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Diuretic Activity of Torasemide and Furosemide in Chronic Heart Failure: A Comparative Double Blind Cross-Over Study

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Summary. The diuretic effects of torasemide and of furosemide were compared in a double blind cross-over study in 13 patients with stable chronic heart failure. Single doses of 10 mg and 20 mg of torasemide and of 40 mg of furosemide were given orally, in a randomized order on 3 consecutive days. In addition, a placebo was administered on the day preceding the 3 active drug treatment days to obtain control data. Each experimental day was divided into three urine collection periods – 0 to 4 h, 4 to 12 h and 12 to 24 h. Urine output, ion excretion and clearance were measured during each of the 3 periods as well as for the 24-h period. Torasemide 20 mg was distinctly more active in each of the 3 collection periods and in the 24-h period than furosemide 40 mg, whereas no significant difference was found between furosemide 40 mg and torasemide 10 mg for most of the experimental data. From 0 to 4 h, both torasemide and furosemide significantly increased the urinary flow rate and the urinary excretion of sodium, chloride and calcium, while they decreased the urinary osmolality when compared to placebo. All the effects persisted in the 4 to 12 h period after torasemide 20 mg in contrast to furosemide, whose effects were limited to the 0 to 4 h period. In the third period (12–24 h), the urine volume fell below the placebo value after furosemide but not torasemide, and only torasemide 20 mg was followed by a persistent decrease in the urine osmolality. Both diuretics increased the free water clearance, but this phenomenon was slightly greater after torasemide. Finally, urinary potassium excretion was increased by both doses of torasemide and furosemide, with no significant difference between the three experiments. Torasemide and furosemide were well tolerated; no clinical or biochemical adverse effects occurred after administration of either of the compounds. Torasemide is a new loop diuretic which may constitute a good alternative to furosemide in the treatment of oedema in chronic heart failure.

Key words: torasemide, furosemide; diuretic activity, chronic heart failure, electrolyte excretion

In a preliminary study in healthy volunteers [1], torasemide was shown to be a potent diuretic of high-ceiling type activity; urinary output and ionic excretion increased while urinary density and osmolality decreased with the logarithm of the dose in the range 2.5 to 20 mg. An other Phase I study [2] showed that torasemide had a terminal half-life of 2.5 h, and that more than 90% was bioavailable by the oral route.

In the present Phase II study, the acute diuretic activity of torasemide was compared with that of furosemide taken as the reference preparation, in patients suffering from chronic heart failure.

Material and Methods

Design of the Study

The study was designed as a double blind randomized cross-over study comparing the effects of single oral doses of 40 mg furosemide (F_{40}), 10 mg torasemide (T_{10}) and 20 mg torasemide (T_{20}). In order to avoid any sequence effect, the three drugs were given in randomized order on three consecutive days: 5 patients began treatment with T_{40}, 4 patients received T_{10} first and 4 patients began treatment with T_{20}. A placebo was administered on the day preceding administration of the active drugs to obtain control data. The study protocol was approved by the Ethical Committees of our institutions.

Subjects

Thirteen patients suffering from chronic heart failure and hospitalized in the Department of Internal Medicine were investigated. Their clinical characteristics were (mean ± SEM): 6 females and 7 males, 67 ± 2 years, 61.5 ± 3.0 kg. All presented oedema of the legs due to right heart insufficiency and/or lung congestion (Killip II or worse) indicating left heart failure.

Their haemodynamic state was quite stable during the week preceding the study. Any diuretic agent was stopped for at least 48 h beforehand, but their other usual medications (digoxin or digitoxin, vasodilators, etc. . . .) were kept unchanged. After receiving a detailed explanation about the purpose of the study and the protocol, all patients gave their formal consent to it.

Protocol

The study was carried out with patients lying down and kept under strict medical supervision. They received a 1600 kcal daily diet containing less than 1 g sodium, and water consumption was limited to 1.5 l/day. The patients, wearing a hospital gown, were weighed every morning at 8 a.m. after voiding. At that time, the drug was ingested with 100 ml water, immediately before breakfast.

