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New Insights into Diuretic Use in Patients with Chronic Renal Disease

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Abstract. Patients with chronic renal insufficiency (CRI) or the nephrotic syndrome frequently manifest diuretic resistance. Factors limiting diuretic responsiveness in patients with CRI may include a reduced basal level of fractional Na^+ reabsorption that places an upper limit on diuretic response, and enhanced NaCl reabsorption in downstream segments, combined with a reduced delivery of diuretic to the kidney. Diuretics are secreted by the recently characterized organic anion transporters (OATs), which are expressed in proximal tubule cells. Secretion may be inhibited by retained organic anions, urate, or acidosis. These limitations necessitate an increased diuretic dosage, up to a defined ceiling level, and consideration of the use of a nonrenally metabolized loop diuretic rather than furosemide. Diuretic responsiveness in patients with the nephrotic syndrome is limited by avid Na^+ reabsorption by the terminal nephron. Experimental studies have shown that a reduced serum albumin concentration can increase the volume of distribution of loop diuretics, reduce their tubular secretion, and enhance the inactivation of furosemide within the kidney by glucuronidization. Binding of loop diuretics can curtail their action in the loop of Henle. Recent clinical investigations have challenged the importance of some of these mechanisms that were identified in animal models. Strategies to improve loop diuretic responsiveness include increasing diuretic dosage, concurrent use of a thiazide diuretic to inhibit downstream NaCl reabsorption and attempts to maximally reduce albumin excretion. Strategies to limit albumin excretion include the use of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker and appropriate limitation of protein intake. These measures are more logical, effective, and less expensive than infusion of albumin solutions.

Diuretics are important in the treatment of most patients with renal disease. This review will highlight new findings concerning the pharmacodynamics (drug action), kinetics (drug disposition), and rational clinical use of diuretics in patients with chronic renal insufficiency (CRI) and the nephrotic syndrome. The genes for the specific proteins that are expressed in the tubular lumen and are the targets for loop diuretics and thiazides have been identified and cloned. These include the bumetanide-sensitive cotransporter one (BSC-1) or $Na^+/K^+/2Cl$ cotransporter and the thiazide-sensitive transporter (TSC) or Na^+/Cl cotransporter. This has prompted the elaboration of detailed models of the cellular action of diuretics (1). Studies of the expression of diuretic target proteins in models of disease will increase understanding of the factors that regulate diuretic responsiveness. New insights into diuretic kinetics should follow from the recent characterization and cloning of the genes for a family of organic anion transporters (OATs) that are expressed in the proximal tubule and mediate diuretic secretion (2).

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Pharmacodynamics and Kinetics in Renal Disease

Chronic Renal Insufficiency

These patients have a reduced GFR and hence a reduced filtered load of NaCl and fluid. To maintain NaCl and fluid balance, the fractional reabsorption and NaCl and fluid by the renal tubules is reduced in proportion to the fall in GFR. The filtered load of fluid and electrolytes represents the substrate delivery to the diuretic site of action. The fractional reabsorption at the target nephron segment represents the basal transport rate that is the site for diuretic action. Therefore, these effects of CRI combine to limit the maximal increase in NaCl and fluid excretion achieved with diuretics. However, there are specific segmental changes in tubular function that modify the response. Chronic renal failure in a rat model of reduced renal mass is accompanied by a decreased reabsorption of NaCl and fluid of the proximal nephron, leading to increased delivery and reabsorption in the loop segment, distal tubule, and collecting ducts (3). Studies of the reduced renal mass model show a corresponding reduction in the expression in the proximal tubule of the Na^+-transporting proteins and the Na^+/K^+ adenosine triphosphatase (ATPase), but a relative increase per residual nephron of three to fourfold in the expression of the protein for the BSC-1 transporter in the cells of the thick ascending limb (TAL) of the loop of Henle and of the TSC transporter in the cells of the early distal tubule. These are the respective targets for loop and thiazide diuretics. The relative

