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Coadministration of thiazides increases the efficacy of loop diuretics even in patients with advanced renal failure

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Coadministration of thiazides increases the efficacy of loop diuretics even in patients with advanced renal failure. It is commonly assumed that thiazide diuretics are ineffective in patients with advanced renal failure (GFR < 30 ml/min/1.73 m^2). Thiazides act on the nephron segment distal to the ascending thick loop of Henle, that is, the site of action of loop diuretics. Blockade of sodium reabsorption in the thiazide-sensitive segment should therefore obliterate the compensatory increase in sodium reabsorption seen after administration of loop diuretics and thus potentiate the natriuretic efficacy of loop diuretics even in advanced renal failure. In a single-blind, randomized, placebo controlled crossover study we compared the natriuretic and chloruretic effect of the loop diuretic, torasemide, given alone or in combination with the thiazide diuretic, butizid, in 10 patients with advanced renal failure (mean C_{In} 13.1 ± 5.9 ml/min/1.73 m^2). For two weeks patients adhered to a diet containing a standardized amount of Na^+ and K^+. On the 6th and 13th study days, two sham infusions were given to patients in order to assess basal 24-hour urinary electrolyte excretion. On the 7th and 14th days they were randomly allocated to receive either 50 mg i.v. torasemide in combination with a sham infusion or torasemide in combination with 20 mg i.v. butizid. Administration of torasemide alone significantly ($P < 0.01$) increased mean cumulative 24-hour excretion of sodium (from 154 ± 30 to 232 ± 59 mmol/24 hr) and chloride (from 128 ± 21 to 233 ± 84 mmol/24 hr) as compared with baseline. Administration of torasemide in combination with butizid caused an even more marked increase of mean cumulative sodium (from 156 ± 33 to 290 ± 76 mmol/24 hr) and chloride excretion (from 128 ± 29 to 309 ± 99 mmol/24 hr). The mean cumulative sodium and chloride excretion was significantly greater with coadministration of butizid as compared with torasemide alone ($P < 0.01$). Despite the high sodium load with the diet three patients had an antinatriuretic rebound after the action of torasemide had dissipated. The rebound was abrogated by coadministration of butizid. In conclusion, thiazide diuretics markedly potentiate the natriuretic and chloruretic action of loop diuretics even in patients with advanced renal failure: (i) by amplifying sodium and chloride excretion and, at least in some patients, (ii) by interfering with the antinatriuretic rebound. Coadministration of thiazide diuretics with loop diuretics is therefore rational even in advanced renal failure.

It is commonly assumed that thiazide diuretics are ineffective in patients with advanced renal failure, that is, in patients with a glomerular filtration rate below 30 ml/min/1.73 m^2 [1–3]. Thiazides interfere with sodium and chloride reabsorption in the distal tubule [4, 5]. Since under normal circumstances only about 5 to 10% of filtered sodium reach the tubular site of action of thiazides, natriuresis can increase only by that amount, so that the increment of sodium excretion rate in the final urine is modest [1–3]. The fractional excretion of sodium (FE_{Na}), that is, the proportion of filtered sodium which is excreted in the final urine, increases even in patients with advanced renal failure after thiazide administration [6], although the net increase in absolute sodium excretion remains modest [6–8].

In patients with nephrotic syndrome and in patients with heart failure addition of thiazides to furosemide markedly increased natriuresis [9–11]. Sigurd, Olesen and Wennevold [11] argued that increased tubular sodium rejection induced by a loop diuretic stimulates net sodium reabsorption in more distal sites as a result of increased delivery of sodium. Some authors suggested that thiazides may abrogate such compensatory stimulation of distal sodium reabsorption [11, 12]. Mechanisms augmenting the transport capacity of the distal tubule in response to chronically increased sodium delivery include epithelial cell hypertrophy [13], increased basolateral Na^+-K^+-ATPase activity [14], increased numbers of thiazide-sensitive NaCl transporters [15], and increased trancellular NaCl transport capacity [16]. These considerations are particularly pertinent in chronic renal failure, when endogenous factors inhibit Na^+ reabsorption in more proximal nephron segments so that a high sodium load is delivered to the distal tubule [1–3].

