C1$^-$ cotransporter in thick ascending limbs.

The permeability properties of the distal convoluted tubule are regulated by antidiuretic hormone (ADH, or *vasopressin*). In hypotonic conditions, ADH secretion by the posterior pituitary is suppressed and the distal convoluted tubule is impermeant to water. Conversely, in hypertonic or volume-contracted states, ADH is released by the posterior pituitary and increases the permeability and water reabsorption by the distal convoluted tubule.

The distal convoluted tubule, along with the collecting duct, is an important site of K^+ transport. The direction (reabsorptive or secretory) and magnitude of K^+ transport is governed by the metabolic state of the individual, the amount and rate of Na^+ and fluid flow through the distal convoluted tubule, and the action of aldosterone. As noted earlier, the main source of urinary K^+ is tubular secretion by distal convoluted tubules and collecting ducts. K^+ secretion also increases during alkalosis and with elevated dietary K^+ intake. *Increases in the rate or amount of Na^+ absorption or of the rate of fluid flow through the distal convoluted tubule stimulate K^+ secretion into the tubular fluid.* These observations are especially important because they account for the elevated K^+ losses that attend the use of diuretics acting in more proximate segments, such as thick ascending limbs and distal convoluted tubules.

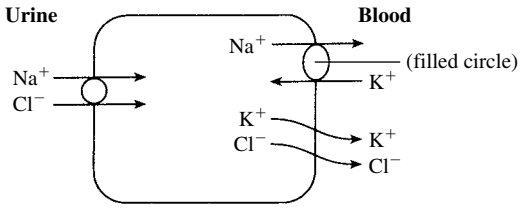

FIGURE 21.4
Na^+-Cl^- cotransport in distal convoluted tubules. This transport protein, shown by the open circle on the apical cell membrane, does not require K^+ for its function. It is a different gene product than the Na^+-K^+-$2Cl^-$cotransporter. Na^+-Cl^-cotransport is limited largely, if not entirely, to the distal convoluted tubules.

In distal convoluted tubules, calcium is transported by an active transport mechanism through rather than between cells. Moreover, in distal convoluted tubules there is a reciprocal relation between the direction and magnitude of calcium on Na^+ transport. As Na^+ absorption increases, calcium decreases, and conversely, reductions of Na^+ absorption are accompanied by elevated calcium reabsorption. This interaction has important implications for diuretics acting in the distal convoluted tubule.

Collecting Ducts

The collecting ducts, which consist of cortical and medullary segments, reabsorb the final 5 to 7% of the filtered Na^+. The epithelium forming the collecting ducts consists of two distinct cell types: *principal cells* and *intercalated cells.* The relative preponderance of the two cell types varies along the length of the collecting duct and between nephron segments. Principal cells are responsible for the reabsorption of Na^+ and the secretion of K^+ (Fig. 21.5). Na^+ enters the principal cell from the tubular fluid through a unique and highly selective epithelial Na^+ channel, ENaC. Intercalated cells reabsorb HCO_3^- and K^+ and secrete H^+. Normally, H^+ is secreted into the urine and HCO_3^- is reabsorbed, while

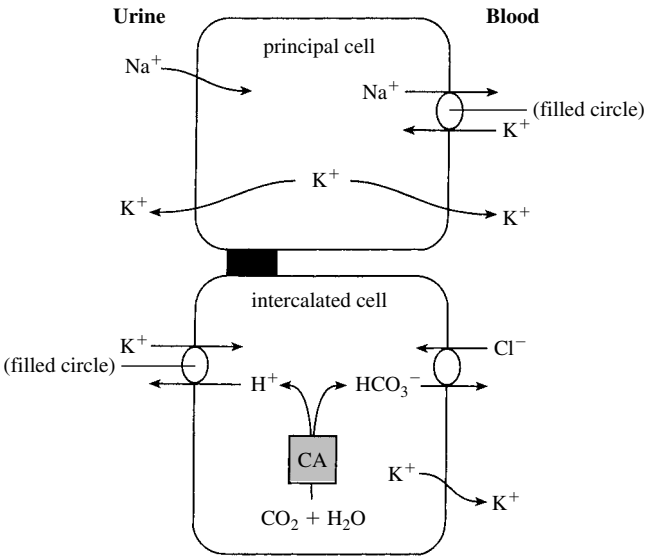

FIGURE 21.5
Principal and intercalated cells of the collecting ducts. Principal (top) cells reabsorb Na^+ and the secreted K^+. Na^+ entry across apical cell membranes is mediated by a Na^+ channel. Na^+ exit across basolateral cell membranes is effected by the Na^+/K^+-ATPase, shown by the filled circle in the principal cell. The rates of Na^+ reabsorption and K^+ secretion are regulated by aldosterone. Intercalated (bottom) cells reabsorb K^+ and $HCO_3^-$and secretes H^+. K^+ entry and H^+ secretion are mediated by an H^+/K^+ ATPase, which is shown by the filled circle in the apical cell membrane of the intercalated cell.

little net K^+ transport occurs under K^+-replete conditions.

Aldosterone stimulates the rates of Na^+ reabsorption and K^+ secretion. This is relevant to the action of spironolactone, a diuretic that is a competitive inhibitor of aldosterone (discussed later). It is also pertinent because administration of diuretics can cause secondary hyperaldosteronism, which may exaggerate the potassium wasting that is a consequence of the increased delivery of Na^+ and enhanced flow through distal convoluted tubules and collecting ducts.

ADH can significantly modify the total urine volume along with its solute concentration. In the absence of ADH, the collecting ducts are essentially impermeable to water. Little fluid is reabsorbed, and the final urine is dilute with respect to plasma. In other words, the clearance of solute-free water (C_{H_2O}) is greater than the osmolar clearance (C_{osm}). ADH increases water permeability, allowing reabsorption of fluid from the tubules into the interstitium. The driving force for water transport is the osmotic gradient between the medullary interstitium and the tubular fluid. NaCl and urea are the two major solutes accounting for the hypertonicity. The NaCl in the interstitium results from the reabsorption of Na^+ by thick ascending limbs. Thus, in the absence of ADH, Na^+ reabsorption contributes to medullary interstitial hypertonicity, water abstraction from the collecting ducts, and the formation of concentrated urine. Diuretics blocking Na^+ reabsorption by thick ascending limbs will therefore attenuate the formation of dilute urine (C_{H_2O}) in hypotonic states when ADH is absent or low. Conversely, in hypertonic conditions, when ADH levels are high and diuretics are blocking Na^+ reabsorption by the thick ascending limbs, the generation of concentrated urine is reduced, and C_{osm} is greater than C_{H_2O}.

DIURETIC DRUGS

Many drugs can enhance urine flow. For example, by increasing cardiac output in the patient with congestive heart failure, digitalis administration will mobilize edema fluid and diuresis. The term *diuretic*, however, is generally restricted to agents that act directly on the kidney. *From a therapeutic point of view, diuretics are considered to be substances that aid in removing excess extracellular fluid and electrolytes.* In the main, they accomplish this by decreasing salt and water reabsorption in the tubules.

