Kirk-Othmer Encyclopedia of Chemical Technology.

DIURETIC AGENTS

Diuresis is defined as the excretion of urine, and is derived from the Greek word *diourein* which means to urinate. It more commonly denotes production of unusually large volumes of urine. Diuretics are agents that increase urine output or flow. The term is generally used to describe all drugs that act on the kidney to increase the production of urine. More specifically, the terms saliuretic or natriuretic are used to describe those agents that exert diuretic effects by primarily increasing the excretion of sodium chloride. Aquaretics are agents that increase urine output by producing a water diuresis but do not promote the urinary excretion of electrolytes. Both the use of diuretics in the treatment of hypertension, and the effects of diuretics on the kidney to promote the excretion of urine to normalize derangements in body fluid distribution leading to edematous states are discussed herein. The use of diuretics in the treatment of congestive heart failure and hypertension is discussed elsewhere (see Cardiovascular agents).

Disturbances in body fluid distribution may occur at three principal sites: (*1*) within the interstitial space, as occurs in peritonitis or cirrhosis with ascites; (*2*) between the interstitial space and the vascular tree, as in the nephrotic syndrome; or (*3*) within the vascular tree, as in congestive heart failure. Thus, the underlying disease may be of cardiac, hepatic, or renal origin. These derangements provide what amounts to a low blood volume signal to the kidneys that activates renal mechanisms to retain salt and water. If the retained salt and water do not terminate the low volume signal, the kidneys continuously retain salt and water, resulting in edema. The clinical outcome of excessive accumulation of salt and water depends on the particular sector of the extracellular space to which the retained fluid is relegated. Clinical signs of edema appear when the volume of the extracellular space is exceeded by several liters. Diuretics are used in the treatment of edematous states because, in most cases, they produce satisfactory mobilization and subsequent prevention of fluid accumulation in the interstitial space, the abdominal cavity, the lungs, and/or thoracic cavity. However, diuretic therapy is symptomatic in nature, and unless the underlying pathology is corrected, the kidneys continue to retain salt and water and the retained fluid and electrolytes are redistributed to the various compartments described. The principal indications of diuretics in the treatment of edema are in congestive heart failure (1); renal disease (2); hepatic cirrhosis with ascites (3); obesity, where salt and water retention are prominent (see also Antiobesity drugs) (4); premenstrual tension (5); edema of pregnancy, including toxemia (6); and steroid administration (7). Edema may also be associated with other clinical conditions such as inflammation or hypersensitivity reactions.

1. Renal Function

In addition to being involved in the formation of urine, the kidney acts as an endocrine organ secreting renin, erythropoietin, prostaglandins (qv), and kinins; it is also capable of synthesizing substances such as 1α,25-dihydroxycholecalciferol [32222-06-3], $C_{27}H_{44}O_3$. One of the principal functions of the kidney is to maintain the body's extracellular fluid composition in relatively narrow concentration ranges by the simultaneous regulation of water and multiple solute excretion. This is of particular interest in regard to the effects of diuretic drugs.

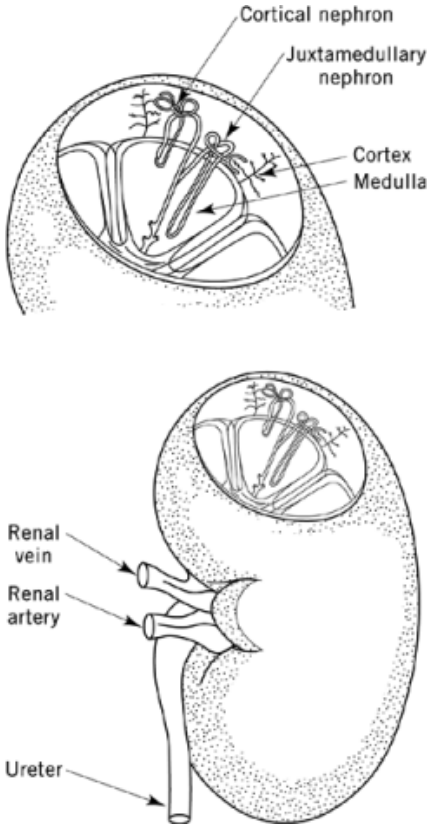


Fig. 1. Position of the two types of nephrons (not drawn to scale) in the kidney.

The kidney also eliminates unwanted metabolic products, drugs, and their metabolites from the body via the urine. The latter effect also may be modified by some diuretic drugs.

Anatomically, the kidneys are bilaterally paired organs located against the posterior abdominal wall in retroperitoneal pockets below the diaphragm. The kidney is divided into an outer cortical region and an inner medullary region. Each kidney contains approximately 1 million distinct functional units called nephrons. The individual nephron consists of a glomerulus, proximal convoluted tubular segment, loop of Henle, distal convoluted tubular segment, and multi-branched collecting duct common for several nephrons. Depending on the anatomical location in the kidney, two types of nephrons can be identified (Fig. 1). The cortical nephron originates in the outer regions of the renal cortex, and the principal portion of the unit is contained in the cortex. The juxtamedullary nephron, which has a longer loop of Henle than the cortical nephron, originates close to the corticomedullary junction, and part of its tubule descends deep into the inner medulla along its osmolar gradient. Although the blood supply to these two types of nephrons may change as a result of a regulatory mechanism, in principle they operate similarly (8, 9).

Under normal conditions, ca 25% of the resting cardiac output passes through the kidney. Blood flowing through the renal artery and the afferent arterioles of all glomeruli is filtered through the glomerular capillary plexus, resulting in ca 120 mL of total glomerular filtrate (ultrafiltrate) per minute. This is also called the glomerular filtration rate (GFR). Owing to the nature of the glomerular membrane, which is said to be as much as 300 times more permeable than other systemic beds, the filtrate contains all of the plasma constituents except

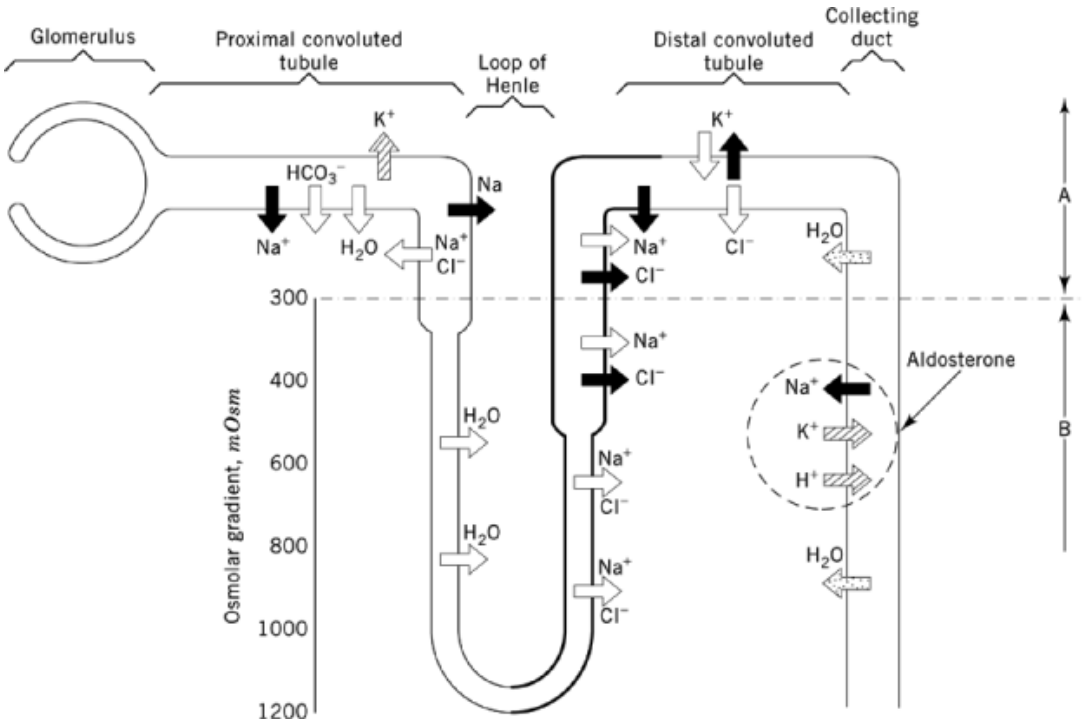


Fig. 2. Schematic representation of relevant electrolyte transport through the renal tubule, depicting the osmolar gradient in medullary interstitial fluid in *mOsm* where➡ represents active transport,⇨ passive transport,⇛ both active and passive transport, and⇨ passive transport of H_2O in the presence of ADH, in A, the cortex, and B, the medulla. An osmole equals a mole of solute divided by the number of ions formed per molecule of the solute. Thus one mole of sodium chloride is equivalent to two osmoles, ie, 1*M*NaCl=2 *Osm* NaCl. ADH=antidiuretic hormone. *mOsm*=milliosmolar=milliosmoles per liter.

lipids, proteins, and protein-bound substances. The driving force is the blood pressure within the glomerular capillaries. On its way through the nephron, where it ends up as urine, the ultrafiltrate rapidly loses its identity by both passive and active transport processes based on physical forces or involving consumption of energy from cellular metabolism, respectively. The final urine volume is ca 1% of the ultrafiltrate. Thus, of the ca 180 L of glomerular filtrate formed daily, only 1–1.5 L reaches the urinary bladder. It is virtually cleared of filtered glucose and amino acids, and contains, with respect to the main plasma electrolytes, only ca 1% of the filtered sodium and chloride ions, together with traces of bicarbonate ion. Substantial fractions of the remaining solutes are reabsorbed, and exogenous organic acids and bases are added to the tubular filtrate by secretion (8, 9).