All urine was collected in 3 successive periods on each day: 0–4, 4–12 and 12–24 h after drug ingestion. On each urine sample the following parameters were measured by classical methods: volume, osmolality, concentration of sodium (Na), potassium (K), chloride (Cl), calcium (Ca), phosphates (P), urea, creatinine and uric acid.

A blood analysis was done 24 h after the ingestion of each drug to determine the following parameters: sodium, potassium, chloride, calcium, phosphates, urea, creatinine, uric acid, osmolality, total proteins, glucose, haematocrit and blood cell count.

Heart rate and arterial blood pressure were determined by conventional methods every hour from 8 to 12 a.m. and at 2, 4 and 8 p.m.

Statistical Analysis

The results were expressed as mean ± SEM. Statistical comparison used Student's *t*-test for paired data.

Results

Urine Data

All the results are expressed as percentage change *versus* the data measured during the control day on placebo, which were taken as the reference (100%) value in each case.

Volume (Fig. 1). The mean urine volume was significantly increased during the first 4 h when compared to the control test: +235% with F_{40}, +128% with T_{10} and +313% with T_{20}. No significant difference was observed between the three diuretic treatments.

During the second period (from 4 to 12 h) T_{20} was the sole treatment in which a significant effect on diuresis was observed when compared to the placebo. During the third period, from 12 to 24 h, the urine volume after F_{40} was significantly lower than after placebo or T_{20}.

As far as the entire 24 h study period was concerned, the total urine volume did not differ significantly between F_{40} and T_{10} and placebo. It was 68% larger ($2p < 0.001$) after T_{20}.

Sodium Excretion (Fig. 1). The changes in urinary sodium excretion in many respects were similar to those in urine volume.

During the first 4 h, a significant increase in natriuresis was observed after F_{40} (+425%), T_{10} (+190%) and T_{20} (+533%) when compared to the placebo. No significant difference was observed between the 3 diuretic treatments.

During the second period from 4 to 12 h (+66%), as well as during the entire 24 h study period (+137%), only T_{20} led to a significant increase in urinary sodium excretion when compared to the day on placebo.

Potassium Excretion (Fig. 1). When compared to the results obtained with placebo, F_{40}, T_{10} and T_{20} significantly increased urinary potassium loss during the first 4 h (respectively +149, +123 et +152%), from 4 to 12 h (respectively +43, +30 et +36%) and throughout the 24 h period (respectively +31, +28 and +31%). No statistically significant difference was observed between the three treatments at any time in the study.

Urinary Sodium/Potassium Ratio (Fig. 1). Inter-individual variation in the urinary Na/K ratio was high in all groups, particularly after placebo administration.

When compared to the placebo results, the urinary Na/K ratio was enhanced during the first 4 h in the three diuretic tests (+144% with F_{40}, +77% with T_{10} and +170% with T_{20}). However, due to the large scatter of the individual results, the difference was only statistically significant with the highest dose of torasemide ($2p < 0.02$). No significant difference from placebo was observed during the other two periods (4–12 h and 12–24 h) or between the three diuretic tests at any time in the study.

