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A Comparison of the Pharmacokinetics and Diuretic Effects of two Loop Diuretics, Torasemide and Furosemide, in Normal Volunteers

L. Dodion[1], Y. Ambroes[2], and N. Lameire[3]

[1] Medical Department, A. Christiaens S. A., Brussels
[2] University Hospital St. Luc, Department of Clinical Biochemistry, Woluwe St. Pierre and
[3] University Hospital, Renal Division, Gent, Belgium

Summary. The diuretic effects of torasemide and furosemide at three different steady-state plasma and urinary drug levels were compared in a randomized cross-over study in 6 healthy volunteers. Each trial with either torasemide or furosemide consisted of four consecutive periods of 90 min, the first being a control period, and during the three other periods, increasing doses of drug were administered. Each 90-min period was itself divided into three 30 min blood sampling and urinary collection periods. The urinary losses of water and electrolytes were compensated within each 30-min period by intravenous infusion of saline (NaCl) and 5% glucose solutions, to which KCl was added. A constant dose of calcium gluconate was given to compensate, at least in part, any calcium loss.

Data from each 30 min control and the 3 drug dose periods, corresponding to full steady-state conditions, were used for clearance determinations and measurement of plasma and urinary drug concentrations.

Urine volume, osmolar clearance, absolute and fractional urinary excretion of sodium, potassium, chloride, calcium and magnesium and creatinine clearance increased similarly after torasemide and furosemide according to the logarithm of the dose of the drug. Free water clearance stabilized at a constant level with torasemide and increased continuously after each dose of furosemide. During each of the three drug administration periods, the plasma levels of torasemide were not significantly different from those of furosemide, whereas the urinary concentrations and absolute excretion rates of torasemide were more than 5-times lower than those of furosemide.

The urinary concentrations and excretion rates of both drugs were significantly correlated with their effect on urinary volume ($p < 0.05$).

It is concluded that torasemide is a potent loop diuretic. It acts at lower urinary levels than furosemide. This might indicate more effective binding of torasemide to luminal tubular receptors or an additional effect of this drug on non-luminal receptors.

Key words: torasemide, furosemide; diuretic effects, pharmacokinetics, adverse effects

Torasemide (1-isopropyl-3-[(4-m-toluidino-3-pyridil) sulphonyl] urea) is a new loop diuretic, which based on animal and human studies, has an effect profile comparable to but 5-10 times more potent than, that of furosemide [1, 2], and with a longer duration of action [3].

Previous pharmacokinetic and pharmacodynamic studies have shown that diuresis and natriuresis increased linearly with the logarithm of the administered dose after furosemide [4-7] and torasemide [8].

In the present cross-over study in normal volunteers, furosemide and torasemide were continuously infused in increasing doses in order to achieve three different steady-state plasma and urinary drug levels. This allowed assessment of the potency of both drugs at the renal tubular site by relating amounts of drug at the urinary site of action to the diuretic response of water and electrolyte excretion. Great care was taken to compensate constantly for urinary losses of water and electrolytes in order to preserve a constant composition of the extracellular volume.

Materials and Methods

Six normal male volunteers, 22 to 55 years old, were selected for the study. Each had a normal medical history, physical examination, electrocardiogram,

chest radiography and complete blood count and blood chemistry. They were instructed to keep to a diet containing 100 mEq sodium and 60 mEq potassium for 5 days before the trial and during the interval between the two periods of drug administrations. They had to refrain from smoking and drinking alcohol, coffee and black tea throughout the investigation period.

Each trial consisted of four consecutive 90-min periods, the first being a control period, and during the other three periods increasing doses of drug were continuously administered. Each 90-min period was itself divided into three blood sampling and urine collection periods of 30 min.

At the end of each 30-min period, the volunteer voided spontaneously, the urinary volume was measured and samples were sent immediately to the laboratory for analysis within 5 min.

The data from the last 30 min period of each control and 3 drug periods were used for the clearance determinations.