The transport processes for relevant electrolytes along the nephron are schematically shown in Figure 2. Under normal circumstances, ca 60% of the ultrafiltrate from the glomerulus is isotonically reabsorbed in the proximal tubule and the thick descending segment of the loop of Henle, where both active and passive transport of sodium ion, Na^+, and passive reabsorption of chloride ion, Cl^-, and water occur. Bicarbonate is also reabsorbed, but the $HCO{-}_3$ is derived from the filtered HCO_3^-. The filtered HCO_3^- combines with H^+ secreted by the proximal tubular cells into the tubular lumen to form H_2CO_3, which in turn dissociates to form CO_2 and water. The CO_2 moves passively into the proximal tubular cell where, depending on cellular carbonic anhydrase activity, it is rehydrated to form H_2CO_3. This H_2CO_3 dissociates into H^+ and HCO_3^-; it is this HCO_3^- that is reabsorbed with actively transported Na^+. Substantial parts of the filtered load of K^+ are also reabsorbed by active and passive transport processes.

Owing to a high water and low NaCl permeability of the thin descending limb of the loop of Henle, the tubular fluid, when it enters the ascending limb, has become hypertonic by osmotic equilibration along the osmolar gradient in the medulla. This effect is not simply reversed when the fluid passes into the ascending limb, as the latter is impermeable to water. On the contrary, as the tubular fluid moves up the ascending limb, it decreases in osmolarity owing to Na^+ and Cl^- reabsorption. Active Cl^- reabsorption, and passive Na^+ and K^+ resorption, without an omostic equivalent of water, provides a hypotonic fluid that moves into the distal convoluted tubule. The reabsorbed NaCl is part of the solute supply to the interstitium, and is necessary for the osmolar gradient in the renal medulla.

The principle of fluid concentration and dilution in the loop of Henle is known as countercurrent multiplication. The ascending limb of the loop of Henle is also referred to as the diluting segment of the nephron, and is the basis of the kidney's ability to produce concentrated or dilute urine. It is here that 20–35% of the filtered sodium ion is reabsorbed. In the distal convoluted tubules and collecting ducts, an additional 5% of the tubular filtrate is reabsorbed by active Na^+ and passive Cl^- reabsorption, whereas K^+ might be secreted or absorbed, depending on the potassium balance of the organism. In the collecting duct, Na^+ is reabsorbed under the influence of aldosterone [52-39-1]. At this part of the nephron, the rate of Na^+ reabsorption is intimately connected to K^+ and carbonic anhydrase-dependent H^+ secretion.

The collecting ducts are distinguished from the other segments of the nephron by changing their water permeability as a result of the action of antidiuretic hormone (ADH), also called vasopressin [9034-50-8], an octapeptide released from the posterior pituitary gland into the systemic circulation when the body is in the hydropenic state. In the presence of ADH, the distal convoluted tubules and collecting ducts are freely permeable to water, which allows back-diffusion of water into the hypertonic interstitial space of the medulla, resulting in a urine of high osmolarity. On the other hand, in the absence of ADH the impermeability to water during hydration leads to water diuresis because the flow of water from these segments into the osmolar medullary interstitium is blocked (8, 9).

2. Pharmacology and Mechanism of Action

2.1. Low Ceiling Diuretics

The designation of low ceiling diuretics denotes that the total excretion of the filtered sodium ion load is less than 10% compared to about 30% for the high ceiling (loop) diuretics (2). There are many chemical classes in this category, ie, thiazides, quinazoline sulfonamides, chlorthalidone, indapamide, etc, but their site of action in the kidney is similar, and they are grouped as thiazide-type diuretics for general discussion (Table 1).

Table 1. Low Ceiling Diuretics (Thiazide-like)

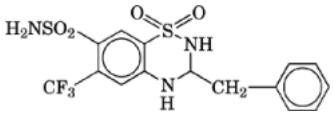
Generic name	CAS Registry Number	Molecular formula	Trade name	Structure
		Thiazides		
bendroflumethazide	[73-48-3]	$C_{15}H_{14}F_3N_3O_4S_2$	BenuronBristuron	

Table 1. ***Continued***

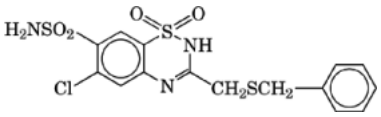
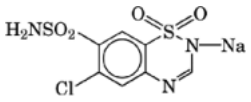
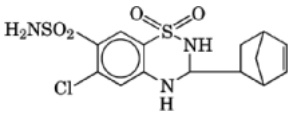
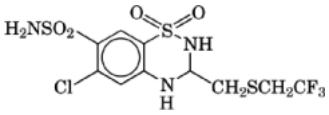
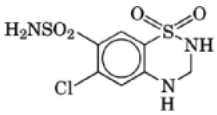
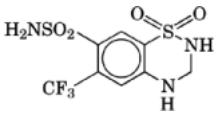
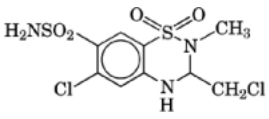
Generic name	CAS Registry Number	Molecular formula	Trade name	Structure
benzthiazide	[91-33-8]	$C_{15}H_{14}ClN_3O_4S_3$	AquatagExnaProaqua	
buthiazide	[2043-38-1]	$C_{11}H_{16}ClN_3O_4S_2$		
chlorothiazidechlorothiazide sodium	[58-94-6] [7085-44-1]	$C_7H_6ClN_3O_4S_2$ $C_7H_5ClN_3NaO_4S_2$	DiurilDiuril Sodium	
cyclothiazide	[2259-96-3]	$C_{14}H_{16}ClN_3O_4S_2$	Anhydron	
epithiazide[a]	[1764-85-8]	$C_{10}H_{11}ClF_3N_3O_4S_3$		
hydrochlorothiazide	[58-93-5]	$C_7H_8ClN_3O_4S_3$	Hydrodiuril	
hydroflumethazide	[135-09-1]	$C_8H_8F_3N_3O_4S_2$	DiucardinSaluron	
methylchlothiazide	[135-07-9]	$C_9H_{11}Cl_2N_3O_4S_2$	AquatensinEnduron	

Table 1. ***Continued***

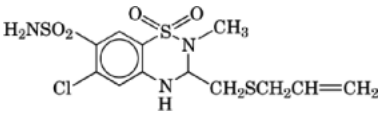
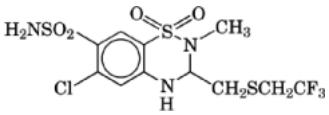
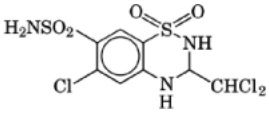
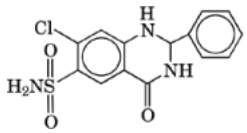
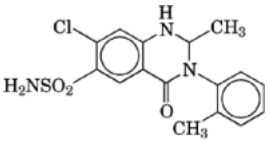
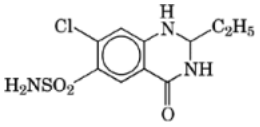
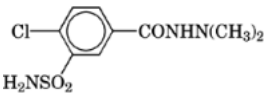
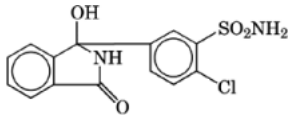
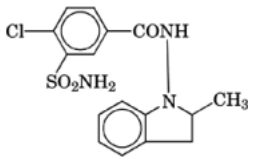
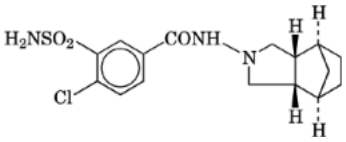
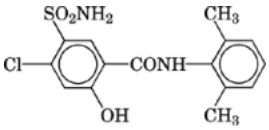
Generic name	CAS Registry Number	Molecular formula	Trade name	Structure
methalthiazide[b]	[5611-64-3]	$C_{12}H_{16}ClN_3O_4S_3$		
polythiazide	[346-18-9]	$C_{11}H_{13}ClF_3N_3O_4S_3$	Renese	
trichlormethiazide	[133-67-5]	$C_8H_8Cl_3N_3O_4S_2$	MetahydrinNaqua	
		Quinazoline sulfonamides		
fenquizone	[20287-37-0]	$C_{14}H_{12}ClN_3O_3S$	Idrolone	
metolazone	[17560-51-9]	$C_{16}H_{16}ClN_3O_3S$	Diulo MycroxZaroxolyn	
quinethazone	[73-49-4]	$C_{10}H_{12}ClN_3O_3S$	Hydromox	
		Other low ceiling diuretics		
alipamide[c]	[3184-59-6]	$C_9H_{12}ClN_3O_3S$		

Table 1. ***Continued***

Generic name	CAS Registry Number	Molecular formula	Trade name	Structure
chlorthalidone	[77-36-1]	$C_{14}H_{11}ClN_2O_4S$	HygrotonThalitone	
indapamide	[26807-65-8]	$C_{16}H_{16}ClN_3O_3S$	Lozol	
tripamide[d]	[73803-48-2]	$C_{16}H_{20}ClN_3O_3S$		
xipamide[e]	[14293-44-8]	$C_{15}H_{15}ClN_2O_4S$	Aquaphor	

[a] Also known as Epitizide-INN [1764-85-8], P-2015, NSC-108164.
[b] Also known as P-2530.
[c] Also known as CI-546; CN-38,474; D-1721.
[d] Also known as ADR-033, E-614.
[e] Also known as MIF 10,938; Be-1293.

