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Pharmacokinetics and pharmacodynamics of lisinopril in advanced renal failure

Consequence of dose adjustment

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Abstract. To prevent drug accumulation and adverse effects the dose of hydrophilic angiotensin-converting enzyme (ACE) inhibitors, e. g. lisinopril, must be reduced in patients with renal failure. To obtain a rational basis for dose recommendations, we undertook a prospective clinical trial. After 15 days of lisinopril treatment pharmacokinetic and pharmacodynamic parameters were determined in patients with advanced renal failure ($n = 8$; endogenous creatinine clearance [CL_{CR}]: 18 ml · min^{-1} · 1.73 m^{-2}) and in healthy subjects with normal renal function ($n = 16$; CL_{CR}: 107 ml · min^{-1} · 1.73 m^{-2}). The volunteers received 10 mg lisinopril once daily, the daily dose in patients (1.1–2.2 mg) was adjusted to the individual CL_{CR} according to the method of Dettli [13].

After 15 days of lisinopril treatment the mean maximal serum concentration (C_{max}) in patients was lower than in volunteers (30.7 vs 40.7 ng · ml^{-1}, while the mean area under the concentration-time curve ($AUC_{0\text{-}24\,h}$) was higher (525 vs 473 ng · h^{-1} · ml^{-1}). ACE activity on day 15 was almost completely inhibited in both groups. Plasma renin activity, angiotensin I and angiotensin II levels documented marked inhibition of converting enzyme in volunteers and patients. Furthermore, average mean arterial blood pressure in patients decreased by 5 mmHg and proteinuria from 3.9–2.7 g per 24 h after 15 days of treatment with the reduced dose of lisinopril.

Adjustment of the dose of lisinopril prevents significant accumulation of the drug in patients with advanced renal failure during chronic therapy. Mean serum levels did not exceed this in subjects with normal renal function receiving a standard dose. Despite substantial dose reduction, blood pressure and proteinuria decreases were observed.

Key words: Lisinopril, Dose adjustment; ACE inhibitors, pharmacokinetics, pharmacodynamics, renal failure

Angiotensin-converting enzyme (ACE) inhibitors are first line drugs in the treatment of high blood pressure in patients with impaired kidney function. They lower blood pressure effectively, have few adverse effects and are well tolerated. Furthermore, experimental [1] and recent prospective clinical trials in patients with renal insufficiency [2–4] have documented that ACE inhibitors arrest the decline of renal function significantly more than alternative antihypertensive agents, despite similar lowering of blood pressure. However, caution is required when hydrophilic ACE inhibitors are administered to patients with renal insufficiency because of accumulation [5–8].

Lisinopril is the lysine analogue of enalaprilat, the active ACE inhibitor metabolite of enalapril. In contrast to enalapril, lisinopril requires no metabolic transformation to become active. After oral administration about 30% of the substance is absorbed and peak serum concentrations are reached within 6–8 h [9]. Lisinopril is not significantly metabolised and is excreted unchanged in the urine [10]. Renal insufficiency is therefore associated with decreased urinary excretion and increased serum concentration of lisinopril. After chronic therapy with lisinopril van Schaik et al. [11, 12] found up to ten times higher serum levels in hypertensive patients with an endogenous creatinine clearance (CL_{CR}) below 30 ml · min^{-1} · 1.73 m^{-2}.

In order to avoid elevated lisinopril serum concentrations due to potential adverse effects in patients with advanced renal failure, dose reduction is recommended. The purpose of the present prospective clinical trial was to investigate whether in patients with advanced renal failure significant accumulation of lisinopril can be prevented by adjusting the dose according to the equation of Dettli [13].

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Materials and methods

Participants

Eight patients with advanced renal failure [mean age 44 (14) years; mean CL_{CR} 18 (5) $ml \cdot min^{-1} \cdot 1.73 m^{-2}$] and 16 healthy volunteers with normal renal function [mean age 29 (5) years; mean CL_{CR} 107 (11) $ml \cdot min^{-1} \cdot 1.73 m^{-2}$] were studied. Three of the patients had biopsy-confirmed glomerulonephritis, in two of them glomerulonephritis was suspected on clinical grounds, one had polycystic kidney disease, one analgesic nephropathy. All participants gave their written informed consent. ACE inhibitors and β-adrenoceptor antagonists were withdrawn in the patients 1 week before the start of the study (run-in phase). The administration of other antihypertensive agents (furosemide, nifedipine or clonidine) was left unchanged. Twenty four-hour-urine was collected by all participants twice during the run-in phase in order to calculate the endogenous creatinine clearance.

