

Diuretics in congestive heart failure

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Introduction

Diuretics (see Table 1.1 for a physiological classification) remain an important part of the medical therapy for patients with congestive heart failure (CHF). They control fluid retention and rapidly relieve the congestive symptoms of heart failure (HF). The American College of Cardiology/American Heart Association assigned them a class I indication in patients with symptomatic heart failure who have evidence of fluid retention [1]. Indeed, diuretics are the only drugs used in the treatment of HF that control fluid retention and that rapidly produce symptomatic benefits in patients with pulmonary and/or peripheral edema. Because diuretics alone are unable to effect clinical stability in patients with HF, they should always be used in combination with an angiotensin converting enzyme (ACE) inhibitor and a β -blocker. Despite the widespread use of diuretics, there have yet to be large randomized clinical trials that evaluate their effects on mortality or morbidity (with the exception of aldosterone antagonists, which will be considered separately). Furthermore, care must be exercised in the use of diuretics as both hypovolemia secondary to over-diuresis and hypervolemia secondary to under-diuresis have profound effects on cardiac pathophysiology. Therefore, questions remain about appropriate diuretic use [2]. This chapter will explore the effects, pharmacokinetics, and clinical utility of diuretics in patients with congestive heart failure.

Vascular effects of diuretics

Diuretics are believed to improve symptoms of congestion by several mechanisms. Loop diuretics induce hemodynamic changes that appear to be independent of their diuretic effect. They act as venodilators and, when given intravenously, reduce right atrial and pulmonary capillary wedge pressure within minutes [3,4]. This initial improvement in hemodynamics may be secondary to the release of vasodilatory prostaglandins [5]. Studies in animals and humans have demonstrated that the loop diuretic furosemide directly dilates veins; this effect can be inhibited by indomethacin, suggesting that local prostaglandins may contribute to its vasodilatory properties [6]. In the setting of acute pulmonary edema from myocardial infarction, Dikshit *et al.* measured an increase in venous capacitance and decreasing pulmonary capillary wedge pressure within 15 min of furosemide infusion, while the peak diuretic effect was at 30 min [7]. Numerous other investigators have found similar results [8]. Other loop diuretics, such as bumetanide, have been reported to have differing effects [9]. There have also been reports of an arteriolar vasoconstrictor response to diuretics when given to patients with advanced heart failure [10]. A rise in plasma renin and norepinephrine levels leads to arteriolar vasoconstriction, resulting in reduction in cardiac output and increase in pulmonary capillary wedge pressure. These hemodynamic changes reverse over the next several hours, likely due to the diuresis. The vasoconstrictor response to loop

Table 1.1 Physiological classification of diuretic drugs.

<i>Proximal diuretics</i>	<i>Loop diuretics</i>	<i>DCT diuretics</i>	<i>CD diuretics</i>	<i>Aquaretics</i>
Carbonic anhydrase inhibitors Acetazolamide	Na–K–2Cl (NKCC2) inhibitors Furosemide Bumetanide Torsemide Ethacrynic acid	Na–Cl (NCCT) inhibitors Hydrochlorothiazide Metolazone Chlorthalidone Indapamide* Many others	Na channel blockers (ENaC inhibitors) Amiloride Triameterene Aldosterone antagonists Spironolactone Eplerenone	Vasopressin receptor antagonists Tolvaptan Lixivaptan

*Indapamide may have other actions as well.

DCT: Distal convoluted tubule. CD: Collecting duct. Aquaretics are pending approval for clinical use.

diuretic administration occurs more commonly in patients treated chronically with loop diuretics [10]. In this situation, chronic stimulation of the renal renin/angiotensin/aldosterone axis may prime the vascular system to vasoconstriction. It is likely that different diuretics have complex and multifactorial actions on the vascular system.

Neurohormonal effects of diuretics

Diuretic drugs stimulate the renin–angiotensin–aldosterone (RAA) axis via several mechanisms. Loop diuretics stimulate renin secretion by inhibiting NaCl uptake into macula densa cells. Sodium/chloride uptake via the loop diuretic-sensitive $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ cotransport system is a central component of the macula densa-mediated pathway for renin secretion [11]. Blocking $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ uptake at the macula densa stimulates renin secretion directly, leading to a volume-independent increase in angiotensin II and aldosterone secretion. Loop diuretics also stimulate renal production of prostacyclin, which further enhances renin secretion. All diuretics can also increase renin secretion by contracting the extracellular fluid (ECF) volume, thereby stimulating the vascular mechanism of renin secretion. ECF volume contraction also inhibits the secretion of atrial natriuretic peptide. Among its other effects, atrial natriuretic peptide inhibits renin release. Interestingly, the combination of aggressive vasodilator therapy and diuresis to achieve improved hemodynamic parameters in turn led to diminished neurohormonal activation [12].

Clinical use of diuretics in congestive heart failure

The mortality benefit of ACE inhibitors (or angiotensin receptor blockers) and β -adrenergic blockers in patients with systolic dysfunction is well documented (see Chapter 4). However, all recent heart failure mortality trials have included patients who were treated with diuretics as diuretics remain an important part of heart failure management. According to the SOLVD (Studies of Left Ventricular Dysfunction) registry, diuretics are the most commonly prescribed drugs for heart failure, used by 62% of patients [13].

When loop diuretics were introduced in the 1960s, they had a significant impact on heart failure treatment. They allowed the physician to aggressively treat fluid retention. However, few multicenter and randomized trials were carried out to assess the efficacy of diuretics and they rapidly became a standard part of the management of patients with this disease [14]. Indeed, it was not until the introduction of ACE inhibitors and elucidation of the neurohormonal pathophysiology of heart failure that regulatory mandates required that new drugs be evaluated with large randomized and placebo-controlled trials. By that time, it was clear to clinicians that diuretics dramatically improve the symptoms of congestion and they had become an inseparable part of the heart failure pharmacopeia.