The most popular diuretics in this class are hydrochlorothiazide and chlorthalidone; there are more potent low ceiling diuretics available (10). The long duration of action of chlorthalidone, 24 to 72 h, makes once a day dosing possible, and achieves good patient compliance. Cyclothiazide, polythiazide, and trichlormethiazide are about 15 to 30 times more potent than hydrochlorothiazide, and about 500 to 1000 times more potent than chlorothiazide, the first member of the thiazide family marketed (2).

The low ceiling diuretics increase urinary sodium excretion by acting directly on the $Na^+ - Cl^-$ transport mechanism in the convoluted distal tubules of the kidney (7, 11–15). The thiazides cause a maximal saluretic response of about 10% of the filtered sodium ion load, or ca 300 mEq/min, increase above the predrug control; about 90% of the sodium ions in the filtrate have been reabsorbed in the proximal tubule and the loop of Henle (12). Diuretic dose-response curves of low ceiling diuretics are rather flat, indicating that increased dosage only causes a small increment of sodium excretion (14). The lowest effective dose should be used to minimize side effects, particularly hypokalemia, ie, potassium-losing effect.

Indapamide has been shown to possess diuretic and independent vasodilatory effects (16). It lowers the elevated blood pressure and reduces total peripheral resistance without an increase in heart rate. Indapamide antagonizes the vasoconstricting effects of the catecholamines and angiotensin II (16), a property not shared by other thiazide-type diuretics. Tripamide is also reported to have direct vasodilatory effects (13).

Weight loss is a good indicator of fluid loss and excretion. The first wave of fluid mobilized is from the periphery. The excretion of chloride and water is considered passive, and the excretion of potassium and magnesium is increased. In long-term use, the excretion of calcium is decreased.

The thiazides are actively secreted into the proximal tubules, where they exert their action on the luminal side of the tubules. The diuretic effect occurs within 1 h after oral administration, and the duration of action varies from 4 to 24 h depending on which thiazide-type diuretic is used. The diuretic effects of the thiazides are not influenced by acid–base conditions of the blood or urine. Probenecid, which also is secreted into the proximal tubules, may block the diuretic effects of the thiazides.

Hydrochlorothiazide and chlorthalidone are absorbed at about 60–70%, and the plasma half-life is about 2.5 and 44 h, respectively (12). About 90% of an oral dose of indapamide is absorbed, and its plasma half-life is about 18 h (18). In the quinazoline–sulfonamide family, quinethazone has the longest experience, and is about 10 to 20 times less potent than metolazone. A newer member, fenquizone (19, 20), is claimed to have less hyperglycemic and hyperuricemic effects as compared to other thiazides.

In long-term treatment, the thiazides may produce hypokalemia, hyperglycemia, hyperuricemia, and a 5% increase in plasma cholesterol; indapamide has been shown not to increase plasma cholesterol or lipids at therapeutic doses (21–23). The decrease of plasma potassium, ie, hypokalemic effect, is dose-dependent, and can be avoided if high doses are avoided (24, 25). Thiazides can cause hyponatremia in patients with large water intake while on the drug (26, 27); hyponatremia may be associated with nausea, vomiting, and headaches.

Paradoxically, the thiazides are efficacious, especially if combined with a prostaglandin synthetase inhibitor such as indomethacin or aspirin, in the treatment of nephrogenic diabetes insidipus, in which the patient's renal tubules fail to reabsorb water despite the excessive production of ADH (28). Thiazides can decrease the urine volume up to 50% in these patients.

2.2. High Ceiling (Loop) Diuretics

The principal action of the loop diuretics (Table 2) is inhibition of sodium and chloride reabsorption in the thick ascending limb of the loop of Henle (7, 11–13, 29–31). They can produce an excretion of 20 to 30% of the filtered sodium ion load. The increase of sodium excretion can be greater than 1000 mEq/min above the predrug control. This pronounced magnitude of sodium excretion cannot be achieved by other classes of diuretics available as of this writing. Most high ceiling diuretics have a rapid onset of action, steep diuretic dose-response curves, and usually are short acting (32, 33).

Table 2. High Ceiling (Loop) Diuretics

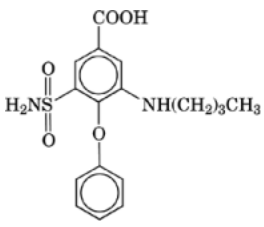
Generic name	CAS Registry Number	Molecular formula	Trade name	Structure
bumetanide	[28395-03-1]	$C_{17}H_{20}N_2O_5S$	Bumex	

Table 2. ***Continued***

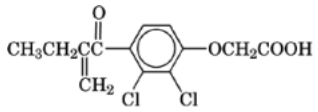
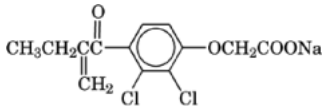
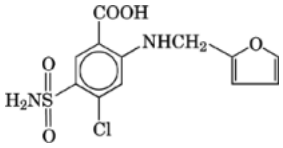
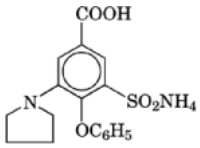
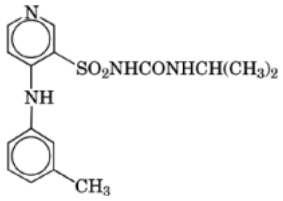
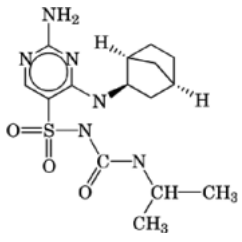
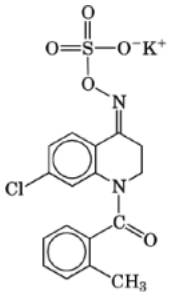
Generic name	CAS Registry Number	Molecular formula	Trade name	Structure
ethacrynic acid[a]	[58-54-8]	$C_{13}H_{12}Cl_2O_4$	Edecrin	
ethacrynic acid sodium	[6500-81-8]	$C_{13}H_{11}Cl_2NaO_4$	Edecrin Sodium	
furosemide	[54-31-9]	$C_{12}H_{11}ClN_2O_5S$	LasixDisal	
piretanide	[55837-27-9]	$C_{17}H_{18}N_2O_5S$	Arelix	
torasemide[b]	[56211-40-6]	$C_{16}H_{20}N_4O_3S$		
AY-31906	[124788-41-1]	$C_{14}H_{21}N_6O_3S$		

Table 2. ***Continued***

Generic name	CAS Registry Number	Molecular formula	Trade name	Structure
M-17055	[114417-20-8]	$C_{17}H_{15}ClN_2O_5SK$		

[a] Also known as Mk-595.
[b] Also known as BM 02 015, or AC 4464.

The most commonly used high ceiling (loop) diuretics are furosemide, bumetanide, and ethacrynic acid. Newer agents available in some countries include torasemide and piretanide. The potency ratio for furosemide:ethacrynic acid:torasemide:piretanide:bumetanide is 1:1:2:4:40. The onset of action is rapid following oral administration, and the duration of action of furosemide, bumetanide, and piretanide is about 2 to 3 h (34, 35). The duration of action of torasemide, an analogue of furosemide, is reported to be much longer and single daily dosing has been reported to be efficacious (35, 36).

After long-term use of a high ceiling diuretic, the extracellular fluid volume contracts and water reabsorption in the proximal and distal tubules increases, thus overriding and diminishing the diuretic's effects. A second high ceiling diuretic may sometimes induce diuresis again. This may be due to additional mechanisms. The high ceiling (loop) diuretics increase urinary excretion of potassium and magnesium, as do the thiazides, but high ceiling (loop) diuretics also increase urinary excretion of calcium; the excretion of chloride ion is greater than that of sodium ion, suggesting the inhibition of active chloride transport by the high ceiling diuretics in the loop of Henle (37, 38). Alkalosis may develop in patients treated with the high ceiling diuretics, and plasma renin activity (PRA) is markedly elevated. The high ceiling diuretics inhibit the ability of the kidney to concentrate urine even in the presence of high concentrations of vasopressin. Like the thiazides, these diuretics act at the luminal side of the tubule so the secretion process of the proximal tubules of the nephron is critical in delivering the drug to the site of action. Probenecid competes for the secretion process, and decreases the efficacy of the loop diuretics. The loop diuretics increase renal blood flow, egg, bumetanide is reported to increase renal blood flow by as much as 40% (39, 40).

