RATIONAL USE OF DIURETICS AND PATHOPHYSIOLOGY OF EDEMA

INTRODUCTION
The use of diuretics for therapeutic purposes is not new. They were used for the treatment of dropsy as early as 16th century. Diuretic drugs increase urine output by the kidney by altering sodium handling. Increased sodium excretion by kidneys leads to increase in water excretion. Most diuretics produce diuresis by inhibiting the reabsorption of sodium at different segments of the renal tubular system. Diuretic use in clinical practice spans conditions like edema, hypertension, metabolic acidosis and hyperkalemia. Patients with nephropathy or heart failure may have a 10 to 30% increase in extracellular and blood volume, even in the absence of overt edema.

CLASSIFICATION
Multiple classes of diuretics are available for use including loop diuretics, thiazides and potassium-sparing diuretics. The level of GFR and need and urgency for reduction in ECF volume dictates the choice of diuretic agent.

THIAZIDE DIURETICS
Thiazide diuretics inhibit the apical Na+-Cl- cotransport system in the distal tubule. Metabolism of thiazide diuretics is variable. Bendroflumethiazide and indapamide are primarily metabolized by the liver; while hydrochlorothiazide and metolazone are metabolized by the kidney. They are delivered to their luminal site of action by organic anion transporters in the straight segment of the proximal tubule, consequent of their extensive protein binding. Considerable protein binding makes role of glomerular filtration inconsequential in entry of thiazide diuretic into the urinary space.

LOOP DIURETICS
Loop diuretics act by inhibiting the Na+-K+-2Cl- cotransporter in the thick ascending limb of the loop of Henle delivered to their luminal site of action by organic anion transporters. By blocking the transporter in the cortical segments, the loop diuretics enhance free water clearance. The bioavailability of loop diuretics is not affected by renal insufficiency. On an average, 50% (range 10-100%) of an orally administered dose of furosemide is absorbed. In contrast, absorption of bumetanide and torsemide, is nearly complete (80-100%). Loop diuretics are primarily bound to albumin. Torsemide is approximately 80% cleared by the liver. Bumetanide is approximately 50% metabolized by the liver and its half-life does not appreciably change in kidney failure. Approximately 50% of the dose of furosemide is excreted unchanged; the remainder is conjugated to glucuronic acid in the kidney. Therefore, in patients with kidney failure, the plasma half-life of furosemide is prolonged.

POTASSIUM SPARING DIURETICS
There are two principal types of potassium-sparing diuretics, those that inhibit epithelial sodium channels (triamicarbene and amiloride) and those that inhibit mineralocorticoid receptors (aldosterone antagonists). For both types, the site of action is in the collecting tubule. The absorption of potassium-sparing diuretics is quite variable. The total protein binding is low for amiloride and high for spironolactone. Amiloride and triamterene undergo significant excretion by the kidney, both by glomerular filtration and tubular secretion by the organic cation secretory pathway. Spironolactone
is metabolized by the liver; its pharmacokinetic property is not significantly affected by chronic kidney disease (CKD).

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<tr>
<th>Loop</th>
<th>Thiazide</th>
<th>Potassium sparing</th>
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<tr>
<td>Pharmacodynamic effects</td>
<td>Increases excretion of Na, K, Ca, Mg</td>
<td>Increases excretion of Na, K, Mg, decrease excretion of Ca</td>
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<tr>
<td>Site of action</td>
<td>Thick ascending limb</td>
<td>Distal tubule</td>
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<td>Transporters affected</td>
<td>Na⁺ K⁺ 2Cl⁻ co transporter</td>
<td>Apical Na⁺ Cl⁻ co transporter</td>
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<tr>
<td>% of filtrate reabsorbed at site of action</td>
<td>20-30%</td>
<td>6-11%</td>
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<td>Bioavailability</td>
<td>50-100%</td>
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**PATHOPHYSIOLOGY OF EDEMA**

