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PHARMACOKINETICS AND DISPOSITION

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Pharmacokinetics of torasemide and its metabolites in end-stage renal disease

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Abstract The pharmacokinetics of torasemide, a new loop diuretic, as well as its active metabolites M1 and M3, and its inactive main metabolite, M5, were studied in 12 patients with end-stage renal failure during single i. v. ($n = 6$) or single oral ($n = 6$) dosing of 200 mg torasemide, and during chronic oral treatment for 9 days ($n = 12$).

The elimination half-life ($t_{1/2}$) of torasemide was unchanged in renal failure, whereas $t_{1/2}$ of the torasemide metabolites M1, M3, and M5 were markedly prolonged. However $t_{1/2}$ as well as the area under the plasma level time curve of torasemide and its metabolites were unchanged during chronic compared to acute administration.

The results of this study suggest that despite the increased half-life of torasemide metabolites M1, M3 and M5 in end-stage renal failure patients, no accumulation of the parent drug torasemide and its metabolites during chronic dosing is demonstrable.

Key words Torasemide; metabolites, end-stage renal disease, pharmacokinetics

Torasemide is a new loop diuretic with a prolonged half-life (in comparison to furosemide) and proven efficacy for treatment of patients with renal failure, hypertension, and heart failure [1, 2]. Torasemide is 1-isopropyl-3-{[4-(3-methyl-phenylamino)pyridine]-3-sulfonyl}urea, and in torasemide metabolite M1, H is substituted by OH at the methyl group of the phenyl ring . Further oxidization of metabolite M1 yields the respective carboxylic acid (M5), whereas metabolite M3 is formed by ring hydroxylation at position 4 of the phenol ring from torasemide. The pharmacodynamics of torasemide have been studied extensively in patients with renal failure, demonstrating a prolonged, marked diuretic effect in a dose-dependent manner in the dose range of 100–200 mg [3–8]. Some authors have observed less kaliuresis with torasemide than furosemide [5, 6].

However, the pharmacokinetics of torasemide and its metabolites have been studied in patients with chronic renal failure only after a single i. v. dose [3, 4]. In these studies the terminal half-life of elimination of the active metabolite, M3, and the inactive main metabolite, M5, was markedly prolonged, whereas the terminal half-life of elimination of torasemide was unchanged [3, 4]. The aim of the present study therefore was to study the pharmacokinetics of torasemide and its active metabolites M1, M3, and, its inactive main metabolite, M5, after single as well as after multiple oral and i. v. dosing.

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Patients and methods

Twelve patients with end-stage renal disease on haemodialysis treatment and with residual urine volume < 1000 ml were studied during single and repeated dosing of 200 mg torasemide. The cause of renal failure was diabetes ($n = 4$), pyelonephritis ($n = 1$), glomerulonephritis ($n = 1$), polycystic kidneys ($n = 1$), radiation nephritis ($n = 1$), multiple myeloma ($n = 1$), and unknown ($n = 3$). The study protocol was approved by the local ethical committee, and all patients gave their informed, written consent. Pharmacokinetic studies were performed at day 1 after oral ($n = 6$, group A) or i. v. ($n = 6$, Group B) administration of 200 mg torasemide and at day 11 after oral ($n = 12$) administration of 200 mg torasemide from day 3 to day 11. Patients of group A were comparable to those of group B with regard to mean age (61 vs 62 years), mean weight (65 vs 59 kg), mean height (171 vs 174 cm) and sex (4 vs 3 men). Torasemide administration was at 8.00 a. m. each day irrespective of the dialysis schedule; however days 1 and 11 were on an interdialytic day. Haemodialysis was as a rule performed 3 times a week with a duration of 4 h using a polysulfone membrane and dialysate and blood flows of 500 ml/min and 200 ml/min respectively. Concomitant medications in our patients consisted of atenolol, betaxolol, bi-

Table 1 Pharmacokinetic parameters of torasemide and its metabolites M3 and M5. Median (range) values for AUC, C_{max}, t_{max}, and $t_{1/2}$ are given for group A (single oral dose), group B (single i.v. dose), group C (group A during steady-state oral dosing), and group D (group B during steady-state oral dosing)

