Comparison of the Effects of Torasemide and Furosemide in Nonazotemic Cirrhotic Patients with Ascites: A Randomized, Double-blind Study

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In a randomized double-blind trial we compared the effects of torasemide, a new loop diuretic, and furosemide in nonazotemic cirrhotic patients with ascites during a 3-day period in association with potassium canrenoate (200 mg/day) administration. Doses of loop diuretics administered in this trial (10 and 25 mg/day of torasemide and furosemide, respectively) had been shown to be equipotent in healthy subjects. Torasemide induced significantly greater natriuresis than furosemide ($p < 0.02$), with a twofold greater percentage increase in basal values (day 1: 130% vs. 50%; day 2: 104% vs. 42%; and day 3: 65% vs. 26%, respectively). Body weight loss was significantly higher during torasemide ($p < 0.02$) administration, and the overall decrease at the end of the treatment was twice as high for furosemide (2.5 ± 0.6 kg vs. 1.3 ± 0.4 kg, respectively). Diuresis was also higher during torasemide administration, but the difference was not significant ($p = 0.08$). The extent of kaliuresis observed during the two treatments was almost identical despite the striking differences in the natriuretic response. The effects of the two treatments on plasma electrolytes, creatinine clearance, blood urea nitrogen, mean arterial pressure, heart rate and plasma arginine vasopressin concentration were similar. Both drugs caused increases in plasma renin activity at the end of the treatment, whereas plasma aldosterone concentration slightly increased only after torasemide administration. Despite the presence of a trend toward a more pronounced effect on these parameters after torasemide administration, no significant difference between the two treatments was observed. Blood ammonia increased compared with pretreatment values after furosemide, whereas it remained unmodified after torasemide administration (from 90 ± 15 μg to 112 ± 19 μg and from 87 ± 15 μg to 80 ± 16 μg NH_3-N/dl, respectively; $p < 0.05$ between treatments). The results of this trial indicate that torasemide is suitable for the treatment of sodium and water retention in cirrhotic patients with ascites. Further investigation is needed to assess the long-term tolerability and effectiveness of this new loop diuretic. (HEPATOLOGY 1991;13:1101-1105.)

Low-sodium diet, diuretic therapy and paracentesis are the main therapeutic tools in the management of cirrhotic patients with ascites (1-3). Aldosterone antagonists, despite their low intrinsic natriuretic potency, are the drugs of choice when glomerular filtration rate is not reduced (4). Addition of loop diuretics, which inhibit sodium chloride reabsorption at the loop of Henle, potentiates the natriuretic effects of aldosterone antagonists (1-3). However, loop diuretic administration may be associated with several complications, including hyponatremia, hypokalemia, prerenal azotemia and hepatic encephalopathy (5). Torasemide—1-isopropyl-3(4-M-toluidino-3-pyridyl)-sulphonyl-urea—is a newly developed loop diuretic that has been shown to be more than twice as active as furosemide on a mole-per-mole basis (6, 7) and to exert very high natriuretic and diuretic action in healthy subjects (7, 8). Preliminary studies have also shown that torasemide exhibits a longer half-life (9-11), greater bioavailability (10, 11) and lower potassium-wasting effects than furosemide (9, 11, 12).

In this randomized double-blind trial we compared the effects of torasemide and furosemide on diuresis, body weight, BUN, urinary and plasma electrolytes, creatinine clearance, the renin-angiotensin-aldosterone system, plasma arginine vasopressin (AVP) concentration, blood ammonia, heart rate and mean arterial pressure in a group of nonazotemic cirrhotic patients with ascites. The effects of torasemide and furosemide on urinary excretion of 6-keto prostaglandin (PG)$F_{1\alpha}$ and thromboxane (TX)B_2, which are reliable indexes of renal PGI_2 and TXA_2 synthesis, respectively (13, 14), were also assessed.