On the day of trial and after an overnight fast, the volunteer lay down comfortably and an intravenous catheter was inserted into one arm for injection of the drug and for the infusion of saline (NaCl) and 5% glucose solutions to which KCl was added. In the other arm, an indwelling catheter was placed for blood sampling.

On the basis of preliminary data obtained from a pilot study with torasemide in another volunteer, the infusion volume was fixed at 0,101-0,201 at the beginning of the first 30-min control period, and at 0,751-1,01, 1,25-1,501 and 1,75-2,251, respectively, at the beginning of the corresponding first 30-min periods for the first, second and third doses of the drug. The final balance was assured within 5-10 min after completion of each of the 30-min periods by exactly adjusting the infusion volume and saline and KCl administration to the preceding urine loss. A standard dose of calcium gluconate was added to either the NaCl or 5% glucose solutions during each of the three drug administration periods. The total cumulative dose of calcium administered was 4.5 mmol.

Drug Administration

Torasemide and furosemide were administered at a one week interval according to a randomized cross-over sequence.

For each drug, a loading dose was injected at the beginning of each 1.5-h administration period, followed by a constant rate infusion throughout the 1.5-h period to maintain a steady-state level. The total dose infused in 1.5 h was calculated on the assumption that both the half-life (2 h) and the diuretic potency of torasemide on a weight basis were double those of furosemide. The loading and infusion doses of the 2 drugs are given in Fig. 1.

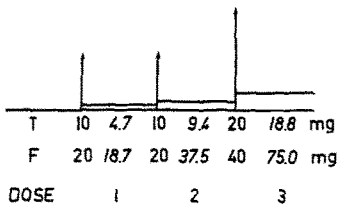

Fig. 1. Protocol of study with an initial bolus followed by continuously infusion of torasemide (T) and furosemide (F). The total cumulative doses were 72.9 mg torasemide and 211.2 mg furosemide. Arrows indicate time of bolus injections. Each interval consisted of 3 consecutive 30-min clearance collections

Blood and urine were analysed for creatinine (Jaffe's reaction), sodium and potassium (flame photometer), chloride (Chloride Color, Wienen) and osmolality (Advanced Osmometer). In addition, calcium, magnesium and phosphate were measured by atomic absorption (Unicam SP 1900) and colorimetry (Phosphorus Rapid Stat Kit, Pierce), respectively. Total protein was measured by the biuret method.

The clearances of creatinine, solutes and free water were computed by standard formulae for the last 30-min period of each of the control and the 3 drug administration periods. Free water clearance (CL_{H_2O}) was calculated as the difference V_{ur}-CL_{osm}.

Fractional urinary electrolyte excretion was calculated as $CL_{EL}/CL_{CR} \times 100$.

The plasma and urinary levels of torasemide were assayed by HPLC, using a Perkin Elmer 601 chromatograph, equipped with an UV-detector set at 290 nm. The method has been described elsewhere [3]. The plasma and urinary levels of furosemide were also assayed by HPLC [10].

Statistical Analysis

Student's *t*-test was used to evaluate differences between the means of the data obtained with torasemide and with furosemide. The balance between the urinary losses and intravenous infusions of water and ions, as well as the stability of the plasma electrolyte levels, blood osmolality and serum creatinine at the 60th-90th min of the control and the three drug administration periods were studied by analysis of variance.

The effects of torasemide and furosemide on water diuresis, creatinine clearance, and urinary excretion and clearance of the electrolytes and free water were studied by regression analysis against the log dose.