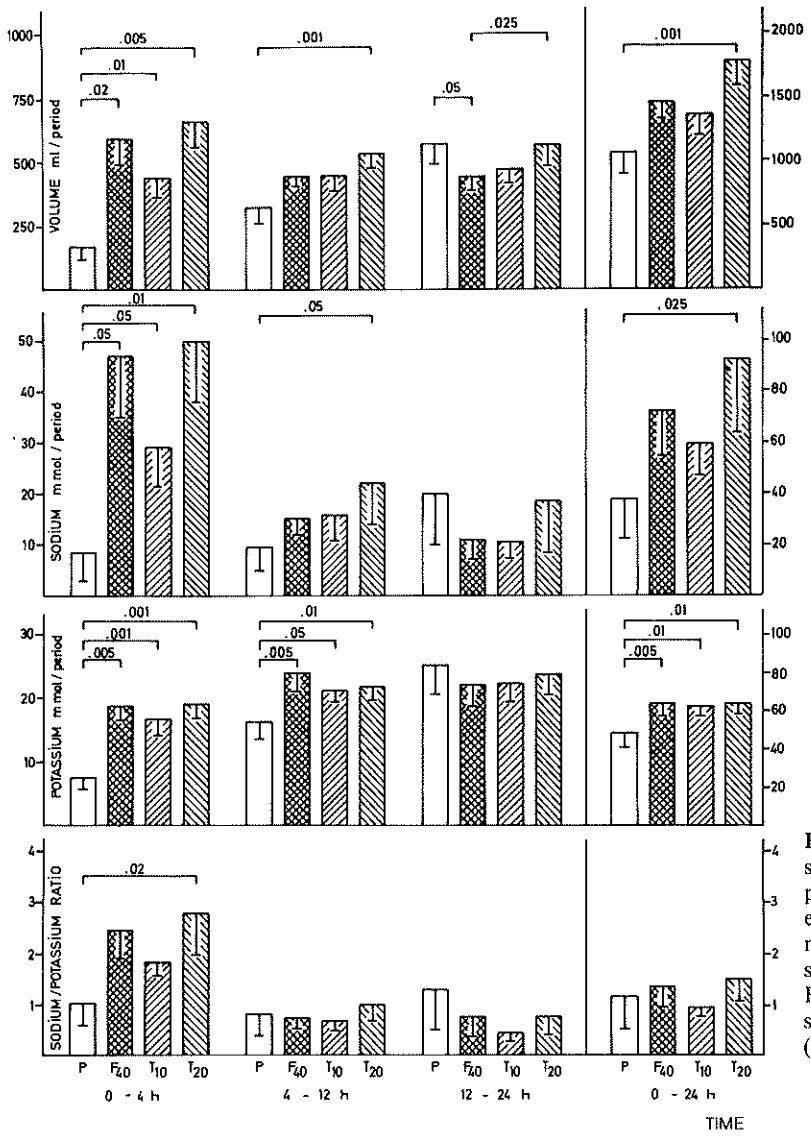

Fig. 1. Urine volume and urinary excretion of sodium and potassium during the three successive periods 0–4 h, 4–12 h and 12–24 h, and during the entire 0 to 24-h study period, after the four treatments: placebo (P), furosemide 40 mg (F_{40}), torasemide 10 mg (T_{10}) and torasemide 20 mg (T_{20}). Results are expressed as mean ± SEM ($n = 13$); the statistical significance is indicated by the 2 p values (Student's t-test for paired data)

Chloride Excretion (Fig. 2). Urinary chloride excretion paralleled the sodium loss, although slightly higher after diuretic ingestion. F_{40} (+499%), T_{10} (+277%) and T_{20} (+508%) significantly enhanced urinary chloride loss during the first period, namely from 0 to 4 h.

During the second period, from 4 to 12 h, a significant increase persisted with F_{40} (+172%) and with T_{20} (+298%).

When the entire 24 h study period was considered, T_{20} was the sole treatment inducing a significant increase in urinary chloride excretion (+246%, $2p < 0.02$). However, there was no statistically significant difference between the three diuretic tests at any time in the study.

Calcium Excretion (Fig. 2). Changes in the urinary calcium excretion were similar to those in urine volume as well as to those in urinary sodium and chloride.

During the first period (0–4 h), there was significantly enhanced urinary calcium excretion in all three diuretic tests: +237% with F_{40}, +197% with T_{10} and +267% with T_{20}. The effect persisted during the second period (4–12 h), but the difference was significant only for T_{20} (+78%). During the third period (12–24 h), urinary calcium loss was significantly lower than in the placebo test with F_{40} (−43%) and T_{10} (−35%), but not with T_{20}.

Consequently, T_{20} was the sole treatment causing a significant increase in urinary calcium excretion during the 24 h study period (+44%, $2p < 0.05$). Again, no significant difference was observed between the three diuretic tests in all the three study periods.

