Diuretics: Still the mainstay of treatment

David J. Wang, MD; Stephen S. Gottlieb, MD

The mainstay of treatment of acute decompensated heart failure is diuretic therapy. While there are no data showing a morbidity or mortality benefit from the use of chronic diuretic therapy, diuretics rapidly improve symptoms associated with volume overload. Thus, despite concerns that some diuretics may cause harm by neurohormonal activation, these agents continue to be the first-line treatment for patients with heart failure. There is no conclusive evidence that one means of diuresis is better than another. When administration of moderate doses of loop diuretics is not sufficient, patients can be treated with higher doses, continuous infusions, or the addition of a thiazide diuretic or aldosterone antagonist. Diuretics improve symptoms but should be used in addition to other agents that improve the long-term outcome of patients with heart failure. (Crit Care Med 2008; 36[Suppl.]:S89–S94)

KEY WORDS: acute decompensated heart failure; diuretic therapy; neurohormonal activation

The mainstay of treatment of acute decompensated heart failure is diuretic therapy. While there are no data from long-term, randomized clinical trials showing a morbidity or mortality benefit from the use of chronic diuretic therapy, it is clear that diuretics rapidly improve symptoms associated with volume overload (1). They promote natriuresis and diuresis, consequently improving symptoms, including pulmonary venous congestion and edema. At present, there are no clear benefits of any particular mode of diuretic therapy, and so any effective means of diuresis is appropriate.

Diuretic Agents

Loop Diuretics. Loop diuretics are the most commonly used diuretics in heart failure. This class of medications includes furosemide, bumetanide, torsemide, and ethacrynic acid, among others. All of the listed loop diuretics are sulfonamide derivatives except for ethacrynic acid. Loop diuretics inhibit the Na^+-K^+-$2Cl^-$ symporter in the thick ascending limb. This portion of the loop of Henle is responsible for as much as 25% of the resorption of filtered sodium. The combination of the large resorptive capacity of the thick ascending limb as well as the inability of the segments of the nephron distal to the ascending limb to reabsorb a large sodium load explains the efficacy of loop diuretics. Furthermore, the thick ascending limb plays a large role in the formation of the hypertonic medullary interstitium. Without this tonicity, the driving force of water out of the collecting duct in the presence of antidiuretic hormone is greatly reduced.

Loop diuretics inhibit the symporter from the luminal side of the nephron. Loop diuretics are highly protein bound, limiting their filtration into the glomerular lumen. The delivery and concentration of loop diuretics depend on active secretion into the lumen of the proximal tubule. Consequently, the ability of loop diuretics to function is dependent on renal plasma flow; decreased renal function slows delivery into the tubular fluid. The elimination of furosemide is dependent on renal excretion (50%) and conjugation to glucuronic acid within the kidney itself (50%). Bumetanide and torsemide are largely metabolized in the liver.

The dose-response curve of loop diuretics is sigmoidal and depends on the concentration of diuretic at the site of action in the loop of Henle (2). Clinically, this relationship is important in establishing a threshold below which there will be no diuretic action. Similarly, at the upper end of the curve, there is a ceiling dose of diuretic, above which no additional diuretic action will take place.

The absorption of oral loop diuretics is often discussed. It has been reported that the absorption of furosemide is highly variable (10% to 100%) (3–5). In contrast, absorption of both bumetanide and torsemide is reliably higher, ranging from 80% to 100% (4–6). Variability has been assessed between individuals; there are no data on variability within a given individual. Thus, the clinical significance of variability in absorption is questionable, as for any given individual the diuretic dose will need to be adjusted for an appropriate response. While it is commonly reported that edematous states can also affect the absorption of loop diuretics, data suggest that edema makes little difference in the pharmacokinetics of oral torsemide and furosemide (7). In a study of massively edematous patients, patients were randomized to oral furosemide or torsemide. Pharmacokinetic measures were made with the first dose of medication and subsequently after the patient had been adequately diuresed (decreased body weight and resolved peripheral edema). There was minimal effect of diuresis on maximal concentration or time to maximum concentration of both furosemide and torsemide.

While loop diuretics are typically used interchangeably, there are some differences in function, although their significance is not clear. Furosemide has weak carbonic anhydrase-inhibiting activity, whereas bumetanide and torsemide do not (8). Torsemide also appears to have

From the Department of Medicine, University of Maryland School of Medicine, and Baltimore Veterans Administration Medical Center, Baltimore, MD.

The authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: sgottlie@medicine.umaryland.edu

DOI: 10.1097/01.CCM.0000296272.68078.6B

Table 1. Pharmacokinetic data for select diuretics

	Oral Availability, %	Half-Life, hrs	Time to Maximum Serum Concentration, hrs
Loop diuretics			
Torsemide	80–100	3.5	~1.4
Furosemide	10–100	1.5	~2
Bumetanide	80–100	0.8	
Ethacrynic acid	~100	1	
Thiazide/thiazide-like diuretics			
Hydrochlorothiazide	70	~2.5	
Metolazone	65	Variable (see text)	
Chlorothiazide	9–56	~1.5	

Data from References 5, 7, 8, and 62.

aldosterone antagonistic effects in the rat kidney (9), although whether this may contribute to outcomes remains to be seen. Two recent open-label studies favored torsemide over furosemide, but these findings need to be verified in a blinded study (10, 11).

Loop Diuretic Ototoxicity. A common concern with the use of high-dose loop diuretics is ototoxicity. The levels at which furosemide becomes ototoxic are not well established; some authors report a serum concentration of >50 μg/mL as being ototoxic (12), while others report a concentration of >100 μg/mL in the face of receiving ototoxic agents (i.e., aminoglycosides) as being ototoxic (13). Rupp (14) measured plasma concentrations of furosemide in patients with renal failure and reported that an infusion rate of 4 mg/min (for intravenous boluses) would not cause levels >40 μg/mL. No patients in that study reported hearing loss. Some studies, however, reported transitory hearing loss with infusion rates of 15–25 mg/min (15, 16), and these authors recommended that infusion rates not exceed 4–6 mg/min. Similar data with other loop diuretics are lacking.

These results, while valid for relatively short infusions, do not address longer term continuous loop diuretic infusion. Dormans and colleagues (19), in studies of continuous furosemide infusion, reported one patient with a creatinine clearance of 14 mL/min/m^2 who, upon receiving 83 mg/hr (total 24-hr dose 2000 mg), had a serum level of 119 μg/mL and had transient hearing loss. In the bolus group of this study (doses ranging from 250 to 2000 mg, mean dose 690 mg), seven patients had plasma concentrations of furosemide >100 μg/mL. Five patients had ototoxicity, although the authors did not explicitly specify that the patients with ototoxicity were from this group of seven patients. In contrast, van Meyel et al. (20) claimed that in patients with a creatinine clearance rate >20 mL/min/m^2, an infusion rate of up to 160 mg/hr (a dose generally accepted to be excessive) was safe. Plasma levels ranged from 26.6 to 134.6 μg/mL (mean 71.1 μg/mL), and only one patient had a level >100 μg/mL. That patient did not have any auditory symptoms. While the data show much variability, the studies suggest that ototoxicity appears to be of concern only with extremely high doses.

Thiazides. Thiazide and thiazide-like diuretics work at the distal convoluted tubules by inhibiting the luminal Na^+-Cl^- symporter. The efficacy of diuretics acting at the distal convoluted tubule is limited, however, as only 10% of the filtered load of Na^+ reaches the distal convoluted tubule; 90% of the filtered load is reabsorbed before reaching it. As with the Na^+-K^+-$2Cl^-$ symporter, the Na^+-Cl^- symporter is found on the luminal side of the tubule. Thiazide diuretics are therefore not effective at glomerular filtration rates <30 mL/min. Thiazide diuretics increase excretion of K^+ by the same mechanism as loop diuretics. However, they do so to a greater degree than loop diuretics for a comparable amount of diuresis (21).

