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Review Article

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Drug Therapy

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DIURETIC THERAPY

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DIURETIC drugs are widely used for the treatment of patients with edema. Among these drugs, loop diuretics such as furosemide are perhaps the most frequently prescribed, and their clinical pharmacology is better understood than is that of other diuretics. This review will therefore focus on this class of diuretics, but others will be discussed as well.

CLINICAL PHARMACOLOGY OF DIURETICS

Pharmacokinetics

The pharmacologic characteristics of all loop diuretics are similar. Therefore, a lack of response to adequate doses of one loop diuretic militates against the administration of another loop diuretic; instead, combinations of diuretics with different mechanisms of action should be given.

Loop diuretics block the sodium–potassium–chloride transporter, thiazide diuretics block the electroneutral sodium–chloride transporter, and amiloride and triamterene block apical sodium channels.[1-6] All diuretics except spironolactone reach these luminal transport sites through the tubular fluid; all but osmotic diuretics are actively secreted into the urine by proximal tubule cells. A high degree of protein binding (>95 percent) limits glomerular filtration,[1-6] even in patients with hypoalbuminemia. In effect, binding to serum proteins traps the diuretic in the vascular space so that it can be delivered to secretory sites of proximal tubule cells. Loop and thiazide diuretics and acetazolamide are secreted through the organic-acid pathway,[1-4] and amiloride and triamterene through the organic-base pathway.[5,6]

About 50 percent of a dose of furosemide is excreted in unchanged form into the urine[7,8]; the other 50 percent is conjugated to glucuronic acid in the kidneys.[9] Thus, in patients with renal insufficiency, the plasma half-life of furosemide is prolonged because not only urinary excretion but also renal conjugation is decreased[7,8,10-14] (Table 1). The other two loop diuretics available in the United States, bumetanide and torsemide, are largely metabolized by the liver (50 and 80 percent, respectively)[4,15-17]; therefore, their half-lives are not prolonged in patients with renal insufficiency, although renal disease impairs their delivery to the tubular fluid. In contrast, in patients with liver disease, the plasma half-lives of these drugs are prolonged, and more drug reaches the tubular fluid[7,18] (Table 1).

Although the pharmacologic characteristics of ethacrynic acid have been characterized as typical of those of loop diuretics, there are no data on its pharmacokinetics. The drug's ototoxic potential is greater than that of other loop diuretics, and it is therefore now given only to patients who have allergic reactions to other loop diuretics.

The pharmacokinetics of thiazide diuretics (Table 1) have been studied less extensively than those of loop diuretics. Some thiazide diuretics are metabolized primarily by the liver (e.g., bendroflumethiazide, polythiazide, and indapamide); others are primarily excreted in unchanged form in the urine (e.g., chlorothiazide, chlorthalidone, hydrochlorothiazide, hydroflumethiazide, and trichlormethiazide). There is little information about the influence of disease on the pharmacokinetics of these drugs.

Since amiloride is excreted by the kidneys, renal disease prolongs its plasma half-life,[19,20] whereas liver disease has little effect on the drug.[20] The pharmacokinetics of triamterene are complicated, because it is converted to an active metabolite by the liver, and the metabolite is then secreted into the tubular fluid.[7,21,22] Renal disease impairs the secretion of this metabolite into the tubular fluid.[21] The amount of metabolite that reaches the tubular fluid is also reduced in patients with liver disease, because of diminished formation of the metabolite in the liver.[22] The pharmacokinetics of spironolactone are even more complex, because it is converted to numerous active metabolites.[23,24]

In addition to the routes of metabolism, the pharmacokinetic features of diuretics that are clinically important are bioavailability and half-life. On average, the amount of an oral dose of furosemide that is absorbed is 50 percent, but it ranges from 10 to 100 percent.[7] This wide range makes it difficult to predict how much furosemide will be absorbed in an individual patient, and different doses must be tried be-

