CHAPTER 61

Loop and Thiazide Diuretics

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OBJECTIVES

This chapter will:

1. Explain the mechanism of action of loop and thiazide diuretics.
2. Discuss pharmacokinetics and pharmacodynamics of loop and thiazide diuretics.
3. Discuss resistance to loop and thiazide diuretics.
4. Discuss the available evidence to guide the use of loop and thiazide diuretics in the acutely ill patient.
5. Discuss the adverse effects and toxicity of loop and thiazide diuretics.

Acute kidney injury (AKI) is an increasingly encountered complication, affecting up to 60% of patients admitted to an intensive care unit (ICU).[1,2] Depending on its cause, as many as 17% of patients with AKI may require renal replacement therapy (RRT) for management of fluid balance, acid base status, or electrolyte disturbances.[3] Patients with AKI have decreased capacity to excrete fluid and solute. Moreover, they often develop AKI in association with conditions precipitating increased capillary permeability, necessitating aggressive fluid resuscitation such as sepsis, major trauma, or burn injury. Therefore these patients are at increased risk for fluid accumulation and complications related to fluid overload. Over the last decades, multiple studies have suggested that a positive fluid balance is associated with increased mortality,[4–6] worsening lung function and oxygenation,[5] and more major surgical complications.[7] Conversely, after initial resuscitation, achieving a neutral or negative fluid balance has been associated with improved gas exchange, greater ventilator-free days, and reduced ICU length of stay.[8,9] Achieving a negative fluid balance in critically ill patients, in particular in the setting of AKI or reduced kidney function, commonly necessitates use of diuretic therapy. In general, in acute and critical care settings, loop diuretics and thiazide are used most commonly. This chapter reviews the mechanism of actions and clinical use of loop and thiazide diuretics.

LOOP DIURETICS

Mechanism of Action

Sodium is filtered by the glomerulus and is part of the ultrafiltrate found in the tubular lumen. Approximately 60% of the filtered sodium is reabsorbed by the proximal tubule, 25% to 30% by the loop of Henle, 5% to 10% by the distal tubule, and 3% to 5% by the collecting duct.[10] It is this variation in fraction of Na+ reabsorption that accounts for the differences in the potency among diuretics. The loop diuretics act predominantly on the medullary

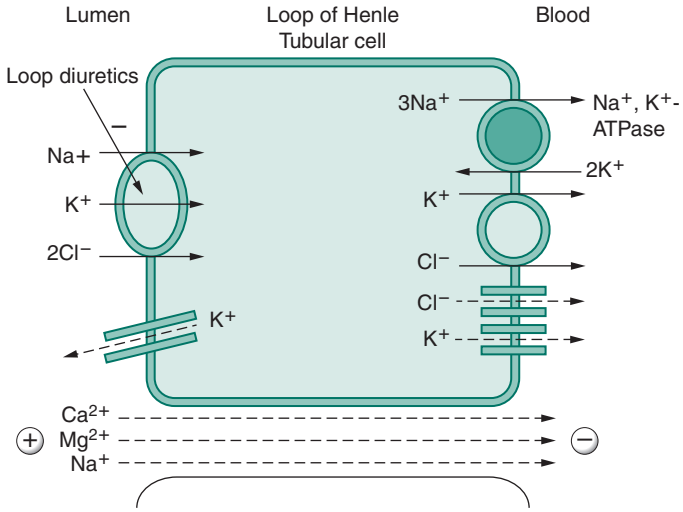

FIGURE 61.1 Mechanism of NaCl reabsorption in the loop of Henle. The Na^+,K^+-ATPase, localized in the basolateral membrane, reduces the cytosolic Na concentration and provides the driving force for the operation of the apical NKCC2 transporter, the site of action of loop diuretics. *Dashed lines* denote passive transport. See text for more details. (Modified from Reeves WB, Molony DA. The physiology of loop diuretic action. *Semin Nephrol.* 1988;8:225–233.)

