LEADING ARTICLE

Drugs 1998 Feb; 55 (2): 165-172
0012-6667/98/0002-0165/$08.00/0

Combination Diuretic Therapy in Severe Congestive Heart Failure

Tom PJ Dormans,[1] *Paul GG Gerlag,*[2] *Frans GM Russel*[3] and *P Smits*[3]

1 Department of Intensive Care, University Hospital Nijmegen, Nijmegen, The Netherlands
2 Department of Internal Medicine, St Joseph Hospital, Veldhoven, The Netherlands
3 Department of Pharmacology, University Hospital Nijmegen, Nijmegen, The Netherlands

Summary

Severe congestive heart failure (CHF) is often characterised by fluid retention. A (chronic) state of overhydration has a negative influence on both the quality of life and prognosis of these patients. Therefore, the use of diuretics remains a cornerstone in the treatment of heart failure. However, diuretic resistance, a failure to correct the hydration state adequately with the use of conventional dosages of loop diuretics, is a frequently occurring complication in the treatment of advanced stages of CHF.

Several intra- and extrarenal mechanisms may be involved in the development of diuretic resistance. An important pathophysiological mechanism leading to diuretic resistance seen after chronic use of loop diuretics is the functional adaptation of the distal tubule. Studies in animals demonstrate that the sodium reabsorption capacity of this nephron segment increases significantly when the sodium delivery to this segment is augmented, as is the case during administration of loop diuretics.

The use of combinations of diuretics acting on different segments of the nephron appears to be an effective option in the treatment of diuretic resistance. Several combinations have been used; however, the combination of a loop diuretic and a thiazide drug acting on the distal tubule appears to be the most effective. However, since the use of this combination may lead to serious adverse effects such as hypokalaemia, metabolic alkalosis and dehydration, careful monitoring of the patient on combination diuretic therapy is necessary.

Heart failure is a major health problem,[1,2] and its incidence is expected to further increase in the next decade.[3] Since no curative therapy is currently available for the majority of patients, the goals of treatment are to improve quality of life and to postpone progression of the disease.[4] Although important advances in the pharmacological treatment of heart failure have recently been achieved, it is still inevitable that a considerable number of patients will progress to the advanced stages of this disease.

The clinical picture of advanced stages of heart failure is often dominated by the presence of oedema and congestion, causing symptoms of dyspnoea, fatigue, nausea and discomfort. Moreover, chronic congestion contributes to further progression of the disease.[5,6] For these 2 reasons, maintenance of an adequate state of hydration is very important. This is usually achieved by use of loop diuretics in combination with salt restriction and a limitation of physical activity. However, as the disease progresses, oedema may reoccur despite these measures. In some of these cases, the decrease in efficacy of diuretic therapy appears to be caused by

diuretic resistance, a phenomenon that can be defined as the failure to create a negative sodium balance despite the use of conventional dosages of furosemide (frusemide) [250mg per day or an equivalent amount of another loop diuretic], a sodium-restricted diet (60 to 80 mmol sodium per day) and restriction of physical activity.

The mechanisms responsible for diuretic resistance are very diverse (table I). In decompensated heart failure, intestinal absorption of orally administered furosemide may be altered, causing inadequate concentrations of loop diuretic on the site of action.[7] Decrease of renal perfusion due to various causes results in a decrease of the capacity of the proximal tubule to secrete furosemide and/or bumetanide into the urine.[8] Endogenous acids and non–steroidal anti-inflammatory drugs compete with loop diuretics for secretion into the tubule by the organic acid pump in the proximal tubule.[9]

In clinical practise the use of combinations of diuretics acting on different segments of the nephron, often referred to as sequential nephron blockade, has shown to be highly effective in the treatment of diuretic resistance in congestive heart failure (CHF).[10] Recent studies give insight in to some of the pathophysiological mechanisms involved in diuretic resistance. In this article, we focus on the mechanisms that explain the synergism of combinations of diuretic drugs in severe heart failure, indications for their use and adverse effects.

