Loop diuretics: from the Na-K-2Cl transporter to clinical use

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Shankar, Sudha S. and D. Craig Brater. Loop diuretics: from the Na-K-2Cl transporter to clinical use. Am J Physiol Renal Physiol 284: F11–F21, 2003; 10.1152/ajprenal.00119.2002.—The diuretic response to loop diuretics in various disease states has consistently been found to be subnormal. One of the key determinants of the degree of diuretic response is the functional integrity of the sodium-potassium-chloride transporter in the loop of Henle. Studies in animal models suggest that expression/activity of the transporter may be affected by factors such as altered natural splicing events of NKCC2 (the gene encoding for the renal transporter), renal prostanoids, vasopressin, and other autacoids. We have reviewed the pharmacokinetics and pharmacodynamics of loop diuretics in health and in edematous disorders for which they are used. On the basis of evidence reviewed in this paper, we propose that altered expression or activity of the sodium-potassium-chloride transporter in the loop of Henle, in conjunction with events occurring in other segments of the nephron, possibly accounts for the altered diuretic response to these agents. Thus the modulators of this altered expression/activity could serve as important therapeutic targets for alternative diuretic regimens in these conditions.

edematous disorders; furosemide

OPTIMAL THERAPEUTIC USE of loop diuretics requires an understanding of their basic pharmacology and how that translates to clinical pharmacology. As will be emphasized, the two complement one another in that discoveries in the domain of pharmacology lead to testable hypotheses as to clinical application. Similarly, clinical observations logically lead to studies best performed at the bench. For example, studies of the pharmacodynamics of loop diuretics in patients with heart failure consistently show that there is a subnormal response to amounts of diuretic reaching the site of action. There are several potential explanations for this observation, each of which dictates a different therapeutic strategy. The possible explanations would be difficult to dissect through clinical studies. For example, one possible explanation is altered expression or activity of the Na-K-2Cl transporter at the loop of Henle. It goes without saying that one could never measure such expression in a clinical study. In contrast, one can imagine addressing such a question in an appropriate animal model. If such a model showed that there was no difference in expression of the transporter, then alternative mechanisms should be explored. If, on the other hand, there were substantial changes in expression or activity of the transporter in heart failure, one would then need to ponder appropriate therapeutic strategies and test them in controlled clinical trials.

PHARMACOLOGY OF LOOP DIURETICS

Loop diuretics act principally by blocking the luminal Na-K-2Cl transporter in the thick ascending limb of the loop of Henle; in other words, this transporter is the receptor for loop diuretics (15, 31, 40, 42, 64, 69, 78, 80). This transporter has been cloned and sequenced, and its expression has been mapped to different segments of the nephron as well as other tissues (66, 69, 70). It is a protein with a core molecular mass of 121 kDa, having 12 putative membrane-spanning domains (42, 70). Loop diuretics bind to portions of transmem-
brane domains 11 and 12, whereas portions of domains 2, 4, and 7 transport Na, K, and/or Cl. It is encoded for by the type 1 bumetanide-sensitive Na-Cl cotransporter (BSC-1/NKCC2 gene on chromosome 2, and rat BSC-1 protein is localized to the apical membrane of epithelial cells in both medullary and cortical segments of the thick ascending limb of the loop of Henle (66, 69, 70). Several investigators have shown that it is expressed throughout the thick ascending limb of the loop of Henle, including the macula densa (66, 69, 70). Interestingly, nitric oxide (NO) synthase is coexpressed in the macula densa, suggesting that the Na-K-2Cl transporter may serve as the sensor of luminal chloride delivery to the macula densa and that NO is a mediator or modulator of subsequent effects in concert with or through locally synthesized prostanoids (77). Expression of Na-K-2Cl is at the luminal membrane but also in cytoplasmic vesicles, suggesting a reservoir of transporters for insertion into the membrane (66, 69). In turn, these vesicles are more predominant in smooth- than rough-surfaced thick ascending limb cells; the former are mainly in the medullary portion of the thick limb. Thus the transporter that serves as the receptor for loop diuretics is expressed at the apical surface of both the medullary and the cortical sections of the thick ascending limb of the loop of Henle, including the macula densa. It resides in cytoplasmic vesicles, offering a mechanism for altered activity of the transporter by way of increasing or decreasing the numbers of transporters inserted into the membrane. In addition to the renal Na-K-2Cl transporter, there is a ubiquitous Na-K-2Cl transporter encoded by BSC-2/NKCC1 that is expressed in many tissues. Loop diuretics have little if any effect on this latter transporter in vivo. In contrast, ex vivo they inhibit its activity. In vivo selectivity derives from three factors. First, the renal Na-K-2Cl transporter has about a four-fold greater affinity for bumetanide and presumably other loop diuretics (41, 49). Second, there are likely differences in access of the loop diuretic to the site of transporter expression. All loop diuretics are highly bound to serum albumin, and this binding restricts their access to many tissues, as might physicochemical properties such as their negative charge and poor lipid solubility. Access to renal Na-K-2Cl receptors occurs via active secretion. One must presume that such an avenue of access is not present at sites of expression of the ubiquitous Na-K-2Cl transporter. Third, once a loop diuretic is secreted into the proximal tubule, as it flows to its site of activity at the thick ascending limb of the loop of Henle, it becomes more concentrated.

