

## PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/22708>

Please be advised that this information was generated on 2021-04-15 and may be subject to change.

# Pharmacokinetics and haemodynamic effects of the angiotensin converting enzyme inhibitor cilazapril in hypertensive patients with normal and impaired renal function

H. J. KLOKE, R. J. AMBROS<sup>1</sup>, H. W. VAN HAMERSVELT, J. F. M. WETZELS,  
R. A. P. KOENE & F. T. M. HUYSMANS

Department of Medicine, Division of Nephrology, University Hospital, Nijmegen, The Netherlands and  
<sup>1</sup>Department of Pharmacokinetics, Roche, Basle, Switzerland

- 1 The pharmacokinetic and pharmacodynamic properties of the angiotensin converting enzyme (ACE) inhibitor cilazapril were studied in 30 hypertensive patients with various degrees of renal function.
- 2 After a single oral dose, apparent cilazaprilat clearance was dependent on renal function being  $16.0 \pm 3.0$ ,  $11.1 \pm 3.0$ ,  $8.7 \pm 3.7$  and  $6.7 \pm 2.1$  l h<sup>-1</sup> (means  $\pm$  s.d.) in patients with creatinine clearances (CL<sub>cr</sub>) of >100, 41–100, 21–40, and 8–20 ml min<sup>-1</sup>, respectively.
- 3 During 11 weeks of treatment with cilazapril, doses were adjusted to the CL<sub>cr</sub> and varied from 0.5 to 5.0 mg once daily. At 24 h after drug administration a clear antihypertensive response was seen only in the low clearance groups (CL<sub>cr</sub> < 40 ml min<sup>-1</sup>). In contrast, and despite higher once daily dosages, the decline of mean arterial pressure was small and cilazaprilat concentrations after 24 h were lower in the high clearance groups.
- 4 This study demonstrates that chronic once daily treatment with cilazapril is effective in patients with impaired renal function at dosages adjusted to creatinine clearance. No accumulation was seen. Since cilazaprilat clearance was high in the high creatinine clearance groups, a clear antihypertensive response in these groups was only seen at 3 h after drug administration.

**Keywords** cilazapril renal failure hypertension pharmacokinetics proteinuria

## Introduction

The ACE inhibitor cilazapril is hydrolysed predominantly in the liver and blood to its active form cilazaprilat. This metabolite is excreted mainly by the kidneys [1]. In patients with normal renal function most of the unbound cilazaprilat is rapidly excreted in the first 8 h after drug administration. However, probably due to the high affinity of cilazaprilat for angiotensin converting enzyme the terminal half-life of this drug is as long as 40 to 50 h [1, 2]. In patients with renal insufficiency only limited pharmacokinetic and pharmacodynamic data on chronic cilazaprilat administration are available [3–5]. Therefore, we investigated the pharmacokinetic properties of cilazaprilat in hypertensive patients with various degrees of renal

insufficiency both after a single dose as well as during chronic treatment. The antihypertensive and antiproteinuric effects of various dosages of cilazapril as well as their relation to creatinine clearance (CL<sub>cr</sub>) and angiotensin converting enzyme (ACE) inhibition were studied at different times after drug administration.

## Methods

Thirty hypertensive patients without other serious cardiovascular disorders and with various but stable levels of renal function were selected. At least 3 weeks before the start of the study all antihypertensive agents and any other drug possibly interfering with blood

Correspondence: Dr H. J. Kloke, Division of Nephrology, University Hospital, Geert Grooteplein Zuid 8, 6500 HB Nijmegen, The Netherlands.

pressure regulation or renal function were discontinued. Patients were divided in four groups: creatinine clearance ( $CL_{cr}$ )  $> 100 \text{ ml min}^{-1}$  (group A),  $CL_{cr}$   $41\text{--}100 \text{ ml min}^{-1}$  (group B),  $CL_{cr}$   $21\text{--}40 \text{ ml min}^{-1}$  (group C) and  $CL_{cr}$   $8\text{--}20 \text{ ml min}^{-1}$  (group D). After three baseline measurements of haemodynamic and laboratory parameters on separate days performed at the same time in the morning, patients received a single (either 0.5 or 1.0 mg) oral dose of cilazapril. During the subsequent 4 days, haemodynamic and laboratory parameters were assessed at regular intervals. Thereafter, patients were treated during 11 weeks with a single daily dose of cilazapril (see below). Control visits were performed at weekly intervals during the first 4 weeks and further at week 7 and 11.

