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Combination of high-dose furosemide and hydrochlorothiazide in the treatment of refractory congestive heart failure

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Objective We studied the synergism between high-dose furosemide and hydrochlorothiazide in patients with severe congestive heart failure and impaired renal function showing diuretic resistance to a daily dose of furosemide of at least 250 mg.

Design and setting An open study. A general hospital in The Netherlands.

Methods In 20 patients with severe congestive heart failure (stage III–IV according to the New York Heart Association) with an oedematous mass of more than 5 kg and a proven diuretic resistance to high-dose furosemide, hydrochlorothiazide (25–100 mg daily) was added to the medication for 3–12 days, leaving the other medication unchanged. After correction of the hydration state, hydrochlorothiazide was withdrawn. Variables included body weight, serum electrolytes, renal function and natriuresis.

Results Addition of hydrochlorothiazide resulted in a mean (± standard deviation) body weight reduction of 6·7 ± 3·3 kg per patient. Mean daily urine volume increased from 1899 ± 958 ml to 3065 ± 925 ml ($P<0·001$). Fractional sodium excretion increased significantly from 3·5 ± 3·2% to 11·5 ± 9·0% ($P<0·001$). The most important side effect of this combination therapy appeared to be hypokalaemia. Mean endogenous creatinine clearance decreased (not significantly) from 32·7 ± 22·5 ml . min^{-1} . 1·73 m^{-2} to 27·6 ± 22·5 ml . min^{-1} . 1·73 m^{-2}.

Conclusions Addition of hydrochlorothiazide to high-dose furosemide is a powerful diuretic tool, even in patients with a significantly reduced renal function. Because of its potentially dangerous side effects (hypokalaemia), it should be used in a carefully controlled setting.
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Key Words: Diuretics, diuretic resistance, oedema, furosemide, heart failure, hydrochlorothiazide.

Introduction

In the majority of patients with congestive heart failure no causal treatment for the underlying disease is available, thus only symptomatic therapy remains. The basis of the management of decompensated patients consists of restriction of both physical activity and sodium intake together with pharmacological therapy. In the management of patients with advanced chronic heart failure, pharmacological treatment comprises angiotensin converting enzyme inhibitors, vasodilators, digitalis and diuretics[1]. Diuretics, most frequently the potent loop diuretics, are universally used once fluid retention occurs.

The usually recommended doses of loop diuretics will lead to clinical improvement in the majority of patients, but in some this fails to reduce oedema. In patients with refractory congestive heart failure, the glomerular filtration rate is often significantly reduced to a level of about 30 ml . min^{-1} due to both pre-renal (low cardiac output, renal vasoconstriction due to sympathetic excitation) and renal (arteriosclerosis) factors[2]. In these cases, conventional doses of loop diuretic appear to be too low to create an adequate concentration in the renal tubule, resulting in an insufficient diuretic response. In these patients, administration of high-dose furosemide (250 to 4000 mg per day) — supplied either orally or as a more effective continuous intravenous infusion — has been shown to be effective and safe[2,3].

However, in a few patients with severe congestive heart failure even chronic therapy with high-dose furosemide fails to reduce the volume of the extracellular compartment to the desired level and again diuretic

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Table 1 Characteristics of study patients and diuretic regimes

Patient no.	Sex M/F	Age (years)	Cause of illness	Furosemide dosage (mg . day^{-1})	Other diuretics (mg . day^{-1})	Hydrochlorothiazide dosage (mg . day^{-1})	Period of combination (days)
1	M	61	CM	2000 PO	TRIAM:50	100	8
2	M	71	CAD	2000 PO	SPIRO:50/AMILO:10	100	4
3	M	58	CAD	2000 PO	—	50	3
4	M	64	CAD	4000 IV	AMILO:10	50/100	3/7
5	M	73	CAD+VD	2000 PO	AMILO:5/TRIAM:50	100	4
6	M	66	CAD	500 PO	—	25/50/100	6/3/3
7	M	69	CAD	2000 PO	SPIRO:100	50	3
8	F	70	VD	500 PO	AMILO:10	50	5
9	M	86	CAD	4000 IV	TRIAM:50	100	3
10	M	78	CAD	1000 IV	TRIAM:50	25	4
11	M	83	CAD	500 PO	TRIAM:50	25	4
12	M	86	CAD	500 PO	AMILO:5	25	5
13	M	51	CM	500 PO	SPIRO:100	25	7
14	F	80	CAD	2000 IV	TRIAM:50	50	15
15	F	81	CAD	1000 PO	—	25	5
16	F	83	CAD	2000 IV	—	25	6
17	M	78	VD	2000 IV	TRIAM:50	25	9
18	M	30	CM	3000 IV	AMILO:10	25	15
19	F	79	VD	250 PO	AMILO:5	25	5
20	F	69	CAD	500 PO	—	25	10