and cortical aspects of the thick ascending limb (TAL). They also act on the macula densa cells in the early distal tubule. After being secreted in the tubular lumen by Organic Acid Transporter (OAT) in the proximal tubule, they reach the TAL, where they bind the chloride-binding site of the Na^+-K^+-$2Cl^-$ cotransporter (NKCC2) located on the apical side of the epithelial cells (Fig. 61.1). Chloride is the rate-limiting step in NKCC2 activation. Its inhibition precludes conformational change in the transporter that allows sodium, potassium, and chloride to shift into the cell. The inhibition of sodium chloride (NaCl) reabsorption in the TAL also abolishes the hypertonicity of the interstitium and so inhibits water reabsorption in the collecting duct. Therefore NKCC2 blockade leads to sodium and water loss. Loop diuretics are also weak inhibitors of carbonic anhydrase.

In a normally functioning TAL, the Na^+-K^+-ATPase pump on the basolateral membrane pumps sodium out of the cell, therefore creating a sodium gradient that allows NKCC2 to move sodium into the cell and with it, potassium and chloride. To avoid potassium depletion on the luminal side, specialized potassium pores allow backleak of this ion out of the cell. This influx of cations creates a positively charged tubular fluid that allows the paracellular absorption of other positively charged ions such as magnesium and calcium through specialized channels (Fig. 61.1). Therefore loop diuretics, by blocking NKCC2, increase not only fractional excretion of sodium, potassium, chloride, and water but also excretion of calcium and magnesium.

The administration of loop diuretics also has an effect on renal and systemic vasculature. Indeed, administration of loop diuretics triggers prostaglandin release by the kidneys, which leads to local afferent arteriole dilatation with an increase in renal blood flow. These prostaglandins also induce systemic venodilation with consequent increase in venous capacitance and decrease in capillary wedge pressure, an effect used in the treatment of patients with pulmonary edema.

PHARMACOKINETICS

There are four loop diuretics currently available: furosemide, bumetanide, torsemide, and ethacrynic acid. Because of significant ototoxicity, ethacrynic acid is used rarely. Because it is the only drug in this class that does not contain sulfa, it can, however, be of help when clinicians face a patient with anaphylactic reactions to this compound. Furosemide is by far the most used loop diuretic, evidenced by the fact that it is the only loop diuretic that figured among the top 20 most prescribed drugs in the United States in 2008,[11] which was confirmed in a recent survey among intensivists.[12]

Absorption

The absorption of oral furosemide is highly variable. Bioavailability ranges from 10% to 90%, depending mainly on intestinal mucosal edema, presence or absence of food, and interindividual variation in enzymes implicated in intestinal metabolism of the drugs. Therefore, to get the same effect as an intravenous (IV) dose, the oral dose generally should be increased by two or three times. In most ICU patients, the IV route is preferred. The bioavailability of ethacrynic acid, bumetanide, and torsemide is almost complete (Table 61.1).

Onset and Peak of Action

Once loop diuretics are absorbed, they are bound to albumin (free fraction < 5%). Because of this low free fraction, only a small proportion is filtered by the glomerulus. Rather, they are secreted into the proximal tubular lumen (S2 segment) by OAT, for which the diuretic has a greater affinity than for albumin. Once secreted in the tubular fluid, it reaches its target receptor in the TAL. Except for torsemide, loop diuretics have similar rapid onset and peak of action (see Table 61.1).

Metabolism and Excretion

Loop diuretics have various rates of renal and extrarenal clearance. Furosemide is the loop diuretic with the lowest extrarenal clearance. About 50% of a dose of furosemide is excreted as unchanged active drug in the urine, the remaining 50% being glucuronidated in the kidney. The metabolism and excretion data for all other diuretics[11] are shown in Table 61.1.

Impact of Loop Diuretics on Outcome in Acute Kidney Injury and the Intensive Care Unit

Despite their widespread use, the evidence that loop diuretics are associated with improved patient-centered outcomes in critical illness and AKI is still lacking, with some data suggesting harm in selected circumstances.