Table I. Cause of treatment failures with conventional dosages of loop diuretics in patients with decompensated heart failure

Noncompliance with medical regimen
Nonadherence to sodium restriction
Nonadherence to drug regimen
True diuretic resistance
Pharmacokinetic causes
Altered intestinal absorption of the loop diuretic
Decreased renal perfusion due to
low cardiac output
hypovolaemia
atherosclerosis, renal artery stenosis, cholesterol emboli
decreased filtration fraction (e.g. due to use of ACE inhibitors or NSAIDs)
Reduced tubular secretion
hypovolaemia
nephrologic pathology
competitive inhibition by NSAIDs, probenecid, endogenous acids (renal insufficiency, gout)
Pharmacodynamic causes
Adaptation of distal convoluted tubule to chronic use of loop diuretics

Abbreviations: ACE = angiotensin-converting enzyme; NSAID = non-steroidal anti-inflammatory drug.

1. Mechanisms of Diuretic Resistance

Under physiological conditions, sodium reabsorption takes place in all segments of the nephron. In the proximal tubule, 60 to 70% of the filtered sodium is reabsorbed; in the loop of Henle, distal tubule and collecting tubule 20 to 25%, 5 to 10% and only 3% of the filtered sodium, respectively, is reabsorbed. This means that more than 99% of filtered sodium is usually reabsorbed in the tubular system.[11] However, in heart failure, with or without diuretic therapy, these numbers are different. Several mechanisms account for the varying contributions of the nephron segments to sodium reabsorption.

1.1 Sodium Reabsorption in Heart Failure

In heart failure, the absolute amount of sodium that is filtered may be decreased due to reduced renal perfusion in a state of low cardiac output. Secondly, heart failure is characterised by activation of both the renin-angiotensin system and sympathetic stimulation. In heart failure the filtration fraction is increased, which is mediated by vasoconstriction of the efferent arteriole. This vasoconstriction is mainly induced by an increased intrarenal production of angiotensin II.[12] As a result, transcapillary hydrostatic pressure and oncotic pressure is decreased, causing increased sodium and water reabsorption in the proximal tubule. Moreover, angiotensin II may exert a direct sodium-retaining effect on the proximal renal tubule[13,14] and it increases sodium reabsorption indirectly in the collecting ducts by an upregulation

of aldosterone secretion. Although the use of angiotensin-converting enzyme (ACE)-inhibitors in heart failure is advocated, angiotensin II levels are often insufficiently decreased in patients with severe heart failure due to intolerance of adequate dosages of ACE-inhibitors.

Catecholamines directly induce an increase of sodium reabsorption by several mechanisms: they stimulate sodium reabsorption in the proximal tubules; indirectly stimulate this reabsorption by stimulation of renin release; and reduce renal perfusion as a result of their vasoconstrictive effects on the afferent arterial system.[15-17] Other mechanisms that play a role in the development of volume overload are the stimulation of the cerebral thirst centre by angiotensin and the enhanced release of antidiuretic hormone in end-stage heart failure.[5]

In addition to activation of sodium-retaining mechanisms, the natriuretic effects of atrial natriuretic peptide are attenuated in heart failure.[5]

These mechanisms may all contribute to the sodium retaining state (and thus the development of oedema) that characterises the advanced stages of CHF. Due to activation of the sodium-retaining mechanisms in severe heart failure, loop diuretics are less effective, and so dose-response curves of loop diuretics are shifted downward and to the right in patients with CHF.[18] In a number of these patients, an extreme activation of the described sodium retaining mechanisms may thus cause diuretic resistance.

1.2 Pharmacodynamic Effects of Diuretics

The administration of loop diuretics has a number of effects:

- Loop diuretics inhibit the Na-K-2Cl cotransporter from the luminal site of the thick ascending limb of the loop of Henle, thereby blocking the sodium reabsorption in this segment of the nephron almost completely. Usually an increased urinary sodium excretion will follow.
- When the commonly used intermittent dosing schedules of loop diuretics are used, no diuretic drug is available at the site of action during a considerable part of the dosage interval. In this so-called 'post-diuretic phase', sodium is avidly reabsorbed, resulting in a rebound sodium retention in the nephron. Moreover, the natriuretic effect of the loop diuretic is attenuated after repeated dosages while the patient is on a salt restricted diet.[19] This phenomenom is often referred to as braking. Both these observations can not completely be explained by enhancement of sympathetic stimulation and further increase of the activity of the renin-angiotensin-aldosterone axis.[20] However, to prevent activation of the latter in heart failure, diuretics are combined with ACE-inhibitors, whenever possible.
- By blocking sodium reabsorption in the loop segment, loop diuretics cause an increase in tubular sodium concentration at the level of the distal convoluted tubule.[11] In studies in rats, it was shown that high rates of sodium delivery to the distal convoluted tubule, induced by chronic furosemide infusion, caused a hypertrophy of this segment of the nephron that was associated with an increased capacity to reabsorb sodium.[21-23] These morphological and functional changes were observed after one week of furosemide infusion. Although the exact mechanisms involved in these structural and functional adaptations are unknown, it was hypothesised that cellular sodium concentrations regulate tubular cell growth directly.[24] Data obtained from a human study indicate that these adaptations to chronic furosemide administration also occur in humans.[25] This mechanism may explain why the diuretic efficacy of loop diuretics after chronic administration attenuates in heart failure.

Thiazides are able to block essentially all sodium reabsorption in the distal convoluted tubule, even after hypertrophy has occurred.[26] This means that thiazides are highly effective, when both the sodium reabsorbing capacity of the distal tubule and the sodium delivery to the distal tubule are increased, as is the case after chronic adminis-

tration of a loop diuretic. It explains the synergistic natriuretic effect of loop diuretics and thiazides.

On the other hand, chronic administration of thiazides induces a reduction of the sodium reabsorption capacity in this part of the nephron.[23] This observation indicates that functional adaptations due to increased sodium delivery in the distal tubule may be avoided or corrected by administration of thiazides.

2. What Diuretic Combinations Are Useful?

Many different combinations of diuretic drugs have been described in the past three decades. In nearly all of the described combinations, loop diuretics form the basis of combination therapy. Although the two most widely used loop diuretics, furosemide and bumetanide, differ with respect to pharmacokinetic properties, the difference in overall response to equipotent amounts of these drugs is subtle and probably of no clinical relevance in patients with CHF.[27] In the following we discuss most of the possible combinations of drugs. Diuretic drugs currently available and their site of action in the nephron include:

- acetazolamide, theophylline and mannitol (proximal tubule);
- ethacrynic acid, furosemide, bumetanide, torasemide and piretanide (loop of Henle);
- hydrochlorothiazide, chlorothiazide, bendroflumethiazide, chlorthalidone and metolazone (distal convoluted tubule); and
- amiloride, triamterene and spironolactone (collecting duct).

As a general rule, combinations of two diuretic drugs acting on the same segment of the nephron will not result in a synergistic effect and therefore should not be combined.

2.1 Loop and Proximal Diuretics

Few studies have been done examining the combination of a loop diuretic with a drug acting on the proximal tubule. Sigurd and Oleson[28] established that the proximally-acting phosphodiesterase inhibitor aminophylline (theophylline ethylenediamine), in combination with long term treatment with bumetanide 2mg 3 times daily in patients with CHF, produced a synergistic effect. Addition of the proximally acting diuretic drug appeared to be superior to monotherapy with bumetanide given in a daily dosage of up to 6mg.[28] It should be noted that theophylline has not only diuretic properties, but also inotropic and chronotropic effects, which may contribute to the improvement of natriuresis in CHF. However, the use of theophylline as a diuretic drug in heart failure may be limited by its chronotropic effects.

In a recent study, it was established that coadministration of the carbonic anhydrase inhibitor acetazolamide, to heart failure patients with an inadequate natriuretic response to furosemide, was very effective.[29]

These studies clearly show that the combination of a loop diuretic and a diuretic acting on the proximal tubule has synergistic diuretic effects in the acute phase. However, no information is currently available on the efficacy of this combination when applied on a long term basis. Moreover, it has not been established whether treatment with diuretics acting on the proximal tubule induces structural and functional changes in the downstream segments of the nephron.