preservation of the target transporters, together with the increased rate of fluid delivery and reabsorption per nephron in the loop segment, is a critical factor in the retained efficacy of loop diuretics even in patients with advanced renal insufficiency. However, thiazide diuretics when used alone become relatively ineffective in patients with a moderate to severe degree of CRI (creatinine clearance below approximately 35 $ml \cdot min^{-1}$), although high doses of thiazide diuretics, such as metolazone, do retain some efficacy in even quite advanced CRI (4). The relatively small response to thiazides in patients with CRI reflects first the fact that the early distal tubule normally reabsorbs only about 3 to 5% of the filtered Na^+ load and that, in the presence of a sharp reduction in the overall fractional Na^+ reabsorption, even complete inhibition of NaCl reabsorption at this site leads to only a modest response. Second, whereas the GFR is normally maintained during therapy with loop diuretics unless there is marked blood volume depletion, hypotension, and prerenal azotemia, thiazide diuretics given alone to patients with CRI reduce the GFR quite sharply, especially when used in the increased doses that are required to be effective in this circumstance (5). This may reflect the fact that loop diuretics block the tubuloglomerular feedback (TGF) response that induces a fall in the GFR when NaCl is delivered to and reabsorbed by the macula densa segment. In contrast, the TGF response is enhanced during volume depletion, as may occur after thiazide diuretic action. This is compounded by an important difference in the response to extracellular fluid volume (ECV) depletion between normal subjects and those with moderate CRI. Thus, dietary salt restriction to reduce the ECV does not change the GFR of normal subjects, even during 3 d of additional furosemide-induced NaCl losses (6). In contrast, patients with CRI sustain a sharp fall in GFR during NaCl restriction even without additional losses associated with diuretic use (7). When used in combination with a loop diuretic that increases NaCl delivery and reabsorption at the distal tubule, large doses of thiazides are effective in promoting fluid loss and reducing hypertension in patients with mild and moderate azotemia (8). However, these benefits are bought at the cost of a sharp further rise in the serum creatinine (S_{Cr}) and blood urea nitrogen (BUN) concentrations and a high incidence of hypokalemia and electrolyte disorders (8). For these reasons, it is preferable to use escalating doses of loop diuretics up to the ceiling dose in patients with CRI and to reserve combined loop and thiazide diuretic therapy for the occasional highly resistant patients.

Approximately 50% of the administered dose of furosemide is eliminated by renal metabolism to the glucuronide. The remainder is eliminated as active diuretic. Only the unmetabolized and secreted fraction is available to inhibit NaCl reabsorption from the tubular lumen in the TAL (9). In contrast, bumetanide and torsemide are metabolized in the liver (9,10). The bioavailability of torsemide is significantly greater than furosemide and its duration of action of approximately 6 h is two to threefold greater than bumetanide or furosemide (11). Net losses of NaCl and fluid during regular diuretic administration are limited by postdiuretic renal NaCl and fluid retention (6). Therefore, a longer duration of action might translate into greater salt and fluid depletion with torsemide (12), but this has not been evident in clinical trials (11,13). In patients with CRI, the elimination of furosemide, unlike bumetanide or torsemide (11), is greatly delayed, thereby prolonging its actions and diminishing any differences in the pattern of response to these drugs (14).

One factor that limits the delivery of diuretics to their sites of action in the tubular lumen in patients with CRI is a reduction in renal blood flow. This reduces the fraction of an administered dose of a diuretic that is presented to the kidney. This is a predictable factor in limiting diuretic delivery to the nephron, providing that nonrenal metabolism of the diuretic is not also impaired in parallel. A reduced renal delivery of bumetanide and torsemide will limit their efficacy. In contrast, the kidney is both the site of action and the major site of metabolism of furosemide (15). Therefore, a decrease in renal blood flow in patients with CRI reduces both the responsiveness and metabolism of furosemide. The reduced responsiveness necessitates an increase in dose. The increase in dose combined with the reduction in metabolism leads to an increase in furosemide plasma concentrations in patients with CRI that is not prominent with bumetanide or torsemide whose hepatic metabolism is unimpaired (11). This may be problematic in patients recovering furosemide, because ototoxicity can occur during prolonged use at high plasma levels (16).