The study protocol was approved by the Ethical Committee of the University Hospital in Nijmegen. All patients gave their written informed consent.

#### Blood pressure measurements

At baseline standard sphygmomanometer supine diastolic blood pressure (BP) was greater than 90 mmHg. All other BP and heart rate (HR) measurements were done by automatic devices (DINAMAP, Criticon Inc., Tampa, Florida or BOSCH EBM502, Bosch GMBH, Berlin, Germany). After 5 min supine rest, BP was measured at 1 min intervals for 3 min in supine position using the same arm throughout the study. During chronic treatment, BP and HR were always measured 24 h after drug administration at the same time in the morning, with additional measurements 3 h after drug administration at weeks 2 and 4. The dose of cilazapril was increased after 2 weeks of treatment (see below) if diastolic blood pressure reduction 24 h after drug administration was less than 10% or if diastolic blood pressure remained higher than 90 mmHg. Thus the cilazapril dose was increased in seven, five, four and four patients of group A, B, C, and D, respectively. Since patient numbers were small, data were analyzed for the combined high and low clearance groups AB and CD, respectively.

#### Drug dosage

In the single dose part of the study patients of groups A and B received 1.0 mg cilazapril orally, whereas those of groups C and D received 0.5 mg. Chronic cilazapril doses were 2.5, 2.5, 1.0 and 0.5 mg once daily in groups A, B, C and D, respectively. If necessary, the dose was increased once at week 2 to 5.0 mg (groups A, B), 2.5 mg (group C) or 1.0 mg once daily (group D). Patient compliance was assessed by capsule counting and measurements of plasma ACE activity and cilazaprilat concentrations.

#### Other assessments

During the single dose part of the study regular measurements of plasma concentrations of cilazaprilat

and ACE activity were performed by radioenzymatic methods [1]. During chronic treatment these were measured at all visits at 24 h after drug administration and additionally at week 2 and 4 at 3 h after drug administration. At each visit serum potassium and creatinine were measured. Other routine blood evaluations remained stable throughout the study. At baseline plasma renin activity (PRA) was determined by radioimmunoassay [6]. In 24 h urine samples, concentrations of creatinine, sodium, potassium, and protein were measured at baseline and during chronic treatment. Patients were advised to adhere to a constant intake of sodium ( $150 \text{ mmol day}^{-1}$ ) and potassium ( $60\text{--}70 \text{ mmol day}^{-1}$ ) which was confirmed by urinary excretion.

#### Data analysis

For analysis, only relative changes of mean arterial pressure (MAP) compared with baseline were used. In one patient of group D the study was discontinued at week 3 because of peritonitis. In this patient only results of the single dose part were used for analysis. For determination of cilazaprilat pharmacokinetics individual data were analyzed by non-compartmental methods [7]. Cilazaprilat peak concentrations ( $C_{max}$ ) and time to peak ( $t_{max}$ ) were directly observed from analytical results. Since the decline of the logarithm of cilazaprilat concentrations is essentially non-linear and may vary widely [2, 8], calculation of the area under the curve (AUC) to infinity may be unreliable. Therefore, the AUC after the first dose was also calculated by the trapezoidal method to 24 h (AUC(0, 24 h)). Since dosages of cilazapril were different in the high (AB) and low clearance groups (CD), AUC (0, 24 h) and  $C_{max}$  were normalized to a dose of 1 mg for comparison of the results in the respective clearance groups. Apparent oral clearance ( $CL_o$ ) was calculated as dose/AUC(0, 24 h).

Analysis of the pharmacokinetic data from the single dose part of the study was performed by ANOVA. Pharmacokinetic and haemodynamic data from the multiple dose part (Table 3) were analyzed by distribution-free repeated measures analysis [9]. All other comparisons were assessed by Wilcoxon's rank sum test and Wilcoxon's signed rank test. Correlations were assessed by determining the correlation coefficient according to Spearman or where appropriate according to Pearson. A *P* value of 0.05 was considered as the level of statistical significance. Unless otherwise indicated, values are given as means  $\pm$  s.d.