In 2002 Mehta et al. published a large observational study showing increased mortality with loop diuretic use.[13] However, this study was highly susceptible to confounding by indication and selection bias, grossly limiting concrete inferences about the direct impact of diuretics on mortality and renal recovery in AKI.[13] Another large observational study failed to demonstrate any significant difference in mortality associated with diuretic exposure in AKI.[14] In 2007 a systematic review of RCTs on the subject found no difference in mortality associated with diuretic use in AKI but rightfully concluded existing data were low quality and had numerous shortcomings prohibiting any clear inferences on their efficacy.[15] Finally, a second analysis of the FACTT trial showed improved survival among AKI patients assigned to a conservative fluid management strategy with entailed a considerable exposure to diuretics; however, this association was mediated largely by fluid status and was insignificant after adjustment for fluid balance.[9] These are important observations, suggesting that in the correct clinical context,

TABLE 61.1

Pharmacokinetics of Loop Diuretics

	FUROSEMIDE	BUMETANIDE	TORSEMIDE	ETHACRYNIC ACID
Relative potency	40 IV	1 IV/PO	15–20 IV/PO	50 IV/PO
Bioavailability (%)	10–90	80–100	80–100	≈ 100%
Protein binding (%)	>95	>95	>95	> 95
Onset of action (min)	5 IV; 30 O	< 5 IV; 30–60 O	10 IV; 60 O	5 IV; 30 O
Peak of action (min)	30 IV; 60–120 O	15–30 IV; 60–120 O	60 IV; 60–120 O	30 IV; 120 O
Elimination (%):				
Renal	90*	60	20	30–65
Hepatic	10	40	80	35–40
Half-life (hr)				
Normal	1.5–2.0	1.0	3.0–4.0	0.5–2.0
Renal dysfunction	2.8	1.6	4.0–5.0	n/a
Liver dysfunction	2.5	2.3	8.0	n/a
HF	2.7	1.3	6.0	n/a
Maximal effective dose (mg)	40 IV; 80 O	1	15–20	50

*50% of a dose is excreted as unchanged active drug in the urine, and 50% is metabolized in the kidney through conjugation with glucuronic acid.
IV, Intravenous; *PO,* oral.

use of diuretics (predominantly loop diuretics) are safe, and although they do not provide a direct survival benefit, may mitigate indirectly improved outcome by facilitating management of fluid accumulation and overload. Early data from the aforementioned trials were significantly confounded by co-interventions (i.e., already receiving RRT, concomitant mannitol, and/or dopamine), were small and often did not include ICU patients. In this context, results of the Trial of the Effect of furoSemide in Critically Ill Patients With eARly Acute Kidney Injury (The SPARK Study) study, a phase II blinded randomized control trial on the effects of diuretics in ICU patients, will be of great interest.[16]

For years, it was believed that oliguria in AKI was a physiologic response to an ongoing kidney insult mediated by glomerulotubular feedback. However, this recently has been challenged. Redfors et al. showed that for each unit of reabsorbed sodium in the tubule, there was a 2.4-fold higher use of oxygen for patients with AKI compared with those who did not have AKI. These data indirectly support a potential "renal protective" role for furosemide.[17] Studies looking at use of furosemide for prevention of AKI in high-risk situations such as cardiac surgery or contrast use have, however, failed to showed such a benefit.[18]

Loop diuretics also have been proposed to hasten recovery of AKI. The systematic review cited above showed shorter duration of RRT by an estimated 1.5 days, shorter delay before decrease in creatinine by 2.1 days, and greater urine output. There was, however, no difference in the proportion of patients who recovered kidney function.[15] A more recent randomized control trial showed improvement in urine output but no difference in time to recovery.[19] In the Fluids and Catheters Treatment Trial (FACTT) trial, there was a trend for decreased use of RRT noted among patients allocated to the conservative fluid group in whom diuretics were used commonly when compared with the liberal fluid group.[8] Conversely, a meta-analysis of nine studies failed to show a decrease in the use of RRT with use of furosemide.[20] Taken together, these data suggest that loop diuretics likely have an adjuvant role for increasing urine output to help manage volume status in ICU patients; however, robust data on kidney specific benefits are lacking.