Furosemide works mainly by inhibiting $Na^+ - 2Cl^- - K^+$ co-transport across the luminal membrane and diminishes free-water clearance and the ability of the nephrons to concentrate urine (30). Both the effects on blood flow and the diuretic effects of furosemide are blocked by cyclooxygenase inhibitors, such as aspirin and indomethacin (40). These observations suggest that the diuretic effects of furosemide, and perhaps other high ceiling diuretics, may be via endogenous prostaglandin formation (41). Prostaglandins and their analogues have been shown to produce diuretic effects (42). Therefore, the concomitant use of nonsteroidal antiinflammatory drugs with the loop diuretics is contraindicated.

Ototoxicity, as evidenced by transient or permanent hearing loss, is a serious side effect of ethacrynic acid, and occurs less frequently with furosemide. Bumetanide is claimed to have only 20% of the ototoxic potential of furosemide (43). It has been reported that patients treated with torasemide at high doses for four weeks did not suffer hearing loss (36).

2.3. Potassium-Sparing Diuretics

Potassium-sparing diuretics act on the aldosterone-sensitive portion of cortical collecting tubules, and partially in the distal convoluted tubules of the nephron. The commonly used potassium-sparing diuretics are triamterene, amiloride, and spironolactone (Table 3). Spironolactone is a competitive aldosterone receptor antagonist, whereas triamterene and amiloride are not (44, 45).

Table 3. Potassium-Sparing Diuretics

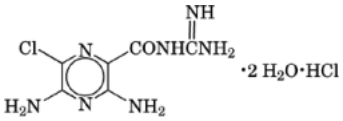
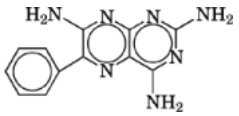
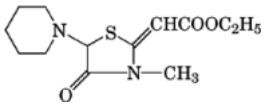
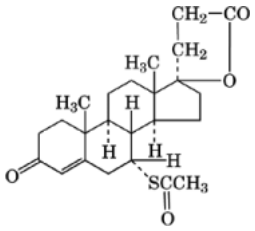
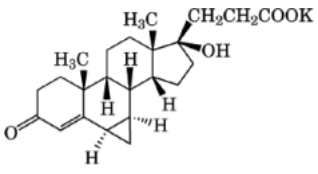
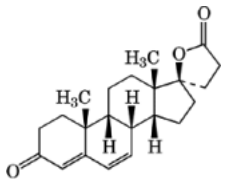
Generic name	CAS Registry Number	Molecular formula	Trade name	Structure
amiloride	[17440-83-4]	$C_6H_8ClN_7O{\cdot}2H_2O{\cdot}HCl$	Midamor	
triamterene	[396-01-0]	$C_{12}H_{11}N_7$	Dyrenium	
etozolin	[73-09-6]	$C_{13}H_{20}N_2O_3S$	Elkapin	
		Aldosterone antagonists		
spironolactone	[52-01-7]	$C_{24}H_{32}O_4S$	Aldactone	
prorenoate potassium	[49847-97-4]	$C_{23}H_{31}O_4K$		

Table 3. ***Continued***

Generic name	CAS Registry Number	Molecular formula	Trade name	Structure
canrenone	[976-71-6]	$C_{22}H_{28}O_3$		

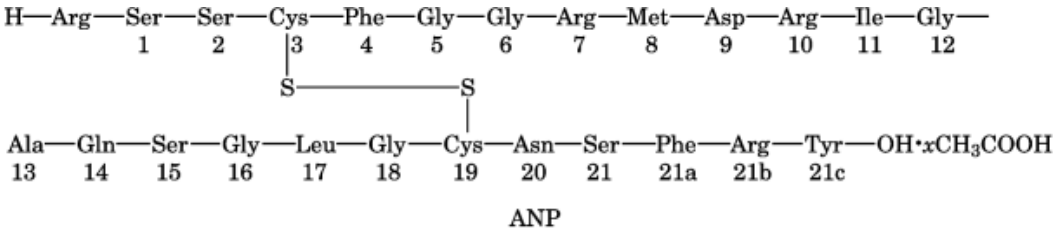
Triamterene and amiloride have been shown to act in the same portion of the nephron by interrupting the Na^+ transport process, and by inhibiting the potassium–sodium exchange mechanism, resulting in a decrease of the electrical potential across the membrane. They exert their effects in the presence or absence of aldosterone. The elimination of the potential gradient may inhibit the secretion of potassium and therefore produce the potassium-sparing or antikaliuretic effects (46–48). Amiloride is far more soluble than triamterene, and is the most widely studied potassium-sparing diuretic. Its natriuretic effect is minimal because only 2 to 3% of the filtered sodium ion load reaches the collecting tubules of the nephron (44). Etozolin (49) is a newer, long-lasting agent that has a gradual onset of action.

Spironolactone antagonizes the effects of aldosterone by binding at the aldosterone receptor in the cytosol of the late distal tubules and renal collecting ducts. Side effects of spironolactone are gynecomastia, decreased libido, and impotency.

Potassium-sparing by diuretic agents, particularly spironolactone, enhances the effectiveness of other diuretics because the secondary hyperaldosteronism is blocked. This class of diuretics decreases magnesium excretion, eg, amiloride can decrease renal excretion of potassium up to 80%. The most important and dangerous adverse effect of all potassium-sparing diuretics is hyperkalemia, which can be potentially fatal; the incidence is about 0.5% (50). Therefore, blood potassium concentrations should be monitored carefully.

2.4. Natriuretic Peptide Diuretics

Atrial natriuretic peptide (ANP), an endogenous diuretic, natriuretic, and vasodilator, is a peptide hormone primarily synthesized and stored by atrial cardiocytes, and secreted by the atria in response to mechanical stretch of the atria. It was discovered in the crude extracts of atria in 1981 (51). ANP is also known as anaritide [95896-08-5], $C_{112}H_{175}N_{39}O_{35}S_3$; atrial natriuretic factor [104595-79-1] (ANF); auriculin; cardionatrin; and atriopeptide. Its primary action is in the kidney and the vascular system. Human ANF is a 28 amino acid residue stored in atrial granules as pro-ANF, a 126 amino acid peptide. It has a very short half-life, and is mainly degraded by neutral endopeptidases, ie, atriopeptidase.



ANP

It has been suggested that both the increased glomerular filtration rate (GFR) caused by ANP and the direct epithelial action in the collecting ducts by ANP are necessary to explain the diuretic effects of ANP. It appears that ANP may increase GFR by relaxing the glomerular mesangial cells resulting in increased surface area for filtration. Due to the augmented GFR, ANP increases the delivery of sodium and water to the renal tubules beyond the distal convoluted tubule. In the collecting ducts, ANP reduces sodium and free-water reabsorption by antagonizing the action of vasopressin. Therefore, the increased loads of sodium and water passing through the collecting ducts without the increased compensatory reabsorption result in profound diuresis and natriuresis (52).

In normal human subjects, ANP infusion for one hour causes increased absolute and fractional sodium excretion, urine flow, GFR, and water clearance (53–55). As shown in many *in vitro* and *in vivo* animal studies, ANP achieves this by direct effect on the sodium reabsorption in the inner medullary collecting duct, ie, by reducing vasopressin-dependent free-water and sodium reabsorption leading to diuresis; and by indirect effect through increased hemodynamic force upon the kidney. ANP inhibits the release of renin and aldosterone resulting in the decreased plasma renin activity and aldosterone concentration (56, 57).

Urodilantin, a 32-amino acid natriuretic peptide synthesized by the kidney and found in urine but not in plasma, is believed to complicate the interpretation of the natriuretic effects of ANP (58). There have been reports of natriuretic peptides related to ANP that have been isolated from several sources, including the brain, eg, brain natriuretic peptide (BNP) [114471-18-0] (59–61).

2.5. Atrial Natriuretic Peptide Potentiator Diuretics

Neural endopeptidase (3.4.24.11) inhibitors or atrial peptidase inhibitors (Table 4) are compounds that inhibit the enzyme that degrades ANP, resulting in higher plasma concentrations, and longer duration of action, of ANP; eg, neural endopeptidase cleaves ANP at the Cys_{105}–Phe_{106} and Ser_{123}–Phe_{124} bonds resulting in the loss of activity of ANP. The diuretic effects of this class of compounds resemble those due to administration of ANP. Compounds such as thiorphan, candoxatril, SCH-34826, and SCH-39370 have been studied in hypertension and congestive heart failure in humans with only limited success (62–67).