Study design

The study protocol was approved by the ethics committee of the University of Heidelberg. The volunteers received 10 mg lisinopril for 15 days in tabletform. The patients received an adjusted oral dose, which was calculated after the equation of Dettli [13]: adjusted dose = 10 mg × individual CL_{CR} ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$) per 120 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$. The mean daily dose in patients was 1.5 (0.4) mg (1.1–2.2 mg) lisinopril as a capsule. The equivalence of both preparations – tablet and capsule – concerning drug release was proven in an in-vitro dissolution test.

Patients and volunteers were examined in a quiet environment in supine position on the first and the 15th day of treatment. All blood and urine samples were obtained in supine position starting at 8.00 a.m. (after 1 h of rest). Standardized meals were given to the participants on both study days; fluid intake was exactly matched to urine excretion. Patients did not take their usual antihypertensive drugs on both days. Blood samples for determination of lisinopril serum levels in patients and volunteers were taken prior to (8.00 a.m.), every hour up to 16 h and 24 h after drug administration. Urine was collected in 3-h-fractions to estimate urinary concentrations of lisinopril. In addition, on days 16, 17, 18 and 19 blood samples for measurement of lisinopril serum concentrations were taken at 8.00 a.m. and 24-h-urine was collected to estimate urinary excretion. Blood samples for determination of ACE activity were taken on day 1 and day 15 prior to (8.00 a.m.), every 3 h up to 16 h and 24 h after lisinopril administration and plasma renin activity (PRA), angiotensin I (ANG I) and angiotensin II (ANG II) levels were estimated prior to (8.00 a.m.), 8 h and 16 h after lisinopril was given. Mean arterial blood pressure (MAP) was monitored in regular intervals throughout on both days. For safety reasons serum potassium and creatinine concentrations were determined on days –7, 1, 2, 15, 16, 17, 18 and 19. In addition, CL_{CR} and urinary protein excretion were estimated on days –7, –1, 16 and 19.

The maximal serum level of lisinopril on day 15 was originally chosen as the primary study endpoint.

Measurements and calculations

Serum and urine concentrations of lisinopril were determined by a modified radioimmunoassay (double antibody technique) with a sheep antiserum and a radioiodinated ligand 351 A (a *p*-hydroxybenzamidine derivative of lisinopril) [14, 15]. The limit of detection amounted to 60 $pg \cdot ml^{-1}$ for plasma and urine. 5.5 % CV for intra- and 9.5 % CV for inter-day variabilities were achieved for both body fluids.

The individual serum and urine concentrations after application of lisinopril were analyzed model-independently. C_{max} represents the observed maximum serum concentration at the corresponding time value t_{max}. Areas under the concentration-time curve (AUC) were calculated using the linear trapezoidal rule for the ascending part of the curve and the logarithmic trapezoidal rule for the descending part of the curve up to 24 h after drug intake. The renal clearance (CL_R) was calculated from the amount excreted into urine during 24 h (Ae) and the corresponding AUC-value as $CL_R = Ae/AUC$. The relevant elimination half-life ($t_{1/2rel}$) and the corresponding elimination rate constant (k_{rel}) were obtained by a computer-aided iterative estimation of the accumulation based on the amounts excreted in urine during the first and the 15th day of treatment (24 h). Assuming that the increase in Ae-values reflects accumulation processes and that bioavailability, volume of distribution and total clearance did not change relevantly in the observation period, the estimation of k_{rel} was performed using the equation $Ae_{15}/Ae_1 = (1\text{-}e^{-15 \cdot krel \cdot T})/(1\text{-}e^{-krel \cdot T})$, where Ae_1 and Ae_{15} represent the amounts excreted via urine during the first and 15th dosage interval T [16, 17]. The relevant half-life ($t_{1/2rel}$) was calculated as $t_{1/2rel} = \ln 2/k_{rel}$. The ratio of accumulation concerning the steady-state ($r\infty$) was determined as $r\infty = (1\text{-}e^{-krel \cdot T})^{-1}$.