CM=cardiomyopathy; CAD=coronary artery disease; VD=valvular disease; PO=supplied orally; IV=supplied intravenously; TRIAM=triamterene; AMILO=amiloride; SPIRO=spironolactone.

resistance ensues. A combination of diuretics acting on different segments of the nephron may then be a possible approach to master diuretic resistance.

The synergism between loop diuretics and thiazides has been described in several studies[4–13]. However, in all studies concerning the synergism of diuretics, loop diuretic doses were relatively low (i.e. oral furosemide lower than 500 mg . day^{-1}) and in most of these studies renal function was fair. While thiazides used as monotherapy are thought to be no longer effective when the glomerular filtration rate falls below approximately 25 to 30 ml . min^{-1}[14,15], there are nevertheless limited data showing that addition of a thiazide to a loop diuretic increases natriuresis in patients with advanced renal failure[10,16].

We studied the effects of the addition of hydrochlorothiazide to high-dose furosemide in patients with severe congestive heart failure who showed an impaired natriuretic response to high-dose furosemide (250–4000 mg), or who were already receiving the drug in combination with a diuretic acting on the collecting ducts.

Patients and methods

After approval of the protocol by the local ethics committee, we selected 20 inpatients (six female, 14 male) with severe congestive heart failure (stage III (n=5) or IV (n=15) according to the New York Heart Association classification) who gave their informed consent for the study, which was performed between December 1989 and October 1994. All patients had an estimated oedematous mass of at least 5 kg and diuretic resistance. Diuretic resistance was defined as a failure to lose weight and/or create a negative sodium balance despite bedrest, restricted salt and fluid intake, a diuretic regime of high-dose furosemide (250 to 4000 mg daily), administered orally or by continuous intravenous infusion, either or not in combination with potassium-sparing diuretics (triamterene, amiloride and/or spironolactone). All studied patients had been using high-dose furosemide for at least 2 weeks before the start of the study. Differences in diuretic regimes between the patients occurred because they were referred for treatment by various departments. During the study 12 patients used angiotensin converting enzyme inhibitors; in four patients enalapril was withdrawn soon after its introduction because of progressive renal impairment, while in two other patients enalapril caused symptomatic hypotension. In two others we could find no reason retrospectively for withdrawal of angiotensin converting enzyme inhibition. Ten patients used digoxin while none used dobutamine and/or low-dose dopamine.

The relevant patient characteristics are presented in Table 1. Mean age was 70·8 years (range 30 to 86 years) and the mean body weight at the start of the study was 73·7 kg (55·2 to 96·8 kg). The underlying cause of heart failure was coronary artery disease (n=13), valvular disease (n=3), cardiomyopathy (n=3) and a combination of coronary artery disease and valvular disease (n=1). The left ventricular ejection fraction, estimated by cross sectional echocardiography, was less than 25% in all patients.

During the entire study the daily dietary sodium intake was limited to 80 mmol and the fluid intake to

1500 ml. Physical examination including measurement of body weight, supine and standing blood pressures, pulse rate, central venous pressure (determined by visual inspection of the neck veins[17]) and assessment of oedematous mass was performed daily. Patients were interviewed daily for recognition of side effects. The total daily output of urine was collected for creatinine, sodium, potassium chloride and protein measurements. Daily blood samples were taken to determine serum sodium, potassium chloride, bicarbonate, albumin, uric acid, creatinine and urea. Monitoring was started at least 2 days before administration and was continued until 2 days after withdrawal of hydrochlorothiazide. Hydrochlorathiazide, either 50 or 100 mg (creatinine clearance >25 ml . min^{-1} . 1·73 m^{-2}: 100 mg hydrochlorothiazide, creatinine clearance <25 ml . min^{-2} . 1·73 m^{-2}: 50 mg hydrochlorothiazide), was added, leaving dosages of other medication (other diuretics included) unchanged. Because three of the patients treated this way showed signs of dehydration several days after withdrawal of hydrochlorothiazide, we decided to lower the starting dose to 25 mg hydrochlorothiazide in an attempt to avoid accumulation of hydrochlorothiazide. In two patients the dosage of hydrochlorothiazide was increased during the study, because the initial dose appeared to be ineffective. Potassium supplements were given when serum potassium was lower than 3·5 mmol . l^{-1}.