## Results

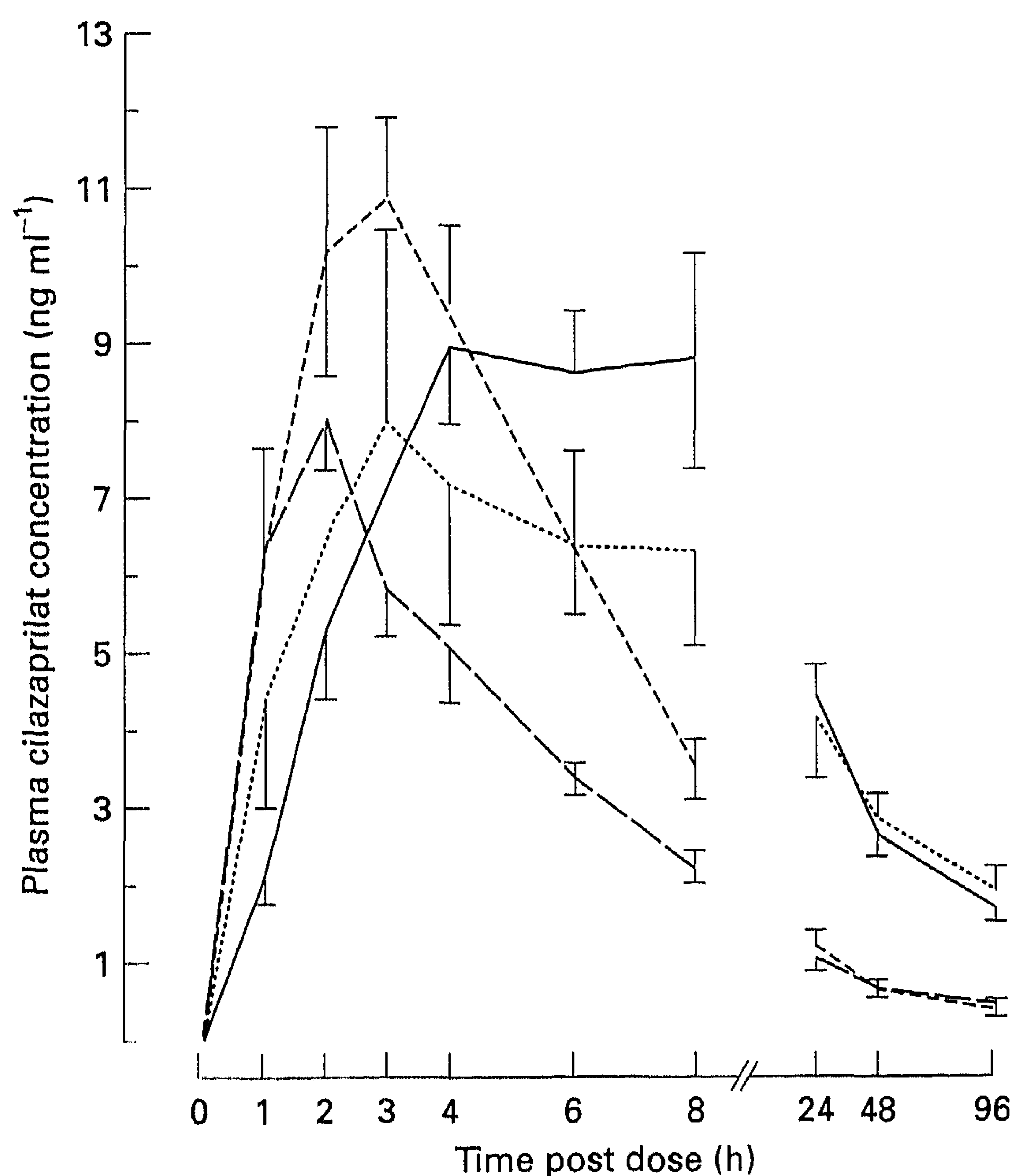
#### Single dose

Patient characteristics are given in Table 1. Pharmacokinetic data are given in Figure 1 and Table 2. In contrast to groups A and B, cilazaprilat concentrations declined slower in groups C and D. Accordingly, AUCs

**Table 1** Patient characteristics at baseline

	Group			
	A	B	C	D
Patients	7	10	5	8
Age (years)	47±10	59±5	49±9	48±14
Male/female	6/1	4/6	3/2	3/5
Body weight (kg)	86±8	70±8	77±10	68±6
BP				
systolic (mm Hg)	157±10	158±11	149±3	158±16
diastolic (mm Hg)	98±4	97±5	98±4	99±9
CL <sub>cr</sub> (ml min <sup>-1</sup> )	130±21	69±13	31±6	15±4
Patients with a proteinuria of more than 1 g day <sup>-1</sup>	0	2	4	4

BP: blood pressure measured by sphygmomanometer; CL<sub>cr</sub>: creatinine clearance; means±s.d. are given.