**Cardiac:** Fluid retention is a consistent finding in almost all acute and most chronic heart failure patients. It manifests as pulmonary and peripheral edema. The pathophysiology of edema in heart failure involves the activation and interplay of multiplemolecular and cellular systems. Pathobiologically important alterations occur in the sympathetic nervous system, the renin-angiotensin-aldosterone system (RAAS), the vasopressin axis, and vasodilatory/natriuretic pathways. These disturbances are translated at the renal circulatory and tubular level in such a way that avid retention of sodium and water occurs. The state of the arterial circulation, as governed by cardiac output and peripheral vascular resistance, is the chief determinant of sodium and water retention in heart failure. In particular, either a primary decrease in cardiac output or arterial vasodilatation brings about arterial underfilling, which activates neurohumoral reflexes that in turn incite sodium and water retention. Sympathetic nervous system activity contributes to peripheral and renal vasoconstriction and to sodium and water retention. Activation of renal sympathetic nerves leads to angiotensin II release, stimulating the renin-angiotensin-aldosterone system. Sympathetic stimulation also prompts release of arginine vasopressin, excess levels of which lead to water retention and hyponatremia. Angiotensin II acts as a potent vasoconstrictor, stimulates aldosterone release from the adrenal gland, and promotes renal tubule sodium reabsorption. Aldosterone increases reabsorption of sodium in the collecting duct.

**Renal:** Chronic renal insufficiency (CRI) leads to alteration in salt and water handling by the kidney. Failure of sodium and free water excretion leads to extracellular volume expansion and total body volume overload manifesting clinically when the GFR falls to less than 10-15 mL/min. As kidney function declines further, peripheral edema and pulmonary edema appears. At a higher GFR, excess sodium and water intake could result in a similar picture if the ingested amounts of sodium and water exceed the available potential for compensatory excretion.

The interstitial inflammation of the kidney has a key role in the pathogenesis of nephrotic edema by inducing primary sodium retention. Both decrease in sodium filtration and increase in net sodium reabsorption occur due to generation of vasoconstrictive substances in the interstitium, driven by the inflammatory cell infiltrate. Reduction in plasma oncotic pressure also plays a key role in the pathogenesis of edema. Thus, hypoalbuminemia effectively buffers the hemodynamic effects of acute increments in blood volume as the fluid overload is sequestered into the tissues and is responsible for the fact that while patients with acute glomerulonephritis show a steep relationship between weight gain and the hemodynamic response, indicating plasma expansion, the patients with nephrotic syndrome do not. Low plasma colloidal oncotic pressure and primary sodium retention combine to overwhelm the mechanisms protecting from changes in interstitial volume and drive the development of edema (Fig. 1).

**Hepatic:** Patients with cirrhosis of liver share a common pathophysiology of arterial underfilling-secondary to decreased cardiac output and decreased systemic vascular resistance, respectively, with eventual stimulation of neurohumoral axis and sodium and water retention. The resultant renal vasoconstriction and sodium and water retention lead to ascites and hepatorenal syndrome in advanced cirrhosis. Two key

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(Fig. 1: Overview of pathophysiology of edema formation in nephrotic syndrome. (Adapted from Rodriguez-Iturbe B, Herrera-Acosta J, Johnson RJ. Interstitial inflammation, sodium retention, and the pathogenesis of nephrotic edema: A unifying hypothesis. Kidney Int 2002; 62: 1379–1384.)
factors are involved in the pathogenesis of ascites formation—
sodium and water retention, and portal hypertension.
There is an overlap between CKD and heart failure11, having a complex bidirectional pathophyslogic state12 that worsens the function of both organs known as cardio renal
syndrome (CRS). In Chronic CRS (Type 2), longstanding heart failure leads to progressive CKD, possibly via episodes of acute kidney injury (AKI). Optimal management of sodium and extracellular fluid volume through low-sodium diet and diuretics is important in prevention of chronic CRS. Many studies indicate that the lowest doses of loop diuretics necessary to maintain hemodynamics are optimal13. Conversely, those patients requiring the highest doses of loop diuretics have the highest rates of CRS and mortality probably by further activation of neurohumoral pathways14. Another form of chronic CRS (Type 4) may be recognized who have repetitive bouts of cardiac ischemia and injury reflected by chest pain, electrocardiogram changes and elevations in cardiac biomarkers. In this form of CRS, worsening kidney function reduces the effectiveness of diuretics.