MATERIALS AND METHODS

Twenty-four cirrhotic patients with ascites being treated in the hospital who did not show adequate response (i.e., body wt loss ≥ 300 gm/day) to a low-sodium diet (40 mEq/day) and bed rest for 5 days were studied. Diagnosis of cirrhosis was

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TABLE 1. Clinical and laboratory data at admission for the two groups of 12 patients undergoing treatment with furosemide or torasemide

Characteristics	Furosemide	Torasemide
Age (yr)	62.6 ± 0.7	57.7 ± 0.8[a]
Sex (M/F)	8:4	11:1
Child class (B/C)	6:6	6:6
Peripheral edema (no.)	4	4
Albumin (mg/dl)	3.11 ± 0.40[a]	3.00 ± 0.30[a]
Bilirubin (mg/dl)	2.55 ± 0.10[a]	2.25 ± 0.13[a]
Prothrombin activity (%)	52.5 ± 1.0[a]	61.7 ± 1.3[a]
BUN (gm/L)	18.7 ± 0.5[a]	18.2 ± 0.5[a]
Creatinine ((mg/dl)	1.00 ± 0.02[a]	1.05 ± 0.02[a]
Creatinine clearance (ml/min)	82.0 ± 2.7[a]	82.5 ± 2.8[a]
Origin (no.)		
Alcoholic	7	6
Postviral	1	2
Cryptogenic	4	4
Urinary sodium excretion (mEq/24 hr)[b]	18 ± 9[a]	20 ± 8[a]

[a]Results are mean ± S.E.M.

[b]Measured after 5 days of low-sodium diet (40 mEq/day) and bed rest.

established by history, by clinical and laboratory findings and by liver biopsy when the procedure was not contraindicated. Presence of ascites was assessed by physical examination and confirmed by ultrasonography and diagnostic paracentesis. All patients showing heart failure, renal failure (creatinine clearance < 30 ml/min), arterial hypertension, diabetes, recent (within the preceding 8 wk) gastrointestinal bleeding, hepatic encephalopathy, HCC or bacterial peritonitis were excluded from the study. A careful interview was carried out to rule out consumption of nonsteroidal antiinflammatory drugs or any other hepatotoxic or nephrotoxic drugs in the previous 4 wk. Sex, mean age and clinical and laboratory parameters of the patients receiving torasemide or furosemide are shown in Table 1.

The study was designed as a randomized, double-blind trial. Patients admitted to the study received the aldosterone antagonist potassium canrenoate (100 mg twice daily for 5 days) while consuming a 40 mEq Na^+, 60 mEq K^+/day diet, with a water intake of 1 L/day. The next day patients were randomly assigned to receive furosemide (25 mg per os once daily for 3 days) or torasemide (10 mg per os once daily for 3 days). Studies performed in healthy subjects have shown equipotency of natriuretic response with oral administration of furosemide and torasemide at this dose ratio (11). Body weight, diuresis, plasma and urinary sodium, potassium, BUN, creatinine clearance (based on 24-hr urinary creatinine measurements), arterial pressure and heart rate were measured on the day before and on each day of loop diuretic administration. Plasma renin activity (PRA), plasma aldosterone concentration (PAC), plasma AVP concentration, blood ammonia and urinary 6-keto $PGF_{1\alpha}$ and TXB_2 excretion were assessed before the administration of the loop diuretic and after 3 days of treatment.

Ammonia was determined in capillary blood immediately after sampling with the Blood Ammonia Checker (Menarini Diagnostici, Florence, Italy) (15, 16). Normal range is 20 to 80 μg NH_3-N/dl.

Blood samples for determination of PRA and PAC were collected in ice-chilled tubes containing EDTA (1 mg/ml blood) and in heparinized tubes, respectively; they were centrifuged at 4° C and the plasma was stored at −25° C. PRA and PAC were assayed as described previously (17).