Table 4. Neural Endopeptidase (Atrial Peptidase) Inhibitors

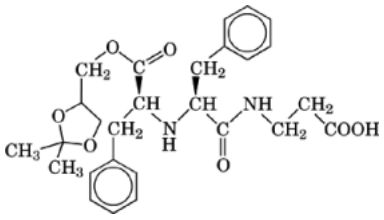
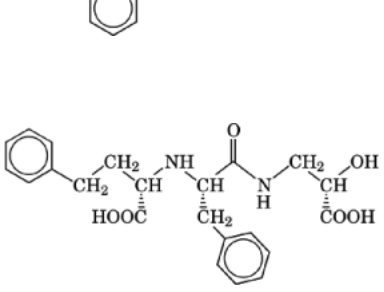
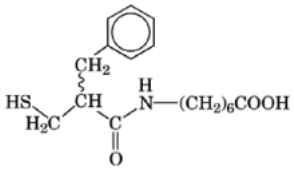
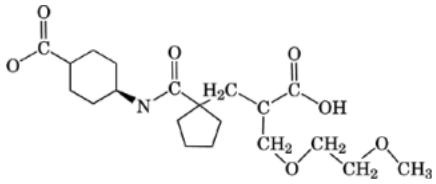
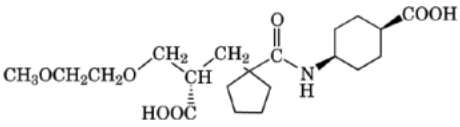
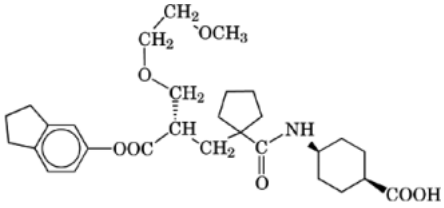
Generic name	CAS Registry Number	Molecular formula	Structure
SCH-34826	[105262-04-2]	$C_{27}H_{34}N_2O_7$	
SCH-39370		$C_{22}H_{26}N_2O_6$	

Table 4. ***Continued***

Generic name	CAS Registry Number	Molecular formula	Structure
SQ-29,072		$C_{17}H_{24}NO_3S$	
UK-69578	[123898-42-0]	$C_{20}H_{33}NO_7$	
candroxatril[a]	[123122-55-4]	$C_{20}H_{33}NO_7$	
candroxatrilet[b]	[123122-54-3]	$C_{29}H_{33}NO_7$	

[a] Also known as UK-79300.
[b] Also known as UK-73967.

2.6. Osmotic Diuretics

An effective osmotic diuretic is a nonionic compound, freely filterable at the glomerulus, not reabsorbed by the tubules of the nephron, and biologically inert except for its osmotic properties. One of the best examples of an osmotic diuretic is mannitol, used to prevent acute renal failure in many major surgeries and traumatic injuries (Table 5) (12, 68). An osmotic diuretic increases urine flow, rather than the excretion of sodium, by maintaining a high osmotic gradient resulting from the presence of large amounts of nonreabsorbable solutes in the luminal side of the proximal tubules. Under such conditions, the reabsorption of water is impaired along the descending loop of Henle as well as the collecting ducts, and urine flow increases. At high concentrations of

an osmotic diuretic, the urinary excretion of sodium is also increased. This is due to the reduced reabsorption of sodium in the proximal tubules.

Table 5. Miscellaneous Diuretics

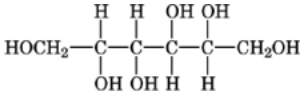
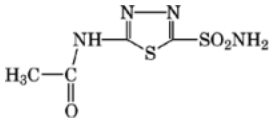
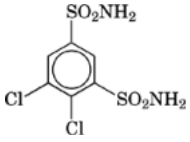
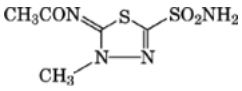
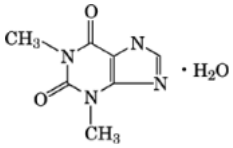
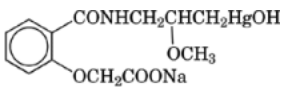
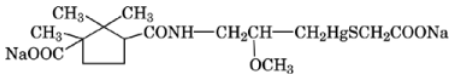
Generic name	CAS Registry Number	Molecular formula	Trade name	Structure
		Osmotic diuretics		
mannitol[a]	[69-65-8]	$C_6H_{14}O_6$	OsmitrolResectisol	
		Carbonic acid anhydrase inhibitors		
acetazolamide	[59-66-5]	$C_4H_6N_4O_3S_2$	Diamox	
acetazolamide sodium	[1424-27-7]	$C_4H_5N_4NaO_3S_2$	Diamox Sodium	
dichlorphenamide	[120-97-8]	$C_6H_6Cl_2N_2O_4S_2$	Daranide	
methazolamide	[554-57-4]	$C_5H_8N_4O_3S_2$	Neptazane	
		Methylxanthines		
theophylline	[58-55-9]	$C_7H_8N_4O_2$	Elixophyllin,	
monohydrate	[5967-84-0]	$C_7H_8N_4O_2H_2O$	Constant-TTheo-Dur TheoventSomophyllin RespbidTheochronDuraphyl Liniphyl	
		Organomercurials		
mersalyl	[492-18-2]	$C_{13}H_{16}HgNNaO_6$	Salyrgan	

Table 5. ***Continued***

Generic name	CAS Registry Number	Molecular formula	Trade name	Structure
mercaptomerin	[20223-84-1]	$C_{16}H_{27}HgNO_6S$		
mercaptomerin sodium	[21259-76-7]	$C_{16}H_{25}HgNNa_2O_6S$		

[a] Also known as D-Mannitol.

2.7. Carbonic Anhydrase Inhibitor Diuretics

Carbonic anhydrase [9001-03-0] accelerates the hydration of carbon dioxide to carbonic acid in aqueous solution, up to 7500-fold as compared to the nonenzymatic reaction. The hydrogen ions liberated from carbonic acid in the epithelial cells of the proximal tubules of the nephron are exchanged for sodium ions in the renal tubular lumen. When the generation of hydrogen ions is inhibited by a carbonic anhydrase inhibitor, the exchange of hydrogen for sodium ions is greatly diminished and the diuretic effect ensues. The site of action of carbonic anhydrase inhibitors (Table 5) is in the proximal tubules. In addition to sodium, the excretion of bicarbonate and potassium is also increased; the maximal excretion is about 2 to 4% of the filtered sodium load. Due to the increased urinary bicarbonate excretion, the urine becomes alkaline and the blood becomes acidotic. The diuretic effect ceases once metabolic acidosis occurs.

Acetazolamide, the best example of this class of diuretics (69, 70), is rarely used as a diuretic since the introduction of the thiazides. Its main use is for the treatment of glaucoma and some minor uses, eg, for the alkalinization of the urine to accelerate the renal excretion of some weak acidic drugs, and for the prevention of acute high altitude mountain sickness.

2.8. Methylxanthine Diuretics

The mild diuretic effect of drinking coffee, from caffeine, and tea, mainly from theophylline, has been recognized for a long time. But the methylxanthines (Table 5) are of very limited efficacy when used as diuretics. The excretion of sodium and chloride ions are increased, but the potassium excretion is normal. Methylxanthines do not alter the urinary pH. Even though the methylxanthines have been demonstrated to have minor direct effects in the renal tubules, it is believed that they exert their diuretic effects through increased renal blood flow and GFR (71).

2.9. Organomercurial Diuretics

Before the advent of the thiazide diuretics, mercurial and organomercurial diuretics were the mainstay therapy for the treatment of edema (72). They have become obsolete and are of historical value only. It is generally accepted that the main site of action of the organomercurial diuretics is in the loop of Henle, although they have also been shown to inhibit sodium and chloride ion reabsorption in the proximal and distal tubules. The organomercurial diuretics, which do not cause the excretion of an amount of bicarbonate equivalent to chloride, produce hypochloremic alkalosis; when this happens the diuretic effect disappears. Metabolic acidosis potentiates their diuretic effects. The organomercurials have to be given parenterally to be effective, and they produce toxic effects on the heart, kidney, and liver. Sudden cardiac death due to ventricular fibrillation has occurred with the use of this class of diuretic agents.

2.10. Water Diuretics (Aquaretics)

A water diuretic, ie, aquaretic, decreases urinary osmolality by influencing the kidney to excrete water selectively without a concomitant proportionally increased excretion of sodium ions (73, 74) (Table 6). A water diuretic should be efficacious for the treatment of hyponatremia, ie, low plasma sodium concentration, and the syndrome of inappropriate antidiuretic hormone secretion (SIADH). In many diseases and conditions, when water is retained to a greater extent as related to sodium ions, hyponatremia results. This is seen in many edema cases arising from congestive heart failure (CHF), hepatic cirrhosis, renal failure, and nephrotic syndrome. In the treatment of these conditions, the conventional diuretics will lose their effectiveness once hyponatremia occurs. Diseases of the brain and the lung, certain surgeries, and some tumors also will cause hyponatremia; in these conditions, with any given plasma osmolality, the plasma antidiuretic hormone (ADH) concentrations are inappropriately high. When this occurs, the patient is inferred to have SIADH.