Although diuretics have not been shown to improve survival in patients with heart failure (a trial that would now be considered unethical), investigators have attempted to gain a better understanding of the long-term benefits and risks

of diuretic use from smaller clinical trials. For example, Odemuyiwa *et al.* [15] demonstrated that diuretic requirements did not decline after the addition of ACE inhibitors in patients with stable heart failure symptoms. Similarly, Grinstead *et al.* [16] evaluated 41 patients with stable, but symptomatic heart failure. After discontinuing diuretic therapy, patients were randomized to either lisinopril or placebo. Of this, 71% of patients restarted diuretic therapy because of worsening symptoms; however, there was no significant difference between the number of patients who restarted therapy in the placebo or lisinopril group. Interestingly, a baseline daily furosemide dose of >40 mg, a left ventricular ejection fraction <27%, and a history of systemic hypertension were independently predictive of the need for diuretic reinitiation.

It is tempting to think that ACE inhibitors would reduce extracellular fluid volume in the absence of other pharmacologic agents; however, in many cases they require the synergistic action of other drugs. The explanation for this paradox lies in the fact that, while diuretics shift the renal function curve to the left (Figure 1.1), permitting sodium excretion to increase at a constant mean arterial pressure and constant dietary salt intake, ACE inhibitors not only shift the renal function curve to the left but also reduce mean arterial pressure through peripheral vasodilation. Thus, in the absence of diuretics, ACE inhibitors are unable to effect a change in urinary sodium excretion because the shift in the renal function curve is offset by the reduction in blood pressure.

In another study that evaluated the effectiveness of diuretic therapy in patients with heart failure, Walma and colleagues evaluated the effects of diuretic withdrawal in a group of 202 elderly patients who were minimally symptomatic and who had not had a recent episode of worsening heart failure [17]. The subjects in this study were randomized to either continued therapy with a diuretic or discontinuation of their diuretic therapy. Diuretic reinstitution was required in 50 of 102 patients in the withdrawal group and 13 of 100 patients in the control arm. Heart failure was the most frequent cause of reinitiating diuretic therapy and 65% of patients who were originally prescribed diuretics for heart failure needed reinitiation of diuretic therapy during the trial. The authors concluded that

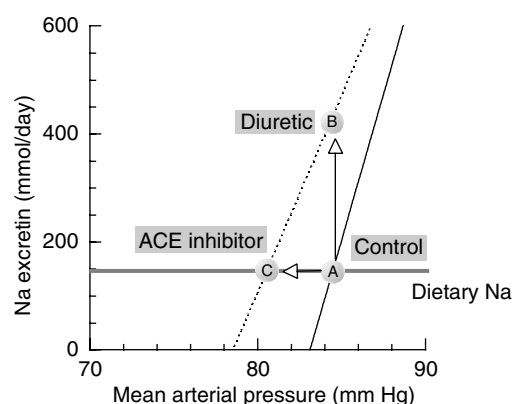


Figure 1.1 Comparison of diuretic and ACE inhibitor effects on sodium (Na) excretion and mean arterial pressure. The figure shows two 'chronic renal function curves' relating dietary Na intake (grey line), urinary Na excretion (ordinate) and mean arterial pressure (abscissa). At baseline (point A), the urinary Na excretion equals dietary Na intake. Both diuretics and ACE inhibitors shift the renal function curve to the left (from the solid to the dotted line). Diuretics do not reduce arterial pressure directly, therefore urinary Na excretion rises (move from point A to point B). In contrast, ACE inhibitors reduce mean arterial pressure as well as shift the renal function curve, so urinary Na excretion is unchanged (move from point A to point C).

clinicians should be cautious while withdrawing diuretic therapy and when withdrawal is required it should be accompanied by assiduous monitoring, especially during the first 4 weeks after therapy is discontinued.

Important information regarding the use of diuretics also come from a number of large multicenter clinical trials that evaluated chronic therapy with diuretics in patients with hypertension, an important risk factor in the development of heart failure. In the Stop Hypertension in the Elderly Program (SHEP) [18], 4736 persons with isolated systolic hypertension were randomized to receive chlorthalidone, a thiazide-like diuretic, versus placebo, in a stepwise approach. The incidence of heart failure was reduced in the active group by 53% with 48 events being seen in the active treatment group and 102 events in the placebo group. Treatment with a diuretic compared to a calcium channel blocker or an ACE inhibitor was also evaluated in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [19]. Chlorthalidone was superior to amlodipine

in preventing the development of heart failure. The amlodipine group had a 38% ($p < 0.001$) higher risk of heart failure and a 6-year absolute risk difference of 2.5%. When all major long-term hypertension treatment trials were reviewed to evaluate the effects of diuretics on the development of heart failure, diuretics were found to decrease the risk of heart failure by 52% [20,21]. Thus, though indirect, the experience in hypertension supports the hypothesis that diuretics are beneficial in patients with heart failure as well as those at high risk of its development.

Adverse effects associated with diuretic use

The adverse effects associated with the use of diuretics are reviewed in Table 1.2. However, the two most serious consequences of diuretic use are the development of arrhythmias and electrolyte abnormalities – the two being linked in many instances.

