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Pharmacokinetics of cilazapril in patients with renal failure

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1 The pharmacokinetics of a single 1 mg dose of cilazapril were determined in six subjects with normal renal function and in 19 uraemic patients with various degrees of renal impairment.

2 Significant decreases in systolic and diastolic blood pressure were noted in all groups of subjects between 2 and 8 h after administration of 1 mg cilazapril.

3 There was a significant correlation between ACE inhbition at 24 h and creatinine clearance (CrCL).

4 For cilazapril, C_{max} and t_{max} were independent of creatinine clearance. AUC(24) was inversely related to CrCL and apparent plasma clearance (CL/*F*) was directly related to CrCL.

5 For cilazaprilat, C_{max} and t_{max} were related to creatinine clearance. AUC(24) was inversely related to CrCl and apparent plasma clearance (CL/*F*) was directly related to CrCL.

6 Dialysis clearance was approximately 2 l h^{-1} for cilazapril and for cilazaprilat.

7 The effects of renal impairment on cilazapril and cilazaprilat kinetics were similar to those observed for other inhibitors of angiotensin-converting enzyme such as captopril, enalapril and lisinopril.

8 It may be necessary to modify doses of cilazapril for the treatment of essential hypertension in uraemic patients. When creatinine clearance was below 15 ml min^{-1} cilazaprilat concentrations were increased, half-lives were prolonged and ACE inhibition remained above 90% for at least 24 h. A reduced dosage is indicated for these patients.

9 In patients requiring haemodialysis, maintenance doses of 0.5 mg given after each haemodialysis session are sufficient.

Keywords cilazapril blood pressure renal impairment angiotensin converting enzyme inhibition creatinine clearance

Introduction

Cilazapril is a new oral angiotensin converting enzyme inhibitor which is used to treat essential hypertension and congestive heart failure. The parent drug is converted *in vivo* to cilazaprilat which is a potent inhibitor of angiotensin converting enzyme. Cilazaprilat is eliminated primarily by renal excretion (Whitehead *et al.*, 1989). Thus, the present study was designed to determine the pharmacokinetics of a single 1 mg dose of cilazapril in patients with various degrees of renal impairment.

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Methods

Subject selection

Six subjects with normal renal function and 20 with various degrees of renal failure were recruited and assigned to one of five groups according to creatinine clearance (CrCL) as follows:-

Group I: Six subjects CrCL > 70 ml min^{-1} 1.73 m^{-2}

Group IIa: Four subjects CrCL < 5 ml min^{-1} 1.73 m^{-2}, requiring periodic haemodialysis

Group IIb: Six subjects CrCL 5–15 ml min^{-1} 1.73 m^{-2}, not requiring periodic haemodialysis

Group IIc: Five subjects CrCL 20–40 ml min^{-1} 1.73 m^{-2}

Group IId: Five subjects CrCL 40–70 ml min^{-1} 1.73 m^{-2}

Subjects in Group IIa were studied twice with an interval of 6–12 weeks between the two single doses. On one occasion, these patients were studied between haemodialysis sessions and on the other occasion they were studied during two haemodialysis sessions 4 and 52 h after dosing.

Each subject underwent a complete medical examination shortly before entering the trial. A 12-lead ECG was performed and samples were obtained for haematology, serum biochemistry, urinalysis and creatinine clearance. Subjects were excluded from the study for the following reasons: cardiac or hepatic insufficiency, gastrointestinal disease, alcoholism, heavy smoking, type I diabetes mellitus, severe hyperkalaemia.

Study procedures

All drug treatment was withdrawn 24 h before dosing and not started again until after the study. The subjects fasted for at least 8 h before dosing with cilazapril. After insertion of an indwelling catheter into an antecubital vein and collection of the predosing samples, each subject received a single oral dose of 1 mg cilazapril with 200 ml of tap water. Subjects remained supine for the first 4 h after dosing and were ambulant thereafter.

A standardized light breakfast was eaten 2 h after drug administration. Blood pressure and heart rate were recorded in the supine position every 15 min during the first 4 h after dosing and then at 6, 8, 10, 24, 36 and 48 h. Recordings were made using an automatic oscillometric device (SENTROM, Bard Biomedical).