When analyzing the effect of a diuretic agent it is important to measure the sodium and chloride excretion not only during the phase of diuresis, but also during the phase of compensatory increase in sodium reabsorption after the action of the diuretic has waned, the so-called "rebound phase" [3, 12]. While such rebound has been well documented in individuals with normal renal function [17–19], it is not clear whether it also occurs in advanced renal failure. This point is of importance since thiazides are uniquely suited to interfere with rebound antinatriuresis because of their long half-life of action. It was the purpose of the present single-blind, randomized, placebo controlled cross-over study to compare natriuresis and chloruresis following intravenous administration of a loop diuretic (torasemide) in combination with either a placebo infusion or infusion of a thiazide diuretic (butizid). The study was performed in 10 patients with advanced renal failure on controlled intake of sodium chloride.

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Table 1. Clinical data of patients studied

Pat.	Age *years*	Sex	Renal disease	S_{Cr} *mg/dl*	GFR (C_{in}) *ml/min/1.73 m²*	RPF (C_{PAH}) *ml/min/1.73 m²*	PTH *pmol/liter*	Antihypertensive drugs
H.L.	61	M	Wegener's gran.	9.6	7.1	31.7	33	enalapril, nitrendipine
C.S.	54	F	AN	7.2	8.6	29.3	49	clonidine
E.S.	55	F	GNS	8.8	8.8	24.8	24	nitrendipine
H.B.	66	M	Renal TBC	8.5	9.1	37.2	30	enalapril, clonidine
J.G.	62	M	IgA GN	6.5	11.1	37.3	46	enalapril
R.N.	61	M	AN	4.3	11.6	59.9	28	nifedipine
M.S.	39	M	IgA GN	5.8	11.8	68.5	51	enalapril
R.N.	48	M	GNS	4.2	17.6	65.6	7	captopril
K.S.	45	M	GNS	3.2	20.2	73.9	5	captopril, clonidine
G.K.	56	M	Hypert. renal dis.	3.2	25.0	99.6	19	nifedipine, atenolol, clonidine, enalapril

Abbreviations are: GN, biopsy confirmed glomerulonephritis; GNS, glomerulonephritis suspected; AN, analgesic nephropathy; S_{Cr}, serum creatinine; GFR, glomerular filtration rate measured with inulin clearance; RPF, renal plasma flow measured with PAH clearance; PTH, parathormone.

Table 2. Mean fractional sodium (FE_{Na}) and chloride (FE_{Cl}) excretion

	Collection periods *h*			
	1–3	3–6	6–12	12–24
FE_{Na} %				
Baseline (S + S)	6.5 ± 3.5	6.6 ± 2.7	3.4 ± 1.4	5.8 ± 2.8
T + S	18.5 ± 7.6	12.1 ± 3.4	4.1 ± 1.6	5.3 ± 3.0
Baseline (S + S)	6.4 ± 4.0	6.5 ± 3.4	3.3 ± 1.3	5.5 ± 2.0
T + B	20.2 ± 5.8	16.1 ± 6.1[a]	5.6 ± 2.5[b]	6.7 ± 3.5[a]
FE_{Cl} %				
Baseline (S + S)	7.1 ± 3.2	7.0 ± 2.9	4.0 ± 2.1	5.7 ± 2.7
T + S	25.3 ± 9.1	17.0 ± 5.8	5.5 ± 2.7	5.8 ± 3.8
Baseline (S + S)	7.2 ± 3.1	7.1 ± 3.4	3.8 ± 2.3	5.6 ± 2.0
T + B	28.5 ± 7.7	23.0 ± 9.4[a]	8.8 ± 3.0[b]	8.5 ± 3.4[b]
FE_{Na}[c]	9%	33%	37%	26%
FE_{Cl}[c]	13%	35%	60%	47%

Abbreviations are: S, sham infusion; T, torasemide infusion; B, butizid infusion.

[a] $P < 0.05$, [b] $P < 0.01$, torasemide plus placebo vs. torasemide plus butizid

[c] FE_{Na} and FE_{Cl} in the combination period (T + B) as percent above FE_{Na} and FE_{Cl} in the monotherapy period (T + S)

Methods

Patients

Ten patients with known advanced renal failure ($C_{In} < 30$ ml/min/1.73 m²) were examined (Table 1) after written informed consent had been obtained. Routine blood chemistry and urine analysis were performed at entry into the study. Diuretic medication was withheld for at least two weeks prior to the start of the study (wash-out phase). Other antihypertensive agents were not washed out, but their dosage was kept unchanged throughout the study (Table 1).