Studies in animal models have explored ways in which expression of the Na-K-2Cl transporter might be altered (Fig. 1). It is now abundantly clear that vasopressin itself, either exogenously or endogenously, or its analogs increase expression of the transporter (24, 55). It is important to note that vasopressin might also cause increased insertion of transporters over and above increasing their expression. Studies with knockout mice (Gβγ knockout) indicate that this effect of vasopressin is through Gβγ, presumably to increase cAMP, which then increases transporter expression via a cAMP regulatory element of the BSC-1/NKCC2 gene (24) (Fig. 1). The net effect would be an increase in solute reabsorption at the thick limb, contributing to sodium retention and also increasing the driving force for water reabsorption (Fig. 1). It is intriguing to note that vasopressin also causes increased aquaporin expression and insertion, thereby increasing the channels available for water reabsorption (2, 59, 97, 103). That effect, coupled with the increased osmotic driving force for water reabsorption noted above and with

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**Fig. 1. Regulation of expression of the Na-K-2Cl transporter at the thick ascending limb of the loop of Henle and the macula densa.**

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*AJR Renal Physiol* • VOL 284 • JANUARY 2003 • www.ajprenal.org
nonosmotically mediated increases in vasopressin in edematous disorders (84, 85), can readily account for the inability to excrete free water and the hyponatremia that is a characteristic of these clinical conditions (Fig. 2). These data suggest that the vasopressin-mediated increase in expression of the Na-K-2Cl transporter amplifies the defect in water excretion in edematous disorders. Might it also be a factor in the changed pharmacodynamics of loop diuretics? As will be discussed subsequently, vasopressin-mediated increased transporter expression alone is an overly simplistic explanation for an altered diuretic response.

The expression of the Na-K-2Cl transporter may also be influenced by alternate natural splicing events of the BSC-1/NKCC2 gene, with various degrees of expression of the different exons (66). In turn, this alternate splicing results in different transporter capacities (36). Disease-induced changes in splicing or distribution of splice variants could conceivably contribute to an altered cumulative response to a loop diuretic.