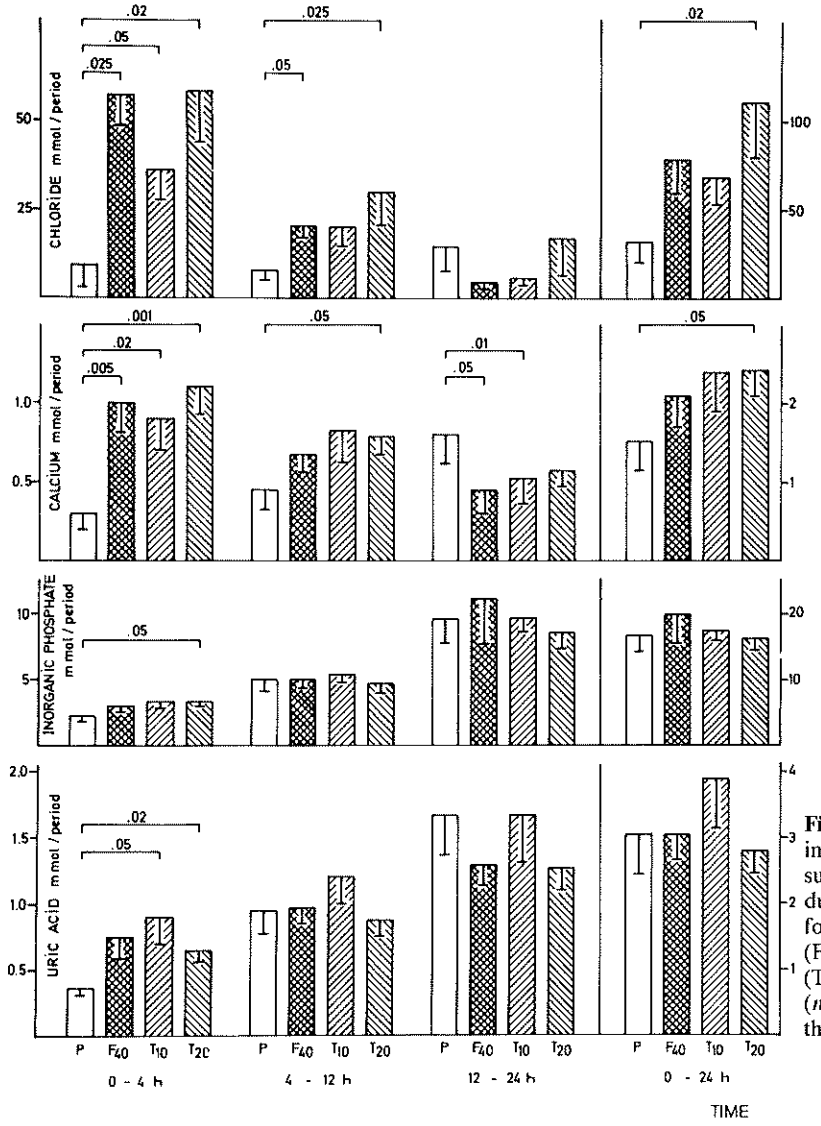

Fig. 2. Urinary excretion of chloride, calcium, inorganic phosphate and uric acid during the three successive periods 0–4 h, 4–12 h and 12–24 h, and during the whole 0 to 24-h study period after the four treatments: placebo (P), furosemide 40 mg (F_{40}), torasemide 10 mg (T_{10}) and torasemide 20 mg (T_{20}). Results are expressed as mean ± SEM ($n = 13$); the statistical significance is indicated by the 2 p values (Student's t-test for paired data)

Phosphate Excretion (Fig. 2). Urinary phosphate excretion was not significantly altered by any of the diuretic drugs at any time (there was a slight increase with T_{20} during the first 4 h which was at the limit of the statistical significance).

Uric Acid Excretion (Fig. 2). When compared to placebo, T_{10} and T_{20} significantly increased urinary uric acid excretion during the first 4 h (respectively +147 and +77%), whereas the rise observed with F_{40}, although of the same order of magnitude (+107%), was not statistically significant. No significant change was observed during the two following periods nor when calculated for the 24-h study period.