Protocol

The protocol of the present study was approved by the ethics committee of the University of Heidelberg. A single-blind, placebo controlled crossover design was used. For two weeks patients adhered to a diet containing a standardized amount of sodium and potassium. The diet was prepared as precooked deep frozen meals with a standardized Na^+ content of 150 mmol/day and K^+ content of 50 mmol/day. In three patients, who required in excess of 120 mg furosemide per day prior to the wash-out phase and who had striking edema in the wash-out phase, only 100 mmol Na^+ per day was given. In addition, patients were instructed to keep the daily fluid intake constant, that is, to drink about 2 liters of $NaHCO_3$-containing mineral water per day.

On study day 6 and day 13 the patients received two sham infusions with 50 ml of 5% glucose solution. On study day 7 and day 14 they were allocated to receive either the loop diuretic torasemide (50 mg i.v. dissolved in 50 ml of 5% glucose solution) in combination with a sham infusion or torasemide in combination with infusion of the thiazide diuretic butizid (20 mg i.v. dissolved in 50 ml 5% glucose solution). The patients were allocated to the different treatment sequences using random numbers. The intravenous route of drug administration was chosen to avoid potential interference with intestinal absorption in uremia. The infusions were given at 8 a.m. over a period of 15 minutes after blood samples for estimation of plasma creatinine and electrolytes had been taken. Mean arterial blood pressure (MAP) was measured at regular intervals before drug administration and thereafter. On the study days patients were examined in a quite environment in recumbent position during the first six hours; afterwards, they were up and about. They collected urine over 24 hours from 8 a.m. to 11 a.m. (3 hr), from 11 a.m. to 2 p.m. (3 hr), from 2 p.m. to 8 p.m. (6 hr) and from 8 p.m. to 8 a.m. of the next day (12 hr) for measurement of urinary sodium, chloride, potassium, calcium and magnesium excretion, urine volume and osmolality. In addition, urinary excretion of torasemide and its main metabolites was assessed in all urine specimens on study days 7 and 14. On study day 6 glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were assessed using the inulin (C_{In}) and paraaminohippurate (C_{PAH}) clearance methods as described elsewhere [20]. Body weight was assessed on all study days.

Torasemide is a loop diuretic with a relative long half-life of action, that is, about six hours. The dose of torasemide chosen (50 mg) is equivalent to about 150 to 200 mg of furosemide [21]. Butizid, or isobutylhydrochlorothiazide (also known as buthiazide), is a thiazide which is derived directly from hydrochlorothiazide by addition of an isobutyl group. The dose of butizid used in the present study (20 mg) is equivalent to about 30 mg of hydrochlorothiazide [22]. The standard dose of butizid in hypertensive patients with normal renal function is 10 mg.

Measurements and calculations

Plasma and urine electrolytes were measured with flame photometry (Eppendorf 5051, Hamburg, Germany), creatinine with