The use of loop diuretics also has been evaluated in hypoproteinemic mechanically ventilated patients with acute lung injury. Martin et al. randomized 37 patients with acute respiratory distress syndrome (ARDS) to albumin and furosemide or placebo. After 24 hours, they observed more diuresis and improvement in PaO_2/FiO_2 ratio in the treatment group.[21] In 2005 they published another randomized control trial comparing the effect of furosemide and placebo to furosemide and albumin on oxygenation in the same population. They showed that combining the medications was more effective than furosemide alone. However, there was no placebo-only group, which would have allowed determining if furosemide is of any benefit compared with placebo.[22] In the FACCT trial, there was also a trend for improvement in the PaO_2/FiO_2 ratio for those allocated to the conservative fluid management strategy.

In summary, data supporting the use of loop diuretics in the ICU are at best of modest quality. The only benefit that seems to be reproducible across studies is the use of loop diuretics to help manage volume status and control of fluid balance. The KDIGO Clinical Practice Guidelines for Acute Kidney Injury have recommended against the use of loop diuretics for the prevention and/or treatment of AKI; however, they suggest that diuretics have an adjuvant role to manage fluid overload.[23]

DIURETIC RESPONSIVENESS AND RESISTANCE

Many patients, especially those with chronic kidney disease (CKD), heart failure, cirrhosis, or nephrotic syndrome become resistant to the effect of loop diuretics. One of the major mechanisms to explain this resistance is the so-called "braking phenomenon," which happens when decreased natriuresis ensues after a dose of diuretics despite a normal rate of excretion in the tubular lumen. This effect is more pronounced for diuretics with short half-lives. Multiple concurrent mechanisms have been proposed to explain this response:

- Activation of the renin-angiotensin system and release of norepinephrine as a consequence of volume depletion increase sodium reabsorption in the proximal tubule
- Distal convoluted tubule hypertrophy mediated by increased flow increase sodium reabsorption in this segment
- Increase in aldosterone as a consequence of volume depletion stimulates sodium reabsorption in the collecting duct
- Increase release of ADH and decreases in natriuretic peptide release

Combining loop diuretics with restricted sodium intake is therefore extremely important. Another approach to overcoming this short-term tolerance is more frequent diuretic administration or the use of continuous infusions.

Diuretic resistance also can occur because not enough drugs are being delivered to the site of action, there is decreased response, or there is increased activity of the receptor. Table 61.2 lists various causes of diuretics resistance. The most clinically relevant are explored in the following sections.

Chronic Kidney Disease

CKD has a variety of influences on the pharmacokinetic and pharmacodynamics response to loop diuretics. The volume of distribution can increase up to 30% as a result of fluid overload; the nephronic mass and blood flow to the glomerulus are decreased, all of which decreases the amount of drug filtered by the glomerulus.[24] Secretion of diuretics in the tubular lumen also is diminished by the presence of multiple acidic molecules in the blood that compete for secretion by Organic Acid Transporter (OAT). This can result in an up to 80% reduction in the amount of

TABLE 61.2

Causes of Resistance to Loop Diuretics

Pharmacokinetic resistance	Reduced bioavailability
	Reduced renal blood flow
	Competition at organic acid transporter
	Hypoalbuminemia
	Albuminemia
Pharmacodynamic resistance	Reduce total fractional sodium reabsorption
	Increased proximal sodium reabsorption
	Increased Na+-K+-2Cl cotransporter expression
	Distal tubular hypertrophy
	Increased distal sodium reabsorption

TABLE 61.3

Maximal Effective Doses of Diuretics in Specific Diseases

DISEASE	FUROSEMIDE (mg)	BUMETANIDE (mg)	TORSEMIDE (mg)
Normal	40	1	15–20
CKD	160–200	8–10	50–100
Heart failure	40–80	2–3	20–50
Liver cirrhosis	40	1	15–20
Nephrotic syndrome	120	3	50

furosemide available in the tubular lumen in patients with stage V CKD.[24] The reduced glomerular filtration rate (GFR) results in a reduction in NaCl reabsorption and in increased synthesis of NKCC2,[25] which further impairs diuretic efficacy. The half-life of loop diuretics is affected unequally by CKD. Furosemide has relatively low extrarenal clearance compared with torsemide and bumetanide. Therefore its half-life and potency are increased significantly (see Table 61.1). The relative potency of furosemide and bumetanide changes from 40:1 in healthy volunteers to 20:1 in patients with renal dysfunction.[11,26] As a result of all these changes, doses have to be modified in CKD (Table 61.3).