RATIONAL FOR USE

Cardiac disease: In heart failure, loop diuretics may improve cardiac function by decreasing cardiac filling pressure, functional mitral insufficiency, ventricular wall stress, and endomyocardial ischemia. In some patients, this may also lead to improved renal function. In patients with acute left heart failure, pulmonary edema is the main abnormality and is usually treated with intravenous loop diuretics. The improvement in symptoms and the accompanying reduction in filling pressures occur even before diuresis is initiated and have been attributed to vasodilatation15.

Renal diseases: In CKD, they reduce ECF volume, lower blood pressure, potentiate the effects of ACE inhibitors, ARBs, and other antihypertensive agents; and reduce the risk of cardiovascular disease in CKD. The addition of diuretics and calcium channel antagonists to RAS inhibitor therapy is also considered to be a rational strategy to reduce blood pressure and preserve renal function. Extracellular fluid volume overload as a result of sodium retention is one of the major causes of hypertension in renal disease16,17. In principle, the mechanism of decreased sodium excretion in CKD is reduced glomerular filtration of sodium, increased tubular reabsorption of sodium, or both. Diuretics act primarily by decreasing tubular sodium reabsorption, thereby increasing sodium excretion, reversing extracellular fluid volume expansion, and lowering blood pressure. Diuretics potentiate the antihypertensive effects of ACE inhibitors and ARBs by stimulating renin and reducing fluid volume, thus making blood pressure more sensitive to the action of these agents16-19. A randomized study designed specifically to test the effectiveness of a diuretic-based treatment on microalbuminuria in diabetic patients with hypertension found that diuretic-based therapy was equivalent to an ACE inhibitor-based therapy20. It is generally recommended that patients with chronic renal disease receive a diuretic along with an ACE inhibitor or ARB as part of the strategy to reach target blood pressure16,21,22.

Increased rate of fluid delivery and reabsorption per nephron in the loop segment and relative preservation of the target transporters is a critical factor in the retained efficacy of loop diuretics even in advanced renal insufficiency. On the other hand, thiazide diuretics when used alone become relatively ineffective in patients with a moderate to severe degree of CRI (creatinine clearance < 35 ml / min), although high doses of thiazide diuretics, such as metolazone, do retain some efficacy in even advanced CRI23.

Loop diuretics have been prescribed to patients with end-stage renal disease (ESRD) in an attempt to slow the rate of loss of GFR. An observational study of 125 patients with ESRD treated by peritoneal dialysis (PD) showed that total sodium and fluid removal by PD were powerful predictors of longer survival24. In contrast, a controlled clinical trial of the effects of furosemide in patients treated with continuous ambulatory peritoneal dialysis (CAPD) showed no benefit of regular diuretic therapy in delaying the loss of residual renal function25. Thus, optimal dialysis, rather than loop diuretic therapy is the best treatment for these patients.

RELEVANT CLINICAL ISSUES

Maximum dose of diuretics

Diuretic action relies on an adequate amount of the drug reaching its site of action at the renal tubule. Once present in the circulation, a diuretic must gain entry into the renal tubule in a sufficient concentration to exceed the threshold for response; thereafter, there exists an optimal rate of drug delivery leading to a rate of a maximal response. Additional diuretic delivery does not produce a greater response16,27. High doses of furosemide can increase urine production in patients with chronic renal failure28. The effects in hemodialysis patients are equivocal. Chronic administration of the drug in doses ranging from 250 to 500 mg orally in these patients has been associated with a remarkably long duration of residual urine production. High dose furosemide increases the urinary excretion of sodium, chloride, and water in CAPD patients without affecting GFR, urea clearance, and creatinine clearance29.

Combination therapy

In patients with nephrotic syndrome, addition of thiazides to furosemide markedly increases natriuresis16,31. But this finding contrasts with repeated recommendations to withhold thiazides in such patients because of their assumed inefficacy32,33. On pharmacokinetic principles, it is usually not
advisable to combine substances with different half-lives of action. In the particular case of loop diuretics (short half-life) and thiazides (long half-life) this approach may, however, have distinct advantages. First, co-administration of thiazide and loop diuretics may help to overcome “resistance” to the action of conventional therapeutic doses of loop diuretics which is frequently observed in patients with advanced renal failure. Administration of high doses of loop diuretics may cause more frequent and severe side effects. Co-administration of thiazide diuretics may therefore permit use of smaller doses of loop diuretics and this may reduce the frequency of side effects. Second, because of the long half-lives, the duration of action of thiazides outlasts that of loop diuretics and thus prolongs the overall duration of natriuresis. Third, administration of a thiazide may interfere with the so-called “rebound effect” following loop diuretic treatment, that is, with antinatriuresis after the short acting natriuretic effect of the loop diuretic has waned.