	A	B	C	D
Torasemide ($n = 6$)				
AUC [ug · h · ml^{-1}]	63.7 (45.0–156.6)	118.5 (47.9–484.1)	57.0 (24.2–190.0)	87.1 (49.2–442.2)
C_{max} [ug · ml^{-1}]	12.9 (7.1–32.7)	29.0 (20.2–119.3)	14.1 (8.4–25.4)	24.0 (13.1–28.2)
t_{max} [h]	1.0 (0.5–8.0)	0.6 (0.5–1.0)	1.2 (1.0–3.0)	1.0 (0.5–1.0)
$t_{1/2}$ [h]	3.3 (2.0–11.2)	4.6 (2.3–19.9)	2.7 (1.7–12.0)	5.4 (2.4–16.1)
Metabolite M3 ($n = 6$[a])				
AUC [ug · h · ml^{-1}]	30.6 (25.8–84.7)	30.9 (14.7–795.0)	13.0 (8.2–30.9)	31.2 (12.5–162.0)
C_{max} [ug/ml^{-1}]	0.8 (0.2–0.9)	0.5 (0.4–13.6)	0.8 (0.5–1.8)	1.8 (0.8–7.4)
t_{max} [h]	8.0 (4.0–10.0)	16.8 (2.8–33.5)	7.9 (2.3–10.0)	5.5 (2.0–10.0)
$t_{1/2}$ [h]	27.9 (25.5–86.1)	29.6 (18.4–42.2)	18.5 (9.8–53.8)	26.8 (13.9–46.8)
Metabolite M5 ($n = 6$)				
AUC [ug · h · ml^{-1}]	104.5 (65.6–328.7)	97.9 (71.9–514.0)	49.2 (18.0–395.1)	124.1 (27.7–184.1)
C_{max} [ug · ml^{-1}]	6.2 (4.2–18.2)	5.7 (3.7–8.0)	4.6 (3.1–21.3)	10.1 (3.1–11.8)
t_{max} [h]	6.0 (4.0–24.0)	5.8 (2.8–30.0)	5.0 (3.0–10.0)	5.5 (2.0–10.0)
$t_{1/2}$ [h]	9.9 (5.2–20.9)	9.2 (5.7–37.5)	12.2 (5.1–28.2)	13.5 (5.9–36.5)

[a] Except A ($n = 5$)

soprolol, metoprolol, clonidine, nifedipine, nitrendipine, diltiazem, isradipine, dihydralazine, prazosin, urapidil, captopril, isosorbide dinitrate, isosorbide mononitrate, molsidomine, digitoxin, calcitriol, calcium carbonate, calcium acetate, erythropoetin, prednisolone, cyclosporin A, allopurinol, insulin, ranitidine, omeprazole, cizaprid, thyroxine, aspirin and antacids. Plasma levels of torasemide and torasemide metabolites M1, M3, and M5 were measured before and 0.5, 1, 2, 3, 4, 6, 8, 10, 24, 30, 34, 48 h after dosing. Urinary excretion of torasemide and its metabolites was measured 0–6, 6–12, 12–24, and 24–48 h after dosing. Concentrations of plasma and urinary torasemide and torasemide metabolites M1, M3, and M5 were measured by means of high-performance liquid chromatography [9]. Non-compartmental kinetic analysis was performed. Calculated pharmacokinetic parameters were maximum plasma concentration (C_{max}), time to peak concentration (t_{max}), terminal elimination half-life $t_{1/2}$, and area under the plasma level-time curve (AUC). Data are given as median (range) and statistical evaluation was by means of the two-sided Wilcoxon matched-pair signed rank test.

Results

The C_{max}, t_{max}, $t_{1/2}$, and AUC values of torasemide, metabolite M3, and metabolite M5 are given in Table 1. These pharmacokinetic parameters, though showing a high inter-individual variability, were not significantly different between acute and chronic dosing. Plasma levels of torasemide metabolite M1 were also not significantly different between acute and chronic dosing (Fig. 1). AUCs of metabolite M1 were in the range of 4.5–430 ugxh · ml^{-1}, C_{max} of metabolite M1 ranged from 0.4–10.6 ug · ml^{-1}, and t_{max} ranged from0.5–47.8 h; $t_{1/2}$ could not be determined for this metabolite.

Since the urine volumes were low and the excretion of torasemide and its metabolites was slight, data are given for the time period 0–48 h during chronic dosing only (amounts excreted in urine as a percentage of the administered dose). 0.35 % (0.02–1.31) or 0.58 % (0.03–0.96) torasemide, 0.72 % (0.03–3.99) or 0.13 % (0.08–1.38) metabolite M1, 0.62 % (0.00–2.35) or 1.04 % (0.04–1.15) metabolite M3, and 2.98 % (0.10–64.63) or 5.35 % (0.34–19.6) metabolite M5 for patient groups C and D (as defined in Table 1), respectively, were excreted during the 48 h after dosing. The ratios $t_{1/2}$ (steady state)/$t_{1/2}$ (single dose) and AUC(steady state)/AUC (single dose) calculated for each individual patient were about 1 for torasemide as well as for torasemide metabolites M1, M3, and M5. These data (not shown in detail) did not support accumulation of torasemide or its metabolites M1, M3, and M5 during chronic dosing.