Blood samples for the measurement of cilazapril, cilazaprilat and ACE were taken before dosing and at the following times after dosing: 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 36, 48 and 52 h. Plasma was separated by centrifugation (15 min at 3000 rev min^{-1}) within 4 h after sampling and frozen at −20° C until assay.

Urine was collected from 0–24 h and 24–48 h after dosing from subjects in groups I and IIb–IId. The total volume of each collection was recorded and two 10 ml aliquots were frozen at −20° C.

For the subjects included in group IIa, during haemodialysis a single 1 mg dose of cilazapril was given 4 h before the start of the first session. The second session started 48 h after the start of the first one and hence 52 h after dosing. Each haemodialysis session lasted for 4 h. The haemodialyses were performed using a TRAVENOL CF 1511 or CF 2308 artificial kidney according to the patient's body surface area. The dialysate flow rate was 500 ml min^{-1} and the blood flow rate was 250–300 ml min^{-1}. Simultaneous arterial and venous blood samples were taken from the arterial and venous lines of the extracorporeal circuit at 0, 0.5, 1, 2, 3 and 4 h during the first session and at 0, 1, 2 and 4 h during the second session.

Haemodialysate was collected from 0–1, 1–2, 2–3 and 3–4 h during each session. A sample of haemodialysate was frozen for drug assay.

Assays

Cilazapril, cilazaprilat and ACE activities were measured by radioenzymatic methods, which have been described previously (Schaik *et al.*, 1987). For cilazaprilat in plasma, samples were heated at 65° C to inactivate endogenous ACE. Then the samples were incubated with added rabbit-lung enzyme in the presence of the artificial substrate [^{14}C]-hippuryl-histidyl-leucine. Liberated [^{14}C]-hippuric acid was determined by liquid scintillation counting. The assay was linear from 0.165 to 675 mg ml^{-1} in three ranges. For cilazapril assays, samples were first subjected to cilazaprilat assay and incubated overnight with hog-liver esterase before the cilazaprilat assay was repeated. Cilazapril concentrations were estimated by difference. Urine and haemodialysate samples were treated in the same ways as plasma but the initial heating was unnecessary. For the measurements of ACE activity, the artificial substrate was added directly to untreated plasma samples.

The pre-study assay validation established intra-assay precision for quality control samples of ± 3% for cilazaprilat, ± 6% for cilazapril and

± 6% for ACE activity. Precisions for standards during the study were ± 5% for cilazaprilat and ± 4% for cilazapril. The limits of assay sensitivity were set at the lowest standard concentration; 0.165 ng ml^{-1} for cilazaprilat and 0.330 ng ml^{-1} for cilazapril, which were determined with mean inter-assay precisions of ± 8% and 7% respectively.

Pharmacokinetic parameters

The peak concentration (C_{max}), the concentration at 24 h after dosing (C_{24}) and the time to peak (t_{max}) were observed values. The area under the concentration AUC(24) *vs* time curve (AUC(24)) was calculated by the trapezoidal method up to 24 h after dosing. Total clearances, CL/*F* were derived from the dosage of cilazapril (1.000 mg) or cilazaprilat (0.9329 mg) divided by AUC(24). Renal clearance CL_R was derived from the urinary recovery in 24 h divided by AUC(24). The elimination half-life 'during the first phase', $t_{½}$ (*F*), in h, was found by weighted log-linear regression from one time point past the peak to the end of the first linear phase. Clearance during haemodialysis CL_D (l h^{-1}) was calculated from

$$CL_D = \frac{DR}{AUC_D}$$

where DR = drug recovery in the dialysate.

The dialysate flow was constant at 20 l h^{-1} giving a total dialysate volume of 120 l in 4 h. AUC_D = area under the arterial plasma concentration *vs* time curve during the dialysis period (ng ml^{-1} h). The volume of dialysate removed as ultrafiltrate was not more than 4 l during a 4 h session and contributed an insignificant amount to the total dialysate volume.