Continuous vs bolus administration

There are potential benefits of continuous infusion when compared with intermittent bolus dosing. Bolus diuretic dosing may be associated with a higher rate of diuretic resistance due to prolonged periods of subtherapeutic drug levels in the kidney. Continuous infusion results in a more constant delivery of diuretic to the tubule, potentially reducing this phenomenon. Additionally, continuous infusion is associated with lower peak plasma concentrations, which may be associated with a lower incidence of other side effects such as ototoxicity, especially at higher doses. A recent meta-analysis from the Cochrane Collaboration comprehensively addresses this question and reviewed studies including a total of 254 patients. Continuous infusion was associated with greater urine output, shorter length of hospital stay, less impairment of renal function, and lower mortality when compared with intermittent bolus dosing. In the Diuretic Optimization Strategies Evaluation (DOSE) study, among patients with acute decompensated heart failure, there were no significant differences in patients’ global assessment of symptoms or in the change in renal function when diuretic therapy was administered by bolus as compared with continuous infusion or at a high dose as compared with a low dose.

In patients who have poor response to intermittent doses of a loop diuretic, a continuous intravenous infusion can be tried. If an effective amount of the diuretic is maintained at the site of action at all times, a small but clinically important increase in the response may occur. Before administering a continuous infusion of a loop diuretic, the physician should give a loading dose in order to decrease the time needed to achieve therapeutic drug concentrations; otherwise, 6 to 20 hours is required to achieve a steady state, depending on the diuretic used.

The frequency of administration of diuretic is determined by its plasma half life. In case of administration of short-acting loop diuretic, sodium reabsorption is increased shortly after the diuretic effect has waned, which may be sufficient to completely nullify the gain from the prior natriuresis. This rebound antinatriuretic effect (braking phenomenon) attenuates the normal dose-response relationship and can last several hours, thus limiting the efficacy of therapy. It can be overcome by administering multiple daily doses of the diuretic.

Predosing for metolazone

The recommendation for pre-dosing metolazone is based solely on the pharmacodynamic rationale of delayed onset of action observed following a single orally administered metolazone dose. Given the lengthy half-life of metolazone, this delayed onset is unlikely to be a concern during ongoing chronic treatment, particularly once steady-state is achieved. However, no published clinical studies have compared pre-dosing to simultaneous dosing. At present, the practice of predosing metolazone prior to a loop diuretic is not supported by the literature.

Diuretic resistance

Refractoriness to diuretics in heart failure is due to blunting of relationship between urinary sodium excretion and the urinary diuretic excretion rate compared with normal subjects. Typically, heart failure patients with mild to moderate disease have a response that is one fourth to one third of that normally observed with maximally effective doses of loop diuretics. The threshold for effect is noticeably increased.

Multiple factors lead to diuretic resistance in CKD. The factors may be increased tubular reabsorption of sodium, use of non-steroidal anti-inflammatory agents, increased plasma levels of organic anions and urate, and metabolic acidosis impairing proximal tubule secretion of diuretics. High dietary intake of sodium may lead to apparent diuretic resistance. The “braking phenomenon” (post diuretic sodium retention) describes avid sodium retention that can develop in response to a rapid diuresis due to hemodynamic and neurohumoral changes produced, thereby limiting response to further doses of diuretics. The braking phenomenon may occur during either short-term or long-term therapy. In CKD, the tubular secretory capacity for a diuretic is lowered in parallel with the reduction in GFR warranting requirement of higher blood levels to affect tubular delivery sufficient to prompt a diuresis.