Patients were treated with a combination of high-dose furosemide and hydrochlorothiazide during a period varying from 3 to 12 days. When the hydration status of a patient was judged appropriate, hydrochlorothiazide was stopped. In two patients the hydrochlorothiazide medication was discontinued despite insufficient weight loss. Because there was a significant increase in natriuresis, we concluded that in these two patients weight loss was not achieved due to poor compliance with the dietary restrictions.

Results are expressed as mean ± SD. The Wilcoxon test was performed when the parameters before and after combined treatment with high-dose furosemide and hydrochlorothiazide were compared.

Results

In the period preceding the combination therapy, when only high-dose furosemide was administered, natriuresis was low in most patients indicating that sodium-retaining mechanisms were activated. However, four patients showed a natriuresis of more than 125 mmol . day^{-1} without weight reduction (range 137–188 mmol . 24 h^{-1}), which can be explained by poor compliance with the dietary restriction. The low natriuresis in the other patients (53 ± 32 mmol . 24 h^{-1}, ranging from 7 to 100 mmol . 24 h^{-1}) confirms the diuretic resistance to high-dose furosemide. A typical example of the effect of the combination therapy is shown in Fig. 1. The average weight reduction during the 5 days preceding the addition of hydrochlorothiazide was 0·6 ± 1·2 kg (n=17); in three patients hydrochlorothiazide had been added already, 2 days after admission to hospital, because of the severity of the symptoms. Patients were treated with a combination of high-dose furosemide and hydrochlorothiazide during a period varying from 3 to 12 days. During this treatment period, body weight reduction varied from 2·2 to 14·0 kg (6·7 ± 3·3 kg). After withdrawal of hydrochlorothiazide, the longest period of weight stabilization was in excess of 2 weeks in 16 patients. During the use of combined diuretic therapy, mean fractional sodium excretion increased from 3·5 ± 3·2% to 11·5 ± 90% ($P<0·001$) (Table 2). After stopping the administration of hydrochlorothiazide, fractional sodium excretion returned to the previous low level. However in three patients, using either 100 mg or 50 mg hydrochlorothiazide, the increased natriuresis lingered on, resulting in dehydration more than 2 days after stopping the combination therapy.

All patients in this study had a reduced renal function. Improvement of the hydration state of these patients induced a (not significant) reduction in endogenous creatinine clearance (32·7 ± 22·5 ml . min^{-1} . 1·73 m^{-2}, (range 4·4 to 110·7 ml . min^{-1} . 1·73 m^{-2}) prior to combination therapy vs 27·6 ± 22·5 ml . min^{-1} . 173 m^{-2} (range 8·9 to 100·8 ml . min^{-1} . 1·73 m^{-2} after)). In six patients correction of the hydration state resulted in an improvement of endogenous creatinine clearance.

Hypokalaemia was an important side effect of the simultaneous administration of high dose furosemide and hydrochlorothiazide; the elevated potassium excretion (65 ± 33 mmol . day^{-1} prior vs 115 ± 55 during combined administration) resulted in hypokalaemia in 15 patients (serum potassium lower than 3·5 mmol . l^{-1}), which could only be corrected by enlarging the potassium intake. The lowest mean serum potassium measured during the combination therapy was 3·3 ± 0·5 mmol . l^{-1} (ranging from 2·2 to 4·2 mmol . l^{-1}). It should be noted, that before hydrochlorothiazide was added to the medication, most of the patients were already using potassium-sparing diuretics (see Table 1) which failed to prevent the development of serious hypokalaemia.