The renal clearance of furosemide in patients with CRI falls in proportion to the reduction in the creatinine clearance (17). All currently marketed diuretics are effective only from the tubular lumen. Carbonic anhydrase inhibitors (CAIs), thiazides, and loop diuretics all are bound strongly to plasma albumin. Thus, very little diuretic is filtered. They gain access to tubular fluid almost exclusively by secretion by the proximal tubule, predominantly by the S_2 segment. Recent studies have characterized this process further. Diuretics are weak organic anions (OA^-). They share peritubular uptake with other weak organic anions, such as paraminohippurate (PAH). Uptake is inhibited by drugs such as probenecid. Four isoforms of an OAT have been cloned and are expressed in the kidney (18,2). OAT-1 has been characterized as a diuretic-transporting protein (19). Peritubular uptake by OAT is a tertiary active process. Energy derives from the basolateral Na^+/K^+ ATPase that provides a low intracellular [Na^+], which drives a coupled uptake of Na^+ and α-ketoglutarate (αKG^-) that maintains a high intracellular level of αKG^- (Figure 1). This in turn drives a basolateral $OA^-/\alpha KG^-$ countertransporter. Thus OAT translocates diuretics into the proximal tubule cell and is inhibited by probenecid. When inside the tubule cell, OA^- and diuretics can be sequestered reversibly in intracellular vesicles. OA^- and diuretics are secreted across the luminal cell membrane by a voltage-driven OAT (20) and by a counter transporter in exchange for urate or OH^- (2). There is competition for peritubular uptake (2,19) and for luminal secretion (20) with organic anions that include urate (18) that accumulate in uremia. Metabolic acidosis depolarizes the membrane potential (Em) of proximal tubule cells (21), which is predicted to decrease OA^- secretion (20). Indeed, diuretic secretion is facilitated by alkalosis (22). Therefore, the increased plasma

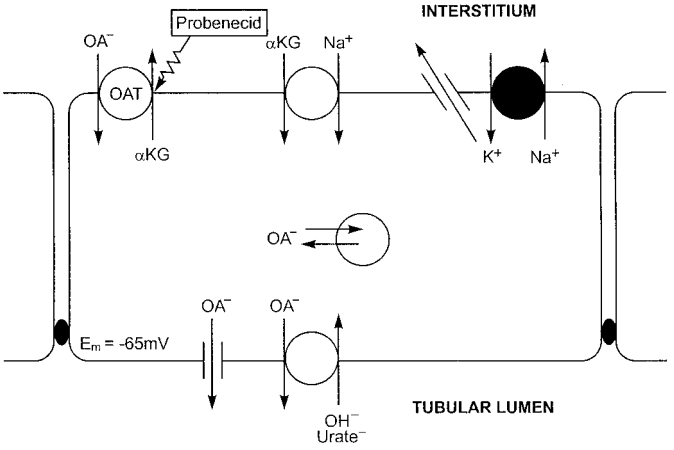

Figure 1. Cell model for secretion of organic anions by proximal tubule cell. OA^-, organic anions; OAT, organic anion transporters; αKG^-, α-ketoglutarate.

levels of organic anions and urate, and the metabolic acidosis that are characteristic feature of CRI, may be a second set of factors that contribute to diuretic resistance in CRI by impairing proximal tubule secretion of diuretics and hence impairing their delivery into tubular fluid to reach their active site in the nephron.