TABLE 1. PHARMACOKINETICS OF DIURETIC DRUGS.*

DIURETIC	ORAL BIOAVAILABILITY	ELIMINATION HALF-LIFE			
		NORMAL SUBJECTS	PATIENTS WITH RENAL INSUFFICIENCY	PATIENTS WITH CIRRHOSIS	PATIENTS WITH CONGESTIVE HEART FAILURE
	%	hr			
Loop					
Furosemide	10–100	1.5–2	2.8	2.5	2.7
Bumetanide	80–100	1	1.6	2.3	1.3
Torsemide	80–100	3–4	4–5	8	6
Thiazide					
Bendroflumethiazide	ND	2–5	ND	ND	ND
Chlorthalidone	64	24–55	ND	ND	ND
Chlorothiazide	30–50	1.5	ND	ND	ND
Hydrochlorothiazide	65–75	2.5	Increased	ND	ND
Hydroflumethiazide	73	6–25	ND	ND	6–28
Indapamide	93	15–25	ND	ND	ND
Polythiazide	ND	26	ND	ND	ND
Trichlormethiazide	ND	1–4	5–10	ND	ND
Distal					
Amiloride	Conflicting data	17–26	100	Negligible change	ND
Triamterene†	>80	2–5	Prolonged	No change	ND
Spironolactone	Conflicting data	1.5	No change	No change	ND
Active metabolites of spironolactone		>15	ND	ND	ND

*ND denotes not determined.

†Values are for the active metabolite.

fore the drug is judged to be ineffective. In contrast, absorption of bumetanide and torsemide is nearly complete, ranging from 80 to 100 percent (Table 1).[18,25,26] There is therefore probably less need for titration of these drugs when one is switching from an intravenous to an oral dose. The variation in the absorption of furosemide may be clinically important; patients with heart failure treated with a completely absorbed loop diuretic (torsemide) may require hospitalization less often and have a better quality of life than patients treated with furosemide.[27] The amount of loop diuretic that is absorbed is normal in patients with edema,[18,25,26,28-32] although absorption is slower than normal, particularly in those with decompensated heart failure.[32]

The plasma half-life of a diuretic determines the frequency of administration. Thiazide and distal diuretics have sufficiently long half-lives that they can be administered once or twice a day. The plasma half-lives of loop diuretics range from about one hour for bumetanide to three to four hours for torsemide; the half-life of furosemide is one and a half to two hours.[7] A truly long acting loop diuretic is not available. Once a dose of a loop diuretic has been administered, its effect dissipates before the next dose is given. During this time, the nephron avidly reabsorbs sodium, resulting in so-called rebound sodium retention,[33,34] which may be sufficient to nullify the prior natriuresis.

Pharmacodynamics

The relation between the arrival of a diuretic at its site of action (determined on the basis of the rate of urinary excretion) and the natriuretic response determines the pharmacodynamics of the drug (Fig. 1).[1,17] This relation holds for all loop diuretics, although the curve may be shifted to the right or the left.[7] This means that in any one patient, the maximal response to each loop diuretic is the same. The same is true for thiazide diuretics. The choice of an agent within either class of diuretics is governed by factors such as pharmacokinetic differences and cost.

Several pharmacodynamic features of diuretics are clinically important. There is a threshold quantity of drug that must be achieved at the site of action in order to elicit a response. The diuretic must therefore be titrated in each patient in order to determine the dose that will deliver enough drug to the site of action to reach the steep portion of the curve shown in Figure 1 (effective dose). In addition, one can determine the lowest dose that elicits a maximal response and that should therefore not be exceeded (maximal dose). In normal subjects, an intravenous dose of 40 mg of furosemide or an equivalent dose of other loop diuretics results in a maximal response, which is the excretion of 200 to 250 mmol of sodium in 3 to 4 liters of urine over a period of three to four hours.
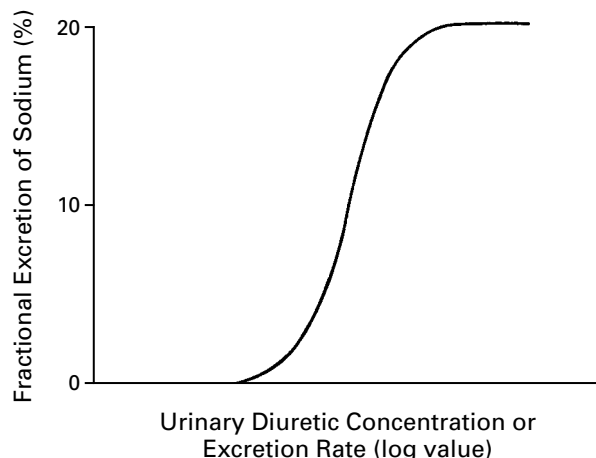
Figure 1. Pharmacodynamics of a Loop Diuretic.
The relation between the natriuretic response and the amount of diuretic reaching the site of action is represented by a sigmoid curve.