**Figure 1** Plasma cilazaprilat concentrations after a single dose of 1.0 and 0.5 mg cilazapril (CL<sub>cr</sub>>40 and <40 ml min<sup>-1</sup>, respectively). Cilazaprilat plasma concentrations of patients with an CL<sub>cr</sub> of less than 40 ml min<sup>-1</sup> are normalized to a dose of 1 mg. Means±s.e. mean are given. — CL<sub>cr</sub> 5–20 ml min<sup>-1</sup>, n=8; - - - - CL<sub>cr</sub> 21–40 ml min<sup>-1</sup>, n=5; ····· CL<sub>cr</sub> 41–100 ml min<sup>-1</sup>, n=10; — · — CL<sub>cr</sub>>100 ml min<sup>-1</sup>, n=7.

were larger in the low creatinine clearance groups. Average time to peak concentration ( $t_{max}$ ) was longer in patients with renal insufficiency. Correlations were found between CL<sub>cr</sub> and CL<sub>o</sub> ( $r = +0.7594$ ,  $P < 0.001$ ), between CL<sub>cr</sub> and AUC(0, 24 h) ( $r = -0.7385$ ,  $P < 0.001$ ) and between CL<sub>cr</sub> and  $t_{max}$  ( $r = -0.6474$ ,  $P < 0.001$ ). Compared with groups A and B, decreases of ACE inhibition were seen later in groups C and D (Figure 2). The correlation coefficient  $r$  between the degrees of ACE

inhibition and cilazaprilat concentrations was  $+0.8325$  ( $P < 0.001$ ) at 3 h after drug administration.

#### Chronic treatment

**Cilazaprilat plasma concentrations, ACE inhibition, PRA levels** Throughout the study cilazaprilat concentrations at 24 h were considerably lower in patients from groups A and B compared with patients from groups C and D (Table 3). Increasing the dose resulted in slightly higher cilazaprilat concentrations only in groups CD. After week 4 cilazaprilat concentrations measured at 24 h remained stable. Together with the lower cilazaprilat concentrations ACE inhibition at 24 h was essentially lower in patients of the high clearance groups. ACE inhibition at 3 h after drug administration at week 2 and 4 was almost complete in all patients. In patients treated with the same ('S') and those treated with an increased ('I') dose, comparable levels of ACE inhibition were seen at week 11 at 24 h:  $62 \pm 9$  and  $57 \pm 12\%$  in the groups AB-S and AB-I (NS), and  $85 \pm 10$  and  $90 \pm 4\%$  in the groups CD-S and CD-I (NS), respectively. PRA plasma concentrations at baseline were  $0.76 \pm 0.79$  and  $0.71 \pm 0.73$  nmol l<sup>-1</sup> u<sup>-1</sup> in group AB and CD (NS), respectively. In patients treated with the same ('S') or an increased ('I') dose PRA concentrations were not significantly different.

**Blood pressure and heart rate** Changes of mean arterial blood pressure are given in Table 3. In patients getting the same dose, blood pressure reduction at 24 h remained essentially the same throughout the study. Increasing the dose at week 2 had no additional effect on blood pressure reduction at 24 h in the high clearance group (AB-I). In contrast, a slight decline of blood pressure after dose increase was observed in the patients of the low clearance group (CD-I). Heart rate did not essentially change in any group. No significant correlation was found between BP decrease on the one hand and baseline MAP, cilazaprilat concentrations, ACE inhibition or urinary sodium excretion on the other.