Several mechanisms may contribute to diuretic resistance in nephrotic syndrome, including intratubular binding of loop diuretic by filtered albumin, decreased GFR, excessive tubular reabsorption of sodium at site proximal to the loop of Henle, or a disease state-related resistance to diuretic action at the cellular level. These patients have an impaired response...
to loop diuretics and there is reduced tubular sensitivity and responsiveness to diuretics. Many patients with advanced nephrotic syndrome have a marked stimulation of plasma renin activity, especially during diuretic therapy. The ensuing hyperaldosteronism further reinforces NaCl reabsorption in the distal nephron and collecting ducts. Four pharmacokinetic mechanisms that could impair the responsiveness to loop diuretics in patients with the nephrotic syndrome are decreased renal diuretic delivery, decreased peritubular diuretic uptake, enhanced renal metabolism of furosemide to the inactive glucuronide and decreased free diuretic levels in tubular fluid.

Treatment of nephrotic syndrome may require high doses of loop diuretics, a combination of loop and thiazide diuretics, or loop diuretics with albumin infusions. With long-term administration of a loop diuretic, the solute that escapes from the loop of Henle floods more distal regions of the nephron. By unknown mechanisms, increased exposure to solute causes hypertrophy of distal nephron segments, with concomitant increases in the reabsorption of sodium. Sodium that escapes from the loop of Henle is therefore reabsorbed at more distal sites, decreasing overall diuresis resulting in long-term tolerance to loop diuretics. Thiazide diuretics block the nephron sites at which hypertrophy occurs, accounting for the synergistic response to the combination of a thiazide and a loop diuretic.

**NEWER METHODS OF DELIVERY**

In nephrotic syndrome, the efficacy of diuretic therapy may be increased by administering a mixture of albumin and a loop diuretic; in several patients with severe hypoalbuminemia, an infusion of 30 mg of furosemide mixed with 25 g of albumin enhanced diuresis. However, in most patients with the nephrotic syndrome, renal tubular secretion of furosemide is normal (unless the patient also has renal insufficiency), and combined infusions are therefore unnecessary. This conclusion may not be applicable to patients with serum albumin concentrations of less than 2 g per deciliter. In such patients, it may be reasonable to try combined infusions.

**DIURETIC THERAPY IN DIVERSE CLINICAL SETTINGs**

**Acute kidney injury**

In the acute care setting, loop diuretics are often prescribed to maintain or increase urine output. Furosemide and other loop diuretics reduce oxygen demand in the medullary thick ascending limb and attenuate the severity of acute kidney injury in animal models. They may protect the human kidney from ischemic injury. There have been several small, randomized, controlled trials of diuretics for the treatment or prevention of AKI in various clinical settings. Some studies showed a reduction in dialysis requirement, reduced urinary albumin and N-acetyl glucosaminidase concentration, or improved dialysis free survival in oliguric patients. Others, however, showed either worsened renal function or no difference in various measured outcomes.

Mehta et al. published an observational study of diuretic use in patients with AKI in the setting of critical illness and showed that, using multivariate analysis and propensity scores, the use of diuretics was associated with an increased risk of death. However, another analysis by Uchino et al. refuted this claim and found that diuretic use in critically ill patients with acute kidney injury is not associated with higher mortality.

**Hypertension**

Many physicians consider thiazides the diuretics of choice for long-term therapy. On average, after adjustment for reductions seen with the use of placebo, thiazides induce a reduction in the systolic and diastolic blood pressures of 10 to 15 mm Hg and 5 to 10 mm Hg, respectively. Hypertension responding preferentially to thiazides is considered to be low-renin or salt-sensitive hypertension. The elderly, blacks, and patients with characteristics associated with high cardiac output (e.g., obesity) tend to have this type of hypertension. Thiazides potentiate the action of other antihypertensive agents when they are used in combination, often producing an additive decrease in blood pressure. For many hypertensive patients, several agents will be needed to achieve desired blood-pressure targets. Combination regimens that include a thiazide can achieve therapeutic synergy while minimizing adverse effects.

Combined meta-analyses and systematic reviews report that, as compared with placebo, thiazide-based therapy reduces relative rates of heart failure (by 41 to 49%), stroke (by 29 to 38%), coronary heart disease (by 14 to 21%), and death from any cause (by 10 to 11%). Despite a long, well-established record of efficacy, the role of thiazides in hypertension therapy continues to provoke debate. Based on the benefits observed in studies in which thiazides were used as initial therapy in a stepped-care approach, with agents added sequentially, guidelines for hypertension therapy in the United States have advocated thiazides as initial treatment. In contrast, British guidelines recommend diuretics more selectively, such as for use in the elderly and blacks. European guidelines endorse several antihypertensive agents, including diuretics, as initial therapy. An update from the Joint National Committee is anticipated in the near future.