2.2 Loop Diuretics and Diuretics Acting on the Distal Convoluted Tubule

Many clinical studies report the synergistic effect of loop diuretics and thiazides or thiazide-like drugs in CHF.[30-42] The guidelines of the American College of Cardiology/American Heart Association and the European Society of Cardiology on the treatment of heart failure recommend the use of this combination in case of diuretic resistance to a loop diuretic.[1,43] As described above (section 1.2), the mechanism behind this synergism consists of functional adaptations in the distal tubule following chronic administration of a loop diuretic.[21,23,44] Many different thiazide and thiazide-like drugs have been used in combination with a loop diuretic. Most of the published data relates to metolazone. However, comparisons of thiazides with respect to

their efficacy when used in combination therapy are sparse.[45] On the basis of the available literature, thiazide drugs are equally effective.

Used as monotherapy, thiazides are ineffective at glomerular filtration rates <30 ml/min. However, coadministration of thiazides increases the efficacy of a loop diuretic in patients both with and without renal failure.[35,41,42]

2.3 Loop Diuretics and Diuretics Acting on the Collecting Duct Tubule

Addition of triamterene or amiloride to a loop diuretic appears to have a limited effect on natriuresis, probably because the sodium reabsorbing capacity of this part of the nephron is small.[11] On the other hand, coadministration of spironolactone (100mg once a day) in CHF refractory to high-dose bumetanide (10 mg per day), improves natriuresis significantly.[46]

3. Indications for Combinations of Diuretics in Heart Failure

In case of an inadequate response to diuretics in a patient suffering from heart failure, a stepwise evaluation may help to find the reason:

- Is the patient really overhydrated? A careful physical examination usually will answer this question. During long term follow-up of a patient, bodyweight is a very important parameter.
- Ensure that there are no causes for oedema other than heart failure. Hypoalbuminaemia and other causes of heart failure that need to be treated by other means [e.g. valvular disease or (constrictive) pericarditis] need to be excluded.
- How is patient compliance to the medical regimen? It should be emphasised that adherence to a sodium-restricted diet is essential for the success of diuretic treatment. This can be evaluated by determination of urinary sodium excretion. If urinary sodium excretion is >100 mmol/day, without any concurrent bodyweight change, poor compliance with dietary therapy (and not diuretic resistance) is the cause of persistent oedema. When poor compliance with drug intake is suspected, urinary drug excretion may be evaluated.
- When noncompliance with the medical regimen is excluded, diuretic resistance is identified as the cause of therapy-resistant oedema.

When diuretic resistance is present, improvement of the efficacy of the loop diuretic prescribed could be the next step:

- Increase the dosage of the loop diuretic. Large doses of furosemide (daily oral dosage up to 2000mg) have been shown to overcome diuretic resistance.[47] Many clinicians feel reluctant to use such high dosages of diuretics, because of the potential for ototoxicity.[48] In our experience, however, irreversible ototoxicity only occurred after coadministration of aminoglycosides. In addition, audiometric evaluations have revealed that short term completely reversible ototoxic adverse effects occurred significantly more frequently after administration of intravenous bolus injections of furosemide than after administration of an equal dosage as a continuous intravenous infusion (TPJ Dormans et al., unpublished data).
- Administer the loop diuretic two or three times a day. This strategy reduces the drug-free intervals, and thus the post-diuretic sodium retention.[49,50] However, inconvenience due to frequent nocturnal voiding should be avoided.

When the effect of these steps is insufficient several additional therapeutic strategies are to be considered:

- Intravenous administration of a loop diuretic increases its bioavailability. The amount of drug delivered to the site of action will be increased. Because the time course of delivery is an important determinant of efficacy, a continuous intravenous infusion is more efficacious than intravenous bolus injections.[51-53] In a recent study it was reported that administration of bumetanide as a continuous infusion triggered less braking than an equal dosage administered as a separate intravenous bolus injection.[54] In other words, the diuretic efficacy is better preserved when using a continuous intravenous infusion.

However, intravenous administration usually makes admission to a hospital necessary.