Logically, ADH receptor antagonists, and ADH synthesis and release inhibitors can be effective aquaretics. ADH, 8-arginine vasopressin [113-79-1], is synthesized in the hypothalamus of the brain, and is transported through the supraopticohypophyseal tract to the posterior pituitary where it is stored. Upon sensing an increase of plasma osmolality by brain osmoreceptors or a decrease of blood volume or blood pressure detected by the baroreceptors and volume receptors, ADH is released into the blood circulation; it activates vasopressin V_1 receptors in blood vessels to raise blood pressure, and vasopressin V_2 receptors of the nephrons of the kidney to retain water and electrolytes to expand the blood volume.

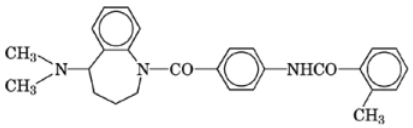
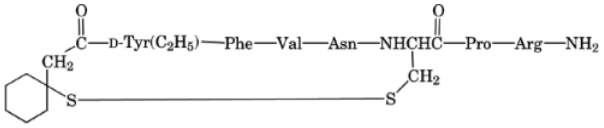
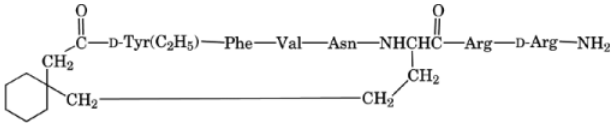
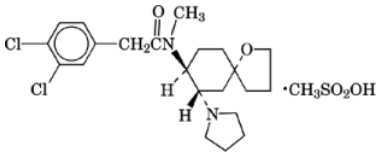
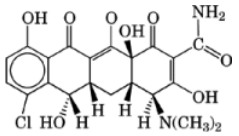
There is no specific water diuretic marketed as of this writing. Demeclocycline has been used clinically with only limited success; in preclinical pharmacology experiments, it has been shown to antagonize the effects of vasopressin in conscious rats (75). Studies in human volunteers have shown a diuretic profile for spiradoline resembling that of an aquaretic by selectively increasing diuresis without increasing excretion of electrolytes (76). Many peptides, including $d(CH_2)_5$[D-Ile^2, Ile^4]AVP, SK&F 101926, and SK&F 105494, have been reported to have vasopressin receptor (V_2-receptor type) antagonistic effects. SK&F 101926 and 105494 have been shown to be *in vitro* and *in vivo* vasopressin V_2-receptor antagonists in rat, dog, and monkey, and in humans, *in vitro.* However, both compounds were found to exert vasopressin V_2-agonist properties in humans *in vivo* (77, 78); the reason for the discrepancy between *in vitro* and *in vivo* results in humans is obscure. OPC-31260 (79, 80), a nonpeptide, has been shown to be 100 times more potent in displacing arginine vasopressin from V_2 than V_1 vasopressin receptors, and has been reported to potently antagonize the antidiuretic effects, ie, V_2-receptor function, of vasopressin in rats. However, OPC-31260 also antagonized the vasoconstricting effects of vasopressin in isolated perfused dog femoral arteries; this indicates that OPC-31260 may not be a highly selective vasopressin V_2-receptor antagonist (79). It has been proposed that the dog femoral artery contains vasopressin V_2 receptors, and these receptors also cause vasoconstriction like the V_1 receptors if activated *in vitro* (79).

3. Health and Safety

Diuretic agents have long been considered relatively safe drugs (81); however, they do produce prominent side effects and toxic effects. The side effects result from the pharmacology of natriuresis, leading to hyponatremia and diuresis, resulting in decreased plasma volume. The decrease in plasma volume reduces cardiac output, which may produce postural hypotension. The decrease in plasma volume may also decrease renal blood flow and glomerular filtration rate producing pre-renal azotemia, or increased proximal reabsorption of uric acid [69-93-2] and distal tubular reabsorption of calcium, leading to hyperuricemia and hypercalcemia, respectively; hypercalcemia may be a prominent feature of thiazide diuretic therapy only.

In an attempt to conserve sodium, the kidney secretes renin; increased plasma renin activity increases the release of aldosterone, which regulates the absorption of potassium and leads to kaliuresis and hypokalemia.

Table 6. Water Diuretics (Aquaretics)[a]

Generic name	CAS Registry Number	Molecular formula	Trade name	Structure
OPC-31260	[137975-06-5]	$C_{27}H_{31}N_3O_2$		
SK&F-101926	[90332-82-4]	$C_{51}H_{74}N_{12}O_{10}S_2$		
SK&F-105494	[114923-99-8]	$C_{54}H_{83}N_{15}O_{10}$		
spiradoline mesylate	[87173-97-5]	$C_{22}H_{30}Cl_2N_2O_2 \cdot CH_4O_3S$		
demeclocycline	[64-73-3]	$C_{21}H_{21}ClN_2O_8 \cdot HCl$	Declomycin	

[a] Antidiuretic hormone (ADH) antagonists.

Hypokalemia is responsible in part for decreased glucose intolerance (82). Hyponatremia, postural hypotension, and pre-renal azotemia are considered of little consequence. Hyperuricemia and hypercalcemia are not unusual, but are not considered harmful. However, hypokalemia, progressive decreased glucose tolerance, and increased serum cholesterol [57-88-5] levels are considered serious side effects or even toxic effects of diuretics.

3.0.1. Hypokalemia

Hypokalemia associated with thiazide diuretic therapy has been implicated in the increased incidence of cardiac arrhythmias and sudden death (82). Several large clinical trials have been conducted in which the effects of antihypertensive drug therapy on the incidence of cardiovascular complications were studied. The antihypertensive regimen included diuretic therapy as the first drug in a stepped care (SC) approach to lowering the blood pressure of hypertensive patients.

One study (83) indicated that in mildly hypertensive male patients treated with an antihypertensive drug, those below the age of 50 or having no clinical evidence of cardiovascular disease had no significant improvement from cardiovascular diseases within 3.3 years; those over the age of 50 or having pre-existing cardiovascular disease benefited significantly.

Another study (84), which enrolled men and women between the ages of 21–55 who had mild hypertension and no recognizable cardiovascular risk factors, showed no significant differences in mortality between drug- and placebo-treated patients. Significant reductions in hypertensive complications were noted, but atherosclerotic complications were not reduced.

A third study (85) enrolled 7825 hypertensive patients (55% males and 45% females) having diastolic blood pressures (DBP) of 99–104 mm Hg (13–14 Pa); there were no placebo controls. Forty-six percent of the patients were assigned to SC antihypertensive drug therapy, ie, step 1, chlorthalidone; step 2, reserpine [50-55-5] or methyldopa [555-30-6]; and step 3, hydralazine [86-54-4]. Fifty-four percent of the patients were assigned to the usual care (UC) sources in the community. Significant reductions in DBP and in cardiovascular and noncardiovascular deaths were noted in both groups. In the SC group, deaths from ischemic heart disease increased 9%, and deaths from coronary heart disease (CHD) and acute myocardial infarctions were reduced 20 and 46%, respectively.

In a study with 3427 male and female patients having DBP of 95–109 mm Hg (12–15 Pa), and no clinical evidence of cardiovascular diseases, half of the patients were placebo-treated and half were SC antihypertensive drug-treated, ie, step 1, chlorothiazide; step 2, methyldopa, propranolol [525-66-6], or pindolol [13523-86-9]; and step 3, hydralazine, or clonidine [4205-90-7] (86). Overall, when the DBP was reduced below 100 mm Hg (13 Pa), there were more deaths in the drug-treated group than in the placebo group. The data suggest reduction of blood pressure by antihypertensive drug treatment that includes a diuretic is accompanied by increased cardiovascular risks.

The Oslo Trial (87) enrolled 785 male patients <50 years of age with DBP <110 mm Hg (15 Pa) and free of clinical evidence of cardiovascular disease. If the initial DBP was <100 mm Hg (13 Pa), there were no differences in mortality or cardiovascular events in the placebo- or drug-treated groups. If the initial DBP was >100 mm Hg, then the incidence of cardiovascular disease was greater in the drug-treated than in the placebo-treated group.

The multiple risk factor intervention trial (MRFIT) (88, 89) examined control of the three primary risk factors, ie, smoking, hypercholesterolemia, and hypertension, in 2338 males ages 40–59 who were assigned either to special intervention care (SIC) or UC antihypertensive drug-treatment groups. The patients had initial DBP >90 mm Hg, and included those with normal and abnormal electrocardiograms (ECG). There were no significant differences in mortality in those patients assigned to the SIC or UC groups if their initial DBP were <100 mm Hg. All patients with initial DBP >100 mm Hg or those with ECG abnormalities in the SIC group had significantly higher mortality. The data were interpreted as suggesting that patients having mild hypertension and ECG abnormalities were at increased risk of mortality from ischemic heart disease.

There is no overwhelming evidence to suggest that patients on thiazide diuretic therapy are at greater risk of CHD. The Oslo Study (87) and MRFIT Study using patients who had baseline ECG abnormalities (88, 89) indicate that patients on diuretic therapy are at greater risk of CHD, whereas the remainder of the studies (83–86) and the MRFIT study using patients having baseline exercise ECG abnormalities (88, 89) indicate that patients on diuretic therapy are not at greater risk of CHD.