Diuretic Tolerance

There are two forms of diuretic tolerance. Short-term tolerance, so-called braking, refers to a decrease in the response to a diuretic after the first dose has been administered. This can be prevented by restoring diuretic-induced loss of volume.[35-37] Teleologically, this response appropriately protects intravascular volume. The mechanism by which short-term tolerance occurs is unclear. It may be mediated by activation of angiotensin II or the sympathetic nervous system, but neither the inhibition of angiotensin-converting enzyme nor adrenergic blockade, separately or together, consistently prevents it.[38-40]

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.[41-45] Sodium that escapes from the loop of Henle is therefore reabsorbed at more distal sites, decreasing overall diuresis. The result is long-term tolerance of the loop diuretic. 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.[46-49] This phenomenon reinforces the logic of using combinations of loop and thiazide diuretics in patients who do not have adequate responses to optimal doses of a loop diuretic.

DIURETIC THERAPY IN PATIENTS WITH EDEMA

Renal Insufficiency

A loop diuretic is the diuretic of choice in patients with renal insufficiency. Although a large dose of a thiazide will cause diuresis in patients with mild renal insufficiency, the response in patients with a creatinine clearance of less than about 50 ml per minute is poor.

In patients with a creatinine clearance of 15 ml per minute, $\frac{1}{5}$ to $\frac{1}{10}$ as much loop diuretic is secreted into the tubular fluid as in normal subjects.[7,8] Thus, a large dose must be given to attain an effective amount of diuretic in the tubular fluid (Table 2). The relation between the rate at which the diuretic is excreted and the response to it is the same in patients with renal insufficiency as it is in normal subjects.[50,51] Thus, the remaining nephrons in patients with renal insufficiency retain their responsiveness to the diuretic; the problem is getting enough drug to the site of action.

A frequent question is, What is the largest single dose of a loop diuretic that can be given to a patient with severe renal insufficiency? The maximal natriuretic response occurs with intravenous bolus doses of 160 to 200 mg of furosemide or the equivalent doses of bumetanide and torsemide,[50,52] and nothing is gained by using larger doses. Some patients may require these large doses several times a day. The maximal response is the excretion of about 20 percent of filtered sodium. In a patient with a creatinine clearance of 15 ml per minute, this means that about 25 mmol of sodium will be excreted. If the patient ingests 75 mmol of sodium per day, then the single dose causing 25 mmol to be excreted must be administered three times per day, and sodium will be retained if the intake is higher. Single intravenous bolus doses of 160 to 200 mg can occasionally cause transient tinnitus,[53,54] but this effect can be minimized by administering the dose over a period of 20 to 30 minutes.

The bioavailability of loop diuretics is the same in patients with renal insufficiency as it is in normal subjects.[25,26,28-32] Therefore, the intravenous and oral doses of bumetanide and torsemide are similar. For furosemide, the usual maximal oral dose is twice the intravenous dose (160 to 320 mg in patients with moderate renal insufficiency and 320 to 400 mg in those with severe renal insufficiency). However, the absorption of furosemide varies from one patient to another. Occasionally, a very small fraction of the dose is absorbed, and very large oral doses are therefore required. Before concluding that a patient has not had a response to furosemide and contemplating the use of dialysis to control volume, the physician should administer larger oral doses of furosemide or a maximal oral dose of either bumetanide or torsemide.