Aldosterone Antagonists. Aldosterone antagonists, such as spironolactone and eplerenone, block the mineralocorticoid receptor (8). The late distal tubule and collecting duct cells have cytosolic mineralocorticoid receptors with a high affinity for aldosterone. The aldosterone-receptor complexes increase the synthesis of multiple proteins, including aldosterone-induced proteins. It is proposed that among the effects of these proteins is the activation of Na^+ channels along the luminal membrane and an increase in the activity of the Na^+-K^- pump along the basolateral membrane. While the details remain to be elucidated, the net effect of aldosterone is to promote absorption of Na^+ from the tubular lumen and secretion of H^+ and K^+ into the tubular lumen. Aldosterone antagonists bind the mineralocorticoid receptors but subsequently prevent the production of aldosterone-induced proteins. Consequently, sodium retention and potassium excretion are reduced. The resultant retention of potassium can produce clinically important hyperkalemia (22, 23). Low doses of spironolactone (e.g., 25–50 mg) were shown to reduce morbidity and mortality in patients with New York Heart Association class III–IV heart failure in the RALES trial (24). There does not appear to be significant diuretic effect at these low doses; rather, it is thought that the benefit in heart failure is due to antagonism of direct myocardial effects of aldosterone.

Choice of Drug (Table 1). Loop diuretics are the most commonly used class of diuretics for the management of volume overload in heart failure. While there are no data to show improvement in mortality, diuretics have been shown to provide symptomatic relief and improve symptoms (1, 25–31). Initial treatment of a patient requiring diuresis can be with a loop diuretic at a dose higher than the patient's chronic dose. While the reflex in the acute setting is to give this initial dose intravenously, there is no clear evidence that intravenous dosing is superior to an oral dose in patients not requiring immediate diuresis. The benefit to intravenous dosing is rapidity in onset of action. In patients on chronic loop diuretics, a dose equivalent to double their chronic dose is a reasonable initial dose. In loop diuretic naïve patients, a reasonable starting dose would be furosemide 20–40 mg intravenously or 40–80 mg orally. Alternatively, an intravenous or oral dose of bumetanide 0.5–1 mg or torsemide 5–10 mg can be used. Patients with compromised renal function and heart failure will require higher doses, and doses higher than previously published ceiling doses may be necessary (32). In these patients, the asymptotic portion of the loop diuretic dose-response curve may be much higher than what is conventionally perceived. Patients should be routinely assessed for adequate response, and if an adequate diuretic response is not seen within 2–3 hrs for an intravenous dose or 4–6 hrs for a oral dose, additional diuretic should be given at a higher dose.

This strategy will be effective in most patients, but some patients may initially

diurese effectively yet not reach a clinically therapeutic end point. While this can often be combated by a simple increase in the diuretic dose, occasionally patients may become resistant to even increasing doses of diuretics.

Diuretic Braking/Diuretic Resistance

The response to administration of a diuretic is a period of diuresis and natriuresis. Following this period, after the diuretic is no longer in the therapeutic range, the body's natural response is to then retain sodium to maintain a net neutral sodium balance (33, 34). Indeed, in patients given a high-sodium diet (270 mmol/day), net sodium balance over a 24-hr period remained neutral (34). This naturally occurring response has been termed by some authors *postdiuretic sodium retention*. Similarly, it has been shown that replacing sodium loses during a period of natriuresis abolishes this increased sodium retention (33).

Another phenomenon that has been described is that of decreased effectiveness of a diuretic following the initial dose. This phenomenon has been termed *diuretic braking* and is related to postdiuretic sodium retention in that it is a natural response by the body to maintain sodium and volume homeostasis. In patients fed a high-salt diet, there was no difference in sodium excretion between the first and third doses of bolus furosemide; in patients on a low-sodium diet, however, there was a marked decrease in urinary sodium excretion. Importantly, however, despite this decrease in urinary sodium excretion, it was only in the low-salt diet group that a negative sodium balance was maintained over the duration of the study; the high-salt diet group was able to replace all diuretic-induced sodium losses during the period of postdiuretic sodium retention (34). While it is clear that this decrease in response to diuretic is mediated by sodium loss and the body's attempt to maintain sodium homeostasis, it is thought that there is a volume component as well. Physiologically, this is a reasonable theory. Experimental models, however, are confounded in that adequate volume replacement is given with sodium (33, 35, 36).