Urea and Creatinine Excretion. When compared to placebo, the three diuretic treatments resulted in significant and similar increases in the urinary excretion of urea during the first 4 h after each dose: from 39.3 ± 4.2 mmol/4 h under placebo to 60.8 ± 9.4 after F_{40} ($2p < 0.025$), 58.0 ± 7.8 after T_{10} ($2p < 0.05$) and 65.1 ± 6.8 after T_{20} ($2p < 0.005$).

Torasemide simultaneously caused a significant increase in the urinary excretion of creatinine: from 1.3 ± 0.1 μmol/4 h after placebo to 1.9 ± 0.2 after T_{10} ($2p < 0.02$) and to 2.1 ± 0.4 after T_{20} ($2p < 0.05$), whereas the corresponding rise observed after F_{40} was smaller and was not significant (from 1.3 ± 0.1 to 1.6 ± 0.3 μmol/4 h).

Urinary urea and creatinine in the two following periods (4–12 h, 12–24 h) and those calculated for the whole 24-h study period were similar in the four groups.

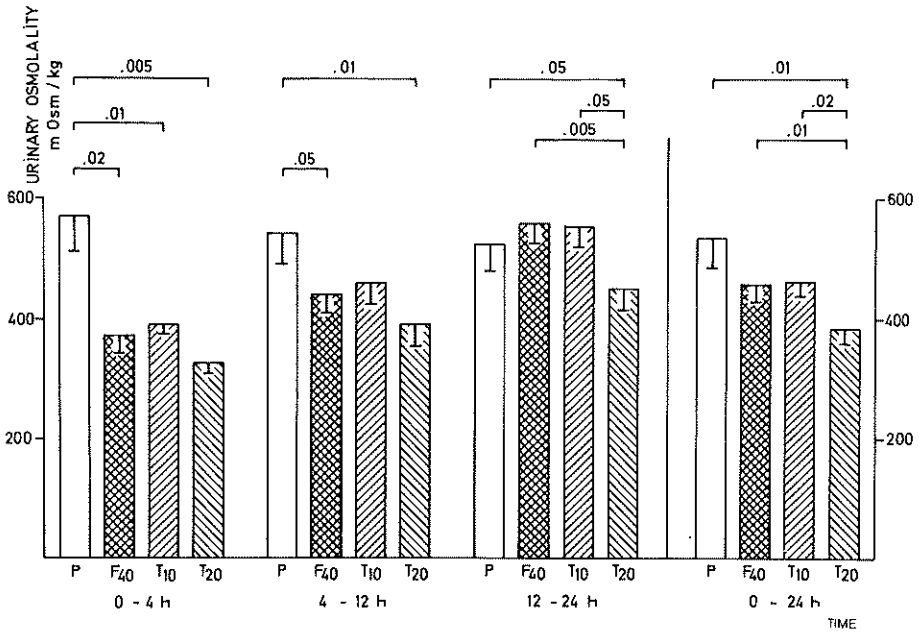

Fig. 3. Urinary osmolality during the three successive periods 0–4 h, 4–12 h and 12–24 h, and during the 0 to 24-h study period after the four treatments: placebo (P), furosemide 40 mg (F_{40}), torasemide 10 mg (T_{10}) and torasemide 20 mg (T_{20}). Results are expressed as mean ± SEM ($n = 13$); the statistical significance is indicated by the 2 p values (Student's t-test for paired data)

Urinary Osmolality (Fig. 3). During the first 4 h, a marked and significant drop in urine osmolality was observed after F_{40} (−35%), T_{10} (−31%) and T_{20} (−42%); no significant differences were observed during the three diuretic tests. During the second period, from 4 to 12 h, the decrease in urinary osmolality when compared to placebo remained slightly more marked with T_{20} than with T_{10} or F_{40}. During the third period (12–24 h), the results obtained with F_{40} and T_{10} were similar to those measured after placebo, whereas T_{20} showed a significant persistent reduction in the urinary osmolality (−19%).

Consequently, as far as the entire 24 h study period was considered, the decrease in urine osmolality was of similar amplitude with F_{40} (−14%) and T_{10} (−11%), and was significantly higher with T_{20} (−29%, $2p < 0.005$).