ACE activity was measured spectrophotometrically as described in detail elsewhere [18]. PRA (normal range: 0.1–2.0 ng ANG I $\cdot ml^{-1} \cdot h^{-1}$) was estimated employing a commercially available angiotensin-I kit [19]. ANG I concentrations (normal range: 0.2–3.3 fmol $\cdot ml^{-1}$) and ANG II concentrations (normal range: 0.8–7.6 $fmol \cdot ml^{-1}$) were measured using RIA after isolation with HPLC as described in detail [20]. The ANG II/ANG I ratio was calculated as an index of in vivo ACE inhibition.

MAP was measured oscillometrically with an automatic device (Dinamap, Critikon Co, USA). Serum potassium levels were measured using flame photometry (AFM 5051, Eppendorf, Germany), and serum and urine creatinine concentrations with an autoanalyzer (Hitachi 705, Boehringer Mannheim, Germany). The endogenous creatinine clearance (CL_{CR}) was calculated as follows: $CL_{CR} = U_{CR} \times UV \times 1.73 m^{-2}/S_{CR} \times 1440 \times$ body surface ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$); where U_{CR} is the concentration of creatinine in urine, UV the urinary volume and S_{CR} the serum creatinine concentration. Protein concentration in urine was measured by the biuret method; 24-h-protein excretion was calculated using UV.

Statistical analyses

For comparison of the primary study endpoint C_{max} on day 15 the geometric mean of this lognormally-distributed parameter with a 95 % confidence interval was estimated in both groups. To achieve a sufficient (–20 %; + 25 %) relative precision of the interval in the reference group we used a two stage design [21] to determine the number of participating volunteers. Proving an agreement concerning all other pharmacokinetic and pharmacodynamic parameters was not an aim of the investigation, therefore they were analyzed descriptively. Unless stated otherwise data are given as mean with SD.

Results

Pharmacokinetics

Mean serum concentration-time profiles of patients and healthy volunteers as well as the corresponding SE-values after the first and 15th lisinopril dosage are shown in Fig. 1. Additional mean pharmacokinetic parameters (C_{max}, t_{max}, AUC, Ae, CL_R and CL_{CR}) are listed in Table 1.

The geometric mean value of C_{max} on day 15, the main target parameter of the investigation, was 37.6

ng·ml^{-1} in the volunteers compared to 28.5 ng·ml^{-1} in the patient group with 95% confidence intervals of (30.1; 47.0) and (22.1; 36.7) respectively, showing that the average maximum serum levels after 2 weeks of treatment were even lower in the patient group than in the volunteers. After 15 days of treatment the volunteers' arithmetic mean C_{max} was about 1.3-fold higher than the respective value after the first dosage [40.7 (17.8) ng·ml^{-1} vs 31.0 (22.1) ng·ml^{-1}]. As expected, the C_{max} levels of the patients who received the reduced dosage were considerably lower on day 1 (arithmetic mean: 4.7 (2.6) ng·ml^{-1}). After 15 days the maximum serum levels were increased about six-fold to 29.7 (9.5) ng·ml^{-1}.