In patients who have poor responses 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.[55] There are other reasons to consider giving a continuous infusion of a loop diuretic.

TABLE 2. THERAPEUTIC REGIMENS FOR LOOP DIURETICS IN PATIENTS WITH DIMINISHED RESPONSES TO INITIAL THERAPY.

FACTOR	RENAL INSUFFICIENCY		PRESERVED RENAL FUNCTION*		
	MODERATE	SEVERE	NEPHROTIC SYNDROME	CIRRHOSIS	CONGESTIVE HEART FAILURE
Mechanism of diminished response	Impaired delivery to site of action		Diminished nephron response, binding of diuretic to urinary protein	Diminished nephron response	Diminished nephron response
Therapeutic approach	Administration of sufficiently high dose to attain effective amount of diuretic at site of action		Administration of sufficiently high dose to attain effective amount of unbound diuretic at site of action, more frequent administration of effective dose	More frequent administration of effective dose	More frequent administration of effective dose
Maximal intravenous dose (mg)†					
Furosemide	80–160	160–200	80–120	40	40–80
Bumetanide	4–8	8–10	2–3	1	1–2
Torsemide	20–50	50–100	20–50	10	10–20

*Preserved renal function is defined as a creatinine clearance of more than 75 ml per minute.

†If the maximal dose is reached without an adequate response, a thiazide diuretic should be administered as adjunctive therapy, with the dose determined according to renal function, and alternative treatment of the primary disease should be considered.

It may be easier for nursing staff to give a continuous infusion than intermittent bolus intravenous doses. In addition, with a continuous infusion, decisions about the timing of doses of an additional diuretic are simplified. Finally, by closely monitoring urinary output, one can unambiguously determine whether the added drug was beneficial.

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 (Table 3); otherwise, 6 to 20 hours is required to achieve a steady state, depending on the diuretic used. The rate of the continuous infusion is governed by the patient's renal function. If an adequate response has not occurred after the drug has been given for an hour, the loading dose should be repeated, and then the infusion rate can be increased, as shown in Table 3.

Another strategy to enhance the response to a loop diuretic is to add an oral thiazide diuretic.[56-58] Metolazone is frequently given in the United States, whereas other thiazides are given elsewhere. The pharmacologic characteristics of metolazone are similar to those of other thiazides. Some formulations of the drug are absorbed poorly and slowly, and it has a long elimination half-life (about two days).[7] Thus, metolazone accumulates over a period of about 10 days. Other thiazides have the same synergistic effects when combined with a loop diuretic.[46-49] Since the absorption of other thiazides, such as hydrochlorothiazide, is more rapid and predictable, they may be preferable to metolazone.

Because thiazide diuretics must reach the lumen of the nephron to be effective, higher doses are required in patients with renal insufficiency than in other patients.[56-58] Patients with mild-to-moderate renal insufficiency require 50 to 100 mg of hydrochlorothiazide per day; those with more severe disease require 100 to 200 mg per day. Thiazides can be administered once or twice a day.

In summary, a patient with edema caused by renal insufficiency should be given increasing doses of a loop diuretic until an effective dose is identified (Fig. 2 and Table 2). The effective dose should be given as often as needed to maintain the response, according to the patient's ability to restrict sodium intake and the duration of action of the drug. If the response is inadequate after the maximal dose has been reached, a thiazide should be added (Fig. 2). If diuresis remains inadequate, the only recourse is dialysis.

The Nephrotic Syndrome

It is often difficult to achieve a satisfactory diuresis in patients with the nephrotic syndrome. In such patients, serum albumin concentrations are frequently low, and the diffusion of diuretics into the extracel-

TABLE 3. DOSES FOR CONTINUOUS INTRAVENOUS INFUSION OF LOOP DIURETICS.

DIURETIC	INTRAVENOUS LOADING DOSE	INFUSION RATE*		
		CREATININE CLEARANCE <25 ml/min	CREATININE CLEARANCE 25–75 ml/min	CREATININE CLEARANCE >75 ml/min
	mg	mg/hr		
Furosemide	40	20 then 40	10 then 20	10
Bumetanide	1	1 then 2	0.5 then 1	0.5
Torsemide	20	10 then 20	5 then 10	5

*Before the infusion rate is increased, the loading dose should be administered again.