Clearance Data

Creatinine Clearance. During the first 4 h, torasemide significantly increased the creatinine clearance from 51.3 ± 5.0 to 84.4 ± 11.0 ml/min after 10 mg ($2p < 0.01$), and to 86.7 ± 13.7 ml/min after 20 mg ($2p < 0.01$). In contrast, the moderate rise from 51.3 ± 5.0 to 68.2 ± 13.5 ml/min observed after F_{40} was not significant. However, no significant difference was observed between the three diuretic treatments.

The values of creatinine clearance were not significantly different between the four groups from 4 to 12 h or from 12 to 24 h, or during the whole study period.

Free Water Clearance. In the patients suffering from cardiac insufficiency, the free water clearance (urinary volume ml/min) (1 − urinary osmolality mOsm/kg/serum osmolality mOsm/kg) was negative during the placebo period (−0.6 ± 0.1 ml/min).

During the first 4 h after administration of the drug, F_{40} and T_{2O} induced a moderate but non-significant increase in free water clearance from −0.52 ± 0.10 ml/min after placebo to −0.30 ± 0.20 and −0.21 ± 0.10 ml/min, respectively.

During the second period (4–12 h), only T_{20} significantly increased the free water clearance from −0.53 ± 0.10 after placebo to −0.33 ± 0.10 ml/min ($2p < 0.05$). The effect of T_{20} persisted from 12 to 24 h (significant rise from −0.72 ± 0.10 after placebo to −0.41 ± 0.10 ml/min, $2p < 0.01$) and became significantly higher when compared to F_{40} (−0.66 ± 0.10 ml/min, $2p < 0.02$) and T_{10} (−0.57 ± 0.10 ml/min, $2p < 0.01$).

Consequently, in the whole 24-h study period, the free water clearance after T_{20} (−0.40 ± 0.10 ml/min) was significantly higher than after placebo (−0.65 ± 0.10 ml/min, $2p < 0.02$) or F_{40} (−0.51 ± 0.10 ml/min, $2p < 0.05$).

However, the free water clearance remained negative in all three diuretic groups during the different periods studied.

Serum Electrolyte Levels (Table 1)

No significant differences were observed between the four experimental conditions as far as the serum levels of sodium, potassium, chloride, calcium, inor-

Table 1. Serum levels of sodium, potassium, chloride, calcium, inorganic phosphate, uric acid, urea, creatinine and total proteins, blood glucose, haematocrit and osmolality in blood samples from overnight fasted subjects 24 h after the ingestion of placebo or of the tested drugs. Mean ± SEM

		Placebo	Furosemide 40 mg	Torasemide 10 mg	Torasemide 20 mg
Na	(mmol/l)	137.6 ± 1.1	137.5 ± 1.1	136.9 ± 1.2	138.3 ± 1.3
K	(mmol/l)	4.3 ± 0.1	4.2 ± 0.1	4.2 ± 0.2	4.1 ± 0.1
Cl	(mmol/l)	100.3 ± 1.6	98.8 ± 1.5	98.3 ± 1.5	99.2 ± 1.6
Ca	(mmol/l)	2.2 ± 0.1	2.3 ± 0.1	2.2 ± 0.1	2.2 ± 0.1
Inorganic P	(μmol/l)	1.05 ± 0.11	1.11 ± 0.06	1.08 ± 0.04	1.13 ± 0.06
Uric acid	(μmol/l)	440.7 ± 28.5	459.8 ± 33.9	472.2 ± 29.1	467.5 ± 38.0
Urea	(mmol/l)	8.4 ± 1.7	9.9 ± 1.2	9.5 ± 0.9	9.6 ± 1.0
Creatinine	(μmol/l)	95.6 ± 7.1	102.7 ± 7.1	99.1 ± 5.3	101.8 ± 6.2
Osmolality	(mOsm/kg)	290.7 ± 5.1	289.1 ± 5.0	291.1 ± 5.2	287.0 ± 4.3
Haematocrit	(%)	39.0 ± 1.6	39.8 ± 1.9[a]	38.9 ± 1.6	39.4 ± 1.9[a]
Total proteins	(g/l)	59.6 ± 3.2	62.7 ± 6.7	61.0 ± 3.4	62.0 ± 2.8
Glucose	(mmol/l)	5.9 ± 0.2	5.7 ± 0.3	5.3 ± 0.2	5.2 ± 0.3