Over the longer term, delivery of high-sodium loads to the distal convoluted tubule can result in adaptation and increased resorption. There is increased ability to transport Na^+ from the tubule lumen in animal models of chronic high-sodium loads (5, 37–39). The increase in Na transport in these cells has also been demonstrated in humans (40). Loon et al. (40) measured baseline increases in sodium excretion in patients who had not recently been on diuretics. Patients were treated with placebo, furosemide (40 mg twice daily), or chlorothiazide (500 mg twice daily) for 1 month in a crossover fashion. Following 1 month of treatment, patients were given furosemide (10 mg intravenous bolus, followed by 15 mg/hr for 3 hrs). In addition, a bolus of chlorothiazide (500 mg intravenously) was given after 150 mins of furosemide infusion. The authors found a response to the furosemide infusion in all three groups. However, the increase in the chlorothiazide and furosemide groups was lower than in the placebo group. After the addition of chlorothiazide, the group that had been on furosemide showed a further increase in fractional excretion of sodium.

Other proposed mechanisms for decreased diuretic effectiveness include increased renal nerve activity, activation of the renin-angiotensin-aldosterone pathway, and hypertrophy of distal tubule epithelial cells. Evidence on the role of renal nerves in the control of renal blood flow, glomerular filtration rate, and sodium retention is conflicting. While stimulation of renal nerves by volume depletion results in increased sodium retention mediated by release of renin, renal denervation has not been demonstrated to affect this response (41–44). The importance of the renin-angiotensin-aldosterone pathway is clear, however. In animal models, hypertrophy of the distal convoluted tubule and collecting duct has been demonstrated and is thought to contribute to the increased distal sodium handling (37, 38, 45–47).

Understanding these mechanisms to decreased diuretic effectiveness gives rise to additional therapeutic options.

Continuous Infusions. There have been many uncontrolled or small reports related to the efficacy of continuous infusions of loop diuretics. Comparison with bolus dosing is difficult, as natriuresis or aquaresis could be increased in either group by increasing the dose used. Thus, while these studies support the efficacy of continuous infusions, they do not prove superiority to appropriate bolus administration.

Some studies of continuous infusions of bumetanide or furosemide have demonstrated higher sodium excretion and urine output compared with boluses at medium to high doses (bumetanide, 12 mg over 12 hrs; furosemide, 180–3840 mg over 24 hrs) (17–19, 48). However, Aaser et al. (49) did not find any difference in urine output or sodium excretion at a lower dose of furosemide (mean 145 mg, range 80–320 mg). Likewise, Kramer et al. (18) found equivalent sodium excretion and urine output in a comparison of bolus torsemide with continuous infusion (total 24-hr dose, 100 mg). A proposed benefit to continuous infusion of loop diuretics is the prevention of potentially detrimental neurohormonal activation with diuretic administration (50). This does not appear to be the case, however. In a study by Aaser et al. (49), plasma concentrations of antidiuretic hormone, norepinephrine, epinephrine, and neuropeptide Y were equivalent in patients treated with a 24-hr continuous infusion or with bolus administration of furosemide.

Ferguson et al. (51) compared the effects of two 3.25-mg bumetanide boluses, given 6 hrs apart, with that of a 0.5-mg bumetanide bolus followed by continuous infusion of 0.5 mg of bumetanide per hour for 12 hrs in a randomized crossover study of eight patients with New York Heart Association class II–III heart failure. At 6 hrs, patients in both groups received a 1-hr 0.45% saline infusion totaling the lesser of one half total urinary volume or 1000 mL. This study is revealing in that sodium excretion up to the point of the sodium load was essentially the same (228 $\pm$ 77 mEq for the infusion group compared with 206 $\pm$ 100 mEq for the bolus group). However, the continuous infusion of bumetanide allowed 86% $\pm$ 15% of the sodium load to be excreted compared with only 29% $\pm$ 30% with the bolus dosing ($p = .0005$). This is consistent with what is known about bumetanide pharmacokinetics; the timing of the sodium load was after the peak effect of bumetanide. This supports the theory that a continuous infusion of loop diuretic can combat the postdiuretic sodium retention. Unfortunately, there are no studies on the diuretic and natriuretic course after a chronic diuretic infusion is discontinued.