Congestive Heart Failure

Loop diuretics are of great help in patients with congestive heart failure (CHF). Multiple small studies have looked at the impact of loop diuretics on outcomes in patients with heart failure. A meta-analysis of diuretic treatment in chronic heart failure demonstrated in 2006 a beneficial effect on mortality, admission for worsening heart failure, and exercise capacity.[27] Two updates of this systematic review found no additional evidence.[28,29]

CHF is associated with avid sodium and water retention resulting from arterial underfilling, resulting in alterations in the sympathetic nervous system, the renin-angiotensin system, the vasopressin axis, and the vasodilatory natriuretic pathway.[30] These factors impair response to loop diuretics:

- Patients with heart failure usually are overloaded, which increases as mentioned above volume of distribution and impairs intestinal absorption when oral route is used.
- The acute tolerance or braking phenomenon is described previously.
- There is decreased renal blood flow provoked by arterial underfilling. This phenomenon triggers renin-angiotensin-aldosterone and sympathetic system activation, which increase salt and water absorption in the proximal tubule with reduced sodium delivery to the TAL, thus decreasing the maximal effect of loop diuretics. Increased aldosterone levels also potentiate sodium reabsorption in the collecting duct.
- There is vasopressin-mediated increase in expression of NKCC2, which may amplify the defect in water excretion and contribute to diuretic resistance.[31] This effect was reversed by the administration of losartan in rat.[32]
- As mentioned in the introduction of the Diuretics Responsiveness and Resistance section above, there are functional and structural adaptations in downstream nephron segments with chronic diuretic use with hypertrophy and hyperplasia in epithelial cells of the distal convoluted tubule, increased expression of the NaCl cotransporter in the luminal membrane, and of the Na^+,K^+-ATPase in the basolateral membrane. This leads to increased reabsorption in this segment, thereby blunting the natriuretic effect and shifting the dose-response curve downward and to the right.

As a result the recommended ceiling doses have to be modified compared with the healthy individual (see Table 61.3).

Conversely to patients with CKD, some evidence suggests that all loop diuretics do not have the same impact on outcomes in heart failure patients. Indeed, one open-label randomized trial showed that torsemide decreased the rate of admission for heart failure by almost 50% at 1 year when compared with furosemide.[33] Similarly, an observational study of 1377 patients found a diminution in 1-year mortality.[34] However, a third study showed improved symptoms but no change in hospitalization or mortality.[35] This potential beneficial effect of torsemide may be explained by its effect on renin-angiotensin system activation. Indeed, it has been shown that torsemide binds to aldosterone receptor and seems to counteract sympathetic system activation, an effect not seen with even high doses of furosemide.[11] This effect seems to translate into smaller left-ventricular end diastolic and systolic volumes and lower brain natriuretic peptide (BNP) levels.[36] These data must be interpreted cautiously because the number of patients included in each study is very small.

Liver Cirrhosis

The physiopathology of edema in liver cirrhosis is similar to what is observed in the heart failure patient. The main difference with heart failure is that underfilling is provoked by vasodilatation as a result of nitric oxide excess.[37] Because secondary hyperaldosteronism is an important cause of water and sodium retention in patients with cirrhosis of the liver, aldosterone antagonists (spironolactone) are first-line treatment for this condition, and the use of loop diuretics is limited mostly to patients whose cirrhosis is resistant to spironolactone and thiazide diuretics.[38]

There is alteration in pharmacodynamic and pharmacokinetics of loop diuretics in patients with cirrhosis. First, the half-life of bumetanide and mainly torsemide are increased because they have a significant hepatic clearance[11] (see Table 61.1). There is also competition by all the waste product from liver insufficiency for the OAT receptors. However, these seem to have mild impact on diuretic responsiveness because the ceiling dose in patients with cirrhosis is unaltered (see Table 6.3). There is not a lot of literature supporting the selection of one loop diuretic over another in patients with cirrhosis. However, some studies suggest that use of torsemide is associated with a greater urine output than furosemide.[38]