**Other assessments, adverse events** In the low clearance groups CD serum creatinine and potassium concentrations had risen slightly from  $364 \pm 102$  at baseline to  $410 \pm 138$   $\mu\text{mol l}^{-1}$  ( $P < 0.05$ ) at week 11 and from  $4.6 \pm 0.4$  to  $5.0 \pm 0.4$  mmol l<sup>-1</sup> ( $P < 0.05$ ), respectively. Body weight essentially did not change. Proteinuria decreased from  $3.5 \pm 2.2$  at baseline to  $2.0 \pm 1.2$  gram day<sup>-1</sup> at week 11 ( $P < 0.01$ ) in the 10 patients with a proteinuria of more than 1 g day<sup>-1</sup>. No additional reduction in proteinuria was seen after increasing the dose at week 2. Compliance assessed by the percentage of capsules used as expected for the number of treatment days was 98 (93–101), 100 (94–102), 100 (99–105) and 99 (97–101)% in group A, B, C, and D, respectively (medians and ranges; percentages of more than 100% were possible since the provided drug bottles had seven capsules in excess of the expected number of treatment days). Two patients had short lasting dizziness during

**Table 2** Pharmacokinetic parameters of cilazaprilat after a single oral dose

	Group				ANOVA
	A	B	C	D	
Patients	7	10	5	8	
CL <sub>cr</sub> (ml min <sup>-1</sup> )	130 ± 21	69 ± 13	31 ± 6	15 ± 4	
AUC(0, 24 h) (ng ml <sup>-1</sup> h)	64 ± 13	97 ± 27	134 ± 60	162 ± 47	**
C <sub>max</sub> (ng ml <sup>-1</sup> )	8.8 ± 1.4	12.2 ± 3.6	8.7 ± 5.0	10.5 ± 3.4	NS
t <sub>max</sub> (h)	2.0 (1-4)	2.5 (1-4)	3.0 (2-8)	6.0 (4-8)	**
CL <sub>o</sub> (l h <sup>-1</sup> )	16.0 ± 3.0	11.1 ± 3.0	8.7 ± 3.7	6.7 ± 2.1	**

Unless otherwise indicated results are given as means ± s.d.; \*\*  $P < 0.01$ . Abbreviations: ANOVA: analysis of variance, AUC(0, 24 h): area under the curve, C<sub>max</sub>: peak concentration, t<sub>max</sub>: time to peak concentration given as medians (ranges), CL<sub>o</sub>: apparent total body clearance. AUC(0, 24 h) and C<sub>max</sub> are normalized to a dose of one mg.

**Table 3** Cilazaprilat plasma concentrations (ng ml<sup>-1</sup>), baseline supine mean arterial blood pressures (MAP) and their percent changes during chronic treatment at 3 and 24 h after cilazapril intake in patients getting the same dose at week 2 ('S') and in patients in which dosage was increased at week 2 ('I')

	Group			
	AB-S	AB-I	CD-S	CD-I
Patients	5	12	4	8
CL <sub>cr</sub> (ml min <sup>-1</sup> )	65 ± 13	*106 ± 34	20 ± 11	23 ± 8
Cilazapril dose (mg)	2.5	5.0	0.5-1.0	1.0-2.5
<i>Cilazaprilat concentrations</i>				
Week 2 (3 h)	50.6 ± 15.6	73.6 ± 23.5	25.1 ± 7.3	*58.9 ± 38.1
(24 h)	2.0 ± 0.6	1.9 ± 0.3	6.7 ± 5.8	5.3 ± 2.2
Week 4 (3 h)	59.8 ± 18.4	68.3 ± 29.5	23.8 ± 7.0	*60.8 ± 25.8
(24 h)	2.3 ± 0.6	2.9 ± 2.3	5.0 ± 2.9	9.3 ± 3.7
Week 11 (24 h)	2.4 ± 0.8	2.3 ± 0.5	5.4 ± 2.7	9.5 ± 3.4
<i>Mean arterial pressure</i>				
Baseline (mm Hg)	111 ± 10	115 ± 8	107 ± 7	118 ± 13
Week 2 (3 h)	-17 ± 8	*-8 ± 6	-7 ± 7	-8 ± 9
(24 h)	-12 ± 4	*-3 ± 4	-11 ± 4	-1 ± 8
Week 4 (3 h)	-17 ± 6	*-7 ± 6	-13 ± 5	-13 ± 11
(24 h)	-11 ± 9	*-1 ± 8	-9 ± 4	-9 ± 8
Week 11 (24 h)	-8 ± 8	*-1 ± 7	-12 ± 3	-9 ± 11