The expression of the Na-K-2Cl transporter is also influenced by renal prostanoids, wherein PGE2 decreases its expression (29) (Fig. 1). PGE2 activates the EP3 receptor, causing decreases in cAMP via G_{i}; through the cAMP regulatory element, expression of the transporter decreases. Such an effect would decrease the driving force for water reabsorption and thereby diminish the hydrosmotic response to vasopressin, a well-known effect of PGE2 (44). This role of PGE2 could also explain the effect of nonsteroidal anti-inflammatory drugs in causing sodium and water retention, an effect that has been shown in clinical studies to occur anatomically at the thick ascending limb (51). It is interesting to note that administration of vasopressin and also edematous disorders are characterized by increases in renal prostanoids. Presumably, this represents a negative-feedback loop to ameliorate the sodium- and water-retentive effects of the edematous disorders. This pathophysiology also likely accounts for the sometimes devastating clinical effects of acute renal failure (16, 20, 83) or decompensation of heart failure (45, 65) that can occur when such patients are administered nonsteroidal anti-inflammatory drugs.

Vasopressin and other autacoids could also affect activity of the transporter in addition to its expression. Extensive studies have been performed with NKCC1 showing numerous fashions by which activity could be modified, including phosphorylation by any of a number of kinases (42). Presumably, the same potential applies to the renal Na-K-2Cl transporter.

From the foregoing, one would predict that increased expression of the Na-K-2Cl transporter occurs in the common clinical conditions treated with loop diuretics. In turn, might increased expression account, at least in part, for the diminished response to loop diuretics that occurs in the edematous disorders? This mechanism is likely overly simplistic. As will be discussed, the response to loop diuretics in the edematous disorders is characterized by a decrease in response to a maximally effective dose. If vasopressin simply caused more transporters to be present in the thick ascending limb of the loop of Henle, one would expect that administration of a dose of loop diuretic sufficient to block all of them would result in an increased maximal response. Thus one must postulate a more complicated scenario of altered activity and/or of events occurring at other segments of the nephron that obviate this manifestation of increased expression. For example, increased proximal and/or distal reabsorption of sodium could contribute. The answers to these questions are open and not only represent scientific opportunities for the future but are also important for the design of future therapeutic diuretic regimens. Importantly, the anticipated availability of vasopressin antagonists for clinical use will allow logical exploration of these different possibilities in parallel with studies at the bench that unravel this undoubtedly complicated pathophysiology.

PHARMACOKINETICS OF LOOP DIURETICS

Loop diuretics reach the Na-K-2Cl transporters that are inserted into the luminal membrane by being actively secreted from the blood into the urine at the proximal tubule (71). High albumin binding (>95%) minimizes glomerular filtration. Binding to albumin traps the diuretic in the plasma and transports it to organic acid secretory sites at the proximal tubule. These secretory pumps have such avidity for the loop diuretic that the diuretic is in effect “stripped” from the albumin and transported across the cell into the lumen, where it gains access to the Na-K-2Cl transporters that are downstream of the secretory sites.

Fifty percent of a dose of furosemide is excreted as active, unchanged drug into the urine (7, 10); the remainder is conjugated to glucuronic acid in the kidney itself (76). In patients with renal insufficiency, the plasma half-life of furosemide is prolonged because both urinary excretion and renal conjugation are decreased (7, 8, 10, 21, 47, 89) (Table 1). Bumetanide and torsemide have substantial metabolism (50 and 80%, respectively), but with these loop diuretics metabolism
is hepatic rather than renal (11, 14, 22, 46). Therefore, their half-lives are not prolonged in patients with renal insufficiency, because the liver provides an alternative route for elimination (Table 1). Just as occurs with furosemide, with these two loop diuretics renal disease impairs delivery into the tubular fluid. In patients with hepatic disease, the plasma half-lives of bumetanide and torsemide are prolonged, allowing more to reach the tubular fluid, an effect that can paradoxically enhance response (10, 86) (Table 1).

Orthoacrylic acid is another loop diuretic; there are no data concerning its pharmacokinetics. Its ototoxic effects have seemed to be greater than that of other loop diuretics, causing its use to be relegated to patients who have allergic reactions to other loop diuretics. It will not be discussed.