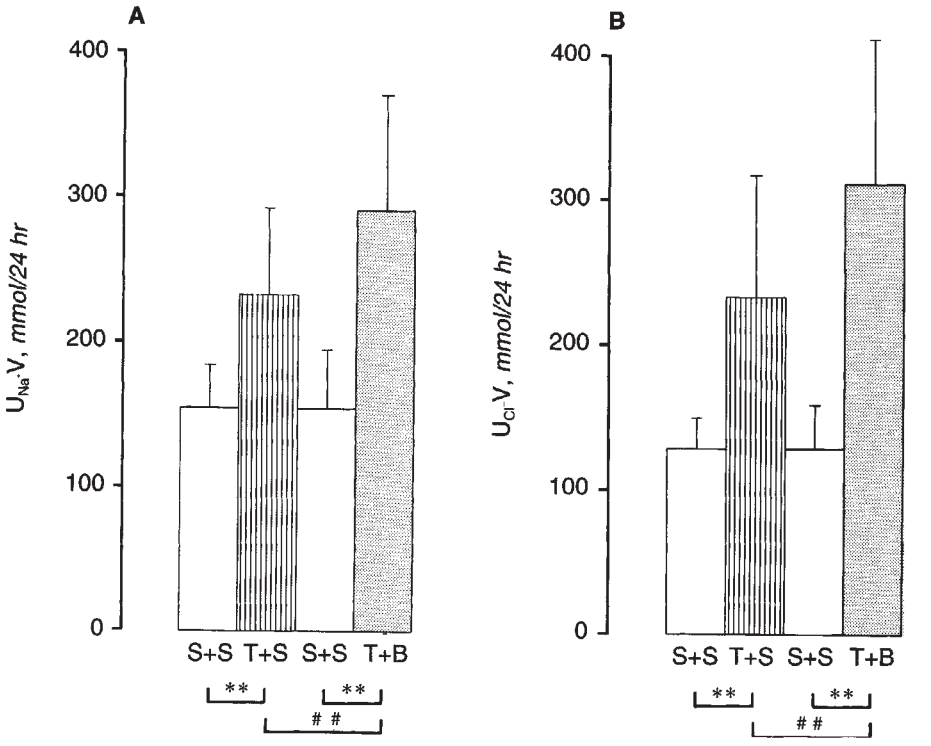

Fig. 1. *Mean 24-hour cumulative sodium (A) and chloride (B) excretion in patients with advanced renal failure (n = 10) after sham infusion (S + S), infusion of torasemide plus placebo (T + S) or in combination with butizid (T + B).* $*P < 0.05$, $**P < 0.01$, sham vs. drug administration; $\#P < 0.05$, $\#\#P < 0.01$, torasemide plus placebo vs. torasemide plus butizid.

autoanalyzer (Hitachi 705, Boehringer Mannheim, Germany), plasma and urine concentrations of magnesium with atomic adsorption-spectometry (Perkins & Elmer, Überlingen, Germany). The concentrations of torasemide and its main metabolites (M1, M3, M5) in urine were determined with high pressure liquid chromatography (HPLC). The detection limit was 50 ng/ml [23]. Inulin was determined enzymatically (Inutest^R, Levosan GmbH, Austria) [24], paraaminohippurate (Nephrotest^R, Biologische Arbeitsgemeinschaft GmbH, Germany) after the method of Braton-Marshall [25]. MAP was measured oscillometrically using an automatic blood pressure monitoring device (Dinamap^R, Critikon Co., USA). The fractional excretions of sodium (FE_{Na}) and chloride (FE_{Cl}) were calculated as the ratio between urinary Na^+ ($U_{Na} \times V$) and Cl^- ($U_{Cl} \times V$) excretion rate and filtered Na^+ ($C_{In} \times$ plasma Na^+) and Cl^- ($C_{In} \times$ plasma Cl^-) load.

Statistics

The primary efficacy parameters were the differences in mean cumulative 24-hour sodium and chloride excretions: (i) after the sham infusions, and (ii) after administration of torasemide plus placebo or torasemide plus butizid, respectively. Because of the relatively small number of patients, data were analyzed using the non-parametrical Kruskal-Wallis test for multiple comparisons, which does not depend on normal Gaussian distribution. If this procedure gave a significant difference, Wilcoxon's test for paired samples was applied to compare the respective treatments. Our analysis also permitted us to exclude a sequence effect [26]. Other parameters were similarly compared with the respective tests. In addition, for descriptive purposes the time course of FE_{Na} and FE_{Cl} after administration of torasemide plus placebo and torasemide plus butizid was analyzed with ANOVA (Table 2). Differences were assumed to be statistically significant at a P level of 0.05. Data are shown as mean ± SD.

Results

Urinary sodium and chloride excretion

Figure 1 shows the mean cumulative 24-hour sodium (Fig. 1A) and chloride (Fig. 1B) excretion in our patients with advanced renal failure. Administration of torasemide alone significantly ($P < 0.01$) increased cumulative 24-hour sodium and chloride excretion over baseline, that is, during sham infusion on the preceding day. The mean cumulative 24-hour sodium and chloride excretion was greater with coadministration of butizid as compared with torasemide alone. In the paired Wilcoxon test the difference between torasemide plus placebo versus torasemide plus butizid was highly significant ($P < 0.01$). Three out of ten patients received 100 mmol Na^+/day instead of 150 mmol Na^+/day (for the safety considerations described above); the variance of mean cumulative sodium (and chloride) excretion was therefore relatively large. The variance was considerably reduced if mean urinary sodium excretion is expressed as percent of daily intake. It was 114 ± 9% with the first sham infusion and 179 ± 60% with infusion of torasemide plus placebo (that is, in the first study arm) compared to 115 ± 10% with the second sham infusion and 223 ± 78% with administration of torasemide plus butizid (that is, in the second study arm).