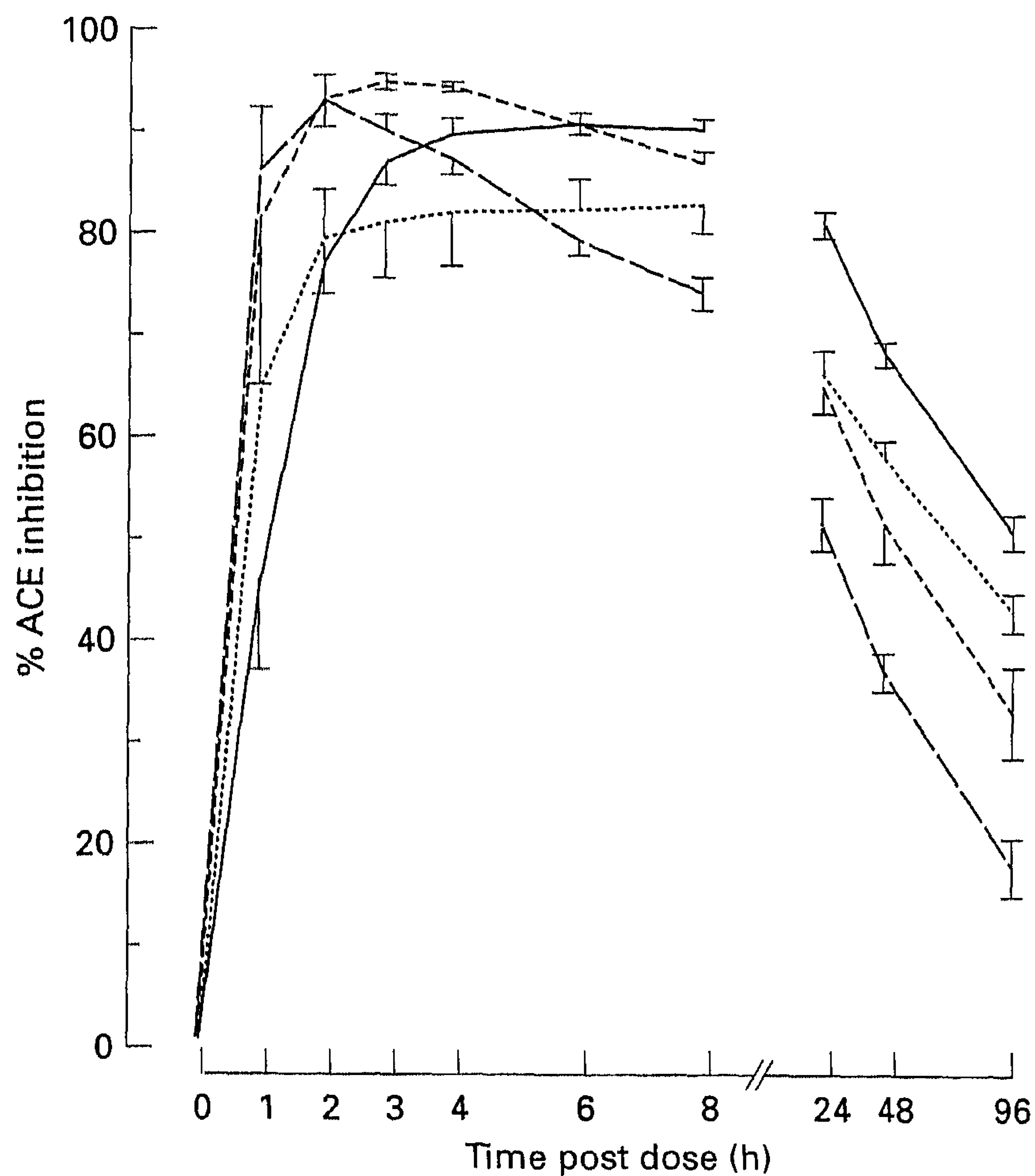
\*  $P < 0.05$  for AB-S vs AB-I and CD-S vs CD-I; results are given as means ± s.d.

the single dose part. In two patients dry cough was probably related to the treatment with cilazapril.