Arrhythmias

Numerous studies have demonstrated an increased incidence of arrhythmias with the use of

non-potassium-sparing diuretics [22]. Siscovick *et al.* demonstrated in a population-based case-control study that the presence and dose of thiazide diuretics was associated with an increased risk of primary cardiac arrest [23]. The SOLVD investigators similarly found that the baseline use of non-potassium-sparing diuretics was associated with an increased risk of arrhythmic death, while potassium-sparing diuretic use was not associated with an increased risk [24]. The presence or absence of ACE inhibitors or potassium supplementation did not affect this relationship and there was not a significant difference in potassium levels between patients who were receiving or not receiving an ACE inhibitor.

Electrolyte abnormalities and other metabolic sequelae of diuretics

Hyponatremia

Hyponatremia develops in the setting of congestive heart failure because of the accumulation of excess free water within the vascular spaces. Free water retention occurs in the setting of increased tubular absorption of sodium and activation of the renin–angiotensin–aldosterone axis [2]. Water retention is caused at least in part by increased

Table 1.2 Complications of diuretics.

<i>Complications</i>	<i>Preventive measures</i>
Electrolyte abnormalities	Periodic electrolyte monitoring when actively diuresing or adjusting ACE inhibitor dose
Hypokalemia	
Hyponatremia	
Hypomagnesemia	
Arrhythmias	Caution with potassium-sparing diuretics
Extracellular fluid volume depletion	Keep serum K 4.0–5.0
Metabolic alkalosis	Daily weights
Azotemia	Regular assessment by clinician
	Regular assessment by clinician
	Medication review, that is, NSAIDs, etc.
Glucose intolerance	Regular assessment by clinician
Hyperlipidemia	
Hyperuricemia	
Erectile dysfunction	
Ototoxicity	Limit rapid boluses, especially in uremia, use of aminoglycosides
	Limit rate of furosemide infusion to less than 240 mg/h
Progressive heart failure	Regular assessment by clinician

levels of vasopressin and subsequent activation of vasopressin receptors in the kidney. Diuretics can contribute to the stimulation of vasopressin by reducing effective arterial volume [25,26]. Indeed, it has been recognized clinically that many patients enter the hospital with normal serum sodium, but develop hyponatremia after receiving aggressive diuresis with loop diuretics. Recent studies have demonstrated that even modest decreases in serum sodium (130 to 135 mEq/L) are associated with a worse outcome in patients hospitalized for worsening heart failure.

The management of hyponatremia includes efforts to improve cardiac function, decrease volume overload, and to restrict free water intake. Some patients may require intravenous inotropic support and/or low doses of dopamine to improve renal perfusion. Because hyponatremia is driven at least in part by an impairment in effective arterial blood volume, the addition of an ACE inhibitor may lead to an improvement in the serum sodium level [27]. The recent development of vasopressin receptor antagonists (so-called aquaretic agents) shows promise in treating the water retention of heart failure and may become an important component of the treatment regimen for hyponatremic patients with heart failure [28,29]. The potential role for vasopressin antagonists will be discussed in Chapter 13.

Disorders of potassium balance

Activation of the renin–angiotensin–aldosterone system leads to hypokalemia because of augmented exchange of sodium for potassium in the renal tubule [2]. Non-potassium-sparing diuretics potentiate this hypokalemia by presenting an increased sodium load to the distal tubule. This leads to urinary excretion of potassium, which has been associated with further activation of the renin–angiotensin–aldosterone axis [30]. As a result, many patients with chronic heart failure develop a reduction in whole-body potassium stores as potassium is released from intracellular storage pools in order to help balance the levels of potassium in the peripheral circulation. Aggressive diuresis in the setting of chronic hypokalemia can further reduce serum potassium levels. Hypokalemia is a significant risk factor for the development of malignant arrhythmias [4]. Although

not evaluated in a randomized, prospective trial, many experts believe that in patients with CHF, potassium concentrations should be maintained in the range of 4.5 to 5.0 mEq/L [2]. Historically, most heart failure patients who were receiving a loop diuretic were prescribed a potassium supplement. However, the incidence of hypokalemia in heart failure patients appears to be decreasing, with the wide utilization of ACE inhibitors/ARBs together with β -blockers and aldosterone antagonists. Indeed, a recent survey showed substantial increases in the rates of hospitalization for potentially harmful hyperkalemia as a result of increased utilization of aldosterone antagonists [31], an area that will be discussed in further detail in the chapter on the use of aldosterone antagonists. Preexisting serum potassium concentrations above 4 mM or even mild chronic kidney disease should prompt special caution in the use of potassium-sparing agents.

Hypomagnesemia

Hypomagnesemia develops by similar mechanisms to hypokalemia; however, the importance of hypomagnesemia in heart failure is less well established. Hypomagnesemia has been associated with an increase in ectopy and mortality in some small trials; however, hypomagnesaemia was not associated with an increase in mortality in the large Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial. Parenthetically, the presence of hypomagnesaemia is difficult to assess as there is poor correlation between serum and tissue magnesium concentrations [32]. Magnesium deficiency is less common in mild to moderate HF; however, there are several populations that are more susceptible including post cardiac transplant patients, patients in intensive care units, and patients with moderately severe to severe symptoms requiring hospitalization, high dose diuretic therapy, or patients who have coexisting hypokalemia [2]. Magnesium replacement should be strongly considered in these populations.

Progressive heart failure

Because diuretic use is associated with activation of the renin–angiotensin–aldosterone system, there is reason to believe that its use may promote the progression of heart failure. In a retrospective

analysis of the SOLVD trial, the risk of hospitalization for, or death from, worsening CHF was significantly increased in patients receiving non-potassium sparing diuretics (i.e. loop diuretics) compared to those patients not being treated with a diuretic or receiving a potassium sparing diuretic [13]. The investigators proposed that loop diuretics induce a loss of sodium that in turn activates the renin–angiotensin system and thereby contributes to disease progression. Thus, diuretics should always be used in conjunction with inhibitors of the renin–angiotensin system including ACE inhibitors, β -blockers, and an aldosterone inhibitor when appropriate.