Hypoalbuminemia and Nephrotic Syndrome

Patients with nephrotic syndrome develop edema mainly because of salt retention.[39] Hypoalbuminemia contribute to edema only when it is severely decreased (i.e., <20 g/L). However, albuminuria and the resulting hypoalbuminemia have an impact on the pharmacodynamic of loops diuretics. It increases their volume of distribution and limits their fixation to NKCC2. As a result, the recommended ceiling dose is increased compared with healthy individuals (see Table 61.3).

To help with the management of this diuretics resistance, some have proposed to combine diuretics with albumin.

In 2011 Ghafari et al. randomized 10 patients to three different regimens of furosemide and albumin, each patient receiving the three regiments in a random fashion. The combination of furosemide and albumin increased urine output and excretion of sodium.[40] Interestingly, a meta-analysis of studies including patients with hypoalbuminemia of all causes showed increased urinary output at 8 but not 24 hours with the combination of furosemide and albumin. However, in the subgroup of patients with nephrotic syndrome the difference was still significant.[41]

CONTINUOUS VERSUS INTERMITTENT ADMINISTRATION

The rationale behind the use of a continuous infusion is to keep a constant diuretic excretion rate in the tubular lumen, thus providing continuous blockade of NKCC2 and sustained natriuresis. Conversely, a bolus infusion will achieve high natriuresis in first 1 to 2 hours and then sodium excretion will decrease to a point at which sodium retention will occur. In clinical practice, data have not confirmed this theory. Indeed, a meta-analysis of eight trials conducted in heart failure patients showed a 271-mL increase in urine output over 24 hours in favor of continuous infusion. This difference, although statistically significant, is probably not clinically important. Other caveats identified in this systematic review were the small numbers of patients included in studies, heterogeneity in case-mix, and subgroup benefit mostly derived by a study in which hypertonic saline was added in the continuous infusion group.[42] More recently, the Diuretic Optimization Strategies Evaluation (DOSE) trial study randomized 308 patients with heart failure to either bolus every 12 hours or continuous infusion of furosemide. At 72 hours there was no difference in patient symptoms. There was also no difference in urine output or in any of the other secondary endpoints. Patients in the bolus group, however, had a higher risk of having the dose increased, resulting in a higher total dose of furosemide given.[43] Since then, other studies including another meta-analysis in patients with heart failure came to a similar conclusion.[44–46] Finally it has been shown that giving a bolus before starting an infusion allows to better achieve target diuresis.[45]

In ICU patients, studies showed no difference in urine output or in clinical outcomes, although in some the dose required to achieve effect was greater with bolus dose.[47,48] The use of loop diuretics may be associated with side effects (see the following section). Meta-analyses have suggested less toxic effects with continuous infusions, mainly ototoxicity.[42]

In conclusion, the available evidence does not show a clear benefit of one strategy over another. However, the safety profile seems to confer a slight advantage to the use of continuous infusion.

Adverse Effects and Toxicity

The major adverse consequences of loop diuretics result from their alterations of fluid, electrolyte, and acid-base balance. The most frequently observed electrolyte disorders are hypokalemia and hypomagnesemia, both of which predispose patients to serious cardiac arrhythmias. Frequent electrolyte monitoring is therefore essential. Loop diuretics block solute reabsorption at nephron sites that are important for concentrating the urine, leading to water excretion in excess of sodium excretion. Hypernatremia therefore can result. Table 61.4 lists complications related to loop diuretics use.