## Discussion

In our patients with normal as well as in those with impaired renal function the pharmacokinetic data of the single dose part were comparable with the results obtained by others [1, 3, 4]. A strong relationship between creatinine clearance on the one hand and AUC and clearance of cilazaprilat on the other hand was observed. Time to peak was longer in patients with more severely impaired renal function. The lower dose given in the low clearance groups was reason for normalization to 1 mg. This may have biased the results regarding time to peak, since the higher dose used in patients with higher creatinine clearances may have resulted in a larger amount of drug absorbed, leading

to higher plasma concentrations of free drug with relatively less binding to ACE and therefore faster elimination. Longer times to peak after lower dosages of cilazapril have also been reported in normal volunteers [2]. In addition, the slower excretion of cilazaprilat in the low clearance groups may have contributed to the longer times to peak. Theoretically, slower intestinal absorption of cilazapril in the low clearance groups may also explain this difference, but studies with other ACE inhibitors are not in favour of such a mechanism [10]. We can not compare our results with the study of Fillastre *et al.* who found a higher C<sub>max</sub> in patients with renal insufficiency [3], since we used a lower dose in patients with a low creatinine clearance. Concentrations of cilazaprilat at 96 h were low and the decline of the logarithm of the cilazaprilat concentration was not linear and showed a wide interindividual variation as reported by others [2, 8]. The area from 96 h to infinity was approximately half of the total area under the curve. Thus, analysis of the total area under the curve



**Figure 2** Degree of ACE inhibition after a single dose of 1.0 and 0.5 mg cilazapril ( $CL_{cr} > 40$  and  $< 40$   $ml\ min^{-1}$ , respectively). Means  $\pm$  s.e. mean are given.

—  $CL_{cr}$  5–20  $ml\ min^{-1}$ ,  $n=8$ ; - - - -  $CL_{cr}$  21–40  $ml\ min^{-1}$ ,  $n=5$ ; ·····  $CL_{cr}$  41–100  $ml\ min^{-1}$ ,  $n=10$ ; - - - -  $CL_{cr} > 100$   $ml\ min^{-1}$ ,  $n=7$ .

from time zero to infinity was inaccurate and therefore only results of  $AUC(0, 24\ h)$  are presented here.

During chronic treatment cilazaprilat concentrations measured at 24 h were considerably lower in the high clearance than in the low clearance groups, in accordance with previously reported data [4, 5, 11]. Only in patients with a low creatinine clearance did the increase in drug dosage cause an increase in cilazaprilat concentrations at 24 h. However, no accumulation was seen in these groups. The duration of ACE inhibition was considerably longer in patients with more severe renal insufficiency. The degree of ACE inhibition was closely related to cilazaprilat concentrations, thereby confirming previous studies [4, 12].

As expected from cilazaprilat concentrations and degree of ACE inhibition a clear antihypertensive effect in all groups of patients was seen at 3 h after drug administration. In agreement with others [13–15], the blood pressure reduction at 24 h remained small also after a dose increase in 12 out of 17 patients of the high clearance groups. In contrast, blood pressure at 24 h was slightly lower after increasing the dose in eight out of 12 patients with a low renal clearance. However, the extent of blood pressure decrease should be interpreted with caution since a placebo control is lacking.

In patients with a proteinuria of more than  $1\ g\ day^{-1}$  cilazapril clearly decreased urinary protein excretion by approximately 40%. Comparable antiproteinuric effects have been reported in the literature [5, 17]. Serum creatinine rose steadily only during the treatment in the low clearance groups. This increase was not influenced by the cilazapril dose or degree of the antihypertensive

response and may be related to the normal course of chronic renal failure in these patients. However, since no control groups were included, this remains difficult to assess.

In conclusion, chronic treatment with cilazapril was safe in patients with an  $CL_{cr}$  of 8–20  $ml\ min^{-1}$  and 21–40  $ml\ min^{-1}$  and a maximal once daily dosage of 1.0 and 2.5 mg, respectively. No cilazaprilat accumulation was seen. Even at 24 h after drug administration cilazaprilat concentrations and degree of ACE inhibition in these low clearance groups were high and blood pressure response was adequate in most of the patients. In contrast, in most patients with an  $CL_{cr}$  of more the 40  $ml\ min^{-1}$  no adequate blood pressure response was achieved at once daily dosing.

A critical review of the pharmacokinetic data was kindly performed by Dr F. Russel, Department of Pharmacology, University of Nijmegen, The Netherlands.