Practical considerations for the use of diuretics

Diuretic choice and dosing

Most patients with a current evidence of volume overload or a history of fluid retention should be treated with a diuretic in combination with an ACE inhibitor and a β -blocker. In patients with new onset of fluid retention, a diuretic should be the first drug used as it will provide the most rapid improvement in symptoms. Some authors suggest that patients with mild symptoms should initially be treated with a thiazide diuretic [33]; however, there are no objective data to support this approach and many heart failure specialists believe that the thiazide diuretics have too little potency in a heart failure population. When patients have moderate to severe heart failure symptoms or renal insufficiency, a loop diuretic is required. Outpatient treatment should begin with low doses of diuretic with incremental increases in the dose until urine output increases and weight decreases (~ 1.0 kg/day). Some patients may develop hypotension or azotemia during diuretic therapy. While the rapidity of diuresis should be slowed in these patients therapy should be maintained at a lower level until euvolemia has been attained, as persistent volume overload may limit and/or compromise the effectiveness of other agents and persistently high filling pressures can enhance maladaptive cardiac remodeling.

A typical starting dose is 20 mg of furosemide in patients with normal renal function, although doses of 40–80 mg may be necessary. Further increases

in dose may be required to maintain urine output and weight loss. In patients with renal insufficiency, larger starting doses are often necessary, such as 40–80 mg of furosemide that may be increased up to 160 mg. Ceiling doses of loop diuretics in treating heart failure, single doses that appear to be maximally effective, have been described [33]. For furosemide, the maximal doses are 40–80 mg IV (160–240 mg PO). For torsemide, the maximal doses are 20–50 mg IV or PO. For bumetanide, the maximal doses are 2–3 mg IV or PO. Because of the steep dose–response curve for loop diuretics, an adequate dose is necessary that causes a clear diuretic response. Some experts recommend doubling the dose until this effect is demonstrated.

Although furosemide is the most commonly used loop diuretic, there are several limitations to its use. For example, its oral bioavailability is only approximately 50% and there is significant intra- and interpatient variability [34]. In patients with hepatic and bowel edema, the bioavailability of furosemide may be markedly decreased because of decreased gastric absorption. Therefore, some clinicians favor the use of bumetanide or torsemide because of their increased and more predictable bioavailability [35].

All of the commonly used loop diuretics are short acting. In CHF, the half-lives of these drugs are increased, but still less than 3 h [34]. After the period of diuresis, the diuretic concentration declines below its threshold and renal sodium reabsorption is no longer inhibited and “postdiuretic NaCl retention” begins [36]. If a patient is not restricting sodium intake, this retention can overtake the original diuresis. For this reason, loop diuretics usually need to be given at least twice daily and salt restriction is an important component of therapy. In addition, patients receiving diuretic therapy should monitor their weight on a daily basis.

Diuretic resistance

An edematous patient may be deemed resistant to diuretic drugs when moderate doses of a loop diuretic do not achieve the desired reduction in ECF volume as noted by a change in weight, the amount of edema, the degree of liver enlargement, or the jugular venous pressure. Before labeling the patient

as 'resistant' to diuretics and considering intensive diuretic therapy or combination therapy, it is important to exclude reversible causes. An inadequate ECF volume reduction does not necessarily indicate an inadequate natriuretic response (see Figure 1.1), Loop diuretics may induce natriuresis without contracting the ECF volume, if dietary NaCl intake is excessive. It should also be emphasized that the 'desired' ECF volume may not lead to an edema-free state; some patients may require a modest amount of peripheral edema to maintain adequate cardiac output: such patients may need to be counseled regarding local measures to reduce edema (support stockings, keeping the feet elevated) and the willingness to tolerate mild edema. When needed, however, intensive diuretic treatment is usually effective in reducing the ECF volume; each of the different approaches to intensive therapy is best employed under specific circumstances.

Combination diuretic therapy

A common and useful method for treating the diuretic resistant patient is to administer two classes of diuretic drug simultaneously. For this discussion, it is assumed that the patient is already being given a loop diuretic at maximal or near maximal doses. Although some authors have advocated alternating two members of the same diuretic class together (such as ethacrynic acid and furosemide) controlled trials suggest little or no benefit from such an approach [37]. In contrast, adding a proximal tubule diuretic or a distal convoluted tubule diuretic (DCT) to a regimen of loop diuretics is often dramatically effective [38–40]. DCT diuretics (thiazides and the like) are the class of drugs most commonly added to loop diuretics and this combination has proven remarkably effective. The combination of loop and DCT diuretics has been shown to be synergistic (the combination is more effective than the sum of the effects of each drug alone) in formal permutation trials [41].

Adding a DCT diuretic to a regimen that includes loop diuretics may enhance NaCl excretion by several mechanisms, none of which is mutually exclusive. DCT diuretics do not appear to potentiate the effects of loop diuretics by altering their pharmacokinetics or bioavailability [42], but DCT diuretics