- Combinations of diuretics are highly effective, but may cause severe metabolic disturbances. Hypokalaemia must be avoided. Other important adverse drug effects are hyponatraemia, dehydration and metabolic alkalosis. This makes frequent control and monitoring of serum electrolytes necessary, especially in the first weeks after addition of the loop diuretic. In addition, it should be remembered that use of combination diuretic therapy may cause too rapid a loss of fluid resulting in hypotension and dehydration. A too vigorous dehydration may result in a temporary decrease of the effective circulatory volume. This may cause hypotension and deterioration of renal function. Therefore, in addition to serum electrolytes and bodyweight, renal function and blood pressure also should be monitored. Finally, noninvasive assessment of the central venous pressure is of value as a valid indicator of the state of hydration.
- It is necessary to tailor the treatment to each individual patient to achieve a gradual reduction of oedema. For these reasons, hospital admission of the patient is preferred when adding a thiazide drug to a loop diuretic.

Although it is generally advocated to increase the dosage of the loop diuretic to the maximum recommended dosage (240mg furosemide per day or an equivalent dosage of another loop diuretic), other strategies have been proven to be successful; firstly, the addition of a thiazide to a low dosage of a loop diuretic in case of an inadequate response to the latter.[55] The theoretical advantage of early introduction of a thiazide in the course of development of diuretic resistance is that the thiazide may prevent functional and structural adaptations in the distal convoluted tubule or reverse them at an early stage.[23] A variation on this treatment schedule is the intermittent addition of thiazides, e.g. twice a week. Titration can be achieved using bodyweight changes as the most important parameter.[10] Secondly, monotherapy with high-dose furosemide (daily dosages varying from 250 to 4000mg) has been shown to be safe and effective.[47,56] Addition of a thiazide to these high dosages of furosemide has been shown to be a powerful diuretic tool in patients with severe CHF.[42]

In cases where even the combined use of a loop diuretic and a thiazide fails to reduce extracellular volume to the desired level, there are still some alternatives. By addition of a inotropic drug, e.g. dobutamine or milrinone, improvement of cardiac output can be achieved. This may lead to an increase of the amount of filtered sodium. In addition, extracorporeal techniques (haemofiltration, haemodialysis, peritoneal dialysis) may lead to short term improvement and restoration of diuretic responsiveness.[57-59] However, in our opinion, the results of the chronic intermittent use of haemofiltration and haemodialysis have been disappointing, and therefore should be reserved for remediable cases of heart failure or as a bridge to heart transplantation.[60]

4. Conclusions

The combined use of a loop diuretic and a diuretic acting on the distal convoluted tubule has been shown to be a very powerful tool in the treatment of diuretic resistance to conventional therapy in CHF. However, adverse effects, especially hypokalaemia, necessitate frequent control and monitoring of serum electrolytes and the clinical condition of the patient after initiation of this therapy. An important mechanism behind this diuretic synergism is the functional adaptation of the distal convoluted tubule after chronic administration of loop diuretics.

References

1. Guidelines for the evaluation and management of heart failure: a report of the American Heart Association Task Force on Practice Guidelines. Circulation 1995; 92: 2764-84
2. Reitsma JB, Mosterd A, Craen de AJM, et al. Increase in hospital admission rates for heart failure in the Netherlands, 1980-1993. Heart 1996; 76: 388-92
3. Rodeheffer RJ, Jacobsen SJ, Gersh BJ, et al. The incidence and prevalence of congestive heart failure in Rochester, Minnesota. Mayo Clin Proc 1993; 68: 1143-50
4. Packer M. Treatment of chronic heart failure. Lancet 1992; 340: 92-5
5. Packer M. Pathophysiology of chronic heart failure. Lancet 1992; 340: 88-92