Nephrotic Syndrome

These patients have an impaired response to loop diuretics, as shown by the relationship between the natriuresis and the log of the rate of renal diuretic excretion. In patients with decompensated nephrotic syndrome, this relationship is shifted to the right and reduced in magnitude. This implies that there is a reduced tubular sensitivity and responsiveness to diuretics. The mechanism of this pharmacodynamic limitation has been studied in an animal model of unilateral nephrotic syndrome created by an intrarenal arterial injection of an aminonucleoside. Comparison of the function of the two kidneys in this model provides clear insight into the effects of proteinuria while controlling for the systemic manifestations of nephrosis that are apparent at the two kidneys. The proteinuric kidney has a sharply reduced rate of Na^+ excretion due to an enhanced Na^+ reabsorption in the collecting ducts (23). There is a diminished response of the collecting ducts to inhibition of Na^+ reabsorption by the atrial natriuretic peptide (ANP) (24). An enhanced Na^+ reabsorption in the terminal nephron would diminish the overall renal sensitivity and responsiveness to all diuretics acting upstream, because more of the NaCl delivered to this site as a consequence of diuretic action upstream would be reabsorbed and less would be excreted. Many patients with advanced nephrotic syndrome have a marked stimulation of plasma renin activity, especially during diuretic therapy. The ensuing hyperaldosteronism will further reinforce NaCl reabsorption in the distal nephron and collecting ducts.

Pharmacokinetic factors have been identified in animal models of the nephrotic syndrome that can limit diuretic responsiveness. The renal secretion of furosemide is strongly dependent on the plasma albumin concentration within the clinically relevant range (25). Even moderate hypoalbuminemia in a rabbit model diminishes the renal clearance of active furosemide (26) but surprisingly enhances its metabolism by the kidney to the inactive glucuronide (27). Co-administration of furosemide to hypoalbuminemic rabbits with a large dose of warfarin to displace the diuretic from albumin increases the metabolism of furosemide and decreases the renal clearance of active furosemide. This is accompanied by a decrease in natriuretic response. However, when furosemide is premixed with albumin before injection, the warfarin-induced changes in furosemide kinetics and dynamics are reversed (28). These studies highlight the importance of plasma albumin concentration and plasma protein binding of furosemide in facilitating its secretion in active form and hence in promoting diuretic action.

Furosemide metabolism and bioinactivation occur predominantly in the early proximal tubule of the kidneys (15). Whereas hypoalbuminemia impairs the uptake and secretion of active furosemide, it enhances the uptake and metabolism of furosemide to its inactive form (27). Thus hypoalbuminemia should simultaneously decrease the delivery of active furosemide to its target in the tubular lumen and enhance its metabolic inactivation (15).

Loop diuretics are >95 to 99% bound to serum albumin. Therefore, filtered albumin in the nephrotic syndrome might bind loop diuretics in the tubular fluid and impair their interaction with the luminal $Na^+/K^+/2Cl^-$ cotransporting proteins. Indeed, in microperfusion studies of the loop of Henle in rats, the action of furosemide to reduce net NaCl reabsorption is prevented by coperfusion with albumin at a concentration found in the urine of patients with nephrotic syndrome (29). The addition of a high dose of warfarin to displace furosemide from the perfused albumin prevents the blockade of furosemide's actions by the perfused albumin.

Finally, studies in an albuminemic rat show a markedly impaired response to furosemide that is attributed to a much enlarged volume of distribution (V_D) for the diuretic. The lack of plasma protein binding allows furosemide to partition out of the plasma and into the interstitial fluid, thereby curtailing its delivery to the kidneys.

These considerations from animal studies demonstrate four pharmacokinetic mechanisms that could impair the responsiveness to loop diuretics in patients with the nephrotic syndrome:

- Increased V_D with decreased renal diuretic delivery.
- Decreased peritubular diuretic uptake.
- Enhanced renal metabolism of furosemide to the inactive glucuronide.
- Decreased free diuretic levels in tubular fluid.