The increment in urinary sodium and chloride excretion over baseline became progressively less with time, but in all collection periods the increment was greater with combined torasemide plus butizid administration than with torasemide plus placebo (Fig. 2 A and B). Table 2 clearly illustrates that the increase of mean

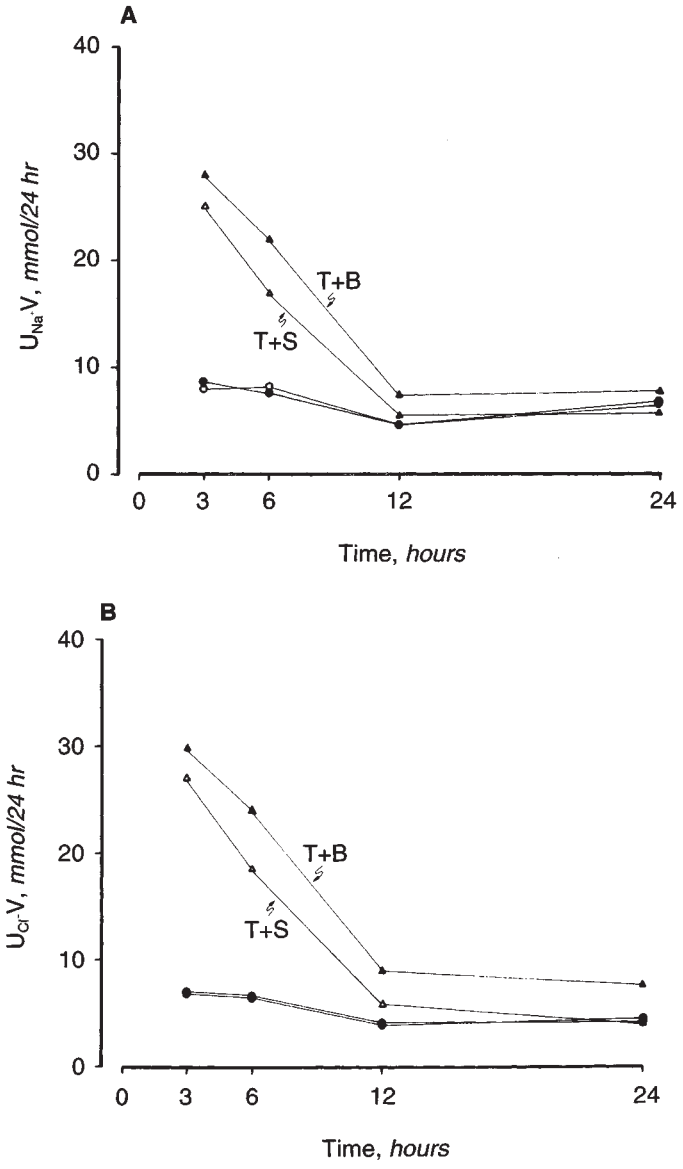

Fig. 2. *Mean hourly excretion of sodium (A) and chloride (B) after sham infusion, infusion of torasemide plus placebo or in combination with butizid.* Symbols are: (○) sham infusion day before infusion of torasemide plus placebo; (●) sham infusion day before infusion of torasemide plus butizid; (△) infusion of torasemide plus placebo; (▲) infusion of torasemide plus butizid.

FE_{Na} and FE_{Cl} in the combination treatment period (torasemide plus butizid) rose progressively with time over mean FE_{Na} and FE_{Cl} in the mono-treatment period (torasemide plus placebo), indicating that the superior efficacy of the combination became more pronounced as time went by.

If antinatriuresis is defined as the decrease of urinary Na^+ excretion below the baseline excretion of the preceding (sham infusion) day, three patients could be identified who had a clearcut rebound phenomenon with torasemide plus placebo. As shown in Figure 3, in all three patients the rebound was abrogated by coadministration of butizid.

Other parameters

Table 3 gives mean cumulative 24-hour urine volume as well as urinary osmolar, potassium, calcium and magnesium excretion and mean 24-hour endogenous creatinine clearance (C_{Cr}). There was no significant difference in mean potassium and magnesium excretion with torasemide plus placebo versus torasemide plus butizid when analyzed with the Kruskal-Wallis test. In contrast, with the combination of diuretics the mean cumulative urinary calcium excretion was significantly less ($P < 0.05$) than with torasemide plus placebo. Mean diuresis (that is, urine volume) was significantly greater ($P < 0.05$) with the combination of diuretics than with torasemide plus placebo, whereas 24 hours C_{Cr} did not change significantly. It remained stable after administration of torasemide plus placebo (1 to 3 hours post-infusion: 15.1 ± 8.9 ml/min/1.73 m^2; 3 to 6 hours post-infusion: 14.5 ± 7.8 ml/min/1.73 m^2) as compared with baseline 24 hour C_{Cr} on the sham infusion day (13.6 ± 6.7 ml/min/1.73 m^2). The same was true for coadministration with butizid (1 to 3 hours post-infusion: 14.9 ± 6.4 ml/min/1.73 m^2; 3 to 6 hours post-infusion: 14.6 ± 6.4 ml/min/1.73 m^2) as compared with baseline 24 hour C_{Cr} (15.0 ± 7.9 ml/min/1.73 m^2).