Other pharmacokinetic features of diuretics that are clinically important are bioavailability and half-life. On average, half a dose of furosemide is absorbed but with a large range (10–100%) (10, 68). This variability makes it difficult to predict how much furosemide will be absorbed in an individual patient. Clinically, this means that one may need to explore a wide range of doses in an individual patient to determine the appropriate oral dose. Absorption of bumetanide and torsemide is essentially complete (34, 68, 86, 94) (Table 1). The variability in furosemide absorption appears to be clinically important. A recent study from our laboratory reports fewer hospitalizations and better quality of life in patients with heart failure treated with a completely absorbed loop diuretic as represented by torsemide compared with furosemide (67). Edematous disorders do not cause malabsorption of loop diuretics (6, 13, 18, 34, 86, 91, 94, 95). Absorption is slowed, particularly in patients with decompensated heart failure (95), but the total amount absorbed is the same as in healthy individuals. The clinical implications of slowed absorption are unclear.

The plasma half-lives of loop diuretics range from ~1 h for bumetanide to 3–4 h for torsemide; that for furosemide is intermediate (10). Neither a truly long-acting loop diuretic nor a sustained-release preparation is available. The traditional dosing intervals of all loop diuretics exceed the duration of time when effective amounts of drug are at the site of action. This means that at the end of the dosing interval there is considerable time during which there are inadequate amounts of diuretic at the site of action. During this time, the nephron avidly reabsorbs sodium, causing so-called “rebound” sodium retention or “braking” (102). This sodium retention can be of sufficient extent as to nullify the prior natriuresis. This is particularly the case if the response is modest, if the time of no drug effect is long (for example, a short half-life coupled with a long dosing interval), and/or if dietary sodium is high relative to response. Dietary intake is particularly a problem if salt indiscretion occurs at the end of a dosing interval wherein most of the sodium is retained (28). As a consequence, it may be wise for patients to take their doses of loop diuretics at times that correspond to sodium ingestion.

In summary, excepting the infrequently used ethacrynic acid, the pharmacokinetic characteristics of loop diuretics are well defined. These data allow logical choices, depending on the needs of individual patients, of which loop diuretic to use. Choice of dose and the frequency of dosing are driven not only by these pharmacokinetic characteristics but also by the pharmacodynamics of loop diuretics in the different clinical conditions in which they are used.

### PHARMACODYNAMICS OF LOOP DIURETICS

The urinary excretion rate of a loop diuretic has been shown to be a reliable measure of amounts of diuretic reaching the site of action and can be used as a surrogate for concentration in a typical concentration-response analysis of diuretic action (10, 19). Urinary concentration has not proven to be a useful measure because the concentration of diuretic in the final urine does not represent that at the site of action. Simplistically, the more diuretic reaching its site of action, the greater the response so that the net result is that diuretic concentration in the final urine is constant. Therein, the diuretic excretion rate is a better reflection of the amount of diuretic that is able to interact with the Na-K-2Cl transporter. The relationship between diuretic delivery and response, measured as urinary sodium excretion, chloride excretion, or fractional excretion of either, is characterized by a sigmoidal-shaped curve, a so-called sigmoidal $\text{E}_{\text{max}}$ model (9). This relationship holds for all loop diuretics, although the position of each on the x-axis differs, because of differences in potency; namely, the excretion rate that causes a half-maximal response being least for bumetanide (~2.5 $\mu$g/min), greatest for furosemide (~100 $\mu$g/min), and intermediate for torsemide (~50 $\mu$g/min). Importantly, efficacy (maximal effect) is the same for all and amounts to a fractional excretion rate of sodium of ~20–25% in a healthy volunteer. This value is important, because it implies that a maximally effective dose of a loop diuretic is capable of completely blocking sodium reabsorption in the thick limb. In turn, once a maximally effective dose is administered, the only way to increase response is to block other segments of the nephron.