Clinical Use in CRI

Loop diuretics are used in patients with CRI to dissipate edema, treat hypertension, and correct metabolic acidosis and hyperkalemia. Patients with CRI have a 10 to 30% increase in extracellular and blood volume, even in the absence of overt edema (30). Depletion of body salt and fluid by dietary restriction and diuretic use is required if edema is contributing to

pulmonary or cardiac dysfunction and reduced exercise ability or causing intolerable inconvenience. However, salt-depleting therapy in CRI is used primarily to combat hypertension. As renal failure progresses, there is an accompanying increase in the proportion of patients with salt-sensitive hypertension (7). Therefore, salt restriction and diuretics are the primary treatment for hypertension in most patients with CRI. Diuretics enhance distal delivery of NaCl and enhance the flow through the terminal nephron, both of which stimulate the activity of the epithelial sodium channel ($E_{Na}C$) and thereby stimulate the distal secretion of K^+ and H^+ (31). Diuretic-stimulated renin secretion, with consequent hyperaldosteronism, enhances these transport processes further. Therefore, regular loop diuretic therapy is the cornerstone of the management of edema, hypertension, acidosis, and hyperkalemia in patients with CRI.

Ceiling doses of loop diuretics in patients with CRI or the nephrotic syndrome have been evaluated. Because of their high bioavailability and nonrenal metabolism, intravenous and oral doses of bumetanide and torsemide are equivalent. Ceiling doses are those that produce a maximal increase in fractional Na^+ excretion. A further increase in dose may produce a further modest increase in Na^+ loss by prolonging the duration of the natriuresis, but repeating the ceiling dose is preferable. Increasing the dose of furosemide above the ceiling increases the plasma level sharply with the possibility of precipitating ototoxicity (16,32). The ceiling doses are shown in Table 1.

Numerous factors in patients with CRI conspire to limit the response of the kidney to loop diuretics (Table 2). This necessitates the use of increased doses (Table 1). A continuous infusion of bumetanide in patients with CRI produces a greater net loss of Na^+ than the same total dose given as divided intravenous injections, although the difference is relatively modest (33). Table 2 summarizes some potential solutions to the problem of limited diuretic efficacy in patients with CRI. An increase in renal blood flow, such as can follow optimization of body fluids, should increase drug delivery to the kidneys.

Fenoldopam, acting on dopamine type 1 receptors, inhibits proximal NaCl reabsorption and increases renal blood flow and should thereby be a valuable adjunct in patients with diuretic resistance (34). However, controlled trials of low-dose dopamine in patients with heart failure or the nephrotic syndrome have been disappointing and have highlighted the potential for dopamine to cause adverse cardiac effects (35) Vargo *et al.* (36) studied eight patients with congestive cardiac failure. An infusion of low-dose dopamine produced only a modest natriuresis and failed to enhance the response to furosemide. Moreover, two subjects had adverse cardiac events. This study does not suggest a role for dopamine to enhance furosemide natriuresis.

Novel adenosine type 1 receptor (A_1) antagonists inhibit NaCl reabsorption in the proximal tubule, block the TGF, and increase the GFR without effects on the heart (37). Brater *et al.* (38) studied the response of patients with heart failure and mild renal insufficiency to an A_1 antagonist. The drug increased the GFR and caused a natriuresis without loss of potassium. Its effects were additive with furosemide; therefore, this therapy has the potential to treat diuretic resistance in a novel manner.