**Heart failure**

Loop diuretics are recommended as the first line of therapy as per the updated guidelines by Heart Failure Society of America. The use of loop diuretics in heart failure may be a double-edged sword. There is, however, a meta-analysis of 3 small randomized trials that concludes a benefit of diuretics on mortality. The use of diuretics in some cardiac failure patients...
occasionally may lead to deterioration of renal function. In general, compared with normal individuals, patients with heart failure need higher doses of loop diuretics to achieve a similar sodium excretion, and the magnitude of the “maximal” response is attenuated

A low sodium diet (less than 2.4 g sodium) and fluid restriction (less than 1.5 l fluid) can reduce the need to use higher doses in advanced heart failure. Non-steroidal anti-inflammatory drugs blunt the effects of diuretics and should be avoided. Diuretics are the mainstay of therapy for symptomatic chronic heart failure but are now rarely used as monotherapy. Together with angiotensin converting enzyme inhibitors they improve patients’ symptoms and in most cases also improve their effort tolerance. Thiazide diuretics can be used in milder cases, particularly if there is no renal impairment. However, in more symptomatic patients (NYHA III–IV) and in patients with renal impairment, loop diuretics are more useful owing to their relatively strong diuretic action and fewer side effects. Consistent with pathophysiological process, evidence for pleiotropic benefits of mineralocorticoid blockade is rapidly emerging. The analysis of SOLVD revealed a significantly lower risk for hospitalization and/or death from heart failure, cardiovascular mortality, and all-cause mortality when a potassium-sparing diuretic was used alone or in combination with a non–potassium-sparing diuretic. Eplerenone is a novel agent that selectively blocks the mineralocorticoid receptor and not those for glucocorticoids, progesterone, or androgens. It has also been shown to reduce morbidity and mortality in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.

**Ascites**

Loop and distal diuretics are the basic drugs for the treatment of ascites. Management of ascites is based on improving the renal sodium excretion with diuretics and dietary sodium restriction. Despite the natriuretic potency of loop diuretics being greater than other diuretics, only half of the nonazotemic cirrhotic patients have satisfactory natriuresis. Reasons for this poor diuretic effect include reduced tubular secretion of furosemide into the lumen, decreased delivery of fluid to the loop of Henle secondary to enhanced proximal sodium reabsorption, and hyperaldosteronism. In a comparative trial in patients with cirrhosis, spironolactone was found to be more effective than furosemide. Thus, patients with marked hyperaldosteronism did not respond to furosemide and required high doses of spironolactone (400 to 600 mg/day). Generally, a “stepped care” approach is used in the management of ascites starting with modest dietary salt restriction, together with an increasing dose of spironolactone. Frusemide is only added when 400 mg of spironolactone alone has proved ineffective.

**Chronic kidney disease**

The choice of diuretics is guided by both the status of ECF volume in the patient and the stage of CKD.

**Thiazide diuretics** can be used in CKD Stages 1-3. In the recommended doses, thiazides are effective in generating diuresis in patients with GFR > 30 mL/min/1.73 m². They may lower blood pressure and reduce cardiovascular risk by mechanisms in addition to reduction in ECF volume. Chlorthalidone is longer-acting than hydrochlorothiazide, resulting in better blood pressure control, but causing higher incidence of hypokalemia. Chlorthalidone may be effective at a lower GFR than hydrochlorothiazide. If blood pressure control worsens or if volume expansion occurs as CKD progresses from Stages 1-3 to Stages 4-5 during treatment with a thiazide diuretic, a loop diuretic should be substituted for the thiazide diuretic. Unlike other thiazide diuretics, metolazone retains effectiveness at GFR below 30 mL/min/1.73 m². Once metolazone has effected a diuresis, it can typically be dosed as infrequently as two to three times a week because of its very long half-life.