6. Stevenson LW, Dracup KA, Tillisch JH. Efficacy of medical therapy tailored for severe congestive heart failure in patients transferred for urgent cardiac transplantation. Am J Cardiol 1989; 63: 461-4
7. Vasko MR, Cartwright DB, Knochel JP, et al. Furosemide absorption altered in decompensated congestive heart failure. Ann Intern Med 1985; 102: 314-8.
8. Brater DC, Seiwell R, Anderson S, et al. Absorption and disposition of furosemide in congestive heart failure. Kidney Int 1982; 22: 171-6
9. Chennavasin P, Seiwell R, Brater DC. Pharmacokinetic-pharmacodynamic analysis of the indomethacin-furosemide interaction in man. J Pharmacol Exp Ther 1980; 215: 77-81
10. Cody RJ, Kubo SH and Pickworth KK. Diuretic treatment for the sodium retention of congestive heart failure. Arch Intern Med 1994; 154: 1905-14
11. Ellison DH. The physiologic basis of diuretic synergism: its role in treating diuretic resistance. Ann Intern Med 1991; 114: 886-94
12. Kelly RA, Smith TW. Drugs used in the treatment of heart failure. In: Braunwald E, editor. Heart disease: a textbook of cardiovascular medicine. Philadelphia: WB Saunders Co., 1997: 471-91
13. Hall JE. Control of glomerular filtration rate and sodium excretion by angiotensin II. Fed Proc 1986; 45: 1431-6
14. Blantz RC. The glomerular and tubular actions of angiotensin II. Am J Kidney Dis 1987; 10 Suppl. I: 2-10
15. Mancia G. Neurohumoral activation in congestive heart failure. Am Heart J 1990; 120: 1532-7
16. Mancia G. Sympathetic activation in congestive heart failure. Eur Heart J 1990; 11 Suppl. A: 3-11
17. Kon V, Yared A, Ichikawa I. Role of sympathetic nerves in mediating hypoperfusion of renal cortical microcirculation in experimental congestive heart failure and acute extracellular volume depletion. J Clin Invest 1985; 76: 1913-20
18. Brater DC, Chennavasin P, Seiwell R. Furosemide in patients with heart failure: shift in dose-response curves. Clin Pharmacol Ther 1980; 28: 182-6
19. Wakelkamp M, Alvan G, Gabrielsson J, et al. Pharmacodynamic modeling of furosemide tolerance after multiple intravenous administration. Clin Pharmacol Ther 1996; 60: 75-88
20. Wilcox CS, Guzman NJ, Mitch WE, et al. Na^+, K^+, and BP homeostasis in man during furosemide: effects of prazosin and captopril. Kidney Int 1987; 31: 135-41
21. Kaissling B, Stanton BA. Adaptation of distal tubule and collecting duct to increased sodium delivery: I. Ultrastructure. Am J Physiol 1988; 255: F1256-68
22. 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: F1269-75
23. Morsing P, Velazquez H, Wright FS, et al. Adaptation of distal convoluted tubule of rats: II. Effects of chronic thiazide infusion. Am J Physiol 1991; 261: F137-43
24. Stanton BA, Kaissling B. Regulation of renal ion transport and cell growth by sodium. Am J Physiol 1989; 257: F1-10
25. Loon NR, Wilcox CS and Unwin RJ. Mechanism of impaired natriuretic response to furosemide during prolonged therapy. Kidney Int 1989; 36: 682-9
26. Ellison DH, Velazquez H, Wright FS. Thiazide-sensitive sodium chloride cotransport in early distal tubule. Am J Physiol 1987; 253: F546-54
27. Brater DC, Day B, Burdette A, et al. Bumetanide and furosemide in heart failure. Kidney Int 1984; 26: 183-9
28. Sigurd B, Olesen KH. The supra-additive natriuretic effect addition of theophylline ethylenediamine and bumetanide in congestive heart failure: permutation trial tests in patients in long-term treatment with bumetanide. Am Heart J 1977; 94: 168-74
29. Knauf H, Mutschler E. Sequential nephron blockade breaks resistance to diuretics in edematous states. J Cardiovasc Pharmacol 1997; 29: 367-72
30. Olesen KH, Dupont B, Flensted Jensen E. The combined diuretic action of quinethazone and furosemide in congestive heart failure: a permutation trial test. Acta Med Scand 1970; 187: 33-40
31. Gunstone RF, Wing AJ, Shani HG, et al. Clinical experience with metolazone in fifty-two African patients: synergy with frusemide. Postgrad Med J 1971; 47: 789-93
32. Sigurd B, Olesen KH, Wennevold A. The supra-additive natriuretic effect addition of bendroflumethiazide and bumetanide in congestive heart failure: permutation trial tests in patients in long-term treatment with bumetanide. Am Heart J 1975; 89: 163-70
33. Ghose RR, Gupta SK. Synergistic action of metolazone with 'loop' diuretics. Br Med J Clin Res Ed 1981; 282: 1432-3
34. Epstein MR, Lepp BA, Hoffman A, et al. Potentiation of furosemide by metolazone in refractory edema. Curr Ther Res 1977; 21: 656-67
35. Wollam GL, Tarazi RC, Bravo EL, et al. Diuretic potency of combined hydrochlorothiazide and furosemide therapy in patients with azotemia. Am J Med 1982; 72: 929-38
36. Brater DC, Pressley RH, Anderson SA. Mechanisms of the synergistic combination of metolazone and bumetanide. J Pharmacol Exp Ther 1985; 233: 70-4
37. Reubi FC. Combination diuretic drug therapy. Cardiovasc Clin 1971; 2: 197-210
38. Oster JR, Epstein M, Smoller S. Combined therapy with thiazide-type and loop diuretic agents for resistant sodium retention. Ann Intern Med 1983; 99: 405-6
39. Kiyingi A, Field MJ, Pawsey CC, et al. Metolazone in treatment of severe refractory congestive cardiac failure. Lancet 1990; 335: 29-31
40. Channer KS, Richardson M, Crook R, et al. Thiazides with loop diuretics for severe congestive heart failure. Lancet 1990; 335: 922-3
41. Fliser D, Schroter M, Neubeck M, et al. Coadministration of thiazides increases the efficacy of loop diuretics even in patients with advanced renal failure. Kidney Int 1994; 46: 482-8
42. Dormans TPJ, Gerlag PGG. Combination of high-dose furosemide and hydrochlorothiazide in the treatment of refractory congestive heart failure. Eur Heart J 1996; 17: 1867-74
43. Task Force of the Working Group on Heart Failure of the European Society of Cardiology. The treatment of heart failure. Eur Heart J 1997; 18: 736-53
44. 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: 113-26
45. 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: 146-50
46. 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-8A