Carbonic Anhydrase Inhibitors

In the late 1930s, it was reported that sulfanilamide and other *N*-unsubstituted sulfonamides could induce diuresis characterized by excretion of an alkaline urine that is high in sodium bicarbonate. It was soon realized that these compounds inhibited *carbonic anhydrase*, an enzyme highly concentrated in renal tissue, and that this enzyme was important for the tubular reabsorption of bicarbonate. The common structural motif of carbonic anhydrase inhibitors is an unsubstituted sulfonamide moiety. These findings led to the synthesis of a series of compounds capable of inhibiting carbonic anhydrase, the most useful of which was acetazolamide (*Diamox*), which is considered the prototype of this class of diuretics. Although the clinical use of carbonic anhydrase inhibitors has greatly diminished since the 1960s, when their use was increasingly supplanted by the more potent thiazide diuretics (discussed later), they have been vitally important in helping to delineate the physiological role of carbonic anhydrase in electrolyte conservation and acid-base balance. Acetazolamide (*Diamox*), dichlorphenamide (*Daranide*), and methazolamide (*Neptazane*) are the carbonic anhydrase inhibitors available in the United States.

Inhibition of proximal tubule brush border carbonic anhydrase decreases bicarbonate reabsorption, and this accounts for their diuretic effect. In addition, carbonic anhydrase inhibitors affect both distal tubule and collecting duct H^+ secretion by inhibiting intracellular carbonic anhydrase.

Renal excretion of Na^+, K^+, and HCO_3^- is increased by carbonic anhydrase inhibition. Diuresis following carbonic anhydrase inhibition consists primarily of Na^+ and HCO_3^-, with only a small increase of Cl^-excretion. This so-called bicarbonate diuresis is unique to carbonic anhydrase inhibitors. The fractional excretion of Na^+ is generally limited to 5%, as a consequence of downstream compensatory Na^+ reabsorption. Although distal nephron sites recapture much of the Na^+, they possess only a limited ability to absorb HCO_3^-. Fractional K^+ excretion, however, can be as much as 70%. *Potassium loss is particularly marked following carbonic anhydrase inhibition*, both because of the presence of poorly reabsorbable HCO_3^- accompanying Na^+ and because of the inhibition of the Na^+–H^+ exchange mechanism. Elevated urinary HCO_3^- excretion leads to the formation of alkaline urine and to metabolic acidosis as a result of both HCO_3^- loss and impaired H^+ secretion.

The main therapeutic use of carbonic anhydrase inhibitors is not for the production of diuresis but in the treatment of glaucoma. This is true especially of the topically applied compound dorzolamide (*Trusopt*). Because the formation of aqueous humor in the eye depends on carbonic anhydrase, acetazolamide has proved to be a useful adjunct to the usual therapy for lowering intraocular pressure. Although acetazolamide has been used in the treatment of epilepsy, particularly absence epilepsy, it is not known whether the beneficial results are due to carbonic anhydrase inhibition or to the resulting acidosis. Oral carbonic anhydrase inhibitors are also useful in preventing or treating acute mountain sickness. Adverse reactions are minor; they include loss of appetite, drowsiness, confusion, and tingling in the extremities. Animal studies have shown some teratogenic potential, so the use of carbonic anhydrase inhibitors is not recommended during the first trimester of pregnancy.

Thiazide Diuretics

Thiazide diuretics consist of two distinct groups: those containing a benzothiadiazine ring, such as hydrochlorothiazide and chlorothiazide, referred to as thiazide diuretics, and those that lack this heterocyclic structure but contain an unsubstituted sulfonamide group. The latter are called thiazidelike diuretics; they include metolazone, xipamide, and indapamide. The major thiazide and thiazidelike drugs available in the United States are bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, and trichlormethiazide; and chlorthalidone, indapamide, metolazone, and quinethazone, respectively.

Despite the structural distinctions, the drugs share the functional attribute of increasing sodium and chloride excretion by inhibiting Na^+–Cl^- cotransport in distal convoluted tubules.

Although chlorothiazide and its subsequently developed congeners (Table 21.2) retain the sulfamyl group SO_2NH_2, which is necessary for carbonic anhydrase inhibition, their primary effect does not rely on carbonic anhydrase inhibition.

The thiazidelike compounds, including chlorthalidone (*Hygroton*), quinethazone (*Hydromox*), and metolazone (*Zaroxolyn*) have similar mechanisms of action, but they differ substantially from one another in their duration of action, the degree of carbonic anhydrase inhibition, and the dose required for maximum natriuretic activity.

Mechanism of Action

Thiazide diuretics act in the distal convoluted tubule, where they block Na^+–Cl^- cotransport (Fig. 21.4). The Na^+–Cl^- cotransport takes place on the luminal surface of distal convoluted tubules. Thus, to exert their diuretic action, the thiazides must reach the luminal fluid. Since the thiazide diuretics are largely bound to plasma proteins and therefore are not readily filtered across the glomeruli, access to the luminal fluid is accomplished by the proximal tubule organic acid secretory system. The drugs then travel along the nephron, presumably being concentrated as fluid is abstracted, until they reach their site of inhibitory action in the distal convoluted tubule.

Especially at higher doses, administration of some of the thiazides results in some degree of carbonic anhydrase inhibition. However, *at usual doses, only chlorothiazide shows any appreciable carbonic anhydrase inhibitory activity.*

Renal Response

When administered at maximal doses, chlorothiazide markedly increases excretion of Na^+, K^+, Cl^-, and HCO_3^-. Maximal diuresis may approach values as high

TABLE 21.2 Some Commonly Prescribed Thiazide and Thiazidelike Diuretics

Generic Name	Trade Names
Bendroflumethiazide	Naturetin
Benzthiazide	Aquatag, Exna
Chlorothiazide	Diuril
Hydrochlorothiazide	Esidrix, HydroDIURIL
Hydroflumethiazide	Saluron, Diucardin
Methyclothiazide	Enduron, Aquatensen
Polythiazide	Renese
Trichlormethiazide	Naqua, Metahydrin
Chlorthalidone	Hygroton
Indapamide	Lozol
Metolazone	Zaroxolyn, Diulo
Quinethazone	Hydromox

as 10% of the filtered load, although fractional Na^+ excretions of 5% are more common. At usual clinical doses, however, the thiazide diuretics generally increase excretion of Na^+ and Cl^-, with an accompanying loss of K^+. Thus, unlike that of the carbonic anhydrase inhibitors, the diuresis produced by thiazide and thiazidelike diuretics is of NaCl and not $NaHCO_3$. The urinary K^+ wasting induced by the thiazides is primarily a consequence of the increased Na^+ delivered to the distal tubule as discussed earlier.