TABLE 61.4

Complications Related to Loop and Thiazide Diuretics Use

	LOOP DIURETICS	THIAZIDE
Fluid / electrolytes/ acid-base related	Acute kidney injury Hypercalcuria Hypernatremia Hypokalemia Hypomagnesemia Hypotension Metabolic alkalosis	Acute kidney injury Hypercalcemia Hyponatremia Hypokalemia Hypomagnesemia Hypotension Metabolic alkalosis
Others	Anaphylaxis Deafness Dyslipidemia Interstitial nephritis Metabolic bone disease Pancreatitis Pulmonary and systemic vasoconstriction Thiamine deficiency Vasculitis	Allergic reaction Diabetes Dyslipidemia Interstitial nephritis Noncardiogenic pulmonary edema Pancreatitis

Thiazide Diuretics

Mechanism of Action

Thiazide diuretics are the results of the chemical modification of sulfanilamide, an inhibitor of the carbonic anhydrase. Thiazides inhibit the NaCl cotransporter (NCC) in the proximal part of the convoluted tubule, the connecting segment, and maybe the cortical collecting tubule. The exact site where they bind to the transporter is unclear but may be the chloride transporter. These segments account for 5% to 10% of sodium reabsorption by the tubule. As a consequence, although they are more potent than carbonic anhydrase inhibitor, their effect on sodium excretion is much weaker than loop diuretics.

Thiazide diuretics also decreased excretion of calcium, an effect that is used in treatment of recurrent nephrolithiasis. The hypocalciuria is probably multifactorial. Evidence suggests it is the result of the downregulation of a calcium transporter on the apical side of the distal tubule (TRPV5), upregulation of a binding protein, and hyperpolarization of the membrane as a result of decrease intracellular chloride.[49] Similar phenomena seem to occur in the cortical collecting tubule. Other evidence suggests that passive absorption of calcium in the proximal tubule as a consequence of increased sodium reabsorption in response to the diuretic effect seems is a key factor.[50] Thiazide diuretics also cause hypomagnesemia. The mechanism by which it occurs remains uncertain, but the most likely hypothesis is that it downregulates TRPM6, a transporter located on the apical side of the distal tubule that plays an important role in magnesium reabsorption.[50]

Thiazide diuretics decrease blood pressure over what would be expected from their diuretic effect. The mechanism is uncertain, but two major hypotheses have been advanced. The first one is that they exert a direct vasodilatory effect mainly via an action on specific potassium channel. The

TABLE 61.5

Pharmacokinetics of Thiazides

DIURETIC	ORAL BIOAVAILABILITY (%)	HALF-LIFE	ELIMINATION	VOLUME OF DISTRIBUTION (L/kg)
Bendroflumethiazide	≈100	2–5	≈70% hepatic (metabolism), ≈30% renal	0.9–1.5
Chlorothiazide	9–56	0.75–2	Renal	
Hydrochlorothiazide	65–75	2.5–14.8	Renal	1.5–7.8
Hydroflumethiazide	≈75	6–25	Renal	?
Chlortalidone	≈65	24–55	Largely renal	3–13
Indapamide	≈93	14–24	Hepatic and renal metabolism	25–60
Metolazone	40–65	8–14	Largely renal	113

Data from Jackson EJ. Diuretics. In Brunton LL, Lazo JS, Parker J, et al., eds. *Goodman and Gilman's the pharmacological basis of therapeutics,* 11th ed. New York: McGraw-Hill; 2006:737–769; and Brater DC. Diuretic therapy. *N Engl J Med.* 1998;339:387–395.

second theory is that vasodilatation occurs as a compensatory mechanism to the decrease in cardiac output induced by diuresis. This effect of thiazide on the vasculature is used widely in the management of hypertension.[51]

Pharmacodynamic and Pharmacokinetic

There are multiple thiazide and thiazide-like diuretics. Table 61.5 provides pharmacokinetic and pharmacodynamic property for the most commonly used. Much less is known about the pharmacology of thiazide diuretics compared with loop diuretics.

All but one thiazide (chlorothiazide) are available only as oral formulation. Therefore significant anasarca may impair intestinal absorption via mucosal edema. There is wide variability in bioavailability between the molecules (see Table 61.5). Once they are absorbed, thiazides are generally highly protein bound. However, the volume of distribution is highly variable, ranging from 0.9 L/kg for bendroflumethiazide to 113 L/kg for metolazone (see Table 61.5). One explanation for this phenomenon is that some of the thiazides have a carbonic anhydrase effect, which allows them to get stored in erythrocytes and thus increase the volume of distribution. As a consequence, the amount of diuretics that reaches the tubular lumen varies widely from 80% for hydrochlorothiazide to 5% with indapamide. Thiazide diuretics reach the tubular lumen using OAT-1 in the proximal segment. Except for indapamide and bendroflumethiazide, they are eliminated by the kidney, which means CKD will increase plasmatic concentration and thus the risk of adverse effects.