do have longer half-lives than do loop diuretics. The first mechanism responsible for the efficacy of combination therapy is that DCT diuretics may prevent or attenuate postdiuretic NaCl retention. As shown in Figure 1.2, the natriuretic effects of a single dose of furosemide, bumetanide, and to a lesser extent torsemide, generally cease within 6 h. Before the next dose of diuretic is administered, intense renal NaCl retention frequently occurs (so called postdiuretic NaCl retention); this NaCl retention can be attenuated by DCT diuretics, which will continue to inhibit renal NaCl absorption after the loop diuretic has worn off. A second mechanism by which DCT diuretics potentiate the effects of loop diuretics is by inhibiting salt transport along the proximal tubule. When the kidney is strongly stimulated to retain NaCl, proximal NaCl reabsorption is enhanced. Most thiazide diuretics inhibit carbonic anhydrase, thereby reducing Na and fluid reabsorption along the proximal tubule. This leads to increase Na and fluid delivery to the loop of Henle [43], which leads to increases in delivery of Na⁺ and Cl⁻ into the collecting duct system. Because the loop diuretic drug is inhibiting loop segment solute reabsorption, the delivery of solute to the distal nephron will be greatly magnified. The importance of carbonic anhydrase inhibition in diuretic synergism is documented by the efficacy of carbonic anhydrase inhibitors (e.g. acetazolamide) when added to loop diuretics. Although carbonic anhydrase inhibitors are relatively weak diuretics when administered alone, they can be very potent when added to a regimen of a loop diuretic [44].

A third mechanism by which DCT diuretics may potentiate the effects of loop diuretics is by inhibiting NaCl transport along the distal convoluted tubule. Chronic loop diuretic administration leads to hypertrophy and hyperplasia of distal convoluted tubule cells, increasing their NaCl reabsorptive capacity by up to threefold [45–47]. Because DCT diuretics can inhibit thiazide-sensitive Na⁺/Cl⁻ cotransport completely even under these stimulated conditions [45], the effects of the DCT diuretics will be greatly magnified in the patient who has developed distal nephron hypertrophy from high doses of loop diuretics. Loon and colleagues [48] showed that the effect of chlorothiazide on urinary Na⁺ excretion in humans is enhanced by one month's prior treatment with furosemide.

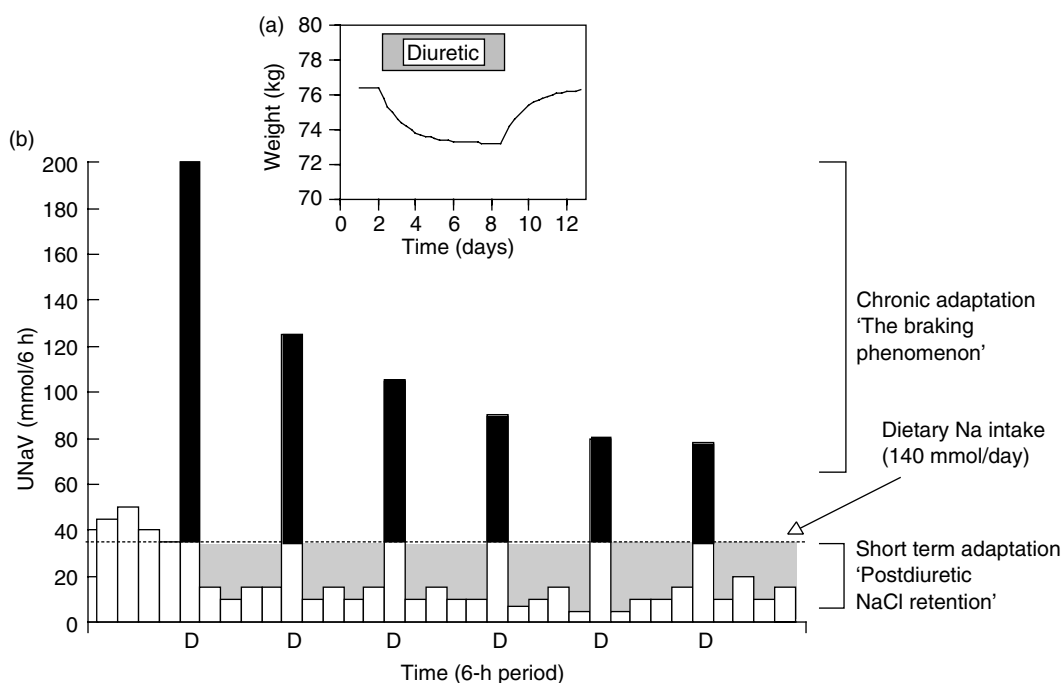


Figure 1.2 Effects of diuretics on urinary Na excretion and ECF volume. (a) Effect of diuretic on body weight, taken as an index of ECF volume. Note that steady state is reached within 6–8 days despite continued diuretic administration. (b) Effects of loop diuretic on urinary Na excretion. Bars represent 6-h periods before (in Na balance) and after doses loop diuretic (D). The dotted line indicates dietary Na intake. The solid portion of the bars indicate the amount by which Na excretion exceeds intake during natriuresis. The hatched areas indicate the amount of positive Na balance after the diuretic effect has worn off. Net Na balance during 24 h is the difference between the hatched area (postdiuretic NaCl retention) and the solid area (diuretic-induced natriuresis). Chronic adaptation is indicated by progressively smaller peak natriuretic effects (The braking phenomenon) and is mirrored by a return to neutral balance [as indicated in (a)] where the solid and hatched areas are equal. As discussed in the text, chronic adaptation requires ECF volume depletion.

These data suggest that daily oral furosemide treatment, even in modest doses, may be sufficient to induce adaptive changes along the distal nephron, changes that may be treated with combination drug therapy.

The choice of drugs for combination diuretic therapy has been controversial [40,44,49–53]. In most cases, it is appropriate to add a DCT diuretic to a regimen of a loop diuretic. Alternative approaches, however, are appropriate in some circumstances and will be discussed later. In general, when a second class of diuretic is added, the dose of loop diuretic should not be altered. The shape of the dose-response curve to loop diuretics is not affected by the addition of other diuretics and the loop diuretic must be given in an effective or maximal safe dose. The choice of DCT diuretic that is to be added is arbitrary. Many clinicians choose metolazone

because its half-life, in the commonly employed formulation, is longer than that of some other DCT diuretics and because it has been reported to remain effective even when the glomerular filtration rate is low. Yet, direct comparisons between metolazone and several traditional thiazides have shown little difference in natriuretic potency when included in a regimen with loop diuretics in patients with congestive heart failure [51].