Correction of metabolic acidosis and prevention of uremic accumulation of organic anions and urate by dietary protein restriction are rational methods to enhance proximal tubule diuretic secretion, but have not been subjected to clinical trial. Several drugs compete with loop diuretics for proximal secretion and thereby may diminish diuretic efficacy (20) (Table 2). Bumetanide and torsemide are metabolized by the liver, whereas furosemide is metabolized by the kidneys. Therefore, when needed for prolonged, high-dosage therapy in CRI, bumetanide or torsemide may be preferable because they do not accumulate. Torsemide has an aldosterone antagonist action in animal models (39) that could perhaps contribute to hyperkalemia in patients with CRI. However, this has not been apparent in clinical studies (11). A strategy in diuretic resistant patients with mild CRI is to combine a loop with a distal acting diuretic, such as a thiazide, to prevent reabsorption of NaCl and fluid in adapted downstream segments (40). In an instructive study, Wollam *et al.* (8) studied the effects of increasing the dose of furosemide or adding escalating doses of a thiazide diuretic to a group of mildly azotemic hypertensive subjects. Doubling the furosemide dosage had little effect on their body weight, BP, or S_{Cr}, thereby demonstrating loop diuretic resistance. In contrast, the addition of 70 mg daily of hydrochlorothiazide normalized the BP and resulted in a substantial loss in body weight. However, the cost of this beneficial effect on BP and body fluid accumulation was a sharp increase in the S_{Cr} and a reduction in the serum potassium concentration (S_K). Therefore, combined therapy with a loop and a thiazide di-

Table 1. Ceiling doses (mg) of loop diuretics

Condition	Furosemide		Bumetanide		Torsemide	
	iv	po	iv	po	iv	po
Chronic renal insufficiency						
moderate (GFR 20 to 50 ml · min^{-1})	120	240	3	3	50	50
severe (GFR > 20 ml · min^{-1})	200	400	10	10	100	100
Nephrotic syndrome with normal GFR		120		3		50

After: Swan SK, Brater DC: Clinical pharmacology of loop diuretics and their use in chronic renal insufficiency. *J Nephrol* 6: 118–123, 1993, and Ellison D, Wilcox CS: Diuretic resistance. In: *Therapy in Nephrology and Hypertension*, edited by H.R. Brady and C.S. Wilcox. Philadelphia: W.B. Saunders, 1998, p. 665–674.

Table 2. Some identified mechanisms and their possible solutions for limited response to loop diuretics in patients with renal insufficiency

Limitation of Response	Potential Mechanism	Potential Solution
Decreased renal diuretic delivery	Decreased renal blood flow	Optimize BP and body fluids to restore renal blood flow
Decreased basal fractional NaCl reabsorption	Limits effects of less-active diuretics	Select a loop, not a thiazide, as initial diuretic
Decreased proximal tubule diuretic secretion	Competition with urate and organic anions for basolateral uptake by OAT	Correct uremic milieu and hyperuricemia
	Acidosis impairs secretion	Correct acidosis
	Competition with drugs for tubular secretion by OAT	Avoid codosing with probencid, NSAIAs, β-lactam and sulphonamide antibiotics, valproic acid, methorexate, cimetidine, and antiviral agents
Maintained metabolic but decreased renal clearance (furosemide only)	Hepatic metabolism of bumetanide and torsemide preserved	Consider bumetanide or torsemide to prevent accumulation and ototoxicity at high plasma levels
Enhanced NaCl reabsorption in downstream segments	Enhanced distal tubule fluid and NaCl delivery	Use thiazide or metolazine with loop diuretic in resistant patients
	Enhanced TSC expression	

OAT, organic anion transporter; TSC, thiazide-sensitive cotransporter.

uretic, when given in high doses to patients with CRI, although effective, requires very close surveillance and appropriate other measures to limit adverse effects. A further short-term reduction in GFR may be the price to pay for normalization of BP. Most patients can be better managed by more modest doses of loop diuretics combined with other effective agents, such as an angiotensin converting enzyme inhibitors (ACEI), an angiotensin receptor blocker (ARB), or a calcium antagonist (CA).

Some physicians prescribed loop diuretics to patients with end-stage renal disease (ESRD) to attempt to slow the rate of loss of the GFR. An observational study of 125 patients with ESRD treated by peritoneal dialysis (PD) showed that total Na^+ and fluid removal by PD were powerful predictors of a good survival (41). In contrast, a controlled clinical trial of the effects of furosemide in patients treated with continuous ambulatory peritoneal dialysis showed no benefit of regular diuretic therapy in delaying the loss of residual renal function (42). Thus, optimal dialysis, rather than loop diuretic therapy, is the best treatment for these patients.