The need for appropriate dosing and the efficacy of close monitoring and frequent adjustments of either bolus or continuous infusions were demonstrated by Schuller et al. (51a) in a randomized trial of medical intensive care unit patients with pulmonary edema. Patients were randomized to treatment with a contin-

uous infusion of furosemide or bolus dosing of furosemide. All patients received a 40-mg intravenous bolus. Patients in the continuous infusion group were then started on a drip at 0.1 mg/kg/hr, which was then titrated to achieve diuresis of 1 mL/kg/hr. The infusion rate was increased hourly by 0.1 mg/kg to a maximal rate of 0.75 mg/kg/hr. The bolus group was reassessed frequently; if the net hourly diuresis was <1 mL/kg/hr, an additional bolus dose, double the previous dose, was given within 1–2 hrs. If the net hourly diuresis was adequate (>1 mL/kg/hr), the previous dose was repeated within 4–6 hrs. Patients were diuresed to what the authors termed a *therapeutic end point*. The authors found no differences in the time to reach the therapeutic end point or in the total amount of diuretic used. Both groups had diuresed ~1.5 L at 6 hrs, and at 24 hrs, the bolus group had diuresed approximately 4 L and the continuous infusion group ~5.5 L (*p* not significant). The amount of furosemide was similar in both groups, ~150 mg administered at 6 hrs, and, at 24 hrs, ~400 mg in the bolus group and ~450 mg in the continuous infusion group (*p* not significant).

Continuous-infusion protocols are highly varied. Doses for bumetanide range from 0.5- to 1-mg loading doses and 0.5 to 1 mg/hr (48, 51). For furosemide, infusion protocols have ranged from 5 to 40 mg/hr, with a loading dose up to 100 mg sometimes given (17–20, 49, 52). It has been recommended that a loading dose be given in order to reduce the time to therapeutic drug concentrations (3). While titration up to 160 mg/hr has been reported (20), few people believe that such high infusion rates are safe or appropriate.

It is difficult to draw any conclusions about outcomes based on the small, heterogeneous studies done with infusion vs. bolus diuretics. None of the studies rigorously examined the period following diuretic infusion, and so true comparisons regarding postdiuretic sodium retention are limited. There currently is no evidence that continuous infusion of loop diuretics prevents postdiuretic sodium retention, nor is there any particular reason to think that this would be the case. Several of the studies comparing bolus with continuous infusion (17–19) discuss "diuretic efficiency" (sodium excretion/diuretic excretion), although the clinical importance of this measure is unclear. It does appear that the effectiveness of loop diuretics is largely based on dose and sodium intake.

Table 2. Doses for continuous infusion of loop diuretics

	Intravenous Bolus, mg	Initial Infusion Rate, mg/hr
Furosemide	40	10–40
Bumetanide	1	0.5–1
Torsemide	20	5–20

Doses based on Reference 3.

Thus, the first step in treating diuretic resistance is to ensure that Na^+ intake is minimized (≤2 g/day) and that the diuretic dose is sufficient. To the extent that a higher dose of diuretic may be given safely with continuous infusion, it may be a better option when extremely large doses are desired. Infusion rates for patients with normal renal function can be on the low end of the infusion range, while patients with renal dysfunction will require higher infusion rates (Table 2). For patients who are already receiving bolus doses of diuretics, the previous dose can be converted to an hourly rate and then increased. Most important, patients should be reassessed regularly and the infusion rate increased or decreased as appropriate. An additional bolus dose can be given with each increase. There is no optimal dosing regimen; adjustments will need to be made for each individual patient.

Dual Diuretic Therapy. Given the ability of the distal convoluted tubule to increase its sodium resorption capacity, another approach to combating diuretic resistance is the addition of a second diuretic agent, such as a thiazide or thiazide-like diuretic (53–58). Hydrochlorothiazide and metolazone, as well as bendrofluazide, have been used, and there is no evidence that one is superior (59). It has been suggested that the diuretic affecting the distal tubule be given before the loop diuretic in order to fully block the distal convoluted tubule (39, 60). Metolazone, however, may have a half-life of as long as 2 days, making this inconvenient dosing regimen unnecessary. For other thiazide diuretics, no benefit of staggered dosing has been demonstrated. This dosing is also clearly not needed when oral loop diuretics are used.

High doses of thiazide/thiazide-like diuretics (metolazone 10 mg, hydrochlorothiazide 50–100 mg) have been recommended previously. Since these doses have been associated with reports of excessive electrolyte and fluid depletion (53), it is advisable to start a lower dose (hydrochlorothiazide 12.5–25 mg or metolazone 2.5–5 mg) when possible. Regardless of the dose chosen, patients' electrolytes should be closely monitored during dual diuretic therapy.