On average, the patients were mildly hyponatraemic (mean serum sodium 136 ± 5 mmol . l^{-1} (reference value 138 to 144 mmol . l^{-1})), which was (not significantly) aggravated during the combination therapy (134 ± 8 mmol . l^{-1}). Although serum uric acid concentration increased (not significantly) during the combined use of high-dose furosemide and hydrochlorothiazide (0·67 ± 0·26 mmol . l^{-1} prior vs 0·79 ± 0.27 mmol . l^{-1} post, $P<0·05$), none of the patients developed attacks of gouty arthritis.

No side-effects of this therapy, in particular hearing loss or tinnitus were recorded. No hypotensive episodes were observed during therapy.

Eight patients were reallocated from NYHA class IV to III as a result of the treatment, and one of five class III patients improved to class II. Fourteen

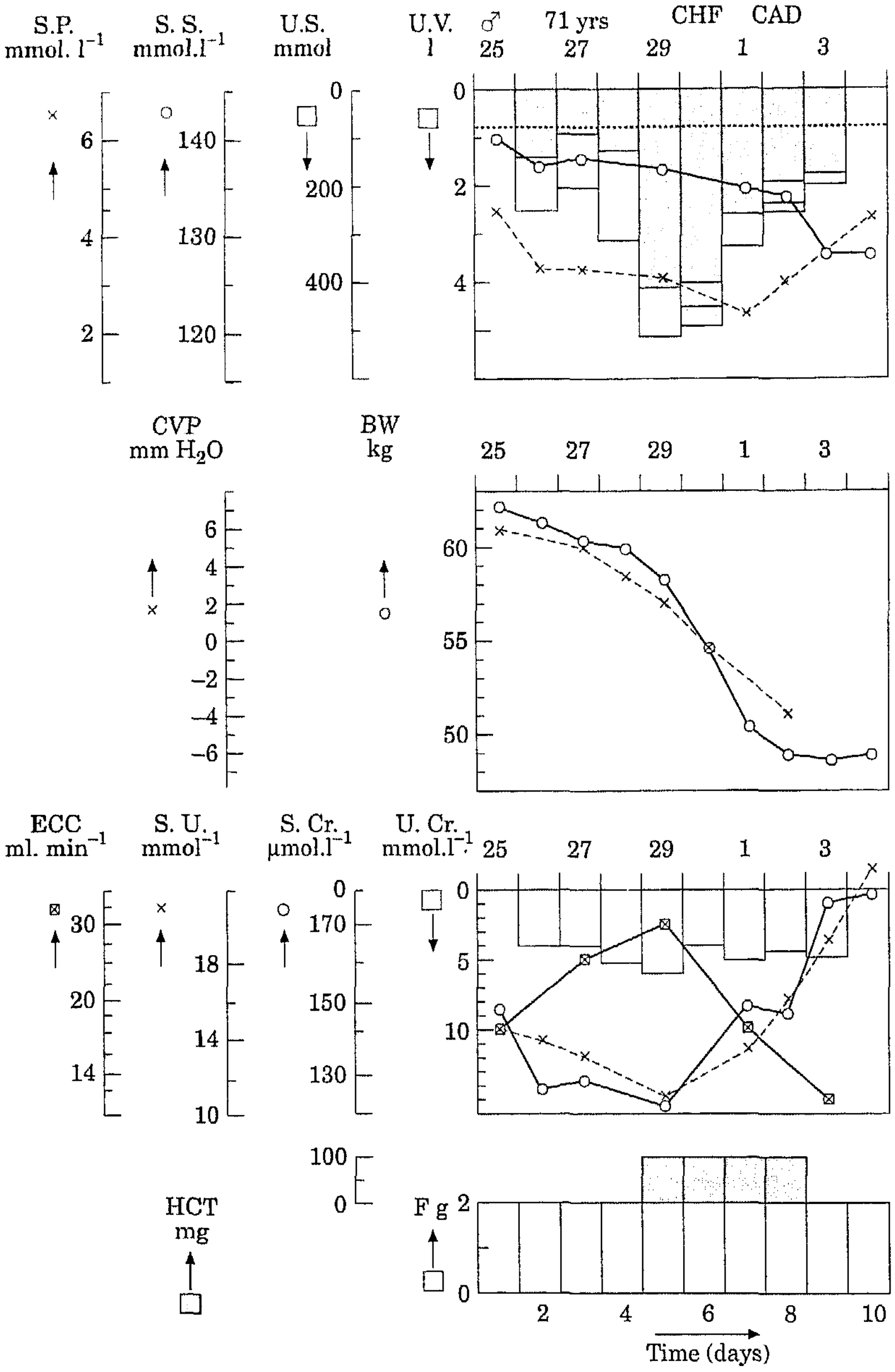

Figure 1 Treatment results in a 71-year-old man with chronic heart failure (CHF) caused by coronary artery disease (CAD, patient 2). The lowest panel shows the diuretic therapy: to 2 g furosemide (F) per day administered orally as the basic regimen, 100 mg hydrochlorothiazide (HCT) was added on 4 consecutive days. The fixed dose of spironolactone (50 mg) and amiloride (10 mg) is not shown. The upper panel shows the daily urine volume (UV), natriuresis (US) and the course of serum sodium (SS) and serum potassium (SP), respectively. The dotted horizontal line represents the daily dietary sodium intake. Note that the lowest serum potassium value was 2·2 mmol . l^{-1} which increased after the potassium chloride intake was raised to 160 mmol per day, in addition to the potassium sparing diuretics. The upper middle panel shows the effects of treatment on bodyweight (BW) and central venous pressure (CVP). The lower middle panel shows the daily creatinine excretion (UCr), the course of serum creatinine (SCr) and urea (SU) levels, and endogenous creatinine clearance (ECC).