Clinical Use in the Nephrotic Syndrome

Fluid retention and loop diuretic resistance becomes increasingly common as the nephrotic syndrome progresses. Whereas some patients, especially those with minimal change glomerulonephritis, have edema primarily because of a decrease in the plasma oncotic pressure and enhanced capillary albumin escape, which redistributes plasma water into the interstitium ("underfill edema"), the majority have "overfill edema" due to a primary NaCl and fluid retention in the collecting ducts (23). Therefore, an enhanced dose of diuretic is required to offset avid NaCl reabsorption by the terminal nephron. Presently, specific strategies to counteract this primary alteration in collecting duct function have not been provided. ANP normally inhibits Na^+ reabsorption in the collecting ducts, but it becomes ineffective in animal models of the nephrotic syndrome (24).

Inoue *et al.* (43) demonstrated that premixing of furosemide with albumin in the syringe before intravenous administration modestly increased the response to the diuretic in hypoalbuminemic patients with the nephrotic syndrome. This was attributed to a reduced V_D and better delivery of furosemide to the kidney. However, the interaction between a drug and serum albumin is dynamic and extremely rapid. This is exemplified by the renal tubular uptake of loop diuretics. Furosemide is delivered to the peritubular capillary blood >98% bound to serum albumin, yet its renal clearance can approach the rate of renal plasma flow. This demonstrates that there can be very little limitation of the passage of diuretics to the interstitium by binding to plasma albumin. Therefore, it is difficult to understand how premixing of a loop diuretic with albumin would increase its action unless sufficient albumin was infused to raise the plasma albumin concentrations. Indeed, a contemporary study failed to detect any improvement in furosemide kinetics or natriuretic response when it was premixed with 25 g of albumin and given intravenously to patients with cirrhosis and ascites (44). This study is not definitive, because the patients had only modest hypoalbuminemia and were very responsive to furosemide alone. Therefore, they did not have loop diuretic resistance.

Even if patients with nephrotic syndrome and diuretic resistance do derive a small increase in diuretic response by pre-

mixing furosemide with albumin in the syringe, the expense of human serum albumin (HSA) and the need to preserve its use for better defined indications dictate that this practice should not be pursued routinely. Moreover, if the problem of diuretic resistance in hypoalbuminemic patients is delivering sufficient furosemide in the blood because of an enhanced V_D, it would be simpler, more predictable, and much cheaper to achieve the desired goal by increasing the administered dose of the diuretic.

Agrawal *et al.* (45) studied the effect of displacing furosemide from albumin by coadministration of sulfisoxazole. When tested in seven patients with the nephrotic syndrome, sulfisoxazole did not affect the natriuresis. The authors concluded that protein binding of loop diuretics in the tubular fluid is not a major mechanism for diuretic resistance in the nephrotic syndrome. However, these patients did not have diuretic resistance because furosemide alone increased natriuresis by 239 mmol, which was eightfold above the level of Na^+ intake. As anticipated (43), blocking albumin binding increased furosemide V_D by 38% and decreased the area under the curve correspondingly, although the total diuretic excretion was not changed. A prolonged time course of delivery of furosemide to the urine increases diuretic responsiveness (46); therefore, these pharmacokinetic changes provide some additional explanations for the results obtained. Nevertheless, this study refutes the possibility that sulfisoxazole should be given to patients with the nephrotic syndrome to enhance diuretic responsiveness, although it does not answer whether a different strategy to reverse binding to filtered albumin might be effective in fully resistant patients.