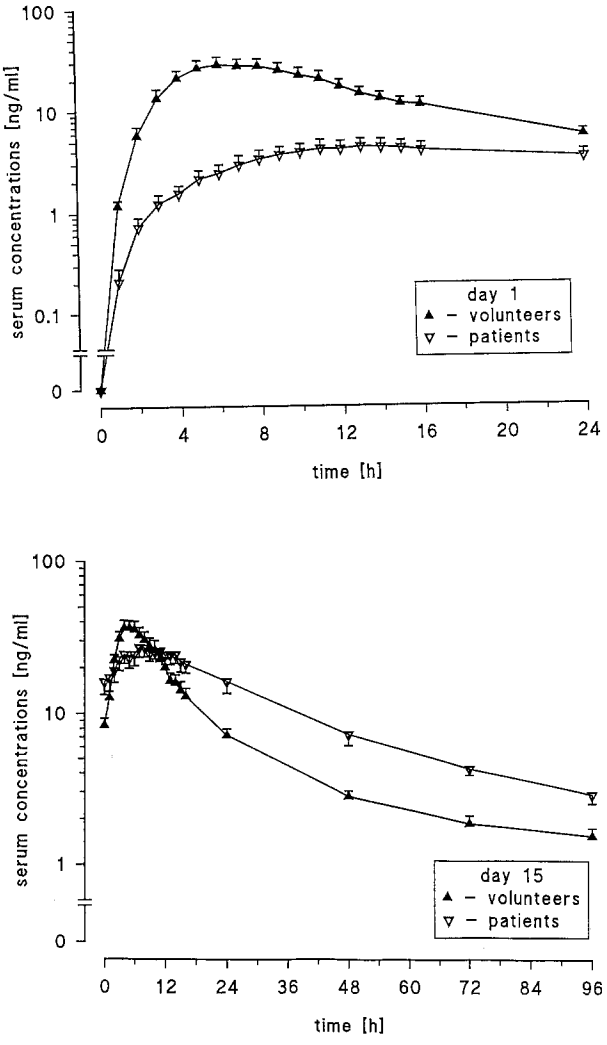

Fig. 1. Mean serum concentration profile curves (mean with SEM) on day 1 and day 15 of lisinopril treatment in patients with advanced renal failure ($n = 8$) and in healthy volunteers ($n = 16$)

The volunteers' mean t_{max} was 6.7 (1.3) h on the first and 4.6 (1.5) h on the 15th day. The respective mean t_{max} for the patients amounted to 12.1 (1.9) h on day 1 and 8.6 (3.1) h on day 15. The increase in the AUC in the volunteers from the first to the 15th day of treatment was in the same range as the corresponding C_{max} increase (1.3-fold), i.e. from 347 (223) to 473 (208) ng·h·ml^{-1}. The patients' mean AUC was 525 (198) ng·h·ml^{-1} on day 15 as compared to 75 (39) ng·h·ml^{-1} on the first day (7-fold increase). The amount of lisinopril excreted into the urine during day 15 in patients was 22.2 (10.6)% of the given (reduced) dose as compared to only 2.4 (1.8)% during the first day. Mean Ae for the healthy volunteers was 22.0 (17.1)% (day 1) and 26.6 (10.8)% (day 15). The calculated renal lisinopril-clearance (CL_R) of the volunteers was in the same range on day 1 and 15 (103.1 (24.5) and 96.8 (17.6) ml·min^{-1}). The respective values of renal lisinopril-clearance in patients' were 6.6 (4.1) and 10.5 (3.6) ml·min^{-1}.

The results concerning the relevant elimination rate constants (k_{rel}), the corresponding half-lives ($t_{1/2\,rel}$) and the deduced factors of accumulation ($r\infty$) are mentioned in Table 2. The model-dependent estimation could be performed in 13 volunteers and in 7 patients. The average k_{rel} for volunteers was 0.058 (0.054) h^{-1}. The corresponding half-life was 20.4 (15.3) h and the respective factor of accumulation $r\infty$ was determined to be 1.68 (0.84). The estimated amount excreted for the volunteers in one dosage interval of steady-state (Ae_{ss}, see Fig. 2) was calculated to be 26.7 (11.0)% of the dosage. For the patients the corresponding mean value for k_{rel} was estimated to be about 0.006 (0.006) h^{-1} and $t_{1/2\,rel}$ was 389 (343) h on average. The respective $r\infty$ was 23.9 (20.6) and the amount of the dose excreted in urine at steady-state (Ae_{ss}) was estimated to be 40.6 (22.9)%.

Table 1. Pharmacokinetic parameters of lisinopril on day 1 and day 15 of treatment in patients with advanced renal failure ($n = 8$) and in healthy volunteers ($n = 16$)