Blood pressure (MAP) and heart rate did not change significantly after the administration of torasemide. Mean MAP changed neither during coadministration of the diuretics nor during sham infusion (Table 4). Mean patients body weight did not change during the study. It was 74.4 ± 7.7 kg on placebo infusion day before the study day when torasemide was infused alone, 74.4 ± 7.9 kg on torasemide infusion day, 74.4 ± 7.6 kg on placebo infusion day before the study day when torasemide was infused with butizid, and 74.4 ± 7.9 kg on the day of torasemide and butizid coadministration.

Pharmacokinetic analyses

Figure 4 shows mean 24 hour cumulative urinary excretion of torasemide and its main metabolites, that is, M1 (less active than torasemide), M3 (as active as torasemide) and M5 (inactive metabolite). No significant differences in urine excretion were found when torasemide was infused with placebo or in combination with butizid.

Discussion

The present study clearly shows that coadministration of the thiazide diuretic, butizid, markedly increases the efficacy of the loop diuretic torasemide in patients with advanced and even preterminal renal failure. This finding contrasts with repeated recommendations to withhold thiazides in such patients because of their assumed inefficacy [1–3]. Maximally effective doses of loop diuretics increase fractional excretion of chloride and sodium to 20 to 30%. This is seen with 200 mg furosemide i.v. and 100 mg torasemide i.v. [27]. In our patients with advanced renal failure FE_{Cl} and FE_{Na} were further increased by more than 30% when an effective intravenous dose of torasemide was combined with butizid. Coadministration of both types of diuretics was shown to increase chloruresis and natriuresis even in patients on maintainance hemodialysis (unpublished data). The remarkable efficacy of thiazides may be related, at least in part, to their long duration of action. When loop diuretics with short half-life are administered, antinatriuresis, that is, a decrease of sodium excretion below baseline, is observed after a few hours. This socalled rebound

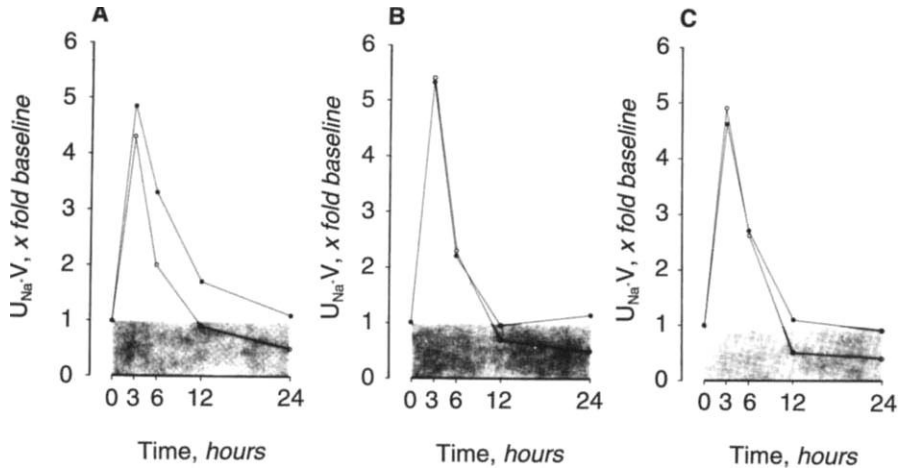

Fig. 3. *Antinatriuretic rebound response in three patients (A, B and C) with advanced renal failure after infusion of torasemide plus placebo or in combination with butizid.* The hourly excretion of sodium is given as multiples of hourly $U_{Na}V$ on the preceding sham day. Symbols are: (○) infusion of torasemide plus placebo; (●) infusion of torasemide plus butizid.