Several features of the sigmoidal shape of the pharmacodynamic relationship are important clinically. First, there is a threshold quantity of drug that must be achieved at the active site to elicit a response. Because of individual differences in sensitivity of the

### Table 1. Pharmacokinetics of loop diuretics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability, %oral dose absorbed</th>
<th>Elimination Half-Life, h</th>
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<tbody>
<tr>
<td></td>
<td>Healthy disease</td>
<td>Renal disease</td>
</tr>
<tr>
<td>Furosemide</td>
<td>50% (Range, 10–100%)</td>
<td>1.5–2</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>80–100%</td>
<td>1</td>
</tr>
<tr>
<td>Torsemide</td>
<td>80–100%</td>
<td>3–4</td>
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</tbody>
</table>

CHF, chronic heart failure.
nephron and individual differences in pharmacokinetic characteristics, the dose that attains this threshold differs among patients. Clinically, this means patients should have doses tailored to their individual needs and that physicians should realize that a process of dose titration needs to occur in each patient. As noted above, the second feature of this pharmacodynamic relationship is that a maximal response can be identified, allowing definition of the ceiling dose of a diuretic, namely, the smallest dose of a diuretic that elicits a maximal response and therefore the dose that should not be exceeded.

In healthy volunteers, an intravenous dose of 40 mg of furosemide, 20 mg of torsemide, or 1 mg of bumetanide causes a maximal response, which is the excretion of 200–250 meq of sodium in a urine volume of 3–4 liters over a time interval of 3–4 h (10). In other words, loop diuretics cause excretion of urine with a sodium content resembling 0.5 normal saline. Knowing this fact can be helpful to clinicians in predicting the amount of sodium excreted based on simple measures of urine volume.

Tolerance to Loop Diuretics

There are two forms of tolerance to loop diuretics. Acute tolerance, or braking, refers to a decrease in response to a loop diuretic early in its use, in fact, within the duration of effect of the first dose. This type of tolerance can be prevented by restoring diuretic-induced loss of volume, implying that volume loss per se is the stimulus for whatever effectors are responsible (4, 43, 100). The mechanism by which acute tolerance occurs is unclear. Potential mediators include angiotensin II, sympathetic nervous system activation, or both. However, neither converting enzyme inhibition nor adrenergic blockade, separately and together, consistently prevents it (54, 75, 101). Thus other as yet unidentified mechanisms must also be involved. Acute tolerance is an important factor in the timing of doses of a loop diuretic and in the frequency of dosing. Because of the short half-lives of loop diuretics relative to their usual dosing interval, there can be a substantial period of time at the end of a dosing interval where amounts of diuretic are below the threshold needed to cause an effect. During this time, when homeostatic mechanisms have been triggered, avid sodium retention can occur. If the patient ingests sodium during these times, most or all of it will be retained, potentially obviating the diuretic effect (28). Several strategies can be used to counter this effect, including more frequent dosing, decreasing overall sodium intake, and/or coordinating diuretic and food ingestion so that the latter occurs at a time when sufficient amounts of diuretic are at the site of action, as, for example, ingestion within 2 h of administration of the diuretic (28). This problem could be most readily overcome by having a truly long-acting loop diuretic or a sustained-release preparation of one of them. Unfortunately, the chemical characteristics of all available loop diuretics have withstood substantial efforts to formulate such a product.

The second type of loop diuretic tolerance occurs with chronic administration. When a loop diuretic is administered, the solute rejected from the loop of Henle floods more distal nephron sites. Increased exposure to solute causes hypertrophy of collecting and connecting duct segments of the nephron, with concomitant increases in reabsorption of sodium (25, 50, 60, 63, 88). Therein, sodium rejected from the loop of Henle is then reclamation at these sites, decreasing overall diuresis. 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 (26, 27, 72, 87). This phenomenon reinforces the logic of using combinations of loop and thiazide diuretics in patients who do not respond adequately to maximally effective doses of a loop diuretic.