	C_{max} (ng·ml^{-1})		t_{max} (h)		$AUC_{0-24\,h}$ (ng·h·ml^{-1})		$Ae_{0-24\,h}$ (% of dose)		$CL_{R/Lis}$ (ml·min)		CL_{CR} (ml·min^{-1})	
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 19
Volunteers												
Mean	31.0	40.7	6.7	4.6	347	473	22.0	26.6	103.1	96.8	106.9	106.6
SD	22.1	17.8	1.3	1.5	223	208	17.1	10.8	24.5	17.6	10.7	13.9
Max	92.8	87.4	9.0	8.0	959	920	67.3	53.6	152.5	120.1	137.0	128.4
Min	10.0	20.0	5.0	2.0	103	214	6.8	14.5	61.1	59.5	91.2	80.3
Patients												
Mean	4.7	29.7	12.1	8.6	75	525	2.4	22.2	6.6	10.5	17.8	16.2
SD	2.6	9.5	1.9	3.1	39	198	1.8	10.6	4.1	3.6	5.0	5.0
Max	9.2	47.5	15.0	13.0	143	924	5.4	13.1	11.2	18.6	26.1	22.6
Min	0.6	20.0	10.0	7.0	10	350	0.0	43.9	0.0	7.8	11.5	9.4

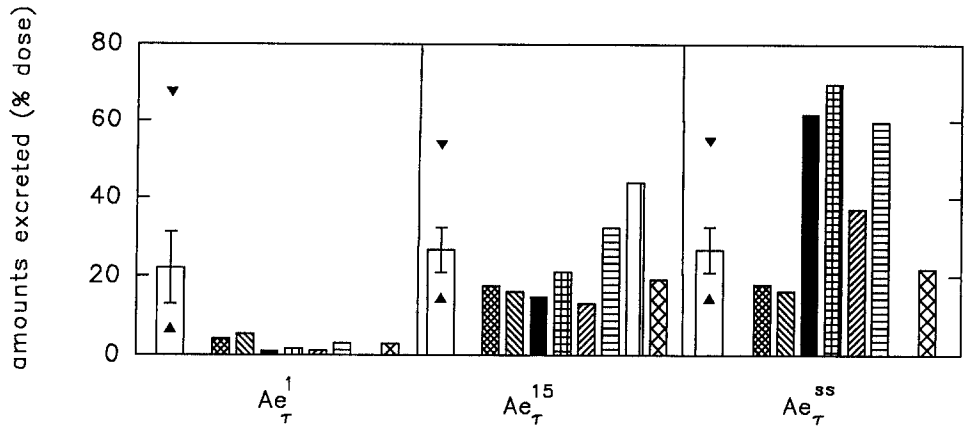

Fig. 2. Measured and estimated renal excretion after administration of lisinopril in healthy volunteers (average values) and patients with severe renal failure (individual values). □ Healthy volunteers; ⊠ - ⊠ Patients with severe renal failure