[a] $2p < 0.05$ versus placebo

ganic phosphate, uric acid, urea, creatinine and osmolality were concerned. There was a slight but significant increase in haematocrit after F_{40} and T_{20}, and simultaneously a discrete rise in total serum protein level was also observed. These changes indicate haemoconcentration after administration of the diuretics. Finally, a slight decrease in blood glucose level was observed after torasemide but not after furosemide.

Body Weight

Body weight fell significantly from 61.2 ± 3.2 kg after placebo to 60.3 ± 3.2 kg after F_{40} ($n = 12$, $2p < 0.005$), from 61.5 ± 3.0 to 60.6 ± 3.1 kg after T_{10} ($n = 13$, $2p < 0.05$) and from 63.1 ± 3.2 to 61.8 ± 3.2 kg after T_{20} ($n = 10$, $2p < 0.01$). The weight loss was similar after the three diuretic treatments.

Haemodynamic Parameters

Analysis of the results for heart rate and arterial blood pressure showed no significant differences between the four experimental conditions at any time in the study, as well as no significant change versus the baseline value recorded at 8 a.m. just before administration of each drug.

Side-Effects

No patient complained of gastro-intestinal, cardio-respiratory or neurological distubances during the four experiments. No particular clinical or biological side-effects were observed.

Discussion

Although in rats and dogs torasemide has been shown to be 5- to 10-times more potent than furosemide on a weight basis (3, 4, 5), previous studies in normal man have indicated that the corresponding oral dose of torasemide when compared to 40 mg furosemide was probably 10 to 20 mg [1, 2]. In a previous Phase II study [6] the comparison was made of three 5-day treatment periods with torasemide 10 mg, torasemide 20 mg or furosemide 40 mg in three different subgroups of oedematous patients, suffering from heart failure or hepatic cirrhosis. The results suggested that torasemide was more effective than furosemide on urine volume and sodium excretion. However, as oedematous patients are often a heterogeneous population, and since it is difficult to appreciate precisely the degree of oedema, it was not possible to be sure that the three subgroups were strictly comparable. Thus, in order to improve the conditions for a comparative trial, the present experiment was designed as a double-blind randomized cross-over study comparing single oral doses of torasemide 10 mg, torasemide 20 mg and furosemide 40 mg. Moreover, all the patients were suffering from pure cardiac insufficiency, excluding hepatic cirrhosis or renal failure. They were in a stable haemodynamic state during the prior week and any diuretic drug was withdrawn for at least 48 h. Finally, the comparative study in each patient was preceded by a control day on placebo.

At the two doses tested, torasemide exhibited potent diuretic activity, with a significant increase in urine volume as well as in the urinary excretion of sodium, potassium, chloride and calcium. Simultaneously, the urinary osmolality was significantly reduced. The changes were qualitatively quite simi-

lar to those reported in normal subjects in whom a clear dose/response curve was observed for doses of torasemide ranging from 2.5 to 20 mg [1]. However, on a quantitative basis, torasemide was much less potent in the cardiac patients, since the urine volume during the first 4 h after drug ingestion was 2.5- to 3-times lower and the urinary sodium excretion was 15- to 20-times lower than in normal subjects.