Table 1. Water, sodium, potassium and chloride balance studies and plasma levels of electrolytes, osmolality and total protein

		Urinary excretion	Infusion	Blood levels (mmol/l) (or g/dl)			
				Control	1st dose	2nd dose	3rd dose
Torasemide							
Water	(l)	11.4 ±1.4	11.5 ±1.43				
Sodium	(mol)	1.11 ±0.178	1.18 ±0.123	0.140 ±0.005	0.141 ±0.005	0.140 ±0.004	0.139 ±0.003
Potassium	(mmol)	117.3 ±6.0	112.9 ±16.7	3.95 ±0.42	4.21 ±0.42	4.23 ±0.61	4.08 ±0.47
Chloride	(mol)	1.26 ±0.158	1.29 ±0.120	0.104 ±0.005	0.105 0.004	0.105 ±0.004	0.104 ±0.003
Calcium	(mmol)	12.6 ±1.5	4.5	2.38 ±0.16	2.20 ±0.10	2.08 ±0.12	2.02 ±0.12
Phosphate	(mmol)	7.65 ±2.50	-	0.867 ±0.159	0.789 ±0.127	0.833 ±0.175	0.871 ±0.145
Magnesium	(mmol)	4.84 ±0.82	-	0.80 ±0.05	0.74 ±0.33	0.67 ±0.04	0.59 ±0.02
Osmolality				284.0 ±3.0	285.7 ±6.4	285.2 ±3.4	284.2 ±15.4
Total proteins				7.0 ±0.4	6.8 ±0.3	6.6 ±0.3	6.8 ±0.3
Furosemide							
Water	(l)	15.0 ±1.6	14.7 ±1.85				
Sodium	(mol)	1.58 ±0.354	1.55 ±0.350	0.142 ±0.006	0.141 ±0.005	0.141 ±0.005	0.139 ±0.004
Potassium	(mmol)	180.6 ±39.0	185.7 ±33.5	4.13 ±0.30	4.43 ±0.60	4.50 ±0.64	4.56 ±0.82
Chloride	(mol)	1.76 ±0.371	1.72 ±0.335	0.106 ±0.002	0.106 ±0.003	0.106 0.005	0.106 ±0.004
Calcium	(mmol)	16.4 ±3.2	4.5	2.43 ±0.10	2.31 ±0.12	2.08 ±0.10	1.70 ±0.15
Phosphate	(mmol)	9.0 ±4.6	-	0.879 ±0.132	0.770 ±0.127	0.740 ±0.097	0.717 ±0.097
Magnesium	(mmol)	5.88 ±0.70	-	0.81 ±0.03	0.75 ±0.05	0.67 ±0.07	0.59 ±0.09
Osmolality				287.2 ±1.5	286.0 ±2.9	283.8 ±1.9	281.2 ±3.9
Total proteins				7.1 ±0.5	7.0 ±0.5	7.1 ±0.6	7.3 ±0.9

Correlations between plasma and urinary drug levels and the effects on electrolyte excretions were studied by regression analysis.

Differences between the parameters were considered non significant (ns) for any p-value higher than 0.05. In all tables, data are given as mean ± SD.

Results

Water and Electrolyte Balance Studies and Blood Electrolyte Levels

As noted in Table 1, there were no differences between the excreted and infused amounts of water and the major electrolytes, indicating that water and electrolyte balance was maintained.

The blood levels of sodium, potassium and chloride were maintained within narrow limits throughout the control and drug periods (Table 1).

The blood calcium levels (Table 1) decreased gradually from the control period to the end of the treatment with torasemide and furosemide; the difference was statistically significant ($p < 0.001$), despite the administration of calcium during each treatment.

The urinary loss of calcium increased to a total of 12.6 ± 1.5 mmol with torasemide and to 16.4 ± 3.2 mmol with furosemide.

Blood phosphate levels varied from an initial control value of 0.867 ± 0.159 mmol/l to 0.871 ± 0.145 mmol/l at the end of the experiment with torasemide. The corresponding figures for furosemide were 0.879 ± 0.132 mmol/l and 0.717 ± 0.097 mmol/l. The fall in phosphate levels was not significant after torasemide but it was for furosemide ($p < 0.01$).

Urinary phosphate excretion was increased to a total of 7.65 ± 2.50 mmol by torasemide, and to 9.0 ± 4.6 mmol by furosemide.