Two renal responses are unique to the thiazide and thiazidelike diuretics. With these compounds, Na^+ excretion is increased, while Ca^{++} excretion is decreased, primarily and directly because of increased distal Ca^{++} reabsorption, secondarily and indirectly because of a compensatory elevation of proximal solute absorption, making this class of diuretics useful in treating hypercalciuria. This effect, which may not be evident upon initial administration of the drug, is particularly beneficial in individuals who are prone to calcium stone formation.

A second unusual action of this class of diuretics is their utility in treating nephrogenic diabetes insipidus. Patients who have an adequate supply of ADH but whose kidneys fail to respond to ADH excrete large volumes of very dilute urine, not unlike those who have an ADH deficiency. The thiazides reduce glomerular filtration modestly and decrease positive free water formation (C_{H_2O}), that is, production of dilute urine. These actions combine to cause patients with nephrogenic diabetes insipidus to excrete a somewhat reduced urine volume with increased osmolality.

Absorption and Elimination

Orally administered thiazides are rapidly absorbed from the gastrointestinal tract and begin to produce diuresis in about 1 hour. Approximately 50% of an oral dose is excreted in the urine within 6 hours. These compounds are organic acids and are actively secreted into the proximal tubular fluid by the organic acid secretory mechanism. There also appears to be an extrarenal pathway for their elimination involving the hepatic–biliary acid secretory system that is particularly important for thiazide elimination when renal function is impaired.

The thiazides have a variable effect on elimination of uric acid, which also is secreted by the renal acid secretory mechanism. Administration of thiazide diuretics, especially at low doses, may elevate serum uric acid levels and cause goutlike symptoms. Following large doses, thiazides may compete with uric acid for active reabsorption and thereby may promote uric acid elimination rather than impair it (see Chapter 37).

Clinical Uses

Thiazides, especially hydrochlorothiazide (*Dyazide, Esidrix, HydroDIURIL, Oretic*), are useful adjunctive therapy in controlling the edema associated with congestive heart failure, cirrhosis, premenstrual tension, and hormone therapy. They are widely used in the treatment of hypertension whether or not it is accompanied by edema (see Chapter 20). They can be used in patients with renal disease; however, their diuretic activity is proportional to the residual tubular functional capacity of the kidney. The thiazides do not prevent toxemia in pregnancy, nor are they useful in the treatment of it.

Adverse Effects

Thiazides should be used cautiously in the presence of severe renal and hepatic disease, since azotemia and coma may result. *The most important toxic effect associated with this class of diuretics is hypokalemia*, which may result in muscular and central nervous system symptoms, as well as cardiac sensitization (see Hypokalemia). Periodic examination of serum electrolytes for possible imbalances is strongly recommended. Appropriate dietary and therapeutic measures for controlling hypokalemia are described later in this chapter. The thiazides also possess some diabetogenic potential, and although pancreatitis during thiazide therapy has been reported in a few cases, the major mechanism contributing to the potential for glucose intolerance is not known.

Hypokalemia and Potassium-sparing Diuretics

Hypokalemia

The chronic use of some diuretics may require the oral administration of potassium supplements or potassium-sparing diuretics that reduce urinary K^+ excretion. This is true especially for patients with congestive heart failure and cirrhosis, who are particularly sensitive to K^+ loss. The presence or absence of clinical symptoms of hypokalemia is quite closely related to serum K^+ concentrations, and even small changes in extracellular K^+ can have marked effects. Most patients begin to show symptoms when serum K^+ levels fall below 2.5 mEq/L (from a normal value of approximately 5 mEq/L).

Neurological symptoms include drowsiness, irritability, confusion, loss of sensation, dizziness, and coma. Other important symptoms of hypokalemia are muscular weakness, cardiac arrhythmias, tetany, respiratory arrest, and increased sensitivity of the myocardium to digitalislike drugs.

Treatment

Hypokalemia can be treated by supplying additional K^+ through the diet, drug treatment, or both. Replacement should be gradual, with frequent evaluation of both serum K^+ concentrations and cardiac activity (electrocardiographic monitoring). K^+ supplements

can be administered in several forms. KCl is generally preferred over other forms such as bicarbonate, citrate, or gluconate, since most patients exhibit concurrent metabolic alkalosis. KCl corrects both the hypokalemia and the alkalosis. When hypokalemia is not attended by metabolic alkalosis, other forms of K^+ supplementation may be preferred. Since KCl solutions have a rather bitter and unpleasant taste, this salt was formerly given as an enteric-coated tablet. However, the rapid release of KCl from the tablet after it entered the small intestine was responsible for a severe local ulceration, hemorrhage, and stenosis, especially when there was a delay in gut transit time; therefore, the enteric-coated tablets have been withdrawn.

Sugar-coated products have been marketed that contain KCl in a wax matrix (*Slow-K* and *Kaon-Cl*) and are purportedly slow- and controlled-release preparations. Available evidence indicates that these slow-release forms of KCl are occasionally capable of causing local tissue damage and therefore probably should be used with caution for K^+ supplementation. Solutions of potassium gluconate, like the tablets, also have been associated with intestinal ulceration. Microencapsulated KCl preparations (*Micro-K, K-Dur*) that are neither enteric coated nor contained within a wax matrix appear to be superior to the wax matrix formulation.

Consumption of potassium-rich foods is the easiest and most generally advised means of counteracting a K^+ deficit. Table 21.3 lists foods that are suitable for K^+ supplementation.

In general, a normal diet plus about 40 mEq per day of K^+ is adequate to prevent hypokalemia. If K^+-rich foods prove inadequate in replacing large quantities of the electrolyte or if the increased caloric intake that is part of the dietary supplementation is not desirable, oral *liquid* therapy is the formulation of choice. A listing of these solutions is given in Table 21.4. Although patients may find many of these products unpalatable, their further dilution with water or fruit juice can be helpful. Finally, the addition of a K^+-sparing diuretic to the therapeutic regimen may prove useful.

TABLE 21.3 Foods Rich in Potassium (approximately 0.5 g portion)

Prune juice (1 cup)
Orange juice (1 cup)
Grapefruit juice (1 cup)
Prunes (7)
Banana (1)
Dates (7)
Figs (4)
Raisins (0.5 cup)
Apricots (6)
Sweet potato (1)
White potato (1)

TABLE 21.4 Potassium Supplementation

Product	Manufacturer	Dosage Form
Kaochlor	Adria	Liquid
Kay Ciel elixir	Berlex	Liquid
Potassium Triplex	Lilly	Liquid
KCL 10%	Purepac	Liquid
KCL 20%	Stanlabs	Liquid
K-Lor	Abbott	Powder[a]
K-Lyte	Mead Johnson	Tablets[a]

[a]This product, although supplied as a solid dose, is dissolved in water before ingestion.

The three principal potassium-sparing diuretic agents produce similar effects on urinary electrolyte composition. Through actions in the distal convoluted tubule and collecting duct, they cause mild natriuresis and a decrease in K^+ and H^+ excretion. Despite their similarities, these agents actually constitute two groups with respect to their mechanisms of action.