The urinary changes induced by torasemide were qualitatively and quantitatively comparable to those observed after furosemide. Torasemide showed a clear dose-response curve, so that the amplitude of the diuretic activity of furosemide 40 mg was mimiced by torasemide 10 to 20 mg. The onset and peak of action of torasemide and furosemide were similar, and their actions both peaked during the first 4 h following ingestion. The results fit with the pharmacokinetic data, since the peak serum level of torasemide is reached 1 h after its oral administration and its biological half-life is estimated to 2.5 h [2]. The action of torasemide appeared to last longer than that of furosemide, as judged from the results obtained during the second period (4–12 h). The results are in agreement with those of Broekhuysen et al. [6], and could easily be explained by the pharmacokinetics, which showed that torasemide had a longer half-life than furosemide (around 1 h; [7–10]). Furthermore, after 20 mg torasemide no secondary fall in diuresis below baseline values was observed during the third period (12–24 h), while the diuresis after furosemide fell below the mean placebo value during the corresponding period. Consequently, over the 24-h period, only torasemide 20 mg induced a significant increase in urine volume and natriuresis when compared to placebo. Torasemide produced a greater chloruresis than natriuresis, as found earlier by Lesne et al. [2] for this compound and by others for several high-ceiling diuretics, such as furosemide, bumetanide and azosemide [11–13].

Furosemide 40 mg and torasemide 20 mg increased the urinary loss of potassium by a similar amount. Since the natriuretic effect of torasemide 20 mg was higher than that of furosemide, the urinary Na/K ratio after the new drug was slightly higher than after furosemide, confirming the results of another Phase II study [6]. However, the urinary potassium excretion was higher after torasemide in the present cardiac patients than in the normal subjects previously tested [1]. Since the natriuresis was lower, the urinary Na/K ratio after torasemide 20 mg reached only 2.8 in this Phase II study, whereas it was 5.1 in the previous work in healthy volunteers [1] and 5.6 in the study of Lesne et al. [2]. The differences can be explained by the salt restriction and the secondary hyperaldosteronism in the patients with heart failure. Nevertheless, in this acute study, serum potassium levels did not change significantly when comparing the three diuretic treatments with the placebo day.

The urinary excretion of inorganic phosphate can be used as a marker of proximal tubular inhibition [14, 15]; the absence of major change with torasemide might then indicate that it had no important effect on this part of the nephron. However, a significant alteration was not found either with furosemide, even though proximal tubular effects with this drug were reported in earlier animal studies [16, 17]. The effect of furosemide on urinary phosphate excretion was shown to be function of the experimental conditions [15, 18]; phosphate excretion increased significantly when urinary loss was replaced, but it remained unchanged if volume contraction occurred, as in the present study.

A significant increase in urinary creatinine and creatinine clearance was found with torasemide but not with furosemide. Increased, unchanged or decreased glomerular filtration rates have been reported in the literature for furosemide and other diuretic agents in various animal species as well in man [reviewed in 19]. The variability might well be explained by the difficulty of obtaining steady-state conditions in diuretic experiments (by adequate water and electrolyte replacement), which is a basic requirement for clearance studies. Thus, in experimental as well as in clinical circumstances, altered creatinine clearance should be considered cautiously and it may not necessarily indicate a corresponding effect on the renal function.

Finally, torasemide induced almost the same increase in free water clearance as furosemide [19, 20]. In the condition of relative hydropenia, both diuretics provoked decreased tubular reabsorption of solute-free water and this effect persisted even after the peak of saliuresis, namely after the 4th hour. The results confirm that the mean locus of action of torasemide is the ascending limb of the loop of Henle, where sodium chloride is reabsorbed in excess of water. Indeed, as a result of studies on free water production in animals and in man, as well as by direct micropuncture and isolated nephron techniques, the high-ceiling diuretics have been shown to act primarily by inhibiting the active transport of the chloride anion at the luminal border of tubule, thereby inhibiting sodium chloride reabsorption in the ascending limb of the loop of Henle [21].

In spite of their potent diuretic effects, torasemide and furosemide were well tolerated. The haemodynamic parameters remained entirely stable, no patient complained of side-effects and no biological abnormalities were detected.

In conclusion, torasemide is a potent diuretic compound, whose mode of action and properties appear similar to those of furosemide, a high-ceiling diuretic. In patients with chronic heart failure, a single oral dose of 20 mg torasemide was significantly more effective than that of 40 mg furosemide, which was not significantly different from 10 mg torasemide. Torasemide, which was clinically and biologically well tolerated, is a new loop diuretic, which may constitute a good alternative to furosemide.

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