While the effectiveness of a thiazide diuretic in combination with a loop diuretic is well described, the diuretic effect of low-dose aldosterone antagonism has been studied less. High doses of spironolactone (100–200 mg daily) are frequently used in ascites and volume overload related to liver cirrhosis. The addition of 100 mg of spironolactone to patients with poor response to bumetanide results in increased natriuresis and diuresis (61, 62). In those patients not prone to hyperkalemia, spironolactone at doses higher than the 25–50 mg used in the RALES trial may be an alternative.

CONCLUSIONS

Administration of loop diuretics in low to moderate doses, given either orally or as intravenous boluses, remains the cornerstone of treating the congestive symptoms in heart failure. The dose of diuretic must be in the therapeutic range (above the threshold). Patients exhibiting decreased responsiveness to diuretics can be treated with higher doses, continuous infusions, or the addition of a thiazide diuretic or aldosterone antagonist.

REFERENCES

1. Faris R, Flather MD, Purcell H, et al: Diuretics for heart failure. *Cochrane Database Syst Rev* 2006; (1):CD003838
2. Brater DC: Diuretic pharmacokinetics and pharmacodynamics. *In:* The In Vivo Study of Drug Action: Principles and Applications of Kinetic-Dynamic Modelling. Boxtel CJv, Holford NHG, Danhof M (Eds). Amsterdam, Elsevier, 1992, pp 253–275
3. Brater DC: Diuretic therapy. *N Engl J Med* 1998; 339:387–395
4. Gehr TW, Rudy DW, Matzke GR, et al: The pharmacokinetics of intravenous and oral torsemide in patients with chronic renal insufficiency. *Clin Pharmacol Ther* 1994; 56: 31–38
5. Vargo DL, Kramer WG, Black PK, et al: Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. *Clin Pharmacol Ther* 1995; 57:601–609
6. Schwartz S, Brater DC, Pound D, et al: Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide in patients with cirrhosis. *Clin Pharmacol Ther* 1993; 54:90–97