Subject 25 was excluded from the pharmacokinetic analyses because she received enalapril until 24 h before the cilazapril dose.

Statistical methods

Univariate statistics for systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate were calculated. Falls in SBP and DBP were compared between group by an analysis of variance and a multiple range test (least significant difference). The variations of heart rate were compared within each group by an analysis of variance. Results are expressed as mean ± s.e.mean.

Mean values were calculated for pharmacokinetic parameters. Statistical analysis was restricted to linear regression of individual values against creatinine clearance.

Results

Eighteen male and eight female subjects with an age range of 20–70 years were recruited to the study. Details are given in Table 1. The single doses of cilazapril were well tolerated by all except one patient. In group IIa, a patient experienced a transient diarrhoea lasting for 4 h. This episode did not recur when cilazapril was re-introduced for the study during haemodialysis.

Changes in blood pressure

Statistically significant decreases in systolic and diastolic blood pressure were noted in all groups of subjects between 2 and 8 h after administration of 1 mg cilazapril. The maximum decrease in diastolic blood pressure in each group is shown in Figure 1. There were no significant differences between groups. Blood pressure returned to baseline values within 24 h except for group IIa (haemodialysed patients) although even for these patients the decrease at 24 h was not statistically significant. There was no significant change in heart rate.

ACE inhibition

Mean profiles of plasma ACE inhibition showed consistently greater inhibition in subjects with more renal impairment (Figure 2). Inhibition at 24 h was highly correlated with creatinine clearance (Figure 3).

Pharmacokinetic parameters

Cilazapril and cilazaprilat results are considered separately.

Cilazapril Peak plasma concentrations were not significantly different in uraemic patients and in healthy volunteers. The overall mean value was 45 ng ml^{-1} for the 1 mg dose of cilazapril. The time to peak varied between 0.5 and 3 h with a mean of 1.25 h. Neither C_{max} nor t_{max} was dependent on creatinine clearance. Post-peak plasma concentrations declined rapidly up to 8 h with a slower decline thereafter. Cilazapril concentrations were undetectable in the control group after 8 h and were measured at 36 h or 48 h only in groups of patients with severe renal failure (CrCL < 40 ml min^{-1}). The 24 h areas under the curves were inversely related to creatinine clearance and so the apparent plasma clearances were directly related (Table 2).

Cilazaprilat Peak plasma concentrations were obtained between 1.5 and 2 h and averaged

Table 1 Details of the patients

Number	*Sex*	*Age (years)*	*Height (cm)*	*Weight (kg)*	*Creatinine clearance (ml min^{-1})*
Group I					
1	M	65	180	84	101
8	M	43	174	88	118
16	M	62	181	74	77
17	M	60	172	74	112
19	M	32	172	80	72
24	M	20	178	63	105
Mean		47	176.2	77.2	97.5
Range		20–65	172–181	63–88	72–118
Group IIa					
18	F	57	165	98	0
20	M	56	154	88	0
21	M	68	176	66	0
23	F	35	160	58	0
Mean		54	163.6	77.5	
Range		35–68	154–176	58–98	
Group IIb					
2	F	52	155	65	12
5	M	64	171	95	8
6	F	53	154	66	9
7	F	59	159	50	12
12	M	48	178	78	9
22	M	62	171	69	6
Mean		56.3	164.6	70.5	9.3
Range		48–64	154–178	50–95	6–12
Group IIC					
11	M	66	166	70	38
13	M	40	169	56	23
14	M	54	164	47	22
25*	F	60	162	57	36
26	M	70	174	71	32
Mean		58	167	60.2	30.2
Range		40–70	162–174	47–71	22–38
Group IId					
3	M	49	190	82	62
4	F	44	148	52	54
9	M	67	172	74	62
10	M	68	155	59	52
15	F	64	160	60	43
Mean		58.4	165	65.4	54.6
Range		44–68	148–190	52–82	43–62

* Subject excluded from pharmacokinetic analyses because of previous enalapril treatment.