The blood magnesium level decreased significantly from 0.80 ± 0.05 mmol/l in the control period to 0.59 ± 0.02 mmol/l in the third torasemide dose period ($p < 0.001$), and from 0.81 ± 0.03 mmol/l to 0.59 ± 0.09 mmol/l in the third furosemide dose period ($p < 0.001$).

The urinary loss of magnesium totalled 4.84 ± 0.82 mmol with torasemide and 5.88 ± 0.70 mmol with furosemide.

The slopes of the regression lines between the urinary excretion of calcium, phosphates and magnesium and the doses of the drugs did not differ between torasemide and furosemide.

Blood osmolality and total protein (Table I) did not change significantly throughout the experiment.

Table 2. Creatinine clearance (CL_{CR}) and creatinine blood levels (C_{CR}) and urinary creatinine excretion ($U_{Cr} \cdot V_{ur}$) after torasemide and furosemide

	CL_{CR} (ml/min)	C_{CR} (μmol/l)	$U_{CR} \cdot V_{ur}$ (μmol/min)
Torasemide			
Control	126.8 ± 21.0	102.0 ± 4.3	12.91 ± 2.57
First dose	129.2 ± 17.3	97.5 ± 6.0	12.08 ± 1.15
Second dose	139.7 ± 22.0	95.1 ± 6.0	12.26 ± 1.92
Third dose	164.8 ± 22.3	89.7 ± 4.6	12.96 ± 1.99
Total			58.21 ± 5.48
Furosemide			
Control	126.5 ± 10.1	96.3 ± 8.8	12.88 ± 1.11
First dose	151.7 ± 2.8	90.3 ± 8.5	12.33 ± 1.34
Second dose	156.5 ± 19.3	85.4 ± 9.1	12.35 ± 0.78
Third dose	164.0 ± 30.4	85.7 ± 4.0	12.20 ± 1.58
Total			53.76 ± 4.24

Creatinine Clearance (CL_{CR}) (Table 2)

The CL_{CR} increased significantly and progressively from 126.8 ± 21.0 ml · min^{-1} in the control period to 164.8 ± 22.3 ml · min^{-1} with torasemide ($p < 0.05$), and similarly from 126.5 ± 10.1 ml · min^{-1} up to 164.0 ± 30.4 ml · min^{-1} with furosemide ($p < 0.05$).

According to analysis of variance, the slope of the regression line of CL_{CR} on the logarithm of the three dose levels of torasemide was not significantly different from that for furosemide.

The increase in creatinine clearance was entirely due to a significant decrease in the absolute serum creatinine level, which was of the same extent with both drugs. The fall in serum creatinine was highly correlated with the infusion volume ($p < 0.01$). The urinary creatinine excretion remained constant.

Table 3. Volumes (V_{ur}), osmolar and free water clearances (CL_{osm} and CL_{H_2O}) and excretion of sodium ($U_{Na} \cdot V_{ur}$), potassium ($U_K \cdot V_{ur}$), calcium ($U_{Ca} \cdot V_{ur}$) and phosphates ($U_p \cdot V_{ur}$) in urine excreted between the 60th and 90th min of the control (C) and the 3 treatment periods with torasemide and furosemide (T_1, T_2 and T_3)