For their support and advice during the study we gratefully acknowledge W. P. L. van Boven M.D. (deceased), St Elisabeth Ziekenhuis, Tilburg; V. M. C. Verstappen M.D., St Maartens Gasthuis, Venlo; M. Koolen M.D., Bosch Medicentrum, 's-Hertogenbosch, The Netherlands.

Cilazapril was kindly supplied by F. Hoffmann-La Roche AG, Basle, Switzerland.

## References

- Williams PEO, Brown AN, Rajaguru S, *et al.* The pharmacokinetics and bioavailability of cilazapril in normal man. *Br J Clin Pharmacol* 1989; **27**: 181S–188S.
- Francis RJ, Brown AN, Kler L, *et al.* Pharmacokinetics of the converting enzyme inhibitor cilazapril in normal volunteers and the relationship to enzyme inhibition: development of a mathematical model. *J Cardiovasc Pharmacol* 1987; **9**: 32–38.
- Fillastre JP, Moulin B, Godin M, *et al.* Pharmacokinetics of cilazapril in patients with renal failure. *Br J Clin Pharmacol* 1989; **27**: 275S–282S.
- Shionori H, Gotoh E, Takagi N, Takeda K, Yabana M, Kaneko Y. Antihypertensive effects and pharmacokinetics of single and consecutive doses of cilazapril in hypertensive patients with normal and impaired renal function. *J Cardiovasc Pharmacol* 1988; **11**: 2–9.
- Kloke HJ, Wetzels JFM, van Hamersvelt HW, Koene RAP, Kleinbloesem CH, Huysmans FTM. Effects of nitrendipine and cilazapril on renal hemodynamics and albuminuria in hypertensive patients with chronic renal failure. *J Cardiovasc Pharmacol* 1990; **16**: 9–930.
- Sealey JE, Laragh JH. Searching out low renin patients: limitations of some commonly used methods. *Am J Med* 1973; **55**: 303–314.
- Gibaldi M. Compartmental and noncompartmental Pharmacokinetics. In *Biopharmaceutics and Clinical Pharmacokinetics*. Philadelphia: Lea & Febiger, 1991: 14–23.
- Meredith PA, Elliott HL, Reid JL, Francis RJ. The pharmacokinetics and angiotensin converting enzyme inhibition dynamics of cilazapril in essential hypertension. *Br J Clin Pharmacol* 1989; **27**: 263S–266S.
- Koziol JA, Maxwell DA. A distribution-free test for tumor-growth curve analyses with application to an animal tumor immunotherapy experiment. *Biometrics* 1981; **37**: 383–390.

- 10 Hoyer J, Schulte KL, Lenz T. Clinical pharmacokinetics of angiotensin converting enzyme inhibitors in renal failure. *Clin Pharmacokinet* 1993; **24**: 230–254.
- 11 Nussberger J, Fasanella d'Amore T, Porchet M, et al. Repeated administration of the converting enzyme inhibitor cilazapril to normal volunteers. *J Cardiovasc Pharmacol* 1987; **9**: 39–44.
- 12 Fasanella d'Amore T, Bussien JP, Nussberger J, et al. Effects of single doses of the converting enzyme inhibitor cilazapril in normal volunteers. *J Cardiovasc Pharmacol* 1987; **9**: 26–31.
- 13 Louis WJ, Conway EL, Krum H, et al. Comparison of the pharmacokinetics and pharmacodynamics of perindopril, cilazapril and enalapril. *Clin Exp Pharmacol Physiol* 1992; **19** (suppl 19): 55–60.
- 14 Lacourcière Y, Poirier L, Provencher P, Pyzyk M. Antihypertensive effects of cilazapril, 2.5 and 5 mg, once daily versus placebo on ambulatory blood pressure following single- and repeat-dose administration. *J Cardiovasc Pharmacol* 1991; **18**: 219–223.
- 15 Belz GG, Lange H, Tschollar W, Neis W. Cilazapril bei essen-tieller Hypertonie. *Med Klin* 1986; **81**: 524–529.
- 16 Resnick LM, Laragh JH. Renin, calcium metabolism and the pathophysiologic basis of antihypertensive therapy. *Am J Cardiol* 1985; **56**: 68H–74H.
- 17 Heeg JE, de Jong PE, van der Hem GK, de Zeeuw D. Reduction of proteinuria by angiotensin converting enzyme inhibition. *Kidney Int* 1987; **32**: 78–83.

(Received 16 November 1995,  
accepted 30 May 1996)