The DCT diuretics may be added in full doses (50–100 mg/day hydrochlorothiazide or 10 mg/day metolazone, see Table 1.3) when a rapid and robust response is needed, but such an approach is likely to lead to complications unless follow-up is assiduous. This approach should be reserved for hospitalized patients since fluid and electrolyte depletion may be excessive. Indeed, in one review of combination diuretic therapy, side effects were noted

Table 1.3 Combination diuretic therapy.*To a maximal dose of a loop diuretic add*

Distal convoluted tubule diuretics:

metolazone 2.5–10 mg PO daily*

hydrochlorothiazide (or equivalent) 25–100 mg PO daily

chlorothiazide 500–1000 mg IV

Proximal tubule diuretics:

acetazolamide 250–375 mg daily or up to 500 mg intravenously

Collecting duct diuretics:

spironolactone 100–200 mg daily

eplerenone 25–100 mg/day

amiloride 5–10 mg daily

*Metolazone is generally best given for a limited period of time (3–5 days) or should be reduced in frequency to three times per week once extracellular fluid volume has declined to the target level. Only in patients who remain volume expanded should full doses be continued indefinitely, based on the target weight. Be very cautious with higher doses of spironolactone or eplerenone in the setting of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, hyperkalemia can occur [31].

to have occurred in about two-thirds of patients receiving therapy [39]. One rational approach to combination therapy is to achieve control of ECF volume by adding full doses of DCT diuretics on a daily basis initially and then to maintain control by reducing the dose of the DCT diuretic to three times weekly. However, many clinicians titrate the dose of the DCT diuretic in each patient and have found that in some patients only a single weekly dose is required to maintain an appropriate level of diuresis. A physiological rationale for such an approach is provided by the observation that chronic treatment with DCT diuretics down-regulates Na^+/K^+ -ATPase activity [54] and transport capacity [55] along the distal convoluted tubule of rat. Thus, it may be speculated that adding a DCT diuretic to a regimen including a loop diuretic may decrease the structural and functional compensatory effects of loop diuretics.

Another approach to combination therapy is to use combination therapy for only a short fixed course. A comparison of different combination diuretic regimens suggested that a limited course of combination therapy may be as effective and perhaps safer than more prolonged courses [51]. Thus, for the outpatient, either a small dose of DCT diuretic, such as 2.5 mg/day metolazone or

a limited and fixed course of a higher dose (3 days of 10 mg/day metolazone) may be recommended as effective therapy that is less likely to lead to side effects. Because DCT diuretics are absorbed more slowly than loop diuretics, it may be reasonable to administer the DCT diuretic 1/2 to 1 h prior to the loop diuretic, although rigorous support for this contention is lacking.

Drugs that act along the collecting duct, such as amiloride and spironolactone, can be added to a regimen of loop diuretic drugs but their effects are generally less robust than those of DCT diuretics. For example, the combination of spironolactone and loop diuretics has not been shown to be synergistic but aldosterone antagonists can prolong life and help prevent hypokalemia [56]. Cortical collecting duct diuretics also reduce magnesium excretion, relative to other diuretics, making hypomagnesemia less likely than when loop diuretics are combined with DCT diuretics [57–60]. However, there is far less experience with these types of diuretics in heart failure patients.

One situation in which aggressive diuretic therapy is often indicated is for hospitalized patients, especially those in an intensive care unit who need urgent diuresis. While the causes of diuretic resistance delineated above may be present in these patients, many also receive obligate fluid and solute loads, some develop electrolyte complications, and many cannot take medications by mouth. Two IV drugs are available to supplement loop diuretics for combination therapy. Chlorothiazide (500–1000 mg once or twice daily) and acetazolamide (250–375 mg up to four times daily) are both available for IV administration: chlorothiazide has relatively potent carbonic anhydrase inhibiting capacity in the proximal tubule. It also blocks the ‘thiazide-sensitive’ $\text{Na}-\text{Cl}$ cotransporter in the distal tubule; and chlorothiazide has a longer half-life than some other DCT diuretics. Both chlorothiazide and acetazolamide have been shown to act synergistically with loop diuretics when given acutely. Acetazolamide is especially useful when metabolic alkalosis and hypokalemia complicate the treatment of edema. Alkalosis may make it difficult to wean a patient from a ventilator and make it impossible to correct K^+ depletion. The use of acetazolamide can often correct these disorders [61] without the need to administer saline,

which would otherwise be used to correct alkalosis in these patients. In other situations, combination diuretic therapy may be targeted at the underlying disease process. Low doses of dopamine are often employed to potentiate the action diuretics by improving renal perfusion. However, one study has suggested that dopamine is not effective as an adjunct to diuretic treatment unless it increases cardiac output [62].

A newer approach may include combining brain natriuretic peptide (nesiritide) with loop diuretic treatment. In animals, this combination was recently shown to result in enhanced natriuresis without stimulating aldosterone secretion [63]. This combination makes it attractive as an option for acutely ill patients, but awaits confirmatory studies in humans and will be discussed in detail in Chapter 11.