		Torasemide				Furosemide			
		C	T_1	T_2	T_3	C	T_1	T_2	T_3
V_{ur}	X	8.07	25.23	39.98	57.45	9.70	38.10	55.13	73.16
(ml · min^{-1})	SEM	1.02	1.57	1.97	4.08	2.39	3.90	3.53	6.71
CL_{osm}	X	3.16	16.73	31.45	49.33	4.44	32.18	48.60	66.36
(ml · min^{-1})	SEM	0.28	0.88	1.15	3.77	0.69	3.59	3.61	6.31
CL_{H_2O}	X	4.88	8.35	7.93	8.04	5.25	5.95	6.55	6.81
(ml · min^{-1})	SEM	0.89	1.10	1.06	0.75	2.06	0.75	0.51	1.18
$U_{Na} \cdot V_{ur}$	X	0.155	1.926	3.984	6.396	0.222	4.034	6.217	8.654
(mEq · min^{-1})	SEM	0.024	0.116	1.659	0.567	0.035	0.461	0.527	0.861
$U_{cl} \cdot V_{ur}$	X	1.67	23.01	45.32	70.66	2.75	45.67	69.20	94.51
(mEq · min^{-1})	SEM	0.22	1.32	1.42	5.27	0.57	4.83	5.08	8.54
$U_K \cdot V_{ur}$	X	0.071	0.291	0.438	0.599	0.134	0.532	0.661	0.839
(mEq · min^{-1})	SEM	0.012	0.020	0.215	0.229	0.030	0.056	0.049	0.670
$U_{Ca} \cdot V_{ur}$	X	0.262	0.980	1.695	2.345	0.337	1.857	2.465	3.092
(mg · min^{-1})	SEM	0.049	0.083	0.058	0.149	0.074	0.177	0.130	0.270
$U_p \cdot V_{ur}$	X	0.313	0.285	0.777	1.160	0.292	0.636	1.023	1.258
(mg · min^{-1})	SEM	0.050	0.147	0.139	0.165	0.089	0.202	0.162	0.190

Table 4a. Plasma levels of torasemide and furosemide in μg/ml

	Torasemide		Furosemide	
	60th min	90th min	60th min	90th min
Dose I	1.91 ± 0.95	1.82 ± 1.54	2.51 ± 0.96[a]	1.50 ± 0.28[a]
Dose II	3.00 ± 1.37	2.33[a] ± 0.69	2.27 ± 0.64	2.78 ± 0.65
Dose III	6.36 ± 2.81	4.63 ± 1.59	3.16 ± 0.09	3.29 ± 0.14

[a] $p < 0.05$

Table 4b. Urinary concentrations (μg/ml) and excretion (mg) of torasemide and furosemide

	Torasemide		Furosemide	
	(μg/ml)	(mg)	(μg/ml)	(mg)
Dose I				
0-30 min	0.63 ± 0.08	0.484 ± 0.171	5.71 ± 1.62	4.32 ± 2.38
30-60 min	0.51 ± 0.06	0.373 ± 0.091	2.33 ± 0.51	2.16 ± 0.97
60-90 min	0.43 ± 0.06	0.328 ± 0.091	1.88 ± 0.40	2.38 ± 1.04
Subtotal		1.185 ± 0.275		8.85 ± 3.60
Dose II				
0-30 min	0.67 ± 0.13	0.863 ± 0.258	4.83 ± 0.53	7.48 ± 2.82
30-60 min	0.60 ± 0.07	0.691 ± 0.094	3.60 ± 0.52	6.62 ± 1.86
60-90 min	0.54 ± 0.10	0.602 ± 0.093	3.23 ± 0.59	5.04 ± 1.82
Subtotal		2.156 ± 0.493		19.15 ± 5.19
Dose III				
0-30 min	1.30 ± 0.29	1.758 ± 0.511	8.37 ± 1.50	16.8 ± 4.63
30-60 min	1.50 ± 0.52	2.302 ± 0.891	5.56 ± 0.84	12.1 ± 4.65
60-90 min	1.86 ± 0.37	1.849 ± 0.645	5.89 ± 1.25	12.6 ± 6.57
Subtotal		6.209 ± 1.564		41.4 ± 6.57
Cumulated total		9.550 (13.1%)		69.405 (32.9%)

Water and Urinary Electrolyte Excretion (Table 3)

The urinary volume between 60 and 90 min after the injection of the first dose of torasemide or of furosemide was significantly higher than the corresponding volumes in the control period. It was further increased after the second and third doses of each compound. The increments were linearly related to the logarithm of the 3 doses of torasemide ($r = 0.904$; $p < 0.001$) and of furosemide ($r = 0.812$, $p < 0.001$).