Renal Insufficiency

Nephrotic
Syndrome

Cirrhosis

Congestive
Heart Failure

Spironolactone,
dose titrated to 400 mg/day

Mild disease

Yes   No

Cl_{Cr}>50 ml/min

Cl_{Cr}>50 ml/min

No   Yes

Yes   No

Add   Add

HCTZ,
25–50 mg bid

Substitute

Loop diuretic

Determine effective dose

Administer as frequently as
necessary to maintain response

Add

Thiazide according to Cl_{Cr}:

<20 ml/min   20–50 ml/min   >50 ml/min

100–200 mg
of HCTZ/day

50–100 mg
of HCTZ/day

25–50 mg
of HCTZ/day

Add distal diuretic drug

If Cl_{Cr}>75 ml/min

For potassium homeostasis

For added natriuresis, if urinary excretion of sodium decreased
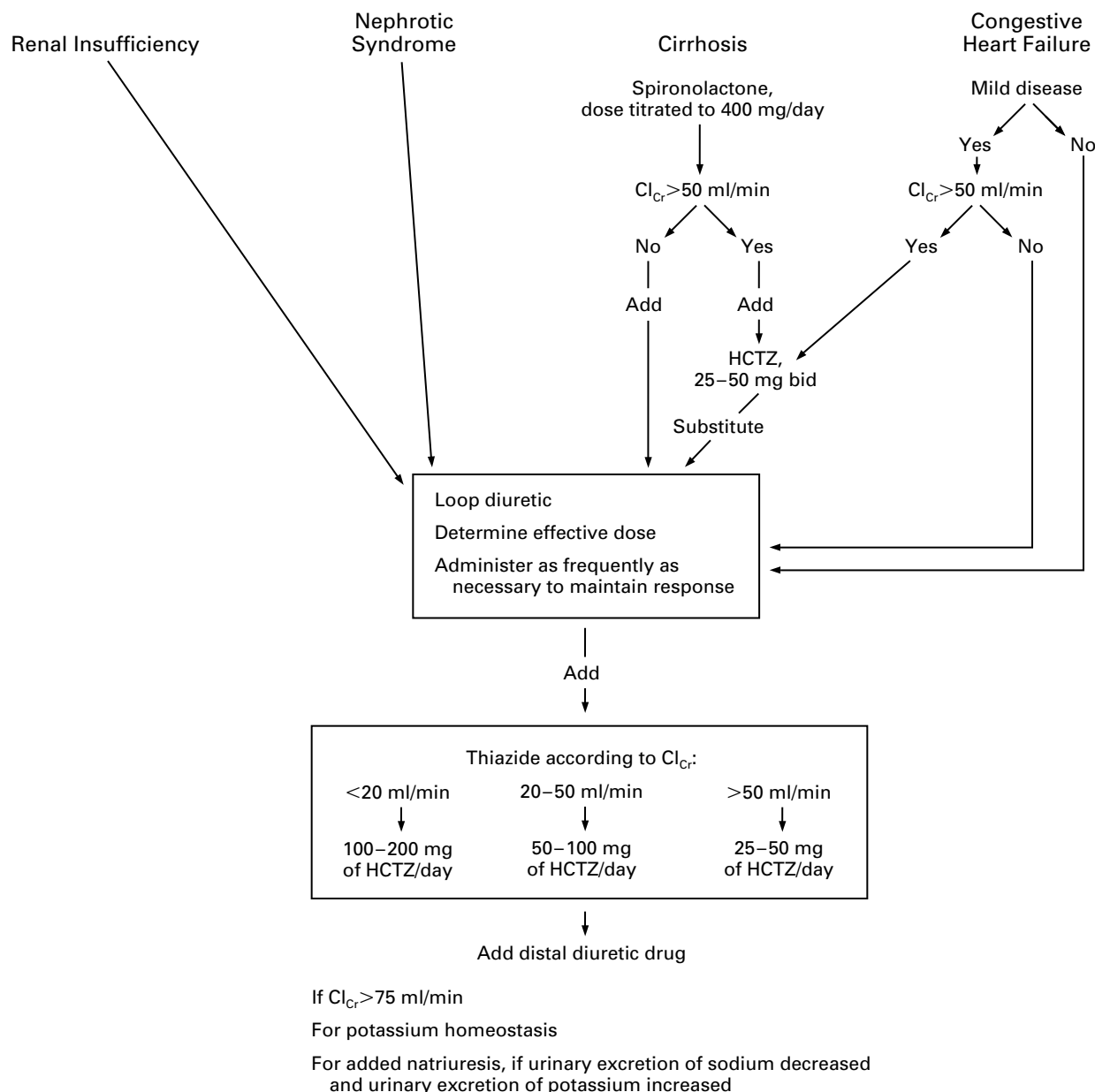and urinary excretion of potassium increased