Pharmacodynamics of Loop Diuretics in Edematous Disorders

**Renal insufficiency.** Patients with a creatinine clearance of 15 ml/min deliver one-fifth to one-tenth as much loop diuretic into the tubular fluid as a healthy volunteer (7, 10). Thus a large dose must be given to attain an effective amount of diuretic in the tubule (Table 2). When sufficient doses are administered to

<table>
<thead>
<tr>
<th>Table 2. Therapeutic strategies for use of loop diuretics</th>
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<tr>
<td>Renal Insufficiency</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Mechanism of diminished response to diuretic</strong></td>
</tr>
<tr>
<td>Impaired delivery to site of action</td>
</tr>
<tr>
<td><strong>Therapeutic strategy</strong></td>
</tr>
<tr>
<td>Sufficient dose to attain effective excretion rates of</td>
</tr>
<tr>
<td>diuretic at site of action</td>
</tr>
<tr>
<td>Ceiling dose, mg (iv)</td>
</tr>
<tr>
<td>Furosemide</td>
</tr>
<tr>
<td>80–160</td>
</tr>
<tr>
<td>Bumetanide</td>
</tr>
<tr>
<td>4–8</td>
</tr>
<tr>
<td>Torsemide</td>
</tr>
<tr>
<td>20–50</td>
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*Preserved renal function (e.g., creatinine clearance >75 ml/min).
attain effective amounts of the loop diuretic in the urine, the relationship between excretion rate of diuretic and response measured as fractional excretion of sodium is the same in patients with renal insufficiency as in healthy volunteers (93, 99). Thus remnant nephrons in patients with renal insufficiency retain their responsiveness. That having been said, a response in terms of total urinary sodium excretion never reaches that for a healthy volunteer because the decrease in renal function limits filtered sodium (Fig. 3). Clinically, this means that a maximally effective dose of a loop diuretic in a patient with renal insufficiency may not result in the needed overall diuresis and that other measures including frequent dosing, combining diuretics, and/or restricting dietary sodium may also need to be employed.

As noted above, the sigmoidal nature of the pharmacodynamic relationship allows definition of a dose of loop diuretic that causes a maximal response. Because this relationship is maintained in patients with renal insufficiency, one can determine the largest dose that needs to be administered in such patients. Clinical studies have shown that a maximal natriuretic response occurs with intravenous bolus doses of 160–200 mg of furosemide, 6–8 mg of bumetanide, and 80–100 mg of torsemide (81, 99). Nothing but the risk of toxicity is gained by larger single doses. Single intravenous bolus doses of this magnitude can occasionally cause transient tinnitus (33, 35). Such effects can likely be minimized by administering the dose by infusion over 20–30 min, although this has never been systematically studied.

As discussed previously, one aspect of the short half-lives of all the loop diuretics is the duration of time at the end of the dosing interval where avid sodium retention can occur. In the appropriate clinical setting, a continuous intravenous infusion can be used to maintain effective amounts of the diuretic at the site of action at all times. This strategy results in a small (20–30%) but sometimes clinically important increase in overall response (82). This approach can be used in all edematous disorders (23, 61, 62, 92). If one intends to use a continuous infusion of a loop diuretic, a loading dose must first be given to decrease the time needed to attain adequate amounts of diuretic at the site of action (Table 3); otherwise, 6–20 h are required to reach steady state, depending on the diuretic used and the patient’s renal and/or hepatic functional status. The rate of the continuous infusion is determined as follows

\[
\text{Desired urinary excretion rate of diuretic} = \text{serum concentration} \times \text{renal diuretic clearance}
\]

\[
\text{Needed serum concentration} = \text{continuous infusion rate} \times \text{serum diuretic clearance}
\]

The desired urinary excretion rate is known from clinical studies in patients with renal insufficiency, where the pharmacodynamic relationship has been defined; renal diuretic clearance and serum diuretic clearance are known from prior pharmacokinetic studies in such patients. The former allows calculation of the needed serum concentration. This value plus serum clearance then allows calculation of the continuous infusion rate (Table 3). Such infusion rates have been tested and validated in appropriate patient groups (23, 61, 62, 82, 92).