3.0.2. Diuretics, Arrhythmias, and Sudden Death

Diuretic-induced hypokalemia may increase the frequency and severity of arrhythmias in patients having preexisting cardiac problems, eg, enlarged hearts, ECG abnormalities, and frequent ventricular ectopic beats. However, the evidence that patients without cardiac problems are at greater risk of sudden death or developing cardiac arrhythmias is not overwhelming. Three studies reported the same number of cases of sudden death

in the control or placebo groups and in the thiazide-treated groups (83, 84, 87), and the MRFIT (88, 89) had a statistically insignificant higher incidence of sudden death in the SIC group who had minor ECG abnormalities than in the UC group; in the group having baseline ECG abnormalities, the incidence of sudden death was approximately four times higher in the usual care group than in the special intervention care group.

3.0.3. Diuretics and Lipid Metabolism

It is well recognized that thiazide diuretics elevate plasma total cholesterol, very low density lipoproteins (VLDL), low density lipoproteins (LDL), triglycerides, and phospholipid concentrations. The levels of high density lipoprotein (HDL), ie, the scavenger lipoprotein, are decreased (83, 90, 91). The changes in lipid profile are characterized as having the potential to increase the risk for coronary heart disease. The mechanism(s) by which the thiazides induce the changes in blood lipids are not well understood (91). However, based on indirect evidence, increased production or decreased clearance of the aforementioned lipids may be involved. The changes are small, ca 5%, but if sustained for several years, these may potentially increase the risk for coronary heart disease. Several studies have re-examined the effects of thiazides on blood lipids. Short-term high dose thiazide diuretic therapy increases plasma cholesterol, but the levels are reduced to or below pretreatment values after several months to a year of daily therapy. The data suggest that long-term thiazide diuretic therapy does not increase the risk for development of atherosclerosis (92).

3.0.4. Diuretics and Glucose Tolerance

The thiazide diuretics have been known for many years to decrease glucose tolerance in patients with established diabetes receiving oral hypoglycemic agents (46, 93). *De novo* glucose intolerance occurs at a rate of ca 9 cases per 1000 persons annually, and appears to be reversible when diuretic therapy is stopped (94, 95). The mechanism by which glucose intolerance occurs may result in part from the hypokalemia induced by the thiazide diuretics (96) because strict control of potassium balance results in minimal disturbances of glucose metabolism (97). Hypokalemia decreases secretion of insulin from the β-islet cells of the pancreas, and decreases insulin-like activity in the blood, probably by inhibiting conversion of proinsulin to insulin (98).

When administered long-term for the treatment of hypertension, diuretics fulfill the goals of preventing cardiovascular disease and increasing longevity. However, diuretic therapy may produce both side and toxic effects that are significant in certain patient subgroups, eg, diabetics and cardiac patients.

4. Therapeutic Uses of Diuretics

Diuretics are one of the drug categories most frequently prescribed. The principal uses of diuretics are for the treatment of hypertension, congestive heart failure, and mobilization of edema fluid in renal failure, liver cirrhosis, and ascites. Other applications include the treatment of glaucoma and hypercalcemia, as well as the alkalinization of urine to prevent cystine and uric acid kidney stones.

4.1. Hypertension

Diuretics were the first drugs used in the stepped care (SC) approach to the treatment of hypertension popular before 1988. They became the cornerstone of all antihypertensive therapies. As of this writing, an individualized or patient-oriented approach, rather than the rigid SC approach, is emphasized, but diuretics, particularly the thiazide-type, still remain one of the first four drugs to be used in antihypertensive therapy (99–102). The importance of the diuretics, especially hydrochlorothiazide (HCTZ), in the treatment of hypertension is evidenced by the large number of combination antihypertensive drug preparations containing HCTZ. HCTZ can be found in combination with almost every class of antihypertensive agents regardless of their mechanism of action, including angiotensin-converting enzyme inhibitors and calcium channel blocking agents. The diuretic

in the combination therapy will counteract the fluid retention side effects of other antihypertensive agents. Therefore, an additive or sometimes a potentiative effect is observed. Diuretics as monotherapy can decrease blood pressure up to 15 mm Hg (2 Pa). They can normalize the blood pressure of about 50% of the hypertensives treated, and are most effective in patients with low plasma renin activity (PRA); they are also very effective in elderly and black patients (103, 104). Indapamide, because of an additional vasodilatory property, can normalize the blood pressure in up to 60 to 80% of the patients; it can decrease the systolic blood pressure up to 20 to 35 mm Hg, and the diastolic up to 10 to 20 mm Hg (105). The main mechanism for lowering the blood pressure of hypertensive patients in long-term diuretic treatment is the contraction of blood volume (106). However, the reduction of excessive sodium and water in the vascular wall induced by the long-term use of a diuretic, rendering the vessel wall less sensitive to neurohormonal stimuli, may play a minor role (106, 107). The possibility of alteration of various ion distribution in the vascular smooth muscle leading to decrease in vascular tone and reactivity also has been proposed. In meta analysis of numerous clinical studies, a reduction of blood volume of 5% is needed before the antihypertensive efficacy of a diuretic is evident. It is emphasized, in the early 1990s, that anti-hypertensive treatment should not be merely to lower the elevated blood pressure, but also to improve quality of life and to lower cardiovascular morbidity and mortality. Diuretics have been shown to significantly protect against stroke but not myocardial infarction; it has been speculated that the undesirable effects of diuretics on blood lipids and potassium may have contributed to the unexpected negative outcome on myocardial infarction. All factors considered, use of diuretics for the treatment of hypertension is considered to be most cost-effective (108). It is particularly suitable for use in patients at high risk of cerebrovascular disease and in hypertensive patients with renal failure.

Furosemide is more efficacious than the thiazides in hypertensive patients with reduced renal functions. Piretanide has been shown to be more efficacious than hydrochlorothiazide in patients with uncomplicated essential hypertension. However, diuretic monotherapy should be avoided in patients with left ventricular hypertrophy or with irregular ventricular heartbeat since diuretics will not reverse cardiac hypertrophy, and can cause additional electrical instability of the heart due to possible serum potassium and magnesium depletion. The lowest effective dose of a diuretic should be used, since this will decrease side effects. Diuretics, particularly potassium-sparing diuretics, should not be used in hypertensive patients with diabetes. It has been shown that low doses of ANP infusions produce a prolonged lowering of blood pressure and increases in heart rate of patients with hypertension (53, 54, 109, 110). Despite some natriuresis, no changes in urine volume or cardiac output were observed. Side effects in some patients included severe postural hypotension and bradycardia (109). Nearly all known antihypertensive agents are more efficacious when combined with a diuretic. Withdrawal of diuretics from patients who have been treated for more than six months may result in low blood pressure for many months.

4.2. Congestive Heart Failure

Congestive heart failure (CHF) occurs when the heart fails as a pump, leading to a decrease in the cardiac output and venous blood pooling. The amount of blood perfusing the vital organs decreases, and receptors on the arterial side of the systemic circulation sense the decrease of the effective volume perfusion and initiate various compensatory mechanisms attempting to correct the deficiency and to restore normal blood supply. The adrenergic nervous system, the renin–angiotensin–aldosterone system, and the vasopressin system are activated. In turn the kidney excretory functions are changed to favor water and salt retention. Capillary pressures finally are increased sufficiently to cause fluid accumulation in the tissue space, resulting in edema. Therefore, the symptoms of CHF are mainly contributed by hemodynamic and neurohormonal forces. Edema through salt retention is one of the factors in increasing ventricular wall stress. Under such conditions, the diuretic can increase renal water and salt excretion so as to facilitate the movement of excess fluid out of the tissues and organs.

Diuretics have become the cornerstone of all treatment regimens of CHF (111–113). They can relieve symptoms of pulmonary and peripheral edema. In mild CHF, the thiazide-type diuretics are adequate unless the GFR falls below 30 mL/min, as compared to 120 mL/min in normal subjects. Diuretics improve left ventricular function in CHF due in part to decrease of preload. Indapamide has been shown to cause reduction of pulmonary arterial pressure and pulmonary wedge pressure.

The high ceiling (loop) diuretics, such as furosemide, bumetanide, and ethacrynic acid, are preferred in moderate CHF because they have higher efficacy and can retain their efficacy until the GFR falls below 5 mL/min. Furosemide has been shown to decrease afterload, as demonstrated by improving left ventricular function. It also causes a reduction of left ventricular filling pressure, improvement of pulmonary compliance, and a decrease of pulmonary wedge pressure. There is evidence to show that the loop diuretics, such as piretanide, will cause a decrease of preload, as demonstrated by decreasing pulmonary wedge pressure and right atrial pressure.