Figure 2. Algorithm for Diuretic Therapy in Patients with Edema Caused by Renal, Hepatic, or Cardiac Disease.
Cl_{Cr} denotes creatinine clearance, HCTZ hydrochlorothiazide, and bid twice a day.

lular fluid is therefore increased. This may reduce the amount of drug delivered to renal secretory sites.[59] If so, 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.[59] However, in most patients with the nephrotic syndrome[60,61] (and in those with cirrhosis[10-14]), renal tubular secretion of furosemide is normal (unless the patient also has renal insufficiency), and combined infusions are there-

fore 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.

The diuretic response is subnormal in patients with the nephrotic syndrome, despite an adequate rate of excretion of drug into the tubular fluid. In animals, and presumably also in humans, diuretics become bound to albumin in tubular fluid, resulting in a diminished amount of unbound, active drug and a decreased diuretic response.[62-65] When urinary albumin

concentrations exceed 4 g per liter, one half to two thirds of the diuretic that reaches the tubular fluid is bound to albumin in the fluid. Consequently, doses two to three times the normal dose are needed to deliver adequate amounts of unbound, active drug to the site of action (Table 2). In addition, patients with the nephrotic syndrome may have a diminished response because of a decrease in the drug's action on cells within the loop of Henle[66] and because of increased proximal or distal reabsorption of sodium.[7] Doses must therefore be sufficient to overcome urinary binding and must be administered more frequently than in other patients, and combinations of diuretics may be necessary.[67]

In summary, several mechanisms result in a decreased diuretic response in patients with the nephrotic syndrome (Table 2). Overcoming the binding of a diuretic to albumin in urine requires the administration of a dose that is sufficiently high to result in normal concentrations of unbound diuretic in the tubular fluid. Concomitant decreases in creatinine clearance make it necessary to increase the dose even more. The diminished response in the loop of Henle mandates frequent doses and often the addition of a thiazide diuretic, the dose of which is governed by the level of renal function (Fig. 2). If these strategies fail and the patient has severe hypoalbuminemia, a trial of a mixture of a loop diuretic and albumin can be tried. Other alternatives entail more aggressive treatment of the nephrotic syndrome.

Cirrhosis

The mainstay of diuretic therapy for patients with cirrhosis who have edema is spironolactone, because secondary hyperaldosteronism is an important cause of sodium and water retention in such patients.[23] Spironolactone causes only a moderate diuresis, which is desirable because greater diuresis may compromise the intravascular volume.[68] Even if patients need additional diuretics, spironolactone should be continued (Fig. 2). Repeated large-volume paracentesis may be used to minimize the need for more potent diuretics.

The initial dose of spironolactone is usually 50 mg per day. The drug and its active metabolites have sufficiently long half-lives that once-daily administration is adequate.[23,24] Its biologic half-life is such that three to four days of treatment are needed to attain steady-state effects. The dose can be increased to as much as 400 mg per day, although doses higher than 200 mg per day are often poorly tolerated.