The slope of the regression line with torasemide was not significantly different from that for furosemide.

A significant increase after the first doses of torasemide as well as of furosemide was observed in the 60 to 90 min osmolar clearance, and in the 60 to 90 min excretion of sodium, potassium, chloride and calcium. Further increases were seen after the second and third doses of both compounds. The linear regression coefficients of the increases against the log dose were significantly different from zero in all instances.

The free water clearance was stabilized at a constant level during the 3 injection periods of torasemide. It increased continuously after the corresponding injections of furosemide. The linear regression coefficients were not significantly different from zero.

The phosphate excretion did not change after the first dose of torasemide, but it increased significantly after the second and third doses of both compounds. However, the changes were not linearly related to the logarithms of the 3 doses.

There was no significant difference between any of the slopes of the regression lines computed for torasemide or for furosemide.

The fractional urinary excretion of water, sodium, potassium, chloride, calcium and phosphates was increased progressively with the three successive doses of torasemide and furosemide (not shown). All the changes were significantly correlated with the logarithms of the doses, but there were no significant differences between the slopes of the regression lines for the two diuretics.

Drug Plasma Levels (Table 4a) *and Urinary Drug Excretion Rates* (Table 4b)

At the end (i.e. 90th min) of each of the 3 drug administration periods, the plasma levels both of tora-

semide and furosemide had progressively increased and the differences between torasemide and furosemide were not significant. The plasma levels were not significantly correlated with the effect on water diuresis, neither for torasemide nor for furosemide.

The urinary concentrations and absolute excretion rates of both drugs are summarized in Table 4b. In each of the 3 drug administration periods, the urinary concentration of torasemide was usually more than 5-times lower than that of furosemide. The total cumulative urinary excretion of torasemide was 7.3-times lower than that of furosemide; the corresponding ratios for total cumulative urinary volume and urinary excretion of sodium were only 1.3-times and 1.4-times, respectively.

The cumulative subtotal urinary excretion of torasemide in 90 min increased progressively from 1.19 ± 0.275 mg with the first dose to 6.21 ± 1.56 mg after the third dose, respectively; the corresponding values for furosemide were 8.85 ± 3.60, and 41.4 ± 13.6 mg, respectively. The urinary excretion of torasemide was significantly lower than that of furosemide in each of the 3 drug administration periods. The total cumulative excretion of torasemide was 9.55 mg, corresponding to 13.1% of the total administered dose. On the other hand, a total amount of 69.4 mg furosemide or 32.9% of the total dose was excreted. Consequently, there was a 5 to 10-fold difference between the clearances of torasemide and furosemide. It ranged from 7 to 14 $ml \cdot min^{-1}$ for torasemide and from 50 to 100 $ml \cdot min^{-1}$ for furosemide.

The effect on urinary volume was significantly correlated with the urinary excretion of torasemide ($r = 0.629$, $p < 0.05$) as well as of furosemide ($r = 0.699$, $p < 0.05$).

Side-Effects

Except for one volunteer, who fainted for a few seconds with a orthostatic fall of blood pressure from 100/70 to 60/0 mmHg after the highest dose of furosemide, with full recovery after lying down for 1 min, the systolic and diastolic blood pressures remained constant throughout the experiment in all the volunteers.

In another subject, a prolonged QT interval with an U on T-wave was found transiently at the end of the second dose of furosemide. At that time, the blood calcium level had decreased from a control value of 5.05 to 4.10 mmol/l, and the corresponding blood magnesium level from 0.83 to 0.67 mmol/l. A 90 mEq dose of calcium was immediately administered i.v., and 10 min later the E.C.G. had returned to normal. No change in heart rate or other side-effect was found in any of the subjects.