As mentioned earlier, the long-term employment of diuretics can cause low serum levels of potassium and magnesium, and can predispose the patients to lethal ventricular fibrillation and sudden cardiac death (112). Therefore, it is highly useful if the regimen includes the use of a thiazide-type diuretic or a loop diuretic in combination with a potassium-sparing diuretic. Attention must be paid to monitor the serum potassium and magnesium levels. Even though diuretics alone can relieve the symptoms of patients with CHF, their disease continues to deteriorate (112). This may be due, in part, to the activation of the renin–angiotensin–system (RAS) by the diuretics, ie, increased plasma renin activity is a common adverse effect of the diuretics. The combined use of a diuretic and an angiotensin-converting enzyme (ACE) inhibitor, such as captopril, enalapril, or lisinopril, will have additive efficacy. Similarly, the combined use of a diuretic with ANP and/or a neutral endopeptidase (atriopeptidase) inhibitor will have beneficial effects, since ANP will suppress the RAS. Diuretics will also enhance the efficacy of vasodilators by counteracting their fluid retention side effects. Furosemide is effective for the treatment of hyponatremia if used concomitantly with hypertonic sodium chloride solution, as it will antagonize the ability of the nephrons to generate free water (114).

4.3. Renal Failure

High ceiling (loop) diuretics, such as furosemide, bumetanide, ethacrynic acid, piretanide, and torasemide, are the drugs of choice for the treatment of acute and chronic renal failure, with or without hypertension. Acute renal failure is characterised by a rapid loss of renal function, leading to a rapid development of azotemia. In acute renal failure that occurs after certain surgical procedures, both mannitol, an osmotic diuretic, and furosemide have been shown to be successful in increasing urine flow and creatinine clearance, but they do not always decrease mortality (115, 116). Chronic renal failure results from destruction of nephrons and much reduced GFR, leading to uremia. In these patients, high ceiling diuretics can increase sodium excretion to >50% of the filtered load. The greater the renal impairment, the higher the dose of diuretic is needed. The half-life of the diuretics can increase two- to fourfold in these patients. Mannitol has been found to be useful in maintaining urine flow even at low GFRs, such as in hypotension and dehydration (116).

4.4. Ascites

Patients with cirrhosis, especially liver cirrhosis, very often develop ascites, ie, accumulation of fluid in the peritoneal cavity. This is the final event resulting from the hemodynamic disturbances in the systemic and splanchnic circulations that lead to sodium and water retention. When therapy with a low sodium diet fails, the drug of choice for the treatment of ascites is furosemide, a high ceiling (loop) diuretic, or spironolactone, an aldosterone receptor antagonist/potassium-sparing diuretic.

Since nonsteroidal antiinflammatory drugs, such as aspirin, an inhibitor of the synthesis of prostaglandins, will block the diuretic effects of furosemide, their concomitant use should be avoided (13, 117).

In severe ascites, therapeutic paracentesis, the nonpharmacological treatment, should be used first, followed by a diuretic to prevent the reaccumulation of fluid in the abdominal cavity (117). Furosemide is effective in only ca 50% of these patients. One of the factors for patients not responding to a high ceiling diuretic may be that they have hyperaldosteronism; in this instance spironolactone has been shown to be more efficacious than furosemide in many patients. The combination of a high ceiling diuretic and spironolactone offers a greater natriuretic effect and a lower incidence of hyperkalemia (117). Patients with ascites may be refractory to diuretic treatment due to the coexistence of functional renal failure; this results in impairment of the delivery of the diuretics to the sites of action in the renal tubules. It has been suggested that the longer-acting loop diuretic, torasemide, is more effective in the treatment of ascites in cirrhosis (118).

5. Economic Impact

Worldwide sales of diuretics in 1991 were $1.602 billion (119). U.S. sales of diuretics in 1992 U.S. dollars were over $650 million (120). Worldwide sales of the leading diuretics Dyazide, ie, triamterene plus hydrochlorothiazide (HCTZ); Moduretic, ie, amiloride plus HCTZ; and Aldactone, ie, spironolactone, were $280, $145, and $206 million, respectively, in 1989–1990 (121, 122). Lozol and Maxzide, a lower dosage form of Dyazide, commanded sales of $74 and $90 million, respectively (123, 124). In the United States, the market shares for potassium-sparing diuretics, the high ceiling (loop) diuretics, and the low ceiling diuretics were 72, 14, and 14%, respectively (125). Between 1984 and 1991, the sales of diuretic agents in constant dollars, adjusted to 1991 prices, declined 40%. In 1992 dollars not adjusted for price increases, sales increased ca 10% (120).

The sales of oral diuretics are declining, and are forecast to continue their decline in constant dollars during the 1990s (119, 120). Several possible explanations can be offered for these trends. The patents of market leaders are expiring, leading to the introduction of generic brands at ca 40% below the cost of the branded market leaders; physicians are switching to newer treatments for hypertension, eg, calcium channel blockers and angiotension-converting enzyme inhibitors; and concerns are growing about the possible adverse effects of diuretics, eg, hypokalemia, the progression of atherosclerosis, and the increase in mortality, serum cholesterol, glucose tolerance, and diabetes (120, 121).

Nomenclature	
acidosis	pH of blood or plasma below normal; the normal range in the adult male is 7.33–7.45
active transport	the movement of materials across cell membranes and epithelial layers resulting directly from the expenditure of metabolic energy
afterload	the load against which cardiac muscle exerts its contractile force; the arterial pressure against which the ventricle must contract; the higher the pressure, the greater the afterload
alkalosis	pH of blood or plasma above normal
angiotensin II	a potent octapeptide vasopressor and stimulant of aldosterone secretion from the adrenal cortex
ascites	accumulation of fluid in the peritoneal cavity
azotemia	an excess of urea or other nitrogenous bodies in the blood
baroreceptor	a sensory nerve ending that is sensitive to changes in pressure, as those in the walls of blood vessels
cardiac output	the quantity of blood pumped into the aorta per minute by the heart

Nomenclature	
catecholamines	one of a group of similar compounds possessing a catechol pharmacophore and having sympathomimetic action, eg, epinephrine, norepinephrine, or dopamine
clearance (renal)	a calculated volume (mL) of blood (plasma, serum) which is cleared of a compound per minute by renal elimination
collecting duct	part of the nephron (Fig. 2); in the original definition of the nephron the collecting duct is excluded
cortex	outer part of the kidney (Fig. 1)
diastole	period of dilation of the heart, especially of the ventricles
diuretic profile	the pattern of urinary volume and electrolyte excretion
glomerulus	the filtering unit of the nephron consisting of Bowman's Capsule and the glomerular capillary network (Fig. 2)
glomerular filtration rate (GFR)	the quantity of glomerular filtrate formed each min in all nephrons of both kidneys
gynecomastia	excessive development of the male mammary glands, even to the functional state
hydropenia	water deficiency
hypercalcemia	serum calcium levels above normal; normal range in humans is 4.5–5.5 mEq/L
hyperkalemia	serum potassium levels above normal; normal range in humans is 3.5–5.0 mEq/L
hypernatremia	serum sodium levels above normal; normal range in humans is 136–145 mEq/L
hypertonic	tonicity (osmolarity) more than isotonic; normal range in humans is 285–295 *mOsm*/kg serum water
hyperuricemia	serum uric acid levels above normal; normal range is 2.5–8.0 mg/dL for men and 1.5–7.0 mg/dL for women
hypocalcemia	serum calcium levels below normal
hypoglycemia	an abnormally diminished concentration of glucose in the blood; normal range in humans is 70–115 mg/dL
hypokalemia	serum potassium levels below normal
hyponatremia	serum sodium levels below normal
hypotonic	tonicity (osmolarity) less than isotonic
interstitium	the interspace of a tissue, eg, of kidney
isotonic	having the same tonicity (osmolarity); usually in comparison with plasma or other body fluids
juxtamedullary	close to the medulla of the kidney
kaliuresis	excretion of potassium in the urine
loop of Henle	part of the nephron between the proximal convoluted tubule and the distal convoluted tubule; divided into a descending limb and an ascending limb (Fig. 2)
medulla	inner part of the kidney (Fig. 1)
nephrogenic diabetes insipidus	a rare congenital and familial form of diabetes insipidus, resulting from the failure of the renal tubules to reabsorb water; there is excessive production of ADH, but the renal tubules fail to respond to it
nephron	the functioning unit of the kidney
osmolarity	the concentration of a solution expressed as osmols (mol wt of a solute in g, divided by the number of ions into which it dissociates in solution) of solute per L of solution
paracentesis	the passage into a cavity of a hollow instrument for the purpose of removing fluid
parenteral	introduced by any other route than by way of the digestive tract
passive transport	the movement of materials into and out of cells and across epithelial layers that is dependent on concentration gradients and not on expenditure of energy
plasma volume	total blood volume minus blood cells
pleural effusion	the presence of fluid in the pleural space
preload	the amount of tension on the cardiac muscle when it begins to contract; the volume of blood in the ventricle at the time of diastole; also known as central venous filling pressure
pulmonary compliance	the extent to which the lungs expand for each unit increase in transpulmonary pressure
systemic	relating to the body as a whole
tubule, distal convoluted	part of the nephron between the ascending limb of the loop of Henle and the collecting ducts (Fig. 2)
tubule, proximal convoluted	part of the nephron between the glomerulus and the descending limb of the loop of Henle (Fig. 2)
uremia	the retention of excessive by-products of protein metabolism in the blood, and the toxic condition produced thereby
uricosuric	increasing the urinary excretion of uric acid

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