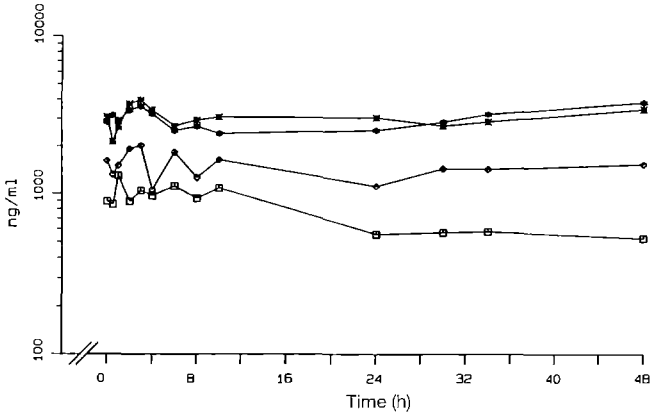

Fig. 1 Serum concentrations of torasemide metabolite M1 in group A (single oral dose; *open squares*), group B (single i.v. dose; *stars*), group C (= group A during steady-state oral dosing; *hexagons*), and group D (= group B during steady-state oral dosing; *diamonds*)

Discussion

$T_{1/2}$ for torasemide, metabolite M1, metabolite M3, and metabolite M5 in patients with normal kidney function were 2–4 h, 1.3, not determined, and 2–4, respectively [3, 10–14]. Torasemide $t_{1/2}$ and AUC were unchanged during chronic dosing in patients with normal renal funtion, however no published data are available with regard to torasemide metabolites during chronic dosing [13, 14]. Administration of a single i.v. dose of 20 mg of torasemide in patients with chronic renal failure (creatinine clearance < 48 ml · min^{-1}) was associated with an unchanged $t_{1/2}$ of torasemide, however $t_{1/2}$ of metabolite M5 was prolonged to 7.4 h [3]. Kult et al. found $t_{1/2}$ to be prolonged 3–4-fold in patients with chronic renal failure (creatinine clearance < 30 ml · min^{-1}) for metabolite M5 (6.3 or 7.3 h) and metabolite M3 (21.1 or 19.5 h) after a single i.v. dose of 100 or 200 mg torasemide [4]. However, no pharmacokinetic data in patients with renal failure were available in the literature with regard to torasemide and its metabolites during chronic dosing. These data are provided by the present study demonstrating that $t_{1/2}$ for torasemide is about 3–5 h, $t_{1/2}$ for the metabolite M3 is about 19–26 h, and $t_{1/2}$ for metabolite M5 is about 12–13 h during chronic dosing (Table 1); $t_{1/2}$ for metabolite M1 could not be determined, but appears to be > 24 h. Most importantly $t_{1/2}$ as well as AUC for torasemide and its metabolites M1, M3, M5 were essentially the same during chronic or acute dosing. Ratios between $t_{1/2}$ or AUC during single dose and $t_{1/2}$ or AUC during chronic dosing were about 1 for torasemide and its metabolites, thus providing evidence against significant accumulation of the parent drug or its main metabolites during chronic dosing. The rather high inter-individual differences of pharmacokinetic parameters in the present study are most likely related to the major hepatic route of elimination of torasemide, whereas kidney function was very similar in all patients.

Urinary excretion of torasemide and its metabolites was low in the present study, being in the range of 0.5 % of the administered dose during 48 h for torasemide and torasemide metabolite M1, 0.8 % for metabolite M3, and 4 % for torasemide metabolite M5. In contrast urinary excretion of torasemide and its metabolites M1, M3 and M5 is 8–25 %, 11–18 %, 2–3 % and 34–55 %, respectively in patients with normal kidney function [10, 12]. Since metabolite M1 has about 1/10 of the diuretic effect of torasemide and metabolite M3 has about the same diuretic effect as torasemide [2], M1 and M3 are thought to cause at least the same diuretic effect as the parent drug, in contrast to healthy controls, where torasemide causes about 80 % of the diuresis [12].

Judging from the results of the present study and from pharmacodynamic studies in patients with severe, chronic renal failure 100–200 mg torasemide per day given as a single dose seems to be appropriate to induce sufficient diuresis and natriuresis [3–8].

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