Discussion

The high-ceiling or loop diuretics are thought to act as inhibitors of sodium chloride reabsorption in the thick ascending limb of the loop of Henle, where their basic mechanism of action appears to be inhibition of active Na-K-Cl-cotransport [9]. Additional effects on sodium chloride reabsorption in the proximal tubule have been reported by Knox et al. [11]. Maximal fractional excretions of sodium and chloride as high as 25% or more can be obtained with loop diuretics, such as furosemide [12]. However, this effect varies markedly with the state of hydration. If the urine volume in an animal is not replaced by saline infusion, fractional reabsorption by the proximal tubule increases and the urine flow falls; conversely, if the loss of extracellular fluid is corrected by infusion of saline, increased reabsorption by the proximal tubule is avoided and the diuretic effect is protracted.

Because of the primary influence of the hydration state, urinary losses in this study were carefully and continuously balanced by a corresponding infusion of water and electrolytes. Plasma levels of total proteins, sodium and potassium did not alter throughout the experimental period. Minor changes in plasma chlorides could be observed in the range of 1-3 mEq/l, corresponding to a maximal error of 1 to 3%. The decrease in blood osmolality after both drugs may be easily accounted for by the increased urinary excretion of calcium and magnesium, which were not fully replaced.

The plasma levels of both these two electrolytes dropped significantly and similarly by approximately 25% after both torasemide and furosemide.

There was a marked linear relationship between the diuretic effect, the urinary excretion of all the electrolytes and the logarithm of the dose of each drug. No basic differences in the effects of torasemide and furosemide could be detected.

A dose-dependent increase in the creatinine clearance was found after both drugs. The urinary excretion of creatinine was not significantly altered throughout the control and the 3 drug administration periods. The increased clearance can therefore be completely explained by a progressive decrease in the plasma creatinine level.

The high infusion rates of water and electrolytes necessary to maintain a steady-state volume in the volunteers might have led to artifical lowering of the plasma creatinine level. Accordingly, the creatinine clearance in this study should not be used as accurate measurement of glomerular filtration rate (GFR), nor should the log dose-related increase in GFR with torasemide or furosemide be interpreted

as evidence of increased glomerular filtration rate and/or renal blood flow.

Decreased [11, 12] or unchanged [13-15] GFRs have been reported after furosemide in various animal experiments and in man. In contrast, in acute studies in patients with reduced glomerular filtration, furosemide usually increases GFR [16].

In spite of their potent diuretic effects, torasemide and furosemide were well tolerated. Urinary flow-related back pain (with a transient vagal reaction in one subject after the highest dose of furosemide) was the only complaint. No other significant symptoms were observed.

The blood pressure and the heart rate remained remarkably stable.

The pharmacokinetics of torasemide and furosemide showed interesting characteristics. The urinary losses of water and sodium, potassium and chloride were well balanced in this study by the intravenous infusion of saline. A steady state was reached with respect to the plasma levels and urinary excretion rates of torasemide and furosemide. Except in the first 30-min period after the first dose of furosemide, the plasma levels and the amount of unchanged drug in the urine remained constant throughout each of the three drug administration periods, and they were associated with completely sustained effects.

This situation permits valid evaluation of the relationship between the diuretic effectiveness and the pharmacokinetics of the drugs. Torasemide was effective at plasma levels similar to those of furosemide. In contrast, the urinary excretion of torasemide was several times lower than that of furosemide and the diuretic effect of each drug was significantly related to its urinary excretion. If the inhibition of sodium chloride and water reabsorption by loop diuretics were to depend on the intraluminal concentration in the nephron [19, 20], the difference with torasemide could be relevant in clinical therapy. The high efficacy of torasemide could then be due to its biotransformation into one or several metabolites, to a more specific binding affinity to luminal tubular receptors involved in the transtubular electrolyte transport, or to an additional effect on nonluminal receptors. Whatever the mechanism, it may be expected that metabolic factors or impaired kidney function might influence the therapeutic response and lead to different effects of torasemide and furosemide in individiual cases.

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N. Lameire
University Hospital
Renal Division
De Pintalaan 185
B-9000 Gent
Belgium