Table 2 Effects of combined administration of high-dose furosemide and hydrochlorothiazide

	Before treatment	During treatment	After treatment
BW (kg)	73·7 ± 13·9		67·0 ± 13·3
BW reduction (kg . day^{-1})	0·1 ± 0·3**	1·3 ± 0·8‡	
UV (ml . 24 h^{-1})	1899 ± 958	3065 ± 925‡	2000 ± 666
U_{Sodium} (mmol . 24 h^{-1})	85 ± 58	206 ± 84‡	84 ± 58
$U_{Potassium}$ (mmol . 24 h^{-1})	65 ± 33	115 ± 55‡	83 ± 33*
$U_{Chloride}$ (mmol . 24 h^{-1})	100 ± 67	243 ± 94‡	116 ± 65
FeNa (%)	3·5 ± 3·2	11·5 ± 9·0‡	2·9 ± 1·9
S_{Sodium} (mmol . l^{-1})	136 ± 5		134 ± 8
$S_{Potassium}$ (mmol . l^{-1})	4·1 ± 0·5	3·3 ± 0·5‡	4·2 ± 0·7
$S_{Chloride}$ (mmol . l^{-1})	94 ± 5		86 ± 8‡
$S_{Bicarbonate}$ (mmol . l^{-1})	28 ± 2		33 ± 4*
$S_{Creatinine}$ (μmol . l^{-1})	148 ± 69		177 ± 78*
S_{Urea} (mmol . l^{-1})	17 ± 6		26 ± 10‡
ECC (ml . min^{-1} 1.73 m^{-2})	32·7 ± 22·5		27·6 ± 22·5
$S_{Albumin}$ (g . l^{-1})	33·0 ± 5·2		35·6 ± 3·9*
$S_{Uric\ Acid}$ (mmol . l^{-1})	0·67 ± 0·26		0·79 ± 0·27†

BW=body weight; UV=urine volume; U_{Sodium}, etc=urine electrolyte excretion; FeNa=fractional sodium excretion; ECC=endogenous creatinine clearance; S_{Sodium}, etc=serum concentrations. Results are mean ± standard deviation.
*=$P<0·05$, †=$P<0·01$, ‡=$P<0·001$, *compared to before treatment with the Wilcoxon-test.*
**=n=17.
The value of serum potassium during treatment represents the nadir of serum potassium during treatment. Administration of potassium supplements was started at a serum potassium value of 3·5 mmol . l^{-1}.

patients were fit enough to be discharged from hospital. Fifteen patients died with a mean survival of 122 ± 129 days (ranging from 0 to 404 days) after termination of the high-dose furosemide and hydrochlorothiazide treatment. Five patients were still alive after a 1-year follow-up period.