In summary, a patient who needs a loop diuretic and who has renal insufficiency should be given increasing doses of a loop diuretic until an effective dose is found or the ceiling dose relative to the individual patient’s renal function is reached (Table 2). When an effective dose is found, its dosing frequency is based on the patient’s response and ability to restrict sodium intake as well as the duration of action of the loop diuretic chosen.

**Nephrotic syndrome.** Several changes occur in nephrotic syndrome that can affect the pharmacokinetics of loop diuretics. Two factors can affect delivery of the diuretic to its site of action, namely, inadequate secretion from blood to lumen of the nephron or alternatively binding of the loop diuretic to albumin in the

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**Table 3. Doses for continuous intravenous infusion of loop diuretics**

<table>
<thead>
<tr>
<th>Creatinine Clearance, ml/min</th>
<th>All levels</th>
<th>Infusion rate, mg/h</th>
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<tbody>
<tr>
<td>Intravenous loading dose, mg</td>
<td>&lt;25</td>
<td>10, then 20, 10</td>
</tr>
<tr>
<td></td>
<td>25–75</td>
<td>0.5, then 1, 0.5</td>
</tr>
<tr>
<td></td>
<td>&gt;75</td>
<td>5, then 10, 5</td>
</tr>
</tbody>
</table>

Before an increase to a higher infusion rate, a repeat loading dose should be administered.
tubular lumen. In terms of the former, studies in analbuminemic rats show that hypoalbuminemia may result in insufficient delivery of drug into the tubular fluid (48). As noted previously, the high degree of binding of loop diuretics to plasma albumin traps the diuretic in the vascular space and carries it to secretory sites in the kidney. In the absence of circulating albumin, loop diuretics are no longer restricted to the plasma (as reflected by a 10-fold increase in volume of distribution in the analbuminemic rat) and reach the secretory sites to a substantially diminished degree; therefore, less diuretic is secreted into the lumen, resulting in inadequate natriuresis (48). In analbuminemic rats, administration of a mixture of albumin and a loop diuretic restores bound diuretic to the animal. This results in a normalization of the volume of distribution and increased delivery of diuretic into the urine, restoring the response (48). That this mechanism might be operative in humans was suggested by a report that administration of 30 mg of furosemide mixed ex vivo with 25 g of albumin enhanced diuresis in several patients with nephrotic syndrome (48).

It is important to emphasize that this therapeutic strategy is aimed at increasing amounts of diuretic in the urine in hypoalbuminemic patients; it is not a strategy to alter the pharmacodynamics of the loop diuretic. Therein, it should be noted that pharmacokinetic studies in patients with both nephrotic syndrome (53, 79) and cirrhosis (32, 52, 90, 96, 98) show that normal excretion rates of furosemide reach the tubular fluid unless the patient also has renal insufficiency. The mechanism of this altered response is unknown. Increased proximal and/or distal reabsorption of sodium may contribute (10). Interestingly, in a rodent model of nephrotic syndrome, a component of the changed response occurs within the loop of Henle itself (58). Might increased expression or altered activity of the Na-K-2Cl transporter occur and how might it influence response? Studies of such expression and activity in animal models would be interesting, as would assessment of the effect of vasopressin antagonists on response to a loop diuretic.

In summary, patients with nephrotic syndrome have at least a pharmacokinetic plus a pharmacodynamic mechanism for decreased loop diuretic response (Table 2). Overcoming binding of diuretic to urinary albumin requires a sufficient dose to attain normal excretion rates of unbound diuretic in the urine. This amount defines the ceiling dose listed in Table 2. The diminished pharmacodynamics of response mandates frequent dosing and often addition of a thiazide diuretic. If these strategies fail and the patient is severely hypoalbuminemic, a mixture of loop diuretic and albumin can be attempted. We recommend mixing a ceiling dose with 25 g of albumin. This strategy should be conducted in a fashion such that response can be closely monitored to allow a definitive conclusion as to whether the combination was effective and should or should not be continued.