If maximal doses of spironolactone do not cause an adequate diuresis, a thiazide diuretic can be added, the dose being determined by the level of renal function (Fig. 2). If diuresis is still inadequate, a loop diuretic can be given instead of the thiazide while spironolactone is continued.

The pharmacokinetics and pharmacodynamics of loop diuretics have been well characterized in patients with cirrhosis. In patients with normal renal function, the diuretic concentration in the tubular fluid is normal.[10-14,18] Thus, a decreased response to a loop diuretic in a patient with cirrhosis is not due to decreased delivery of the drug to its site of action, and there is no need to administer large doses, unless the patient has concomitant renal dysfunction.

Responses to loop diuretics are decreased in patients with cirrhosis because the relation between the excretion rate and the natriuretic response (Fig. 1) is shifted downward and to the right, so that the response to a maximally effective dose is substantially less than the normal response.[10-14,18] The cause of this shift is unknown. The maximal response in a patient with severe cirrhosis may be the excretion of only 25 or 30 mmol of sodium, as compared with 200 to 250 mmol in normal subjects. This response is not increased with larger doses, but more frequent doses, given alone or with a thiazide diuretic, may be effective.

In summary, spironolactone is the mainstay of diuretic therapy for patients with cirrhosis, with the addition of a thiazide, a loop diuretic, or both as necessary (Fig. 2). Single high doses of a thiazide or loop diuretic are inappropriate; instead, moderate doses should be given several times daily, and dietary sodium restriction should be encouraged.

Congestive Heart Failure

Patients with edema caused by mild congestive heart failure should be treated initially with a thiazide diuretic (Fig. 2), but most will require a loop diuretic. In patients with normal or nearly normal renal function, the delivery of loop diuretics to the tubular fluid is normal.[69-71] The rate of absorption of loop diuretics is slowed in patients with severe heart failure; therefore, the maximal response occurs four hours or more after the dose has been administered.[32] Since the delivery of loop diuretics to the site of action is normal, patients do not need large doses of these diuretics unless they have concomitant renal insufficiency (Table 2). However, renal responsiveness to loop diuretics may be decreased.[26,72] As compared with normal subjects, patients with New York Heart Association class II or III heart failure have one fourth to one third the natriuretic response to maximally effective doses of loop diuretics,[26,72] and the response is even smaller in patients with more severe heart failure. The response is not increased by giving large doses, but it may be increased by giving moderate doses more frequently (Table 2).

If loop diuretics and dietary sodium restriction are not adequate, a thiazide diuretic should be added in a dose determined according to the patient's renal function (Fig. 2). A synergistic response can result in a profound diuresis with cardiovascular collapse.[73] In addition, through sequential blocking of nephron sites at which potassium is normally reabsorbed, sub-

stantial kaliuresis usually occurs. Patients given combinations of a thiazide and a loop diuretic should therefore be followed closely to prevent volume and potassium depletion.

In some patients, the addition of a potassium-sparing diuretic that acts at distal nephron sites may increase sodium excretion slightly. This response can be predicted by measuring urinary electrolyte excretion. If urinary sodium and potassium concentrations are both low, then a distal diuretic will not be effective because the amount of sodium delivered to the distal nephron is not sufficient for the diuretic to have an effect. If the urinary sodium concentration is low and the urinary potassium concentration is high, sodium is being exchanged for potassium distally, and the addition of a diuretic that acts on distal tubules will result in a natriuresis.[74,75]

In summary, patients with congestive heart failure have normal delivery of loop diuretics to the tubular fluid and therefore do not require large doses, but the doses should be given more often than in other patients (Table 2). Loop diuretics are the mainstay of therapy, but the addition of a thiazide and sometimes triamterene or amiloride may be helpful.