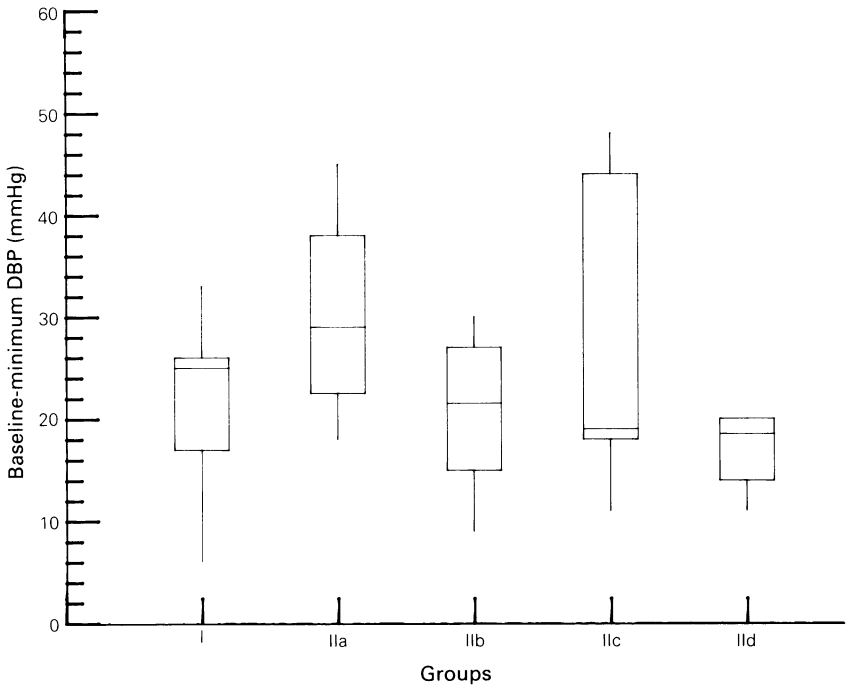

Figure 1 The maximum decrease in diastolic blood pressure (DBP) in each group (Box and Whisker plots).

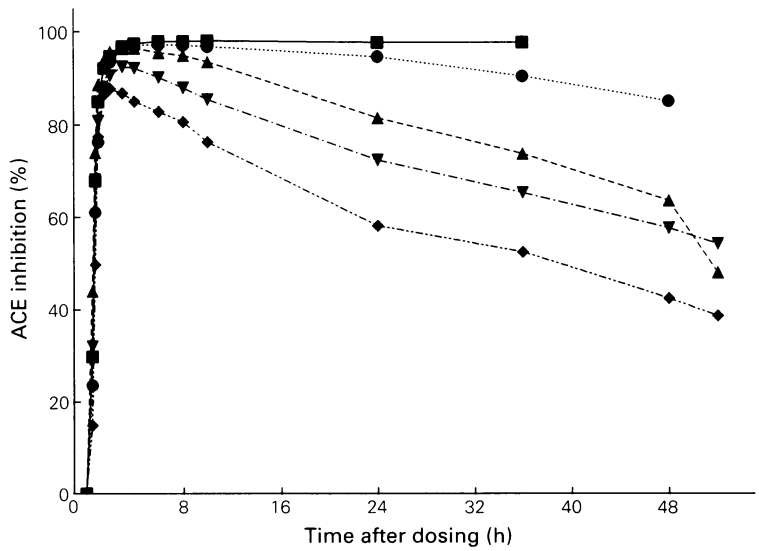

Figure 2 Mean profiles of ACE inhibition (■ Group IIa (0 ml min^{-1}), ● Group IIb (6–12 ml min^{-1}), ▲ Group IIc (22–38 ml min^{-1}), ▼ Group IId (43–62 ml min^{-1}) and ◆ Group I (72–118 ml min^{-1})).