Several additional mechanisms have been identified in experimental studies whereby a reduction in the serum albumin concentration or an increase in the quantity of albumin filtered into tubular fluid contributes to diuretic resistance (Table 3). A logical first approach to a patient with the nephrotic syndrome and diuretic resistance is to pursue a vigorous strategy for limiting albuminuria. This strategy may also combat other adverse effects of the nephrotic syndrome, such as coagulopathy, dyslipidemia, edema, and progressive loss of renal function. The cornerstones of treatment are the use of escalating doses of ACEI or ARB with sequential measurements of 24-h albumin excretion. This can be combined with attempts, where feasible, to limit protein intake, because this reduces protein excretion. A reasonable goal is a daily protein intake equivalent to the sum of the daily protein excretion plus 0.8 to $1.0 g \cdot kg^{-1}$. More severe restriction to $0.6\ g \cdot kg^{-1}$ can be attempted, but further reduction can lead to protein malnutrition. This strategy is preferable to the use of large volumes of intravenous HSA. This expensive therapy is rather ineffective in raising the serum albumin concentration or blood volume or in improving diuretic responsiveness because of rapid loss of infused albumin into the interstitium and its excretion in the urine. The infused albumin constitutes a substantial NaCl load (47). Salt pure HSA is normally administered as an isooncotic infusion with saline. Therefore, each liter delivers 150 mEq of sodium and chloride, which is twice the daily salt intake recommended for diuretic resistance patients. A graphic example of this problem is provided by a study in which albumin saline was infused daily over 3 d into hypoalbuminemic patients with the nephrotic syndrome to produce a sustained increase in plasma volume of 20% (48). Although this therapy led to a modest increase in renal sodium excretion, the renal Na^+ losses were substantially less than the increased Na^+ load delivered by the therapy. The result was a progressive accumulation of body Na^+. An additional problem is that albumin infusion increases renal albumin excretion, thereby perhaps contributing to a decline in renal function. These considerations leave little doubt that such therapy should be abandoned

Table 3. Some identified mechanisms and their possible solutions for limited response to loop diuretics in patients with the nephrotic syndrome

Limitation of Response	Mechanism	Potential Solution
Decreased diuretic delivery to the kidney	Decreased serum albumin concentration increases V_D and reduces renal diuretic delivery	Premix intravenous diuretic with albumin in syringe
Decreased tubular secretion of active diuretic	Decreased serum albumin concentration limits proximal secretion	Decrease albuminuria with an ACEI or ARB and protein restriction
Increased renal metabolism of furosemide	Decreased serum albumin concentration increases tubular uptake and inactivation by glucuronidization	Consider bumetanide or torsemide, which are hepatically metabolized
Decreased blockade of tubular NaCl reabsorption	Binding of free drug to filtered albumin	Decrease albuminuria with an ACEI or ARB and protein restriction
Adaptive enhancement of reabsorption in downstream nephron segments	Functional adaptation of the distal tubule collecting duct	Consider thiazide use with loop diuretic
Enhanced reabsorption in the collecting ducts	ANP resistance	Increase dose of diuretic

ACEI, angiotension-converting enzyme inhibitor; ARB, angiotension receptor blocker; ANP, atrial natriuretic peptide.

except as required to restore a reasonable circulating blood volume and BP in the occasional severely hypovolemic, hypotensive individual.

Conclusions

Recent evidence from animal studies and clinical investigations have thrown new light on mechanisms that contribute to diuretic resistance in models or patients with CRI or the nephrotic syndrome. These have provoked a reexamination of strategies for restoring natriuresis. The complexity of the pharmacokinetic and pharmacodynamic mechanism so far identified makes it likely that several factors may need to be addressed concurrently in such patients. Important general measures to combat diuretic resistance include the appropriate restriction of fluid intake (1.5 L daily) and NaCl intakes (Na^+ intake of 2 g daily) combined with use of escalating doses of loop diuretics up to established ceiling levels. Judicious use of a second diuretic acting at a downstream site can produce substantial synergism, but it carries the potential for adverse effects due to fluid and electrolyte disturbances. Measures designed to reduce renal proteinuria in patients with nephrotic syndrome are more logical and more effective than measures based on albumin administration.

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