For plasma AVP measurement, blood was collected in chilled EDTA tubes and centrifuged within 30 min at 4° C. Plasma was stored at −80° C until assayed. Aliquots of acidified plasma (2 ml) were extracted with Sep-Pak C_{18} cartridges (Waters Chromatography Division, Millipore Corp., Milford, MA) previously activated with methanol and 4% acetic acid, eluted with 3 ml of methanol, evaporated to dryness by a centrifugal concentrator (Univapo 150 H; Uni Equipe, Martinsted, FRG), and reconstituted in 250 μl assay buffer (50 mmol/L PBS, pH 7.4, containing BSA and 10 nmol/L EDTA). Samples and standards (0.1 ml) (Peninsula Laboratory Inc., San Carlos, CA) were incubated with a rabbit antibody (0.025 ml; Amersham Ltd., Buckinghamshire, UK) and (3-[^{125}I] iodotyrosyl^2) vasopressin [Arg^8] (0.025 ml; Amersham Ltd.) at 4° C for 24 hr. Bound/free separation was performed by activated charcoal (Norit GSX; BDH Italia, Milan, Italy) and dextran (mol wt 60,000 to 90,000; Sigma Chemical Co., St. Louis, MO). Blank values were always less than 2% and mean recovery of synthetic vasopressin was between 70% and 80% when 0.25, 2.5 or 25 fmol was added to 2 ml plasma. Sensitivity of the RIA was 0.1 fmol/tube (99% confidence). Values are expressed in fmol/ml.

Urinary 6-keto $PGF_{1\alpha}$ and TXB_2 were extracted by different aliquots of the same urine sample, separated by HPLC and assayed by RIA according to previously described methods (18, 19). The characteristics of the antisera employed and validation of the assay procedures – including comparison with gas chromatography–mass spectrometry – have been reported elsewhere (18-20).

Plasma and urinary sodium and potassium were determined by flame photometry (BT 601; Biotecnica, Rome, Italy). Plasma and urinary creatinine was measured by the creatinine test (Sclavo Diagnostics, Siena, Italy). All other determinations were carried out by standard techniques. Mean blood pressure was calculated as diastolic blood pressure + ⅓ pulse pressure.

Results are expressed as mean ± S.E.M. Statistical analysis was performed by analysis of covariance.

The study protocol was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the University of Florence Ethical Committee in May 1988. Informed consent was obtained from each patient.

RESULTS

All patients completed the trial. No significant differences between the two groups were observed in the baseline parameters shown in Table 1. Data on diuresis and urinary sodium excretion are illustrated in Figure 1. Comparison of the two treatments showed that the mean percentage increase in natriuresis induced by torasemide during the 3 days was two times greater than that induced by furosemide (day 1: 130% vs. 50%; day 2: 104% vs. 42%; day 3: 65% vs. 26%). Analysis of covariance revealed a statistically significant difference between the treatments in the 3-day period. Torasemide also caused a higher diuretic response than did furosemide (mean percentage increase, day 1: 60% vs. 26%; day 2: 35% vs. 27%; day 3: 31% vs. 24%), although the difference did not reach statistical significance ($p = 0.08$). Consequently, the extent of body weight loss induced by the two treatments was significantly different ($p < 0.02$), with a 2.5 ± 0.6 kg vs. 1.3 ± 0.4 kg overall decrease at the end of the treatments with torasemide and furosemide, respectively. The extent of