Aldosterone Antagonists: Spironolactone

The mechanism by which Na^+ is reabsorbed in coupled exchange with H^+ and K^+ in the collecting duct has been discussed previously; that is, Na^+-driven K^+ secretion is partially under mineralocorticoid control. Aldosterone and other compounds with mineralocorticoid activity bind to a specific mineralocorticoid receptor in the cytoplasm of late distal tubule cells and of principal cells of the collecting ducts. This hormone–receptor complex is transported to the cell nucleus, where it induces synthesis of multiple proteins that are collectively called aldosterone-induced proteins. The precise mechanisms by which these proteins enhance Na^+ transport are incompletely understood. However, the net effect is to increase Na^+ entry across apical cell membranes and to increase basolateral membrane Na^+–K^+–ATPase activity and synthesis.

Mechanism of Action

Spironolactone (*Aldactone*) is structurally related to aldosterone and acts as a competitive inhibitor to prevent the binding of aldosterone to its specific cellular binding protein. Spironolactone thus blocks the hormone-induced stimulation of protein synthesis necessary for Na^+ reabsorption and K^+ secretion. *Spironolactone, in the presence of circulating aldosterone, promotes a modest increase in Na^+ excretion associated with a decrease in K^+ elimination.* The observations that spironolactone is ineffective in adrenalectomized patients and that the actions of spironolactone can be reversed by raising circulating al-

dosterone blood levels (surmountable antagonism) support the conclusion that spironolactone acts by competitive inhibition of the binding of aldosterone with receptor sites in the target tissue. *Spironolactone acts only when mineralocorticoids are present.*

Pharmacokinetic Properties

Spironolactone is poorly absorbed after oral administration and has a delayed onset of action; it may take several days until a peak effect is produced. It has a somewhat slower onset of action than triamterene and amiloride (discussed later), but its natriuretic effect is modestly more pronounced, especially during long-term therapy. Spironolactone is rapidly and extensively metabolized, largely to the active metabolite *canrenone*. Canrenone and potassium canrenoate, its K^+ salt, are available for clinical use in some countries outside the United States. Canrenone has a half-life of approximately 10 to 35 hours. The metabolites of spironolactone are excreted in both the urine and feces. New selective aldosterone receptor antagonists (SARA), such as eplerenone, have been developed but have not yet been introduced into clinical practice. Eplerenone and canrenone exhibit fewer steroidlike side effects (gynecomastia, hirsutism).

Clinical Uses

Spironolactone has been used clinically in the following conditions:

1. *Primary hyperaldosteronism*. Used as an aid in preparing patients with adrenal cortical tumors for surgery.
2. *Hypokalemia*. Used in patients with low serum K^+ resulting from diuretic therapy with other agents. Its use should be restricted to patients who are unable to supplement their dietary K^+ intake or adequately restrict their salt intake or who cannot tolerate orally available KCl preparations.
3. *Hypertension and congestive heart failure*. Although spironolactone may be useful in combination with thiazides, the latter remain the drugs of first choice. Fixed-dose combinations of spironolactone and a particular thiazide (e.g., *Aldactazide*) generally offer no therapeutic advantage over either component given separately and tend to restrict the ability of the clinician to determine the optimal dosage of each drug for a particular patient.
4. *Cirrhosis and nephrotic syndrome*. Spironolactone is a mild diuretic and may be useful in treating the edema that occurs in these two clinical conditions, that is, when excessive K^+ loss is to be avoided.

Adverse Effects

Serum electrolyte balance should be monitored periodically, since potentially fatal *hyperkalemia* may occur, especially in patients with impaired renal function or excessive K^+ intake (including the K^+ salts of coadministered drugs, e.g., potassium penicillin). Spironolactone can induce hyponatremia and in cirrhotic patients, metabolic acidosis. A variety of gastrointestinal disturbances may accompany spironolactone administration. These include diarrhea, gastritis, gastric bleeding, and peptic ulcers. Spironolactone is contraindicated in patients with peptic ulcers. Spironolactone may also cause elevated blood urea nitrogen, drowsiness, lethargy, ataxia, confusion, and headache. Gynecomastia and menstrual irregularity in males and females, respectively, can occur. Painful *gynecomastia* (directly related to dosage level and duration of therapy), which is generally reversible, may necessitate termination of therapy. Animal studies demonstrating tumorigenic potential support the clinical judgment that spironolactone alone or in combination should not be used for most patients who require diuretic therapy and its unnecessary use should be avoided.

Nonsteroidal Potassium-sparing Drugs: Triamterene and Amiloride

Triamterene (*Dyrenium*) or amiloride (*Midamor*) administration results in changes in urinary electrolyte patterns that are qualitatively similar to those produced by spironolactone. The mechanism by which these agents bring about the alterations in electrolyte loss, however, is quite different. *Triamterene and amiloride produce their effects whether or not aldosterone or any other mineralocorticoid is present.* The action of these two drugs is clearly unrelated to endogenous mineralocorticoid activity, and *these drugs are effective in adrenalectomized patients.*

Mechanism of Action

Both agents appear to affect Na^+ reabsorption in the cortical collecting duct. A site in the connecting tubule also may be involved. Although amiloride has been more extensively studied than triamterene, *both diuretics specifically block the apical membrane epithelial Na^+ channel* (*ENaC*) (Fig. 21-5). The reduced rate of Na^+ reabsorption diminishes the gradient that facilitates K^+ secretion. K^+ secretion by the collecting duct principal cells is a passive phenomenon that depends on and is secondary to the active reabsorption of Na^+.

In addition to their effects on distal Na^+ and K^+ transport, *all of the K^+-sparing diuretics inhibit urinary H^+ secretion by the late distal tubule and cortical collecting duct.* The mechanism of this inhibitory action is not totally clear.

Pharmacokinetic Properties

Both triamterene and amiloride are effective after oral administration. Diuresis ensues within 2 to 4 hours

after administration, although a maximum therapeutic effect may not be seen for several days. Both drugs cause a modest (2–3%) increase in Na^+ and HCO_3^- excretion, a reduction in K^+ and H^+ loss, and a variable effect on Cl^- elimination. Approximately 80% of an administered dose of triamterene is excreted in the urine as metabolites; amiloride is excreted unchanged.

Clinical Uses

Triamterene can be used in the treatment of congestive heart failure, cirrhosis, and the edema caused by secondary hyperaldosteronism. It is frequently used in combination with other diuretics except spironolactone. Amiloride, but not triamterene, possesses antihypertensive effects that can add to those of the thiazides.

These K^+-sparing diuretics have low efficacy when used alone, since only a small amount of total Na^+ reabsorption occurs at more distal sites of the nephron. These compounds are *used primarily in combination* with other diuretics, such as the thiazides and loop diuretics, to prevent or correct hypokalemia. The availability of fixed-dose mixtures of thiazides with nonsteroidal K^+-sparing compounds has proved a rational form of drug therapy. Both triamterene and amiloride are available alone or in combination with hydrochlorothiazide.