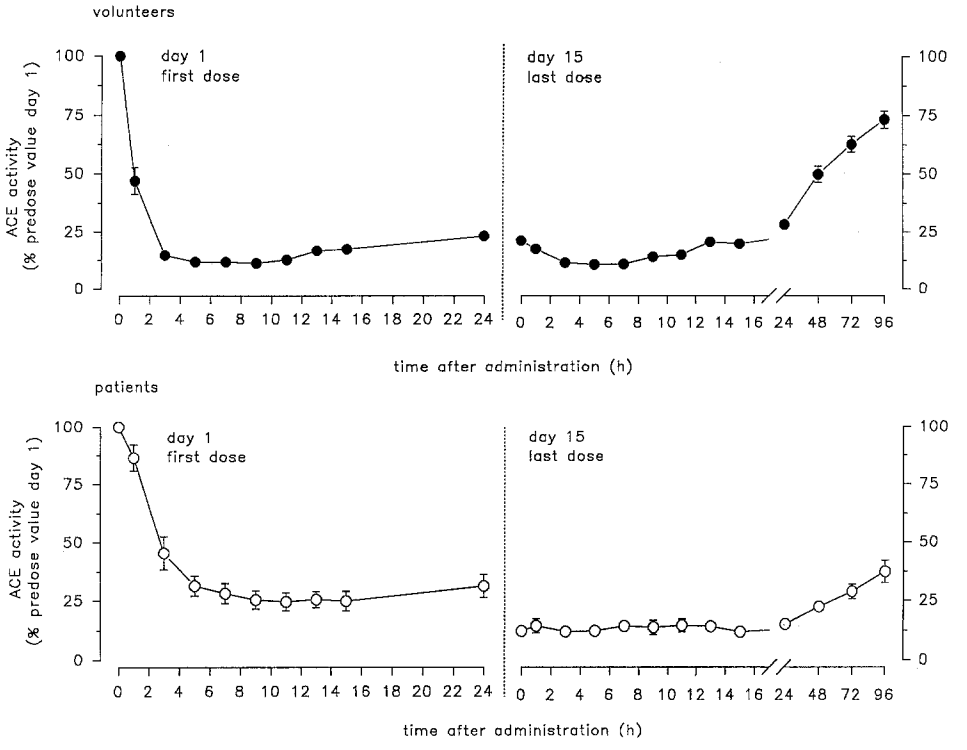

Fig. 3. Mean serum ACE activity profiles (mean with SEM) on day 1 and day 15 of lisinopril treatment in healthy volunteers in patients with advanced renal failure

Table 2. Measured and estimated amounts excreted in urine after administration of lisinopril; estimation for steady-state (Ae_{ss}) is based on the renal amounts excreted during the first and 15th treatment day in patients ($n = 7$) and in volunteers ($n = 13$)

	$t_{1/2\,rel}$ (h)	k_{rel} ($1 \cdot h^{-1}$)	r_∞	Ae_{ss} (% of dose)
Volunteers				
Mean	20.4	0.058	1.68	26.7
SD	15.3	0.054	0.84	11.0
Max	62.4	0.216	4.28	54.6
Min	3.2	0.011	1.00	14.5
Patients				
Mean	389	0.006	23.9	40.6
SD	343	0.006	20.6	22.9
Max	911	0.071	55.3	69.6
Min	41	0.001	3.0	16.2

Pharmacodynamics

Mean serum ACE activities on the first and 15th day of treatment for both groups are shown in Fig. 3. In addition, ANG II/ANG I ratios are listed in Table 3. After the first lisinopril dose (day 1) mean serum ACE activity was more than 70% inhibited in patients. The inhibition with the standard dose of 10 mg lisinopril in healthy subjects was more than 85%. After chronic administration mean serum ACE activity was almost completely inhibited both in volunteers and in patients.

Mean PRA, ANG I and ANG II levels and MAP on day 1 and day 15 are shown in Table 3. Mean baseline ANG I concentration on the first day of lisinopril administration was higher in patients than in healthy subjects; after the first dose of the ACE inhibitor it rose in both groups. After chronic treatment (day 15) these values became much higher both in patients and in volunteers. Following lisinopril administration mean ANG II levels decreased in both

Table 3. Mean PRA, ANG I and ANG II levels, ANG II/ANG I ratios and MAP in patients ($n = 7$) and volunteers ($n = 16$) before (8.00 a.m.), 8 h after (4.00 p.m.), and 16 h after (12.00 a.m.) lisinopril administration on the first and 15th day of treatment

		8 am (baseline)	4 pm	12 am
PRA				
Patients:	Day 1	1.50 (0.30)	1.27 (0.24)	0.85 (0.15)
	Day 15	4.39 (1.00)	3.44 (1.09)	2.34 (0.65)
Volunteers:	Day 1			
	Day 15	0.53 (0.07)	2.57 (0.62)	1.08 (0.20)
		3.24 (0.45)	10.2 (1.54)	3.67 (0.61)
ANG I				9.71 (1.42)
Patients:	Day 1	11.0 (2.85)	14.5 (3.26)	29.7 (8.42)
	Day 15	52.6 (15.4)	44.1 (13.51)	
Volunteers:	Day 1	5.01 (0.72)	35.7 (7.68)	15.7 (2.19)
	Day 15	44.5 (6.22)	121 (22.1)	45.8 (8.69)
ANG II				
Patients:	Day 1	1.71 (0.48)	0.57 (0.09)	0.64 (0.16)
	Day 15	0.78 (0.17)	0.59 (0.10)	0.77 (0.11)
Volunteers:	Day 1	2.64 (0.37)		
	Day 15	3.01 (0.53)	0.97 (0.21)	0.83 (0.16)
			2.22 (0.34)	2.70 (0.48)
ANG II/ANG I				
Patients:	Day 1	0.23 (0.05)	0.06 (0.01)	0.07 (0.00)
	Day 15	0.03 (0.00)	0.02 (0.00)	0.04 (0.00)
Volunteers:	Day 1	0.60 (0.05)	0.05 (0.00)	0.07 (0.00)
	Day 15	0.06 (0.00)	0.02 (0.00)	0.08 (0.01)
MAP				
Patients:	Day 1	112 (12)	113 (12)	114 (11)
	Day 15	107 (12)	107 (13)	108 (11)
Volunteers:	Day 1	88 (7)	82 (4)	85 (9)
	Day 15	81 (5)	79 (9)	81 (6)