High dose diuretic therapy

High doses of loop diuretics are frequently employed to treat severe volume overload, especially when treatment is urgent. Maximal effective doses of furosemide, bumetanide, and torsemide have been estimated (see “diuretic choice and dosing” discussed earlier), although some have used higher doses [64]. In diuretic sensitive patients, the most common complications of loop diuretics result directly from the diuresis and natriuresis. Hypokalemia, hyponatremia, and hypotension frequently result because of excessive fluid and electrolyte losses. For diuretic *resistant* patients, however, drug toxicity, most commonly ototoxicity, may also occur and is an important consideration during high dose or prolonged therapy. All loop diuretics have been reported to cause ototoxicity in experimental animals and clinical ototoxicity has been reported following ethacrynic acid, furosemide, and bumetanide administration [65,66]. Ototoxicity is usually reversible, but has been irreversible occasionally; its incidence may be increased in patients exposed to other ototoxic agents, such as the aminoglycosides. Ototoxicity may be especially common following ethacrynic acid administration. It appears to be related to the serum concentration of the drug. It has been suggested, and clinical experience seems to confirm, that ototoxicity of furosemide can be minimized by administering it no

faster than 15 mg/min [67]. Comparable data are not available for bumetanide and torsemide, but it seems reasonable to avoid rapid bolus administration of loop diuretics in general. Myalgias appear to be more common following high doses of bumetanide [68]. The avoidance of high peak levels and the concomitant toxicity is one reason that continuous infusion of diuretics (discussed later) has become popular as an alternative approach to treat diuretic resistant patients.

It has long been appreciated that many patients suffering from CHF experience symptomatic relief from IV boluses of loop diuretics before significant volume and NaCl losses have occurred. In some patients, loop diuretics reduce pulmonary capillary wedge pressure acutely [7]. Loop diuretics are also known to stimulate secretion of vasodilatory prostaglandins. Pretreatment of animals with indomethacin greatly attenuates furosemide-induced venodilation, suggesting that prostaglandin secretion contributes importantly to the effects of loop diuretics by altering vascular reactivity. Although venodilation and improvements in cardiac hemodynamics frequently result, other reports suggest that the hemodynamic response to IV loop diuretics may be more complex. In two series, 1–1.5 mg/kg furosemide boluses, administered to patients with chronic CHF, resulted in transient *deteriorations* in hemodynamics during the first hour [10,69] and exacerbation of CHF symptoms. These changes were related to activation of both the sympathetic nervous system and the renin–angiotensin system by the diuretic. Although these data provide cautionary information concerning the use of loop diuretics in acute cardiogenic pulmonary edema, it should be emphasized that IV loop diuretics remain the most important and useful form of therapy for these patients because they rapidly ameliorate symptoms in most patients. Furthermore, they contribute to symptomatic improvement once natriuresis begins, an effect that should begin within 15 to 20 min of diuretic administration.

Another interesting complication of high dose furosemide treatment may be thiamine deficiency [70–74]. Studies in experimental animals have shown that chronic furosemide administration can lead to thiamine deficiency. In humans, several groups have reported thiamine deficiency in patients treated chronically with furosemide [74].

In one study, patients with CHF who received furosemide 80 mg daily for at least 3 months were randomized to receive IV thiamine or placebo. Intravenous thiamine led to improved hemodynamics and a natriuresis, compared with placebo, and to an improvement in the thiamine-pyrophosphate effect on erythrocyte transketolase activity [72].

Continuous diuretic infusion

For hospitalized patients who are resistant to diuretic therapy, another approach is to infuse diuretics continuously. Continuous diuretic infusions have several potential advantages over bolus diuretic administration. First, because it avoids troughs of diuretic concentration, continuous infusion prevents intermittent periods of positive NaCl balance (postdiuretic NaCl retention). When short-acting diuretics, such as the loop diuretics, are administered by bolus infusion or by mouth once or twice a day, a period of natriuresis and diuresis lasting about 6 h ensues. When diuretic serum concentrations decline, urine NaCl concentrations also decline to levels below basal. Because 24-h renal NaCl excretion is the sum of the natriuretic and antinatriuretic responses, negative salt balance may be limited, especially when dietary salt intake is high. Clearly, a constant infusion that leads to constant serum diuretic concentrations will minimize periods of sodium retention and might be expected to be more efficacious. Second, constant infusions appear to be more efficient than bolus therapy. In one study of patients with chronic renal failure, a continuous infusion of bumetanide was 32% more efficient than a bolus of the same drug when the amount of NaCl excreted per milligram of administered drug was compared [68]. In a crossover study of nine patients with NYHA class III–IV CHF (see Figure 1.2), 60–80 mg/day was more effective when given as a continuous infusion following a loading dose (30–40 mg) than when given as boluses three times daily (30–40 mg/dose) [75]. Third, some patients who are resistant to large doses of diuretics given by bolus have responded to continuous infusion [64]. Most studies of efficacy in diuretic resistant patients have not compared strictly equivalent doses or administered them in a randomized manner. Regardless, several studies do provide suggestive evidence that continuous

infusion may elicit diuresis in some patients resistant to large boluses. Fourth, diuretic response can be titrated; in the intensive care unit where obligate solute and fluid administration must be balanced by solute and fluid excretion, control of NaCl and water excretion can be obtained by titration of diuretic dose. While this is important in every postoperative patient, it is especially important in patients who are hemodynamically compromised. Magovern reported successful diuresis of hemodynamically compromised patients after cardiac surgery by continuous furosemide infusion [76]. Because continuous infusion of loop diuretics may reduce the sympathetic discharge and activation of the renin–angiotensin system, continuous infusions may be the preferred mode of therapy for hemodynamically unstable patients in need of diuresis. Finally, drug toxicity from loop diuretics, such as ototoxicity (observed with all loop diuretics) and myopathies (with bumetanide), appear to be less common when the drugs are administered as continuous infusions. In fact, total daily furosemide doses exceeding 2 g have been tolerated well when administered over 24 h. Dosage regimens for continuous IV diuretic administration are shown in Table 1.4. Of note, although natriuretic efficacy may vary linearly with loop diuretic dose, high infusion rates (e.g. 2 g per day of furosemide) might lead to toxic serum concentrations if continued for prolonged periods. This is especially true in patients with renal failure, in whom larger doses are often required to initiate diuresis. Special care should be taken when administering large daily doses of loop diuretics over prolonged periods; in patients with renal failure, a drug such as torsemide that is cleared, in part, by hepatic metabolism, may be preferred when high or prolonged therapy is attempted.