Adverse Effects

Because the actions of triamterene and amiloride are independent of plasma aldosterone levels, their prolonged administration is likely to result in hyperkalemia. Both amiloride and triamterene are contraindicated in patients with hyperkalemia. Triamterene should not be given to patients with impaired renal function. Potassium intake must be reduced, especially in outpatients. A folic acid deficiency has been reported to occur occasionally following the use of triamterene.

High-Ceiling, or Loop, Diuretics

The compounds known as *high-ceiling* or *loop diuretics* are the most efficacious agents available for inducing marked water and electrolyte excretion. They can increase diuresis even in patients who are already responding maximally to other diuretics. The drugs in this group available for use in the United States include furosemide (*Lasix*), bumetanide (*Bumex*), torsemide (*Demadex*), and ethacrynic acid (*Edecrin*). Although these agents differ somewhat, they share a common primary site of action, which underlies their effectiveness.

Mechanism of Action

The site of action of loop diuretics is the thick ascending limb of the loop of Henle, and diuresis is brought about by inhibition of the Na^+–K^+–$2Cl^-$ transporter. This segment of the nephron is critical for determining the final magnitude of natriuresis. As much as 20% of the filtered Na^+ may be reabsorbed by the loop of Henle. The importance of the loop is further emphasized by the realization that drugs that primarily inhibit proximal Na^+ and fluid reabsorption have their natriuretic response reduced by the ability of the ascending limb to augment its rate of Na^+ reabsorption in the presence of an increased tubular Na^+ load. Thus, *any agent that greatly impairs active reabsorption in the thick ascending limb may induce a very large Na^+ and water loss.* Furthermore, the relatively limited capacity of the distal tubule and collecting duct for Na^+ reabsorption makes it impossible to recapture much of the suddenly increased tubular Na^+ reaching them.

Since the thick ascending limb is responsible for initiating events that lead to the hyperosmolar medullary interstitium (and therefore providing the driving force for water reabsorption from the collecting ducts under the influence of ADH), it is this nephron segment that underlies urinary concentration. Thus, drugs that interfere with this concentrating function will have marked effects on urinary output.

Diuretic Response

During the peak effect of the loop diuretics, urine flow is greatly augmented, as is the excretion of Na^+ and Cl^-, corresponding to as much as 20 to 30% of their filtered load. K^+ loss also occurs as an indirect effect of the large Na^+ load reaching the distal tubules and is 2 to 5 times above normal levels of K^+ excretion. With low or moderately effective doses, these drugs do not appreciably affect HCO_3^- or H^+ excretion.

Furosemide (*Lasix*), torsemide (*Demadex*), and bumetanide (*Bumex*) possess some carbonic anhydrase inhibiting activity (about one-tenth that of chlorothiazide). This property may account for the increased bicarbonate and phosphate excretion seen after large doses of these diuretics. The elevated HCO_3^- loss probably indicates some proximal tubular effects for furosemide and bumetanide.

Pharmacokinetic Properties

All of the loop diuretics are available for both oral and parenteral administration. Their onset of action is rapid, usually within 30 minutes after oral and 5 minutes after intravenous administration. They produce peak diuresis in about 2 hours, with a total duration of diuretic action of approximately 6 to 8 hours. Loop diuretics are extensively bound to plasma proteins and are eliminated in the urine by both glomerular filtration and tubular secretion. Approximately a third of an administered dose is excreted by the liver into the bile, from where it may be eliminated in the feces. Only small amounts of these compounds appear to be metabolized by the liver.

The loop diuretics must be present in the tubular fluid before they can become effective. Because of their extensive binding to plasma proteins, filtration across the glomerular capillaries is restricted. Like the thiazides, however, the loop diuretics are weak organic acids that are substrates for the organic acid secretory system in the proximal tubule. A consequence of this active secretion is that the presence of other organic acids or certain forms of renal disease may impair the therapeutic usefulness of the loop diuretics.

Clinical Uses

Because diuresis may be extensive, loop diuretics should be administered initially in small doses; multiple doses, if needed, should be given in early morning and early afternoon. During the remainder of the day, when the drug is not acting, the body can begin to compensate for any derangements in fluid and electrolyte balance that may have occurred as a result of drug therapy. These drugs should be restricted to patients who require greater diuretic potential than can be achieved by other diuretic drugs. In addition to being used in the usual edematous states associated with congestive heart failure, cirrhosis, or renal disease, the loop diuretics can be used in emergencies, such as acute pulmonary edema, when rapid onset of action is essential. They are not recommended for use during pregnancy.

Adverse Effects

Frequent serum electrolyte analysis is essential during therapy with the high-ceiling diuretics. Overdose may result in a rapid reduction of blood volume, dizziness, headache, orthostatic hypotension, hyponatremia, and hypokalemia. Nausea, vomiting, diarrhea, and loss of appetite are especially common with ethacrynic acid.

Ototoxicity has been reported during therapy with all loop diuretics. This effect seems to be dose related and is most common in patients with renal insufficiency. Deafness is usually reversed when these drugs are discontinued, but irreversible hearing loss has been reported after administration of ethacrynic acid, and this has led to a marked decrease in its use.

Furosemide, torsemide, and bumetanide are sulfonamide derivatives, hence chemically related to the thiazides. They share the thiazides' adverse effects of serum uric acid elevation and diabetogenic potential. Ethacrynic acid (*Edecrin*) is chemically unrelated to other diuretics and does not appear to have diabetogenic potential.

Osmotic Diuretics

Osmotic diuretics owe their effects to the physical retention of fluid within the nephron rather than to direct action on cellular sodium transport. These compounds are not electrolytes, and they are freely filtered at the glomerulus and not reabsorbed to a significant extent. Ideally, these drugs should be water-soluble compounds, well absorbed after oral administration, freely filtered at the glomerulus, poorly reabsorbed by the tubule, and devoid of pharmacological effects. The prototype is mannitol (*Osmitrol*), an unmetabolizable polysaccharide derivative of sucrose. Other clinically available osmotic diuretics include glycerin (*Glycerol, Osmoglyn,* and the topical agent *Ophthalgan*), isosorbide (*Ismotic*), and urea (*Ureaphil, Urevert*). Since these osmotic agents act in part to retard tubule fluid reabsorption, *the amount of diuresis produced is proportional to the quantity of osmotic diuretic administered.* Therefore, unless large quantities of a particular osmotic diuretic are given, the increase in urinary volume will not be marked.

Ideally, the distribution of osmotic diuretics should be largely confined to the vascular system, although this can lead to excessive expansion of the vascular compartment. Such an overexpansion could precipitate pulmonary edema or increase cardiac work or both. This is largely the result of rapid transfer of fluid from the interstitial to the vascular compartment. Practically speaking, however, few osmotic diuretics are available for therapeutic use. *These agents, therefore, should be given cautiously to patients with compromised cardiac function.*

Mechanism of Action

The renal response to osmotic diuretics is probably due to the interplay of several factors. The primary effect involves an *increased fluid loss* caused by the osmotically active diuretic molecules; this results in reduced Na^+ and water reabsorption from the proximal tubule.