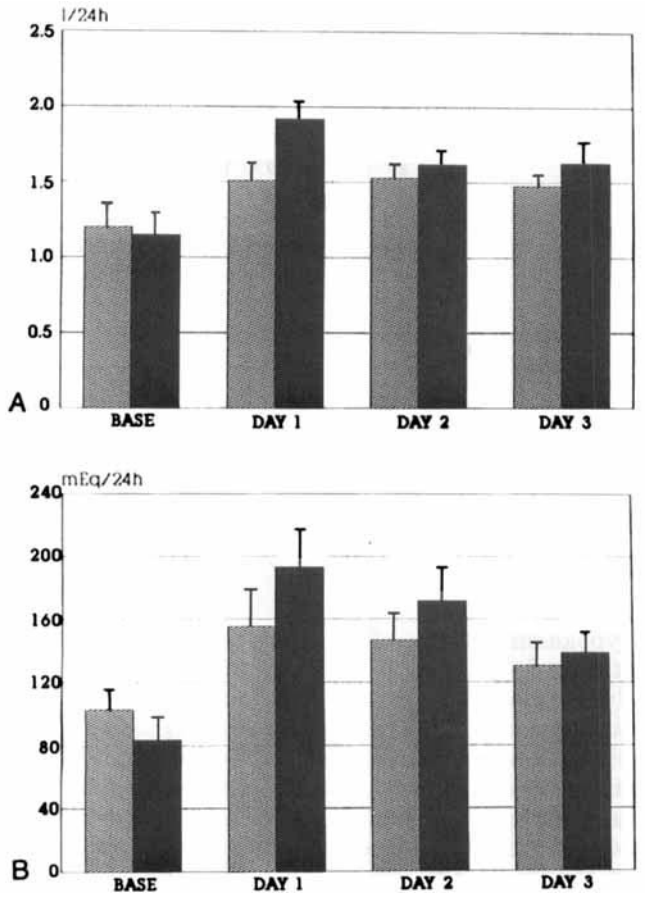

FIG. 1. Diuresis (A) and urinary sodium excretion (B) measured in two groups of 12 cirrhotic patients with ascites after 5 days of 200 mg/day potassium canrenoate administration *(BASE)* and addition of furosemide *(hatched columns)* or torasemide *(black columns)* (mean ± S.E.M.). In (B), torasemide vs. furosemide, $p < 0.02$.

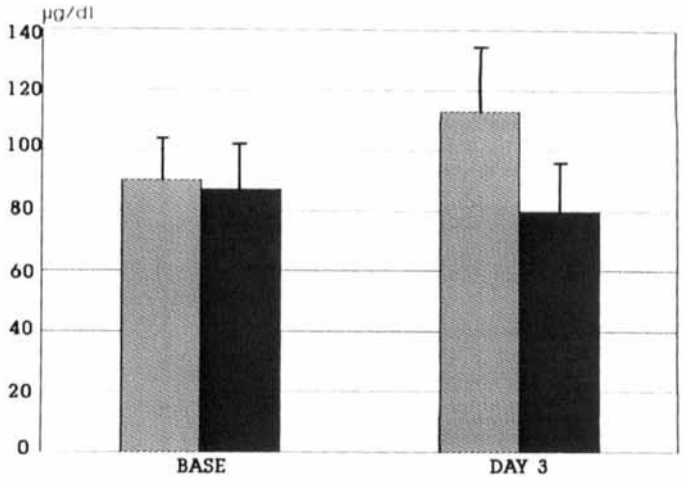

FIG. 2. Blood ammonia after 5 days of 200 mg/day potassium canrenoate administration *(BASE)* and addition of furosemide *(hatched columns)* or torasemide *(black columns)* in two groups of 12 cirrhotic patients with ascites. Torasemide vs. furosemide, $p < 0.05$.

kaliuresis (Table 2) observed after the two treatments was almost identical despite the striking difference observed in the natriuretic responses. As shown in Table 2, the two drugs did not affect plasma electrolytes, BUN and creatinine clearance differently. Both drugs caused an increase in PRA at the end of the treatment, whereas PAC slightly increased only after torasemide administration (Table 3). Despite a trend toward a more pronounced effect on these parameters after torasemide administration, no significant difference between the two treatments was observed. Plasma AVP moderately increased after administration of both torasemide and furosemide, without significant differences between the two diuretics (Table 3). As shown in Table 2, no significant differences in mean arterial pressure or heart rate were observed when the two treatments were compared. Remarkably, blood ammonia was significantly higher after furosemide administration ($p < 0.05$; see Fig. 2). Urinary excretion of 6-keto $PGF_{1\alpha}$ and TXB_2 (Table 3) increased after furosemide administration, whereas it remained unmodified by torasemide. However, the difference between the treatments was not statistically significant.

No relevant side effects occurred during the study period.