Ultrafiltration

In contrast to loop diuretics, ultrafiltration has much more modest effects to stimulate the renin–angiotensin–aldosterone axis because it does not activate the macula densa mechanism [77]. Subsequent reports have corroborated that ultrafiltration is safe and can be an effective adjunct to diuretics, but controlled trials are still lacking [78].

Table 1.4 Continuous infusion of loop diuretics.

	Bolus (mg)	Infusion rate (mg/h)		
		<25 mL/min	25–75 mL/min	>75 mL/min
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

At high continuous doses, toxicity may develop, especially during furosemide infusion in patients with impaired renal function. Doses derived from Brater [88].

Table 1.5 Adequacy of diuresis.

Adequacy of diuresis
Jugular venous distension
Hepatojugular reflex
Hepatomegaly
Ascites, peripheral and sacral edema
Pulmonary rales
Cough, dyspnea on exertion
Orthopnea, paroxysmal nocturnal dyspnea
Documented elevated filling pressures by cardiovascular testing (i.e. cardiac catheterization, echo cardiography)

Evaluation of adequacy of diuresis

Clinicians use various methods to determine the extent and adequacy of diuresis (Table 1.5). However, some of the more commonly used signs, such as resolution of pulmonary rales, are insensitive when determining adequacy of diuresis in patients with chronic heart failure. Many clinicians use measures of renal function as an indicator of overdiuresis; however, increased blood urea nitrogen (BUN)/serum creatinine ratio can be a marker for rapid diuresis rather than overdiuresis. Patients may be temporarily intravascularly depleted while evidence of increased total body fluid still remains. In patients with azotemia or hypotension but continued evidence of fluid retention, diuresis should continue, although at a slower rate. Overdiuresis that leads to hypotension may contribute to renal insufficiency in patients on vasodilators and ACE inhibitors. In this setting, hypotension can be managed by reducing the dose or frequency of diuretics. In some patients with advanced, chronic heart failure, elevated BUN and creatinine concentrations may be necessary to maintain control of

congestive symptoms. Once patients are believed to be adequately diuresed, it is important to document this “dry weight” and have patients weigh themselves daily.

Natriuretic peptides are increasingly being used as both diagnostic and prognostic tools in CHF. Some investigators have encouraged their use to titrate therapy. Both b-type natriuretic peptide (BNP) and N-terminal-pro-BNP plasma concentrations have been demonstrated to improve with heart failure pharmacologic therapy [79–82]. In a study by Troughton *et al.* [82], patients with impaired systolic function and symptomatic heart failure were randomized to receive treatment guided by either N-BNP concentration (N-BNP < 200 pmol/L) or standardized clinical assessment. After a median of 9.5 months, there were fewer total cardiovascular events (death, hospital admission, or heart failure decompensation) in the BNP group compared to the clinical group (19 versus 54, $p = 0.02$). However, titration of heart failure therapy was accomplished by a predetermined protocol that first maximized ACE inhibitors and then increased the dose of the loop diuretics. Unfortunately, there have not been studies that investigate the role of natriuretic peptides in titration of diuretics in patients already maximized on ACE inhibitors and β -blockers.

Monitoring the efficacy of diuretic therapy

Patients with CHF who are on diuretics should be monitored for complications of diuretics on a regular basis (Table 1.2). The interval for reassessment should be individualized based on severity of illness, recent medication changes, past history of electrolyte imbalances, or need for active diuresis.

The earliest indication of volume retention is usually a consistent or dramatic increase in weight. In some patients, they can be instructed to take an extra dose of their routinely prescribed loop diuretic. Metolazone or other long-acting thiazide diuretics also can be used to improve diuresis. A dose of 2.5 to 5.0 mg of metolazone in addition to routine loop diuretics can be used periodically. While the effectiveness of volume management by heart failure nurses and multidisciplinary heart failure clinics is well established [83–85], this commonly prescribed practice of patient-guided management of diuretics has not been adequately studied [86]. Some clinicians in cognitively intact and motivated patients have used this practice in order to prevent heart failure hospitalizations [87]; however, this practice could lead to over treatment with diuretics. Therefore, it should be reserved for those patients who are hemodynamically stable, well motivated, and consistently compliant. Routine use of extra diuretics should prompt reevaluation by a clinician.

Summary

Diuretics are a mainstay of therapy in patients with heart failure. They rapidly produce an improvement in symptoms, can be effective in alleviating pulmonary and peripheral edema, and can adequately control fluid retention with chronic therapy. However, diuretics must be utilized with care. First and foremost, they must be used in combination with an ACE inhibitor and a β -blocker in order to optimize their effectiveness and decrease risk. Furthermore, care must be taken to avoid inappropriately high doses of diuretics and resultant volume contraction as well as to avoid underutilization and associated hypervolemia. Furthermore, care should be taken to avoid alterations in serum electrolyte levels that can accompany diuretic use. Although appropriate cautions are warranted, it should be recognized that an optimal use of diuretics serves as a cornerstone in the treatment of patients with heart failure.

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