An additional contributing factor to the diuresis induced by osmotic diuretics is the *increase in renal medullary blood flow* that follows their administration. This medullary hyperemia reduces the cortex–medullary osmolar gradient by carrying away interstitial Na^+ and urea. This partial reduction of the osmolar gradient impairs normal reabsorption of tubular water, which occurs from the descending limb of Henle and the collecting duct.

Finally, there is an additional *increase in electrolyte excretion* due to impairment of ascending limb and distal tubule Na^+ reabsorption; this occurs as a result of lowered tubular Na^+ concentration and the increased tubular fluid flow rate.

Individual Agents

Mannitol

Mannitol (*Osmitrol*) is a six-carbon sugar that does not undergo appreciable metabolic degradation. It is not absorbed from the gastrointestinal tract and there-

fore must be given intravenously. Humans do not reabsorb it in the proximal tubules.

Mannitol is particularly useful in clinical conditions characterized by hypotension and decreased glomerular filtration. These symptoms are usually the result of some physical trauma or surgical procedure. Mannitol is useful in maintaining kidney function in these conditions, since even at reduced rates of filtration, a sufficient amount of the sugar may enter the tubular fluid to exert an osmotic effect and thus continue urine formation. However, if circulatory failure is profound and glomerular filtration is severely compromised or absent, not enough mannitol may reach the tubules to be effective. The ability to maintain urine flow when renal shutdown might otherwise be expected aids in preventing kidney tubular damage. In addition, mannitol has been used to reduce cerebral edema during neurosurgery, to reduce intraocular pressure before surgery for glaucoma, and to promote the elimination of ingested toxic substances.

The major characteristics of the renal response to mannitol diuresis include a fall in urine osmolality and a decrease in the osmolality of the interstitial fluid of the renal medulla. *The quantity of urine formation and Na^+ excretion is generally proportional to the amount of mannitol excreted.* Although there is a significant inhibition of proximal water reabsorption, the effects of mannitol on proximal Na^+ reabsorption are not marked.

The major adverse reactions associated with mannitol administration are headache, nausea, vomiting, chest pain, and hyponatremia. Too rapid an administration of large amounts may cause an excessive shift of fluid from the intracellular to the extracellular compartment and result in congestive heart failure.

Glycerin

The primary use of anhydrous glycerin (*Ophthalgan*) is as an osmotic agent that is applied topically to reduce corneal edema. Orally administered glycerin (*Glycerol, Osmoglyn*) is used to reduce intraocular pressure and vitreous volume before ocular surgery.

Urea

The use of urea (*Ureaphil, Urevert*) has declined in recent years owing both to its disagreeable taste and to the increasing use of mannitol for the same purposes. When used to reduce cerebrospinal fluid pressure, urea is generally given by intravenous drip. Because of its potential to expand the extracellular fluid volume, urea is contraindicated in patients with severe impairment of renal, hepatic, or cardiac function or active intracranial bleeding.

Isosorbide

Isosorbide (*Ismotic*) is an orally effective, osmotically active drug that is most commonly used for the emergency treatment of acute angle-closure glaucoma. It should not be confused with isosorbide dinitrate, an antianginal drug.

USES OF DIURETICS

The ability of certain drugs to increase both fluid and electrolyte loss has led to their use in the clinical management of fluid and electrolyte disorders, for example, edema. *Regardless of the cause of the syndrome associated with edema, the common factor is almost invariably an increased retention of Na^+.* The aim of diuretic therapy is to enhance Na^+ excretion, thereby promoting negative Na^+ balance. This net Na^+ (and fluid) loss leads to contraction of the overexpanded extracellular fluid compartment.

Congestive Heart Failure

Diuretics may have considerable value in reducing the edema associated with congestive heart failure; however, each patient must be evaluated individually, since diuresis is not considered mandatory in all patients. Digitalis and salt restriction may be sufficient to decrease the associated symptoms of pulmonary congestion and peripheral edema. *In patients who require a diuretic as adjunctive therapy, the usual choice should be a thiazide or thiazide-type diuretic rather than one of the loop diuretics (e.g., bumetanide or furosemide).* This is true especially in mild congestive heart failure. The more efficacious compounds probably should be reserved for those who fail to respond to one of the thiazides. A K^+-sparing diuretic also can be given with the thiazide to maintain serum K^+ levels, which might otherwise be depleted. Hypokalemia predisposes patients to digitalis intoxication.

Hypertension

The use of diuretic drugs, either alone or in combination with other agents, in the management of mild to moderate hypertension is frequent. Diuresis and restriction of salt intake are often sufficient for all hypertensive patients except those with severe, malignant, or complicated hypertension. The mechanisms by which the diuretics lower arterial pressure are not precisely known, although it is thought that the initial response is due to a reduction of plasma volume with a consequently diminished cardiac output. However, after a few weeks, the initial degree of extracellular volume reduction is not maintained, probably owing to a gradual increase in aldosterone production (i.e., increased Na^+ retention and K^+ loss). Nonetheless, the antihypertensive effect is sustained.

Although the arterial pressure in hypertensive patients is related to intravascular volume, the changes in

plasma volume are primarily caused by alterations in total body Na^+. *Strict dietary Na^+ restriction can lower arterial pressure in hypertensive patients, whereas a large Na^+ intake will reverse the hypotensive effects of thiazide diuretics.* It appears quite plausible that all of the hypotensive effects of the diuretics can be attributed to some aspect of Na^+ depletion, that is, either directly on extracellular fluid volume or perhaps indirectly through the effects of Na^+ loss on autonomic nervous function (e.g., diminished norepinephrine storage capacity in sympathetic nerves) or vascular smooth muscle reactivity.

Diuretics are frequently used in combination with other antihypertensive agents. The appropriateness of this combination becomes even more apparent when it is realized that nondiuretic antihypertensives (e.g., hydralazine or diazoxide) produce some increase in plasma volume that if not corrected, would lead to an eventual decrease in their activity (see Chapter 20).

Hepatic Ascites

Cirrhosis and other liver diseases may result in the formation of excessive amounts of fluid in the abdomen (*ascites*). The primary causes of ascites are usually elevation of pressure in the portal vein and a decreased amount of hepatic plasma protein production. Both factors tend to reduce the ability of the vascular compartment to retain fluid. The resultant ascites may contribute to decreased appetite and respiratory difficulties, among other symptoms. When these symptoms are present, careful reduction in the fluid volume through the use of diuretics is desirable.

Since patients with cirrhosis vary widely in their response to diuretics, conservative initial diuretic therapy is called for. *The mainstay of treatment, however, remains restriction of dietary Na^+.* A common finding in patients with cirrhosis is decreased glomerular filtration, despite the increase in total blood volume caused by the extensive pooling of blood in the splanchnic vessels. Diminished renal perfusion leads to increased aldosterone secretion, which in turn increases Na^+ retention and K^+ loss. Thus, in addition to diuretics, most patients require K^+ supplementation. *The thiazides remain the drugs of first choice.* The use of a high-ceiling drug, such as furosemide, leads more frequently to such complications as hypokalemia, hyponatremia, and azotemia. K^+-sparing diuretics may be useful adjunctive (but not sole) agents if extensive hypokalemia is present.