Data are given as mean with (SEM)

groups compared to the day before treatment. A similar response to lisinopril was also seen after the last dose was given on day 15. Mean MAP in healthy subjects decreased after lisinopril administration on day 1 and remained low on the 15th day of treatment. Administration of the reduced ACE inhibitor dose in patients did not acutely reduce MAP on the first or on the 15th day. The average MAP in patients, however, was about 5 mm Hg lower after 15 days of treatment as compared with the first day.

Mean urinary protein excretion in patients decreased from 3.9 (3.2) $g \cdot 24\ h^{-1}$ (day –1) to 2.7 (2.3) $g \cdot 24\ h^{-1}$ (day 16), whereas in volunteers it was unchanged [0.03 (0.02) $g \cdot 24\ h^{-1}$ on day –1 and day 16]. Mean serum potassium levels increased slightly with lisinopril treatment both in volunteers (3.8 (0.2) $mmol \cdot l^{-1}$ on day 1 vs 4.0 (0.1) on day 15) and in patients (4.3 (0.8) vs 4.6 (0.9) $mmol \cdot l^{-1}$). In two of our patients serum potassium temporally increased to 5.5 and 5.7 $mmol \cdot l^{-1}$ respectively. Mean CL_{CR} was virtually unchanged with chronic lisinopril administration in volunteers [107 (11) $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ on day –1 and day 16] and in patients [18 (5) and 17 (5) $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$]. In patients a slight increase in mean serum creatinine from 4.8 (1.0) $mg \cdot dl^{-1}$ on the first day to 5.1 (1.0) $mg \cdot dl^{-1}$ on the 15th day was observed, whereas mean serum creatinine was stable in volunteers (0.9 (0.1) $mg \cdot dl^{-1}$ both on day 1 and day 15).

Discussion and conclusions

C_{max}- as well as t_{max}-values found for the healthy volunteers were in accordance with published results [9, 10, 22]. Mean C_{max} as well as the lower and upper limits of the 95%-confidence interval found for the patients' day 15 were significantly below the corresponding values for the volunteers, while the mean AUC-value slightly exceeded that of the volunteers. This was to be expected because of smaller fluctuations in the serum concentration-time curve as a result of the reduced lisinopril dose and increased relevant elimination half-lives. It may therefore be assumed that maximum serum concentrations in patients treated with the adjusted lisinopril dose will not exceed the values found in healthy volunteers treated with a standard dose, even if AUC-values in patients increase 2-fold further.

For the volunteers the estimated mean amount excreted in one dosage interval at steady-state (Ae_{ss}) concurred with the measured value on day 15. Though the underlying model is limited it can be assumed that the volunteers had reached steady-state on the last day of treatment with lisinopril. Of course, the results out of the corresponding estimation for the patients are not as reliable as for the volunteers. The influence of possible disorders will have a significant effect on the small lisinopril serum levels on day one. The pharmacokinetic behavior of lisinopril in healthy volunteers as well as in patients with advanced renal failure was characterized by marked inter- and intra-individual variabilities reflecting fluctuations in bioavailability (variations up to 10-fold). For example, the AUC- and Ae-values in some healthy volunteers were higher on the first day (acute administration) than on the 15th day (chronic treatment) of the study. Since such fluctuations are typical for drugs with low bioavailability like lisinopril, intra-individual variability had to be expected for the patients too. Retrospectively, it was not possible to perform a clinical investigation where all patients would have reached steady-state. Despite its limitation the estimation model gives a good indication of lisinopril serum levels in long-term treatment of patients with severe renal failure.

Comparing the pharmacokinetic behaviour of lisinopril in both groups it becomes evident that there is a significant delay according to t_{max} for the patients which can not entirely be explained by a predominance of invasion compared to elimination processes in the patients with advanced renal failure. The profiles of serum concentration-time curves are similar to saturation curves indicating that the first portion of the absorbed substance may accumulate in a blood compartment which is not notably involved in elimination processes. In previous investigations Beermann et al. [23, 24] suggested that this compartment may be equivalent with binding to serum ACE (about 3 $mol \cdot l^{-1}$). The reduced first dosage administered to the patients would have been enough to saturate the converting enzyme located in the blood. This hypothesis is also supported by investigations of Wade et al. [25] concerning enalapril.