**Loop diuretics** can be used in all stages of CKD and hence are the most commonly used diuretics. The maximal natriuretic response occurs with intravenous bolus doses of 160 to 200 mg of furosemide, or the equivalent doses of bumetanide and torsemide. Larger doses have little incremental value. Loop diuretics are not as effective as thiazide diuretics in lowering blood pressure in CKD Stages 1-3. In CKD Stages 4-5, loop diuretic therapy is a useful adjunct therapy in the treatment of hypertension. One may use the most bioavailable drug, torsemide, when using the oral route and the drug with the least hepatic elimination, furosemide, when using the intravenous route.

**Potassium-sparing diuretics** must be used with caution in CKD consequent to risk of hyperkalemia. The risk is especially high in patients with GFR < 30 mL/min/1.73 m² receiving concomitant therapy with ACE inhibitors or ARBs or other conditions that raise serum potassium. Indications for potassium-sparing diuretics in CKD are persistent hypokalemia or resistant hypertension. The presence of hyporeninemic hypoaldosteronism is a contraindication to their use.

**ADVERSE EFFECTS**

Loop diuretics may have detrimental effects in patients with heart failure. Administration of loop diuretics may result in a significant increase in glomerular filtration rate in some patients with heart failure, presumably due to renin-angiotensin-aldosterone system and sympathetic nervous system activation with related changes in renal blood flow and glomerular filtration pressure.

New-onset diabetes has been reported in patients receiving...
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thiazides; however, newly diagnosed diabetes occurs over time in many hypertensive patients, regardless of which class of antihypertensive agent is used. Use of thiazides over several years may lead to an excess of 3 - 4% of new cases of diabetes as compared with other antihypertensive agents. But no analyses of ALLHAT data have indicated that the development of diabetes obviates the benefit of the thiazide.

Depending upon the site and mode of action, some diuretics increase excretion of potassium, chloride, calcium, bicarbonate, or magnesium. Some can reduce renal excretion of electrolyte-free water, calcium, potassium, or protons. Consequently, electrolyte and acid-base disorders commonly accompany diuretic use. Except for the mildly natriuretic collecting duct agents, which are used mainly to limit potassium excretion, all diuretics can cause volume depletion with prerenal azotemia. Loop agents and thiazides, produce hypokalemic and hypochloremic metabolic alkalosis. Carbonic anhydrase inhibitors produce less hypokalemia and volume depletion but at the cost of inducing metabolic acidosis that is often symptomatic. The potassium-sparing agents like spironolactone may also produce metabolic acidosis. Hyperkalemia is a leading complication of the potassium-sparing agents, especially in patients with an underlying tendency. Whether diuretic-induced hypokalemia increases cardiovascular risk is controversial. All diuretics promote excretion of sodium. Hyponatraemia, a frequent accompaniment of use of loop agents and thiazides may cause permanent neurologic damage, especially with thiazides use. Loop agents may cause dose-related reversible or irreversible ototoxicity. Some diuretic agents have the potential to cause nephrocalcinosis, nephrolithiasis, hypomagnesemia, and hyperuricemia. Reported idiosyncratic reactions to diuretics include interstitial nephritis, noncardiogenic pulmonary edema, pancreatitis, and myalgias.

CONCLUSION

Multiple classes of diuretics are available for use including loop diuretics, thiazides and potassium-sparing diuretics with use primarily focused in edema of various causes. The pathophysiology of edema involves the activation and interplay of multiple neurohumoral and cellular systems with alterations in the sympathetic nervous system, the renin-angiotensin-aldosterone system, the vasopressin axis, and vasodilatory/ natriuretic pathways. These disturbances are translated at the renal circulatory and tubular level in such a way that avid retention of sodium and water occurs resulting in edema.

High doses of loop diuretics can increase urine production in patients with chronic renal failure. Loop diuretics combined with thiazides have distinct advantages especially in resistant cases. Continuous infusion of loop diuretics offer potential benefits compared with intermittent bolus dosing. Treatment of diuretic resistance may require high doses of loop diuretics, a combination of loop and thiazide diuretics, or loop diuretics with albumin infusions. The level of GFR and need for reduction in ECF volume dictates the choice of diuretic agent. Electrolyte and acid-base disorders commonly accompany diuretic use and thus their use should be prudent and in tune with the clinical profile of the patient.

REFERENCES

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