Table 3. Cumulative 24-hour urine volume (UV) and solute excretion and 24-hour endogenous creatinine clearance (C_{Cr})

	UV *ml/24 hr*	U_{Osm} *mOsm/24 hr*	U_{K^+}	$U_{Ca^{++}}$	$U_{Mg^{++}}$	C_{Cr} *ml/min/1.73 m²*
			mmol/24 hr			
Baseline (S + S)	2340 ± 424[b]	771 ± 157[b]	52 ± 10	1.3 ± 0.6[a]	3.1 ± 0.9	13.6 ± 6.7
T + S	2956 ± 603	898 ± 186	61 ± 15	2.5 ± 1.6	3.4 ± 1.0	13.4 ± 6.9
Baseline (S + S)	2343 ± 508[b]	746 ± 135[b]	51 ± 17	1.2 ± 0.4[a]	3.1 ± 0.9	15.0 ± 7.9
T + B	3216 ± 737[c]	1011 ± 238[c]	64 ± 20	2.1 ± 1.2[c]	3.7 ± 1.0	13.0 ± 5.7

Abbreviations are: S, sham infusion; T, torasemide infusion; B, butizid infusion.
[a] $P < 0.05$, [b] $P < 0.01$, sham vs. drug administration
[c] $P < 0.05$, torasemide plus placebo vs. torasemide plus butizid

Table 4. Mean arterial blood pressure (MAP) and heart rate

	MAP *mm Hg*[a]			Heart rate *beats/min*		
	8 a.m.	11 a.m.	2 p.m.	8 a.m.	11 a.m.	2 p.m.
Baseline (S + S)	101 ± 18	104 ± 11	110 ± 18	71 ± 18	67 ± 16	66 ± 15
T + S	101 ± 12	105 ± 10	107 ± 15	72 ± 12	67 ± 10	68 ± 10
Baseline (S + S)	101 ± 15	106 ± 12	106 ± 13	71 ± 15	66 ± 12	66 ± 14
T + B	100 ± 14	103 ± 11	103 ± 15	70 ± 14	67 ± 11	67 ± 15

Abbreviations are: S, sham infusion; T, torasemide infusion; B, butizid infusion.
[a] Patients did not take their usual (antihypertensive) medication on the study days

phenomenon tends to negate a beneficial long-term effect of loop diuretics on sodium balance [12, 19]. Inhibition of chloride and sodium reabsorption by butizid was demonstrable throughout the observation period, and the difference between torasemide monotherapy and combination therapy with torasemide plus butizid increased progressively with the time of observation. As discussed below, thiazides may therefore be uniquely suited to interfere with the rebound phenomenon. Fractional excretion of chloride (FE_{Cl}) increased more than FE_{Na}. The greater responsiveness of FE_{Cl} is well explained by more distal exchange of sodium for other ions.

With respect to the mechanisms underlying the enhanced potency of loop diuretics in combination with thiazides, it is obvious that neither changes in systemic hemodynamics nor changes in GFR are involved, since blood pressure, heart rate and endogenous creatinine clearance remained unchanged with diuretic administration in our patients. A further potential confounding variable may be a pharmacokinetic interaction between torasemide and butizid. It is well known that the action of diuretics, especially of loop diuretics, depends on their luminal concentration within the renal tubule [3, 21]. Our pharmacokinetic evaluation documented that urinary concentrations of torasemide (and the urinary concentrations of its main metabolites) did not differ whether it was given alone or in combination with butizid. Because no suitable assay for butizid is available, its concentration in the urine could not be measured.

The results of our study are in line with uncontrolled clinical observations which showed that addition of a diuretic acting on the distal tubule tended to increase natriuresis in patients with elevated serum creatinine who had been pretreated with loop diuretics [28]. However, this therapeutic approach had so far never been validated in controlled clinical studies. The mechanisms by which thiazides enhance sodium and chloride excretion in patients with advanced renal failure treated with loop diuretics deserve comment. Thiazide diuretics are usually considered to be low ceiling diuretics, since they act late in the nephron and increase sodium excretion only by 5 to 10% [1–5]. This is,