DISCUSSION

Torasemide, a newly developed loop diuretic derivative of sulfanylurea, has been considered suitable for a broad spectrum of clinical settings including heart failure (9, 12), hypertension (21) and chronic renal failure (22, 23). In this study we compared the effectiveness of torasemide and furosemide in nonazotemic cirrhotic patients with ascites. Although the standard method of comparing drug efficacy is by dose-response testing, we administered a single dose of each loop diuretic. In fact, in healthy subjects the dose-response curves for furosemide and torasemide have been shown to be linear in a dose range between 12.5 and 50 mg and 2.5 and 20 mg, respectively (24, 25).

In this study torasemide induced twice the natriuresis of furosemide, together with a higher diuretic response and body weight loss. The two loop diuretics administered in this trial differ in pharmacokinetic and pharmacodynamic properties. Torasemide exhibits almost complete bioavailability, estimated at 90% (10, 11), whereas furosemide is only partially absorbed by the gastrointestinal tract, with a bioavailability between 40% and 60% (26). However, because we administered doses equipotent in healthy subjects (11), the differing bioavailability cannot be taken into account to explain the different natriuretic potency exhibited by the two drugs in this setting. In fact, furosemide bioavailability has been shown to be normal in cirrhotic patients (27). Conversely, their differing natriuretic potencies are more likely to be related to a different metabolic fate. Furosemide is mainly cleared by the kidney, and nonrenal clearance is unchanged in cirrhotic patients (28). On the other hand, renal clearance contributes only about 25% to the total clearance of torasemide, which is mainly eliminated by hepatic metabolism and excretion (10, 29). In fact, torasemide is hydroxylated at the

TABLE 2. Values after 5 days of 200 mg/day potassium canrenoate administration (base) and after addition of furosemide or torasemide

Values	Drug	Baseline	Day 1	Day 2	Day 3
Urinary potassium excretion (mEq/24 hr)	F	28.4 ± 4.1[a]	37.3 ± 4.0	34.9 ± 2.8	34.9 ± 2.4
	T	26.5 ± 3.5	42.4 ± 4.9	38 ± 4.4	33.3 ± 2.5
Plasma sodium concentration (mmol/L)	F	140 ± 2	138 ± 2	140 ± 1	137 ± 1
	T	138 ± 1	137 ± 1	139 ± 1	138 ± 1
Plasma potassium concentration (mmol/L)	F	4.4 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	4.2 ± 0.1
	T	4.4 ± 0.1	4.1 ± 0.1	4.2 ± 0.2	4.1 ± 0.1
BUN (gm/L)	F	17.4 ± 8.6	17.6 ± 9.2	18.9 ± 9.3	19.2 ± 9.1
	T	15.6 ± 5.2	15.8 ± 4.1	18.8 ± 4.6	18.4 ± 4
Creatinine clearance (ml/min)	F	68.1 ± 3.7	67.9 ± 3.7	67.8 ± 3.6	66.8 ± 3.6
	T	71.5 ± 4.2	69.8 ± 4.1	69.4 ± 4	69.0 ± 4.1
Mean arterial pressure (mm Hg)	F	86.2 ± 3.2	84.6 ± 1.8	84.1 ± 2	83.8 ± 2.6
	T	90.7 ± 2.2	88.2 ± 1.8	91.7 ± 2.1	90.9 ± 2.5
Heart rate (beats/min)	F	76.8 ± 3.8	75.3 ± 3.3	78.8 ± 2.9	75.9 ± 3.2
	T	78.4 ± 1.6	76.7 ± 1.9	74.8 ± 2.8	76.1 ± 2

F = furosemide; T = torasemide.
[a]All results are given as mean ± S.E.M.

TABLE 3. Values after 5 days of 200 mg/day potassium canrenoate administration (base) and addition of furosemide or torasemide in two groups of 12 patients with cirrhosis and ascites