OTHER TREATMENT REGIMENS

Acetazolamide plus Loop Diuretics

Acetazolamide has been used in patients with edema, usually those with congestive heart failure refractory to high doses of loop diuretics, and in patients with metabolic alkalosis. In such patients, increased proximal tubular reabsorption of sodium results in decreased distal delivery, rendering loop diuretics ineffective.[76-79] In a study of normal subjects with increased proximal tubular reabsorption of sodium as a result of severely restricted dietary sodium intake, acetazolamide had a synergistic effect with furosemide.[80] No studies have examined the efficacy of acetazolamide in patients with severe heart failure. Acetazolamide should be given only if a thiazide and a loop diuretic are ineffective. A single 500-mg intravenous dose can be given in addition to a continuous intravenous infusion of a loop diuretic.

Dopamine

Low-dose infusions of dopamine (≤ 3 μg per kilogram of body weight per minute) may improve renal hemodynamics and increase the response to loop diuretics. However, recent reports have questioned these indications and have emphasized that even low doses of dopamine may have adverse effects.[81-83] In one study involving patients with heart failure, dopamine did not increase the response to a maximally effective dose of furosemide.[84]

Mannitol

Mannitol exerts a diuretic effect at the proximal tubule and loop of Henle.[84] It must be filtered into the urine to be effective. If it is unfiltered, as in patients with renal insufficiency, it increases vascular volume.[85,86] The risks associated with mannitol, coupled with the availability of other highly effective diuretics, relegate its use to nondiuretic indications, such as cerebral edema.

ADVERSE REACTIONS AND DRUG INTERACTIONS

Thiazide and loop diuretics may cause skin reactions and interstitial nephritis. Loop diuretics may cause ototoxicity, usually in patients receiving both very high doses and other ototoxic drugs, particularly aminoglycoside antibiotics.[87,88] Ototoxicity is usually transient. Large doses of spironolactone can cause gynecomastia.[89]

The most serious adverse effects of diuretics are abnormalities in fluid and electrolyte homeostasis.[90] Both loop and thiazide diuretics cause loss of potassium and magnesium in the urine, and when administered in combination, they may result in substantial depletion of these cations. Oral supplements will suffice in many patients, but some patients require the addition of a potassium-sparing diuretic. Loop diuretics block solute reabsorption at nephron sites that are important for concentrating the urine and thus impair urinary concentrating ability. As a result, water is excreted in excess of sodium, an effect that can help correct hyponatremia. Thiazides block solute reabsorption at nephron sites involved in the dilution of urine. Thus, the use of these agents impairs the ability to dilute urine, which entails a risk of hyponatremia, particularly in patients who drink large amounts of hypotonic fluids. More distal nephron sites also contribute to urinary dilution. Although distal diuretics have not been associated with hyponatremia, the addition of distal diuretics to thiazide diuretics increases the risk of hyponatremia.[90] Loop diuretics increase urinary calcium excretion and can be used to treat hypercalcemia; thiazide diuretics cause urinary calcium retention and may cause hypercalcemia or may be given to treat hypercalciuria.

Nonsteroidal antiinflammatory drugs diminish the response to loop and thiazide diuretics,[91] because they increase solute reabsorption at the thick ascending limb of the loop of Henle.[92] These agents can cause hyperkalemia by decreasing the secretion of renin and aldosterone.[90] Presumably, the use of a nonsteroidal antiinflammatory drug combined with a potassium-sparing diuretic would entail an increased risk of hyperkalemia. Other drugs that impair potassium excretion, such as angiotensin-converting–enzyme inhibitors and trimethoprim, would also increase the risk of hyperkalemia if they were combined with a potassium-sparing diuretic.

Organic acids such as probenecid can diminish proximal tubular secretion of thiazides and loop diuretics,[1-4] and organic bases such as trimethoprim

and histamine H_2–receptor antagonists can compete for the secretion of amiloride and triamterene,[5,6] but clinically important interactions have not been reported. Spironolactone can decrease the renal excretion of digoxin.[93]

CONCLUSIONS

An effective diuresis can be attained in most patients with renal, hepatic, or cardiac disease by using a systematic approach to diuretic therapy. The therapeutic strategies differ according to the type of disorder, because each type affects the metabolism and action of different diuretics in different ways. Diuretic therapy should therefore be tailored first to the primary disease process and then to the individual patient. With such tailoring, treatment failure should be infrequent.

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