Discussion

In the past 20 years the synergism between loop diuretics and thiazides has been described in several studies[4–13]. However, administration of loop diuretics in these studies in relatively low doses (i.e. oral furosemide lower than 500 mg . day^{-1}) and to our knowledge this is the first study describing this synergism in patients with severe congestive heart failure and advanced renal failure showing diuretic resistance to high-dose furosemide.

Under physiological conditions, approximately 25% of the filtered NaCl is reabsorbed in the loop of Henle, while 5% to 10% is reabsorbed in the distal tubule. However, the distal tubules have the ability to increase NaCl transport capacity when the delivered load in this segment of the nephron increases[18–20]. Furosemide acts from the tubular lumen on the thick ascending limb of the loop of Henle and blocks the major part of the sodium reabsorbing capacity in this part of the nephron. As a result, more sodium is delivered to the distal parts of the nephron. In rats, a chronic increment of sodium delivery to the distal tubules appeared to induce hyperplasia of the cells and an increase of the sodium transport capacity in this segment[18,21,22]. It was shown that the sodium retaining capacity of the distal convoluted tubule was increased substantially after chronic use of loop diuretics and this seems to be an important cause of diuretic resistance[18,19,21,22].

Administration of high-dose furosemide, preferably given as a continuous intravenous pump infusion, has been demonstrated to be a safe, efficient and controllable method of overcoming diuretic resistance to usually recommended doses (40 to 250 mg daily) in chronic heart failure[2,3]. The patients presented here all used high doses of furosemide (at least 250 mg daily), administered either orally or by continuous intravenous pump infusion, for at least 2 weeks, prior to combined use of high-dose furosemide and hydrochlorothiazide. During this phase, fractional sodium excretion was low in all patients, reflecting diuretic resistance. It is also possible that diuretic resistance to high-dose furosemide was the result of decreased tubular excretion of furosemide, because we did not measure renal furosemide excretion. In an animal experimental study it was shown that triamterene (and not amiloride or spironolactone) inhibits the tubular secretion of furosemide in a non-competitive manner[23]. However, in the latter study, as well as in the studies on the coadministration of furosemide and triamterene in humans, this coadministration resulted in increased natriuresis[24,25]. Therefore, it is unlikely that administration of triamterene together with high-dose furosemide (n=7) will attribute the diuretic resistance to high-dose furosemide, as observed in the

patients in this study. Another possible cause for this diuretic resistance to high-dose furosemide could be a reduced response in the loop of Henle. However, the striking natriuretic response during combined use of high dosages of furosemide and hydrochlorothiazide in the patients presented here suggests that these furosemide doses are able to reduce sodium reabsorption in the loop, even after prolonged use.

In most of the studies describing the synergism between loop diuretics and thiazides, the former was combined with metolazone, a diuretic agent which is registered in only a few countries in Europe. Metolazone is structurally related to the benzothiadiazines, with pharmacological effects similar to hydrochlorothiazide [14,26]. The major action of hydrochlorothiazide, like other thiazides, is from the luminar surface on the distal convoluted tubule. Used as monotherapy, hydrochlorothiazide has no significant diuretic effect on diuresis in patients with a considerably impaired renal function (endogenous creatinine clearance lower than 30 ml . min^{-1} . 1·73 m^{-2})[15,26]. One patient was subsequently treated with high-dose furosemide alone, hydrochlorothiazide alone and a combination of high-dose furosemide and hydrochlorothiazide (data not shown). Only the latter treatment resulted in increased natriuresis.

For these reasons, it seems unlikely that hydrochlorothiazide could by itself account for the natriuresis during the period of combined use of furosemide and hydrochlorothiazide in the patients presented. Therefore, it is most probably the increased sodium reabsorbing capacity of the distal tubules and the collecting ducts in these patients that causes a diminished natriuretic response to high-dose furosemide. Evidence for the presence of this mechanism in humans was found in a previous study[27]. Animal studies showed that even the increased sodium reabsorbing capacity of the distal tubule after chronic furosemide treatment could be almost completely blocked by thiazides[19,28].

Thus, the simultaneous administration of high-dose furosemide and hydrochlorothiazide leads to decreased sodium reabsorption in the loop of Henle and to a block of the increased sodium transport capacity in the distal tubule, resulting in a significant increase in fractional sodium excretion.