Use of Thiazide Diuretics

For the clinician working with acutely ill patients, the primary use for diuretics is fluid overload. As such, loop diuretics are much more potent. However, when patients have resistance to loop diuretics as in nephrotic syndrome, heart failure, cirrhosis, or advanced CKD (see Diuretic Responsiveness and Resistance), the addition of a thiazide diuretic may be of great help. Indeed, as mentioned above, chronic use of loop diuretics leads to distal tubule hypertrophy. As a consequence the distal segment of the tubule may reabsorb up to 80% of the sodium that escapes from the loop of Henle. Therefore adding a thiazide to avoid this reabsorption will make perfect physiologic sense.

In patients with heart failure, multiple studies looking at the impact of adding thiazide diuretics have been published over the last 40 years. However, most of them are from before 2000, are observational and small in numbers (only 300 patients for a total of 50 reports). Among the most recent is an observational study of 21 patients in whom metolazone was added to high-dose furosemide, which results in a decrease in weight, but in a significant increase in creatinine and urea as well as hypokalemia.[52] This lack of good evidence should be overcome by the Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure (CLOROTIC) trial, a large double-blind trial that will randomize patients with acute decompensated heart failure on high-dose loop diuretics to either hydrochlorothiazide or placebo.[53] In patients with reduced GFR, there has been a concern for years that thiazide diuretics may be ineffective. However, multiple old studies showed that when appropriate doses are used, increases in urine output and weight loss ensue even in patients with stage V CKD. In ICU patients, effectiveness is extrapolated mainly from an old study.[54]

Some considerations are necessary in deciding which route of administration and which molecule to use. First, there is no evidence to support the use of one thiazide over another. As for the route of administration, only chlorothiazide is available IV. Loop diuretics have a faster peak of action than thiazide. As a result, two choices are available. The first one is to give both diuretics by the same route. Conversely, if an intravenous loop diuretic is used with an oral thiazide, the latter should be given 2 to 5 hours before the former.

In conclusion, the addition of a thiazide diuretic to a loop diuretic in patients with resistant edema is a widely spread practice, although most of the evidence comes from an old, small observational study. Thiazide diuretics retain effect in CKD. When combination is used, the clinician should monitor closely electrolytes and renal function.

Side Effects of Thiazide Diuretics

One of the most important side effects of thiazide diuretics is hyponatremia. Its incidence ranges from 11% to 13%.[55,56] Risk factors include old age, female sex, lower body weight, hypokalemia, and concurrent use of other medications that impair free water excretion. Thiazides block sodium and chloride absorption in the distal tubule. At the same time, they increase water reabsorption by ADH-dependent and independent mechanism. As a consequence the proportion of water to sodium in the body increases and hyponatremia ensue. Thiazide diuretics have multiple other side effects (see Table 61.4).

In conclusion, thiazide diuretics act by blocking the sodium-chloride cotransporter in the distal tubule. They are of great value in combination with loop diuretics in acutely ill patients. Their main side effects relate to electrolyte disturbance.

Key Points

1. Loop diuretics are the most potent diuretics; they act by blocking the NKCC2 cotransporter in the loop of Henle.
2. Renal failure, congestive heart failure, liver cirrhosis, and hypoalbuminemia are associated with resistance to loop diuretics.
3. Adverse effects of loop diuretics include hypokalemia, hypomagnesemia, hypocalcemia, metabolic alkalosis, ototoxicity, and interstitial nephritis.
4. Thiazide diuretics act by blocking NCC in the distal tubule.
5. One of the main side effects of thiazide diuretics is hyponatremia, which can happen at any time in the course of treatment.
6. Strategies to overcome diuretic resistance include sodium and fluid restriction, increased diuretic doses, increased frequency of administration, continuous infusions, and/or combination therapy with thiazides.

Key References

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