47. Gerlag PG, van Meijel JJ. High-dose furosemide in the treatment of refractory congestive heart failure. Arch Intern Med 1988; 148: 286-91
48. Rybak LP. Furosemide ototoxicity: clinical and experimental aspects. Laryngoscope 1985; 95: 1-14
49. Brater DC. Resistance to loop diuretics: why it happens and what to do about it. Drugs 1985; 30: 427-43
50. Hammarlund Udenaes M, Benet LZ. Furosemide pharmacokinetics and pharmacodynamics in health and disease – an update. J Pharmacokinet Biopharm 1989; 17: 1-46
51. Kaojarern S, Day B, Brater DC. The time course of delivery of furosemide into urine: an independent determinant of overall response. Kidney Int 1982; 22: 69-74
52. 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: 360-6
53. Dormans TPJ, van Meyel JJM, Gerlag PGG, et al. Diuretic efficacy of high-dose furosemide in severe heart failure: bolus injection versus continuous infusion. J Am Coll Cardiol 1996; 28: 376-82
54. Ferguson JA, Sundblad KJ, Becker PK, et al. Role of duration of diuretic effect in preventing sodium retention. Clin Pharmacol Ther 1997; 62: 203-8
55. 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
56. 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: 329-34
57. Simpson IA, Rae AP, Simpson K, et al. Ultrafiltration in the management of refractory congestive heart failure. Br Heart J 1986; 55: 344-7
58. Rimondini A, Cipolla CM, Della Bella P, et al. Hemofiltration as short-term treatment for refractory congestive heart failure. Am J Med 1987; 83: 43-8
59. Rubin J, Ball R. Continuous ambulatory peritoneal dialysis as treatment of severe congestive heart failure in the face of chronic renal failure. Report of eight cases. Arch Intern Med 1986; 146: 1533-5
60. Dormans TPJ, Huige RMC, Gerlag PGG. Chronic intermittent haemofiltration and haemodialysis in end stage chronic heart failure with oedema refractory to high dose frusemide. Heart 1996; 75: 349-51

Correspondence and reprints: Dr *Tom PJ Dormans*, Department of Intensive Care, University Hospital Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands.
E-mail:tom.dormans@pi.net