The addition of hydrochlorothiazide in patients after chronic administration of loop diuretics (all patients in this study used high-dose furosemide for at least 2 weeks) instead of simultaneous introduction of the two diuretic drugs might be even more powerful because of the increased sodium reabsorbing capacity of the distal tubule in these patients. This increased reabsorbing capacity could also explain why hydrochlorothiazide is still effective in those patients with a reduction of the renal function below the level where thiazides as monotherapy are reported to become ineffective. This observation is confirmed by the results of a recent study, showing that coadministration of thiazides increased efficacy of loop diuretics in patients with advanced renal failure[16].

In this study, we did not analyse the effects of the addition of a diuretic acting specifically on the proximal tubule, to furosemide and hydrochlorothiazide on natriuresis. In some of our patients we observed that the natriuretic effect of the combination of diuretics described persisted some days after administration of hydrochlorothiazide was stopped. Three patients showed signs of dehydration some days after withdrawal of hydrochlorothiazide, and required intravenous rehydration. The reason for this prolonged effect might be the reduced renal clearance of hydrochlorothiazide in these patients (who all used 50 mg or 100 mg hydrochlorothiazide) with an impaired renal function resulting in a longer half life and accumulation of hydrochlorothiazide[26]. A better cardiac output after amelioration of the hydration state or a stronger osmotic diuretic effect of the higher serum urea are other possible explanations for the improved natriuresis after the combined treatment.

It should be emphasized that the combination of high-dose furosemide and hydrochlorothiazide should only be used under carefully controlled circumstances. Besides side-effects like hyponatraemia, alkalosis, dehydration and loss of renal function, severe hypokalaemia should be avoided most of all. Daily clinical and laboratory examinations should be performed until a new equilibrium has been achieved. The (not significant) reduction in renal function can be caused by slight dehydration or by a direct effect of hydrochlorothiazide[29]. Since the appearance of ototoxic side effects is positively related to the plasma furosemide concentration, patients treated with intravenously administered high-dose furosemide and a reduced renal function (and thus a reduced renal clearance of furosemide) are at risk for ototoxicity[30]. On the other hand, in an earlier study on the use of high-dose furosemide in chronic haemodialysis patients there were no audiometric signs of ototoxicity[31]. To avoid ototoxic plasma concentrations, the patients in this study were mainly treated orally and in all of those receiving furosemide intravenously, furosemide was administered as a continuous infusion. None of the patients in this study complained of hearing loss or tinnitus. However, this study did not comprise an audiometric evaluation.

Left ventricular performance was significantly reduced in all patients studied. They all had end-stage congestive heart failure with a very short life expectancy. Whether survival was prolonged by combined use of high-dose furosemide and hydrochlorothiazide, which is merely a symptomatic therapy, could not be proven because of the absence of a matched control group. The quality of life was definitely improved by reducing peripheral oedema and avoiding symptoms of lung oedema, as demonstrated by the reduction in NYHA class. On the other hand, this therapy may worsen the prognosis. Although chronic diuretic therapy may lead to a decrease in the hyperactivity of the sympathetic nervous system[32], diuretic treatment will cause further stimulation of the renin angiotensinogen system, causing negative haemodynamic effects[33–35]. To reduce these

effects, angiotensin converting enzyme inhibitors and diuretics should be used simultaneously, whenever possible. Furthermore, diuretic therapy can be associated with cardiac arrest[36].

A further benefit of this combination therapy is that an overhydrated state could be treated without the use of invasive techniques such as haemofiltration, haemodialysis or continuous ambulatory peritoneal dialysis, for example to bridge a period to a heart transplantation, as in one of the patients included in this study.

In conclusion, we observed that high-dose furosemide (500 to 4000 mg daily dosage) and hydrochlorothiazide have a powerful synergistic diuretic effect in patients with severe congestive heart failure showing diuretic resistance to high-dose furosemide despite a significantly reduced renal function (mean endogenous creatinine clearance $32{\cdot}7 \pm 22{\cdot}5$ ml . min^{-1} . $1{\cdot}73$ m^{-2}). Because of its side effects, this combination therapy should only be used in a carefully controlled setting and should be reserved for a selected group of patients not responsive to other diuretic regimes.

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