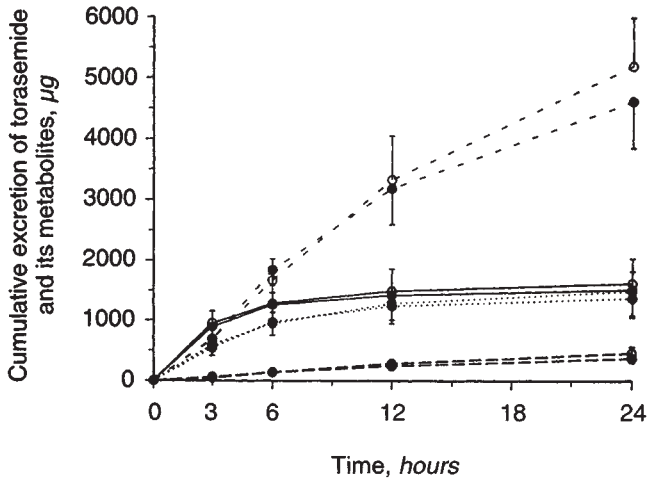

Fig. 4. *Mean urinary excretion of torasemide (T) and its main metabolites (M1, M3 and M5) in patients with advanced renal failure (N = 10) after torasemide infusion plus placebo or in combination with butizid.* Symbols are: (○) infusion of torasemide plus placebo; (●) infusion of torasemide plus butizid; (– – –) M_3; (• • •) M_1; (——) torasemide; (- -) M_5.

however, not due to an intrinsically low diuretic potency of the substance, but only due to the delivery of small amounts of sodium (and chloride) to the site of action of thiazides. Since under normal circumstances only about 5 to 10% of filtered sodium reaches the distal tubule, natriuresis can increase only by that proportion with thiazide treatment. In contrast, if sodium delivery to this site is increased, thiazides are highly effective diuretics. This was documented in patients with normal renal function and edema refractory to loop diuretic treatment in whom coadministration of a thiazide induced a vigorous diuresis and natriuresis [29, 30].

On pharmacokinetic principles, it is usually not advisable to combine substances with different half-lives of action. In the particular case of loop diuretics (short half-life) and thiazides (long half-life) this approach may, however, have distinct advantages. First, coadministration of thiazide and loop diuretics may help to overcome "resistance" to the action of conventional therapeutic doses of loop diuretics which is frequently observed in patients with advanced renal failure [29–31]. Administration of high doses of loop diuretics [32, 33] may cause more frequent and severe side effects, particularly hypokalemia, hypocalcemia and hypomagnesemia. Furthermore, drug toxicity, for example, ototoxicity in the case of furosemide [34], may develop. In our patients who received standard doses of both diuretics, plasma K^+ and Mg^{++} levels were not significantly different with administration of torasemide alone or in combination with butizid. The calcium excretion was, however, significantly lower with butizid coadministration; the latter finding is not surprising in view of the known anticalciuric action of thiazide diuretics [2, 3]. Coadministration of thiazide diuretics may therefore permit use of smaller doses of loop diuretics in the treatment of hypertension and/or edema in patients with advanced renal failure, and this may reduce the frequency of side effects. Second, because of the long half-lives, the duration of action of thiazides outlasts that of loop diuretics and thus prolongs the overall duration of natriuresis. In the present study this is illustrated by the observation that coadministration of torasemide and butizid caused more pronounced diuresis particularly from 3 to 24 hours postdosing as compared to torasemide alone. Third, administration of a thiazide may interfere with the so-called "rebound effect" after loop diuretic treatment, that is, with antinatriuresis after the short acting natriuretic effect of the loop diuretic has waned [17–19]. The mechanisms of the rebound phenomenon are not completely understood. Reduction of extracellular volume may play a role, since it is reduced by a high salt intake [18]. Post-diuretic activation of the renin-angiotensin system or the sympathetic system is not a prerequisite, since ACE inhibition and α-adrenergic receptor blockade do not obliterate the antinatriuretic rebound [17, 35, 36]. In addition, there is evidence that volume-independent intrinsic renal mechanisms of sodium retention are also involved [37, 38]. While the antinatriuretic effect has been well documented in subjects with normal renal function, it has so far not been clear whether it occurs in patients with impaired renal function as well. Volume expansion, commonly present in such patients may interfere with rebound. In the present study we documented antinatriuresis at least in some patients in spite of a high dietary sodium load. Coadministration of butizid clearly prevented such antinatriuresis after torasemide.

In conclusion, thiazides markedly increase the natriuretic and chloruretic potential of loop diuretics even in patients with advanced renal failure: (i) by amplifying sodium and chloride excretion and, at least in some patients, (ii) by interfering with the antinatriuretic rebound. Coadministration of thiazides with loop diuretics is therefore a rational therapeutic strategy even in patients with advanced renal failure.

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