Despite a substantial reduction of the lisinopril dose in patients with renal failure the pharmacodynamic action of the ACE inhibitor was satisfactory. After the first dose

serum ACE activity, both measured and calculated (ANG II/ANG I ratio), was already more than 70% inhibited in patients as compared with 85% in healthy subjects. After chronic administration ACE activity was almost completely inhibited both in volunteers and in patients. A similar (complete) inhibition of ACE activity in patients with chronic renal failure was documented in a study of Shionori et al. [26] after chronic therapy with a standard dose of 10 mg lisinopril. Ninety-six hours after the last drug intake mean serum ACE activity in our patients was below the corresponding value found in the volunteers. According to the extended elimination half-life of lisinopril in patients one can conclude that ACE activity reflects the pharmacokinetic data. Furthermore, patients' data on PRA, ANG I and ANG II concentrations all document a marked inhibition of the converting enzyme after chronic treatment with the adjusted dose. In both study groups mean baseline PRA was much higher on day 15 than on the first treatment day. Whereas PRA increased after lisinopril administration on both study days in volunteers, it clearly decreased in patients. This paradoxical may be explained by prestimulated renin secretion in patients whose antihypertensive therapy was not completely washed-out. In contrast, the more sensitive ANG I concentration increased in volunteers as well as in patients after the first dose of lisinopril, indicating a small effect of the reduced lisinopril dose on the renin-angiotensin system. After chronic treatment baseline ANG I concentrations on day 15 were highly elevated indicating a markedly inhibited conversion of angiotensin I to angiotensin II. The most sensitive index of renin-angiotensin system inhibition is provided by ANG II concentrations. A substantial fall in mean ANG II concentration in volunteers and in patients was observed even after the first dose of lisinopril (day 1). In addition, despite much lower ANG II baseline levels in patients on day 15 as compared to the first treatment day, ANG II concentration further decreased after the last dose. These results are remarkable, since the patients received a mean of only 1.5 mg lisinopril daily as compared to 10 mg in healthy subjects.

In parallel to the decrease in MAP (about 5 mm Hg) a decrease of proteinuria (from 3.9 (3.2) to 2.7 (2.3) g per 24 h) was observed in our patients after treatment of limited duration. Since antihypertensive agents (with the exception of ACE inhibitors and β-adrenoceptor-antagonists) were not washed out, we have to guard our conclusions concerning the pharmacodynamic actions of the adjusted lisinopril dose in patients. Nevertheless, our data are comparable with those of Heeg et al. [27], who documented a significant decrease in MAP and a decrease in urinary protein excretion from 4.2 (3.2) to 2.9 (2.9) g per 24 h in 13 patients with impaired renal function ($CL_{CR} < 30\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) after 4 weeks of therapy with a mean lisinopril dose of 8.9 mg per day. In addition, the tolerability and safety of the small lisinopril dose in our patients was excellent. Serum potassium increased to 5.5 or 5.7 $mmol \cdot l^{-1}$ after the start of the ACE inhibitor therapy in only two patients. The increase was reversible and no subjective or objective signs of hyperkalemia were noted. In comparison, in the study of Heeg et al. [27] 5 out of 13 patients experienced an increase in serum potassium level of more than 1.0 $mmol \cdot l^{-1}$ and in 8 patients an increase above 5.5 $mmol \cdot l^{-1}$ was seen. Similar observations in patients with impaired renal function and prolonged lisinopril therapy were also reported by Jackson et al. [28] and Donohoe et al. [29].

In conclusion, after dose adjustment according to the equation of Dettli [13] serum lisinopril levels in patients with advanced renal failure did not significantly differ from those of healthy subjects after chronic treatment with a standard dose. The expected pharmacodynamic actions on blood pressure and proteinuria were observed despite dose reduction. The dose adjustment permits safe serum concentrations without compromising drug actions. Therefore, the production of a tablet containing about 2 mg can be recommended.

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