Cirrhosis. Patients with cirrhosis receive loop diuretics only if their disease is so severe that spironolactone and thiazides are not effective; even then, loop diuretics are added to a regimen of spironolactone. The pharmacokinetics and pharmacodynamics of loop diuretics have been amply quantified in patients with cirrhosis. Unless patients have diminished renal function, they deliver normal amounts of diuretic into the urine (32, 34, 52, 90, 96, 98). Thus a diminished response in patients with cirrhosis occurs by pharmacodynamic mechanisms, wherein the relationship between excretion rates of diuretic and natriuretic response is shifted downward and to the right so that the response to a maximally effective dose is substantially less than oc-
curs normally (32, 34, 52, 90, 96, 98). As was discussed above with nephrotic syndrome, the cause of this shift is unknown. It may entail increased solute reabsorption more proximal and/or more distal to the loop of Henle but also may implicate changes at the loop itself.

**Congestive heart failure.** In patients with congestive heart failure and preserved renal function, delivery of loop diuretics to the tubular fluid is normal (5, 39, 74). Historically, the possibility has been raised that patients with overt heart failure likely have gut wall edema causing diuretic malabsorption; studies have shown that the same quantity of loop diuretic is absorbed in such patients as occurs in healthy control subjects (6, 13, 92, 95). Thus malabsorption does not occur. However, the rate of absorption is slowed, particularly in patients with decompensated heart failure; therefore, the time of maximal response is delayed to 4 h or more (95). Whether this change is important clinically has not been studied.

Because the pharmacokinetics of loop diuretics are essentially normal in patients with heart failure, it is pharmacodynamic mechanisms that account for diminished response (12, 94). In fact, patients with heart failure have a pattern of response that is similar to that of patients with nephrotic syndrome or those with cirrhosis, with a shift in the relationship between diuretic excretion rate and response downward and to the right (12). In patients with mild-to-moderate heart failure, this results in a natriuretic response in these patients that is one-fourth to one-third that which occurs normally to maximally effective doses of loop diuretics (12, 94). The response in patients with more severe disease is smaller yet. The response is not improved by large doses of loop diuretic; the therapeutic strategy is to administer modest doses more frequently (Table 2).

Many patients with heart failure do not respond adequately to a loop diuretic alone even if accompanied by dietary sodium restriction. In such patients, a thiazide diuretic is often added, wherein it is not uncommon for patients to have a synergistic response with a profound diuresis (26, 27, 73, 87). The mechanism of this synergy is that discussed above in terms of the interaction of thiazide diuretics so that their blockade results in the delivery of loop diuretics into the urine and do not require large doses; rather, doses must be given more frequently (Table 2). The possible mechanisms of the altered pharmacodynamics are as were discussed previously; particularly intriguing is the possibility of altered expression and/or activity of Na-K-2Cl transporters and the potential role of vasopressin therein.

**SUMMARY**

The pharmacokinetics and clinical pharmacodynamics of loop diuretics have been well characterized in all the edematous disorders in which they are used. Such data allow more rational designs of therapeutic regimens than was possible in the past. More recent data on the receptor for loop diuretics, namely, the Na-K-2Cl transporter, offer the exciting prospect of linking changes in expression and/or function of this transporter to pharmacodynamic observations. Doing so should allow even better therapeutic strategies in the future. More specifically, questions that are highly pertinent are whether altered expression and activity of the transporter occur in models of heart failure, cirrhosis, and nephrotic syndrome and by which mechanism(s) that increase occurs. In particular, what is the role of nonosmotically released vasopressin? Is the function of the transporter altered? If so, what are the mediators of such changes and the implications therein for therapeutic strategies? Most importantly, the tools are now in hand to dissect these mechanisms and attack these common clinical conditions from a mechanism-based strategy as opposed to the more empirical approaches that have heretofore characterized this area.

This work was supported by the General Clinical Research Center (MO1 RR-00750) and by National Institutes of Health Grants R01-DK-37994 and R01-AQ-07631.

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