Pulmonary Edema

The usual cause of pulmonary edema is acute left ventricular failure. The sequelae of events after left heart failure roughly follow the pattern of reduced stroke volume, leading to increased end-systolic and diastolic volume, which elevates left ventricular end-diastolic pressure. Pressure then increases in the left atrium, pulmonary vein, and finally in the pulmonary capillaries. Elevated pressure in the pulmonary capillaries results in the passing of more fluid into the pulmonary interstitial space, and this compromises gas exchange, diminishes total lung gas volume, and increases airway resistance. *With acute pulmonary edema of cardiac origin, the traditional treatment has included administration of the efficacious, rapidly acting loop diuretics.* These agents, given parenterally, can reduce total blood volume rapidly and thus may help to prevent recurrence of pulmonary congestion. The value of immediate and vigorous use of the loop diuretics has been questioned. The problems of excessive fluid and K^+ loss indicate a conservative approach to diuresis even in this medical emergency.

Increased Intracranial Pressure

A rise in intracranial pressure results in the appearance of a number of symptoms, including headache, vomiting, edema of the optic discs, changes in vital signs, and possibly death. Dehydrating measures, including the use of diuretics, can help lower the pressure, particularly if the elevated intracranial pressure is of a nontraumatic origin. *The parenteral administration of a hypertonic solution of one of the osmotic diuretics, urea or mannitol, can relieve the pressure through its osmotic effects.* The oral administration of glycerol also has been used in neurosurgical procedures when increases in intracranial pressure are anticipated.

Renal Edema

Nephrotic Syndrome

Nephrotic syndrome is characterized by proteinuria and edema due to some form of glomerulonephritis. The resulting fall in plasma protein concentration decreases vascular volume, which leads to diminished renal blood flow. This in turn causes secondary aldosteronism characterized by Na^+ and water retention and K^+ depletion. Rigid control of dietary Na^+ is essential. *Therapy of the nephrotic syndrome using a thiazide (possibly with a K^+-sparing diuretic) to control the secondary aldosteronism, is a useful initial approach to treatment.* Since nephrotic edema is frequently more difficult to control than cardiac edema, it may be necessary to switch to a loop diuretic (and spironolactone) to obtain adequate diuresis.

Chronic Renal Failure

The loop diuretics are usually required in treating chronic renal failure, since drugs with lesser intrinsic activity are not sufficiently effective when tubular function has been compromised greatly. Larger than normal amounts of furosemide are frequently employed, and thus it is especially important to monitor the patient for

excessive volume depletion. Intermittent therapy may be the best approach.

Acute Renal Failure

The principal rationale for the use of diuretics in acute renal failure is to prevent complete renal shutdown. Whether renal failure is caused by some underlying disease or by drug-induced renal toxicity, the continued production of even a small amount of urine is probably important in reducing further kidney tubular damage. *Most commonly employed are the osmotic diuretics, with intravenous mannitol generally being the agent of choice.* Osmotic diuresis is possible only if glomerular damage, tubular damage, or both have not progressed too far.

Premenstrual Edema and Edema of Pregnancy

Many women retain fluid during pregnancy and during the last days of the menstrual cycle. Breast fullness and subcutaneous swelling or puffiness are the most commonly observed symptoms; they are largely the result of elevated circulating hormone levels in the blood. Estrogens possess some mineralocorticoid activity, and thus, when present in relatively high concentrations, may produce some expansion of the extracellular fluid compartment. Excessive premenstrual edema frequently responds well to thiazide therapy. *Recent experience has diminished enthusiasm for use of any diuretics in pregnant women.* Since the edema of pregnancy is frequently well tolerated, concerns of compromised uteroplacental perfusion, possible ineffectiveness of diuretics in preeclampsia, and the risk of adverse effects of diuretics on the baby (e.g., thiazides can both cross the placental barrier and appear in breast milk, producing electrolyte disturbances and thrombocytopenia in newborns) have led to diminished routine use of these agents in pregnancy.

Resistance to Diuretic Administration

Since the effectiveness of many diuretics ultimately depends on establishing a negative Na^+ balance to mobilize edema fluid, *restriction of dietary Na^+ intake is generally an essential part of diuretic therapy.* Therefore, one cause of therapeutic failure or apparent patient refractoriness to diuretics could be the patient's continued ingestion of large quantities of NaC1.

Some of the older diuretic drugs were self-limiting; that is, prolonged administration resulted in a gradual diminution of their effectiveness. This problem was corrected through the use of intermittent diuretic therapy. Such a program of several days of diuresis followed by several days of drug withdrawal delayed refractoriness to the drug by preventing excessive disturbances in body electrolyte composition.

Many diuretics (e.g., thiazides and loop diuretics) must reach the tubular lumen before they begin to be effective. Because these compounds are organic acids and are bound to plasma proteins, they reach the luminal fluid by secretion. Any disease condition or drug that impairs *secretion* will affect the access of the diuretics to the luminal fluid and hence to their ultimate site of action (e.g., distal tubule or ascending loop). For example, renal dysfunction may lead to a buildup of *endogenous* organic acids that decrease drug secretion and thereby alter the patient's expected response to the diuretic. Patients with azotemia frequently require large doses of organic acid diuretics to achieve a satisfactory response. The concomitant administration of other drugs that are substrates for the organic acid secretory system (e.g., probenecid or penicillin) may result in an apparent resistance to diuretic action. It should now be obvious that *in addition to disease and electrolyte imbalances, the pharmacodynamic handling of the diuretics themselves may be a factor in diuretic resistance.*

Although most individuals respond well to the usual doses of loop diuretics, a small number of patients are refractory to these drugs. These patients may be vulnerable to ototoxicity or other adverse effects if larger amounts of the diuretic are employed. Compensatory proximal tubular sodium absorption may contribute to or be responsible for the resistance to loop diuretics. Combinations of diuretics may be used as an alternative approach to treating diuretic resistance once it has been verified that satisfactory Na^+ restriction is being followed and that the drug is being adequately absorbed. Administration of a carbonic anhydrase inhibitor may be sufficient to enhance Na^+ delivery to thick ascending limbs, where its reabsorption can be blocked by loop diuretics. Alternatively, thiazide diuretics may be combined with the loop diuretic to limit absorption by distal convoluted tubules. The thiazidelike diuretic metolazone, which has some proximal tubule effects unrelated to carbonic anhydrase, appears to be the most effective of the thiazide and thiazidelike drugs in this regard.