7. Gottlieb SS, Khatta M, Wentworth D, et al: The effects of diuresis on the pharmacokinetics of the loop diuretics furosemide and torsemide in patients with heart failure. *Am J Med* 1998; 104:533–538
8. Jackson EK. Diuretics. *In:* Goodman and Gilman's the Pharmacological Basis of Therapeutics. Brunton LL (Ed). New York, McGraw-Hill, 2006, pp 737–769
9. Uchida T, Yamanaga K, Nishikawa M, et al: Anti-aldosteronergic effect of torasemide. *Eur J Pharmacol* 1991; 205:145–150
10. Murray MD, Deer MM, Ferguson JA, et al: Open-label randomized trial of torsemide compared with furosemide therapy for patients with heart failure. *Am J Med* 2001; 111:513–520
11. Cosin J, Diez J: Torasemide in chronic heart failure: Results of the TORIC study. *Eur J Heart Fail* 2002; 4:507–513
12. Beermann B, Dalen E, Lindstrom B, et al: On the fate of furosemide in man. *Eur J Clin Pharmacol* 1975; 9:51–61
13. Brown CB, Ogg CS, Cameron JS, et al: High dose frusemide in acute reversible intrinsic renal failure: A preliminary communication. *Scott Med J* 1974; 19(Suppl 1):35–39
14. Rupp W: Pharmacokinetics and pharmacodynamics of Lasix. *Scott Med J* 1974; 19(Suppl 1):5–13
15. Vargish T, Benjamin R, Shenkman L: Deafness from furosemide. *Ann Intern Med* 1970; 72:761
16. Heidland A, Hennemann H, Rockel A, et al: Clinical pharmacology of high-dose furosemide in terminal renal insufficiency. *Bratisl Lek Listy* 1971; 56:620–629
17. Lahav M, Regev A, Ra'anani P, et al: Intermittent administration of furosemide vs continuous infusion preceded by a loading dose for congestive heart failure. *Chest* 1992; 102: 725–731
18. Kramer WG, Smith WB, Ferguson J, et al: Pharmacodynamics of torsemide administered as an intravenous injection and as a continuous infusion to patients with congestive heart failure. *J Clin Pharmacol* 1996; 36:265–270
19. Dormans TP, van Meyel JJ, Gerlag PG, et al: Diuretic efficacy of high dose furosemide in severe heart failure: Bolus injection versus continuous infusion. *J Am Coll Cardiol* 1996; 28:376–382
20. van Meyel JJ, Smits P, Dormans T, et al: Continuous infusion of furosemide in the treatment of patients with congestive heart failure and diuretic resistance. *J Intern Med* 1994; 235:329–334
21. Morgan DB, Davidson C: Hypokalaemia and diuretics: An analysis of publications. *BMJ* 1980; 280:905–908
22. Shah KB, Rao K, Sawyer R, et al: The adequacy of laboratory monitoring in patients treated with spironolactone for congestive heart failure. *J Am Coll Cardiol* 2005; 46:845–849
23. Juurlink DN, Mamdani MM, Lee DS, et al: Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004; 351:543–551
24. Pitt B, Zannad F, Remme WJ, et al: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; 341:709–717
25. Wilson JR, Reichek N, Dunkman WB, et al: Effect of diuresis on the performance of the failing left ventricle in man. *Am J Med* 1981; 70:234–239
26. Robson AO, Kerr DN, Ashcroft R, et al: The diuretic response to frusemide. *Lancet* 1964; 13:1085–1088
27. Richardson A, Bayliss J, Scriven AJ, et al: Double-blind comparison of captopril alone against frusemide plus amiloride in mild heart failure. *Lancet* 1987; 2:709–711
28. Patterson JH, Adams KF Jr, Applefeld MM, et al: Oral torsemide in patients with chronic congestive heart failure: Effects on body weight, edema, and electrolyte excretion. Torsemide Investigators Group. *Pharmacotherapy* 1994; 14:514–521
29. Parker JO: The effects of oral ibopamine in patients with mild heart failure—A double blind placebo controlled comparison to furosemide. The Ibopamine Study Group. *Int J Cardiol* 1993; 40:221–227
30. Bayliss J, Norell M, Canepa-Anson R, et al: Untreated heart failure: Clinical and neuroendocrine effects of introducing diuretics. *Br Heart J* 1987; 57:17–22
31. Anand IS, Kalra GS, Harris P, et al: Diuretics as initial and sole treatment in chronic cardiac failure. *Cardioscience* 1991; 2:273–278
32. Ellison DH: Diuretic resistance: physiology and therapeutics. *Semin Nephrol* 1999; 19: 581–597
33. Almeshari K, Ahlstrom NG, Capraro FE, et al: A volume-independent component to postdiuretic sodium retention in humans. *J Am Soc Nephrol* 1993; 3:1878–1883
34. Wilcox CS, Mitch WE, Kelly RA, et al: Response of the kidney to furosemide. I. Effects of salt intake and renal compensation. *J Lab Clin Med* 1983; 102:450–458
35. Hammarlund MM, Odlind B, Paalzow LK: Acute tolerance to furosemide diuresis in humans: Pharmacokinetic-pharmacodynamic modeling. *J Pharmacol Exp Ther* 1985; 233: 447–453
36. Wakelkamp M, Alvan G, Gabrielsson J, et al: Pharmacodynamic modeling of furosemide tolerance after multiple intravenous administration. *Clin Pharmacol Ther* 1996; 60:75–88
37. Ellison DH, Velazquez H, Wright FS: Adaptation of the distal convoluted tubule of the rat: Structural and functional effects of dietary salt intake and chronic diuretic infusion. *J Clin Invest* 1989; 83:113–126
38. Kaissling B, Stanton BA: Adaptation of distal tubule and collecting duct to increased sodium delivery. I. Ultrastructure. *Am J Physiol* 1988; 255:F1256–F1268
39. Ellison DH: The physiologic basis of diuretic synergism: Its role in treating diuretic resistance. *Ann Intern Med* 1991; 114:886–894
40. Loon NR, Wilcox CS, Unwin RJ: Mechanism of impaired natriuretic response to furosemide during prolonged therapy. *Kidney Int* 1989; 36:682–689
41. DiBona GF, Sawin LL: Renal nerve activity in conscious rats during volume expansion and depletion. *Am J Physiol* 1985; 248:F15–F23
42. Petersen JS, DiBona GF: Effects of renal denervation on sodium balance and renal function during chronic furosemide administration in rats. *J Pharmacol Exp Ther* 1992; 262:1103–1109
43. Mizelle HL, Hall JE, Montani JP: Role of renal nerves in control of sodium excretion in chronic congestive heart failure. *Am J Physiol* 1989; 256:F1084–F1093
44. Kon V, Yared A, Ichikawa I: Role of renal sympathetic nerves in mediating hypoperfusion of renal cortical microcirculation in experimental congestive heart failure and acute extracellular fluid volume depletion. *J Clin Invest* 1985; 76:1913–1920
45. Stanton BA, Kaissling B: Adaptation of distal tubule and collecting duct to increased Na delivery. II. Na^+ and K^+ transport. *Am J Physiol* 1988; 255:F1269–F1275
46. Scherzer P, Wald H, Popovtzer MM: Enhanced glomerular filtration and Na^+-K^+-ATPase with furosemide administration. *Am J Physiol* 1987; 252:F910–F915
47. Mernissi GE, Doucet A: Stimulation of Na-K-ATPase in the rat collecting tubule by two diuretics: Furosemide and amiloride. *Am J Physiol* 1984; 247:F485–F490
48. Rudy DW, Voelker JR, Greene PK, et al: Loop diuretics for chronic renal insufficiency: A continuous infusion is more efficacious than bolus therapy. *Ann Intern Med* 1991; 115: 360–366
49. Aaser E, Gullestad L, Tollofsrud S, et al: Effect of bolus injection versus continuous infusion of furosemide on diuresis and neurohormonal activation in patients with severe congestive heart failure. *Scand J Clin Lab Invest* 1997; 57:361–367
50. Francis GS, Siegel RM, Goldsmith SR, et al: Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure: Activation of the neurohumoral axis. *Ann Intern Med* 1985; 103:1–6
51. Ferguson JA, Sundblad KJ, Becker PK, et al: Role of duration of diuretic effect in preventing sodium retention. *Clin Pharmacol Ther* 1997; 62:203–208