Values	Drug	Baseline	Day 3
PRA ($ng \cdot ml^{-1} \cdot hr^{-1}$)	F	4.2 ± 1.2[a]	5.4 ± 1.8
	T	5.8 ± 1.5	9.4 ± 1.8
Plasma aldosterone concentration ($ng \cdot ml^{-1}$)	F	0.54 ± 0.16	0.52 ± 0.15
	T	0.79 ± 0.15	0.94 ± 0.14
Plasma AVP (fmol/ml)	F	1.81 ± 0.30	2.16 ± 0.38
	T	1.29 ± 0.37	1.69 ± 0.45
Urinary 6-keto $PGF_{1\alpha}$ excretion (ng/hr)	F	14.7 ± 3.7	24.1 ± 12.2
	T	22.0 ± 13.3	15 ± 7.8
Urinary TXB_2 excretion (ng/hr)	F	12.1 ± 5.8	21.6 ± 7.6
	T	15.9 ± 2.6	14.3 ± 2.8

F = furosemide; T = torasemide.
[a]All results are given as mean ± S.E.M.

methyl group of the phenyl ring to metabolite M_1, which is further oxidized to the respective carboxylic acid M_5. Only small amounts of torasemide are ring hydroxylated, thus yielding metabolite M_3. The potency ratios of M_1 and M_3 compared with torasemide are 0.25 and 1, respectively, whereas M_5 has no natriuretic effect (10). The overall renal excretion of torasemide and its metabolites was shown to be comparable in healthy subjects and in patients with cirrhosis (30). However, in the latter group, analysis of the concentration time curves for torasemide showed persistently higher levels of the drugs and a larger area under the curve than in healthy controls. An increase in the serum levels of the metabolite M_1 and delayed appearance of M_5 were also observed in cirrhotics (30). These data are consistent with a reduced oxidative metabolism of the drug caused by impairment of liver function. The resulting larger amounts of circulating unchanged torasemide can explain the greater natriuretic and diuretic effect compared with furosemide.

Hypokalemia is one of the more frequent side effects related to loop diuretic administration (5); it is more likely to develop in cirrhotic patients (31). Despite its striking natriuretic potency, torasemide exerted a kaliuretic action comparable to that of furosemide. The relatively lower potassium wasting capacity exhibited by torasemide has also been observed in studies performed in healthy subjects (11) and in patients with congestive heart failure (9, 12).

Neither torasemide nor furosemide exerted an adverse effect on BUN or glomerular filtration rate in our nonazotemic ascitic patients. The increase in PRA and PAC observed at the end of torasemide administration was slightly higher compared with furosemide. This finding may be explained by the greater natriuretic and diuretic effects of torasemide. An alternative explanation is related to the observation that loop diuretics stimulate renin secretion, even in the absence of volume depletion, by directly inhibiting sodium chloride transport at the macula densa (32, 33).

An additional finding of this study is the different action of the two drugs on blood ammonia levels. In fact, torasemide administration did not affect blood ammonia, whereas furosemide produced a 25% increase. Increased ammonia generation during diuretic therapy is mainly related to development of hypokalemia (34), but in this study no differences in kaliuretic response and kalemia between the two drugs were observed.

Diuretic and natriuretic responses induced by furosemide have been suggested to be dependent, at least in part, on augmented renal prostaglandin synthesis (35, 36). In this study torasemide did not affect urinary 6-keto $PGF_{1\alpha}$ or TXB_2 excretion. However, considering the limitations on our study in assessing renal prostaglandin metabolites by a single 24-hr urine collection, data obtained in this study cannot definitively exclude a role of urinary arachidonic acid metabolites in modulating the natriuretic effects of torasemide.

In summary, our study shows that torasemide exerts strikingly higher natriuretic and diuretic action than

does furosemide in cirrhotic patients with ascites in the absence of any adverse effect on plasma electrolytes, BUN or creatinine clearance, at least in our 3-day study. The greater natriuretic effect of torasemide is likely due to impaired hepatic metabolism of the drug. Despite the higher natriuretic and diuretic potency exhibited by torasemide, urinary potassium excretion was not affected differently by the two treatments, thus confirming the relatively lower potassium-wasting effect of torasemide. Unlike furosemide, torasemide did not increase blood ammonia at the end of the treatment. These data indicate that torasemide is suitable for the treatment of sodium and water retention in cirrhotic patients with ascites. However, larger and more prolonged clinical trials will be necessary to establish the long-term tolerability and effectiveness of this new loop diuretic.

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