Excessive Diuresis

Excessively vigorous diuresis may lead to intravascular dehydration before removal of edema fluid from the rest of the extracellular compartment. This is especially dangerous if the patient has significant liver or kidney disease. *Once the initial correction of fluid and electrolyte derangement has been achieved, the effect sought is maintenance of homeostasis, not dehydration.* Drug dosage, frequency of administration, and Na^+ intake should be adjusted to achieve homeostasis.

If diuresis has been too vigorous, as may occur after injudicious use of loop diuretics, or if extensive fluid and

electrolyte loss has occurred following severe diarrhea or vomiting, replacement therapy may be required. A number of available solutions resemble extracellular fluid and are useful for the repair of water and electrolyte deficits (Table 21-5).

Since the 1950s, diuretic therapy has changed dramatically. Earlier, the major diuretics were acid-forming salts, xanthines, organomercurial compounds, and carbonic anhydrase inhibitors. Either because of toxicity or lack of efficacy, these agents are rarely if ever used.

TABLE 21.5 Solutions Resembling Extracellular Fluid

Solution	Manufacturer
Normosol-R	Abbott
Plasma-Lyte	Baxter
Inosol D-CM	Abbott
Polysal	Cutter
Lactated Ringer's	(Several)

Most of these solutions contain electrolytes in the following mEq range: sodium (130–150), potassium (4–12), chloride (98–109), bicarbonate (50–55), calcium (3–5), and magnesium (0–3).

Study Questions

1. When a patient is treated with a thiazide diuretic for hypertension, all of the following are likely EXCEPT:
(A) The fall of blood pressure that occurs in the first 2 weeks of therapy results from a decrease of extracellular volume.
(B) The sustained fall in blood pressure that occurs after several weeks of therapy is due to a decrease of intravascular resistance.
(C) After the blood pressure is reduced, hypokalemia remains a complication.
(D) Hyperuricemia may occur.
(E) Hypoglycemia may occur.

2. Furosemide increases the excretion of all of the following EXCEPT:
(A) Na^+
(B) K^+
(C) Ca^{++} and Mg^{++}
(D) Uric acid

3. Which of the following drugs is an appropriate initial antihypertensive therapy in an otherwise healthy adult with mild hypertension?
(A) Bumetanide
(B) Triamterene
(C) Hydrochlorothiazide
(D) Aldactone

4. When furosemide is administered to a patient with pulmonary edema, there is often symptomatic relief within 5 minutes of starting treatment. This relief is primarily due to:
(A) A rapid diuretic effect
(B) An increase in venous capacitance
(C) A direct effect on myocardial contractility
(D) Psychological effects

5. All of the following statements are true regarding patients with renal insufficiency who exhibit a reduced diuretic response EXCEPT:
(A) When the GFR drops below 30 mL/minute, thiazide diuretics are virtually useless.
(B) The combination of a thiazide plus a potassium-sparing diuretic may yield an adequate diuretic response.
(C) An 80-mg dose of IV furosemide followed an hour later by a 500-mg dose of IV chlorothiazide will probably yield the highest possible response.
(D) Metolazone is contraindicated.

ANSWERS

1. E. There is no evidence that the thiazides have any effect on blood sugar. Initial reductions of blood pressure are due to decreased extracellular volume and cardiac output. The beneficial effect of the sustained reduction of blood pressure is due to reduced vascular resistance. Extracellular volume remains modestly reduced and cardiac output returns to pretreatment levels. Hypokalemia does not ameliorate over time and is associated with an increased risk of ventricular fibrillation and malignant arrhythmias. The magnitude of hypokalemia produced by thiazide and thiazidelike diuretics is dose dependent. However, the degree to which individual patients are affected varies, though chronic administration of even small doses causes some K^+ depletion. Hyperuricemia is thought to have two causes. One is competition of the thiazide class of diuretics, which are weak organic acids, with uric acid for secretion by proximal tubules. This leads to diminished uric acid excretion. Serum concentrations of uric acid are further elevated by the reduced extracellular volume. Diuretic-induced hyperuricemia may cause acute gouty attacks.

2. D. Increased Na^+ excretion is a direct consequence of diuretic treatment. In thick ascending limbs, the site of furosemide action, calcium and magnesium transport is largely determined by the magnitude of

sodium absorption. Decreases of Na^+ absorption are accompanied by diminished Ca^{++} and Mg^{++} absorption. K^+ wasting is due to increased K^+ secretion by late distal tubules and collecting ducts. Uric acid excretion decreases as a consequence of competition for the proximal tubule organic acid secretory mechanism.

3. **C.** Although still highly controversial, the initial use of a thiazide diuretic for monotherapy has been recommended by the Joint National Committee on Detection, Evaluation and treatment of High Blood Pressure. Triamterene and Aldactone are rarely used alone and exhibit no antihypertensive activity. A recent study found that the loop diuretics bumetanide and furosemide effectively reduced blood pressure. Serum lipid levels were less affected than with thiazide diuretics or chlorthalidone. However, thiazide diuretics are a more conservative and approved approach for the initial treatment of hypertension that avoid the more dramatic fluid and electrolyte shifts that occur with loop diuretics.
4. **B.** Intravenous furosemide causes a significant decrease in pulmonary capillary wedge pressure and right atrial pressure, concomitantly decreasing stroke volume and increasing vascular resistance. This effect in many cases occurs before diuresis begins.
5. **D.** Metolazone would be expected to be very effective, particularly in combination with a loop diuretic.

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Case Study Furosemide Resistance

A 26-year-old woman with nephrotic syndrome comes to your office because of worsening edema. Her medications include clonidine 0.1 mg orally twice daily and furosemide 200 mg orally twice daily. On physical examination, her blood pressure is 120/85 mm Hg, and she has generalized massive edema (anasarca). The rest of the examination is unremarkable.

Labatory Studies

Serum creatinine	1.9 mg/dL
Serum albumin	2.0 g/dL
24-hour urine protein excretion	13.0 g
24-hour urine sodium excretion	74.0 mEq

Which of the following factors may contribute to resistance to furosemide in this patient?

(A) Reduced bioavailability
(B) Reduced active tubular secretion of furosemide by the proximal tubule organic acid secretory mechanism
(C) Sequestration of furosemide by intraluminal albumin thereby reducing its inhibition of the Na-K-2Cl cotransporter
(D) Increased reabsorption of sodium downstream to the thick ascending limb of Henle's loop
(E) All of the above

E. Intestinal absorption of furosemide is reduced in patients with anasarca due to edema of the intestinal mucosa. All loop diuretics are highly protein bound; therefore the GFR of these agents is negligible. Availability at the luminal site depends on the activity of the organic acid secretory pump in the proximal tubule. In this patient, secretion of loop diuretics is limited because of reduced renal blood flow and accumulation of organic acids in renal insufficiency, which can compete with furosemide for proximal tubule secretion. In animals, albumin in the tubular fluid binds furosemide, preventing its access to the Na-K-2Cl cotransporter. After prolonged use of furosemide, hypertrophy of the distal tubule epithelial cells occurs, indicating compensatory increased reabsorptive capacity.