51a. Schuller D, Lynch JP, Fine D: Protocol-guided diuretic management: Comparison of furosemide by continuous infusion and intermittent bolus. *Crit Care Med* 1997; 25: 1969–1975

52. Howard PA, Dunn MI: Aggressive diuresis for severe heart failure in the elderly. *Chest* 2001; 119:807–810
53. Oster JR, Epstein M, Smoller S: Combined therapy with thiazide-type and loop diuretic agents for resistant sodium retention. *Ann Intern Med* 1983; 99:405–406
54. Wollam GL, Tarazi RC, Bravo EL, et al: Di-

uretic potency of combined hydrochlorothiazide and furosemide therapy in patients with azotemia. *Am J Med* 1982; 72:929–938
55. Fliser D, Schroter M, Neubeck M, et al: Co-administration of thiazides increases the efficacy of loop diuretics even in patients with advanced renal failure. *Kidney Int* 1994; 46: 482–488
56. Knauf H, Mutschler E: Sequential nephron blockade breaks resistance to diuretics in edematous states. *J Cardiovasc Pharmacol* 1997; 29:367–372
57. Knauf H, Mutschler E: Diuretic effectiveness of hydrochlorothiazide and furosemide alone and in combination in chronic renal failure. *J Cardiovasc Pharmacol* 1995; 26:394–400
58. Kiyingi A, Field MJ, Pawsey CC, et al: Metolazone in treatment of severe refractory congestive cardiac failure. *Lancet* 1990; 335: 29–31
59. Channer KS, McLean KA, Lawson-Matthew P, et al: Combination diuretic treatment in severe heart failure: A randomised controlled trial. *Br Heart J* 1994; 71:146–150
60. Steinmuller ST, Puschett JB: Effects of metolazone in man: Comparison with chlorothiazide. *Kidney Int* 1972; 1:169–181
61. van Vliet AA, Donker AJ, Nauta JJ, et al: Spironolactone in congestive heart failure refractory to high-dose loop diuretic and low-dose angiotensin-converting enzyme inhibitor. *Am J Cardiol* 1993; 71:21A–28A
62. Shankar SS, Brater DC: Loop diuretics: from the Na-K-2Cl transporter to clinical use. *Am J Physiol Renal Physiol* 2003; 284: F11–F21