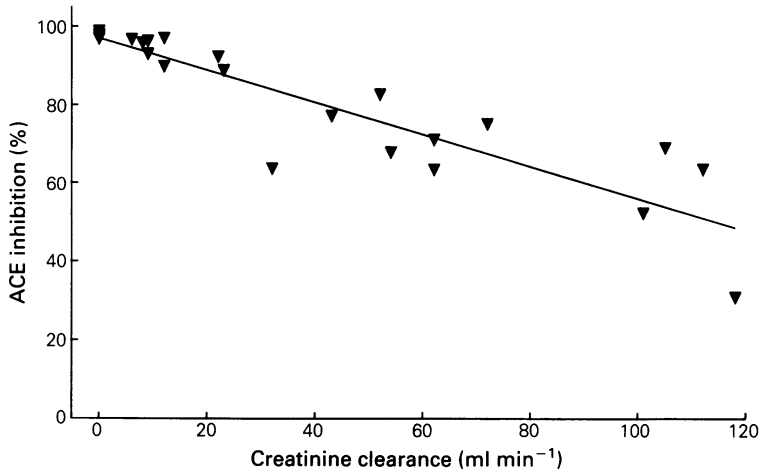

Figure 3 ACE inhibition at 24 h after dosing *vs* creatinine clearance. ▼ ACE inhibition at 24 h, —— $0.410 \cdot x + 97.0$, $r^2 = 0.803$, $P < 0.0001$.

Table 2 Pharmacokinetic parameters of cilazapril (mean ± s.d.)

	Group				
	I	*IIa*	*IIb*	*IIc*	*IId*
C_{max} (ng ml^{-1})	38.71 ±21.80	52.76 ± 6.25	47.52 ±27.89	51.18 ±17.86	38.57 ±22.21
t_{max} (h)	0.87 ± 0.14	1.19 ± 0.37	1.37 ± 0.54	1.12 ± 0.48	1.70 ± 1.25
AUC(24) (ng ml^{-1} h)	131 ± 143	319 ± 89	239 ± 131	210 ± 96	99 ± 65
CL/*F* (l h^{-1})	13.21 ± 7.11	3.31 ± 0.84	5.53 ± 2.95	5.49 ± 2.29	13.52 ± 7.41
CL_R (l h^{-1})	4.65 ± 3.30	—	—	—	3.96 ± 3.10

11 ng ml^{-1} in subjects with a normal renal function. These were similar in patients with mild renal failure but t_{max} appeared later between 3 and 4 h (group IIa). C_{max} was higher (mean value 26 ng ml^{-1}) and t_{max} was later (13 h) for patients of group IIa (CrCL < 5 ml min^{-1}). C_{max} and t_{max} depended on creatinine clearance (Table 3).

Post-peak concentrations declined rapidly up to 8 h for group IIa patients with a mild renal insufficiency (half-lives were 4.8 h group IIa compared with 5.1 h for the control group). For other groups, a slower terminal phase was evident and there was a major increase of half-life only for patients with creatinine clearance below 40 ml min^{-1}. Thus, cilazaprilat plasma concentrations were 1.54 ± 0.39 ng ml^{-1} at 24 h for the control group and 20.1 ± 5.53 ng ml^{-1} at the same time for uraemic patients with a creatinine clearance below 5 ml min^{-1}. Similarly, the 24 h areas under the curves were inversely related to creatinine clearance and the apparent plasma clearances were directly related. Linear regression of cilazaprilat plasma clearance against creatinine clearance gave a significant correlation ($r^2 = 0.486$, $P < 0.01$) (Figure 4). Cilazaprilat renal clearances were more highly correlated with creatinine clearance ($r^2 = 0.818$, $P < 0.0001$ (Figure 5).

Patients undergoing haemodialysis The four patients in group IIa were also studied during two successive haemodialysis sessions, initiated 4 and 52 h after a 1 mg single oral dose of

Table 3 Pharmacokinetic parameters of cilazaprilat (mean ± s.d.)

	Group				
	I	*IIa*	*IIb*	*IIc*	*IId*
C_{max} (ng ml^{-1})	10.81 ± 5.95	26.26 ±10.94	20.03 ±10.14	22.47 ± 1.86	11.83 ± 7.01
t_{max} (h)	1.46 ± 0.51	12.50 ± 7.72	5.33 ± 1.03	3.00 ± 0.81	2.90 ± 1.14
AUC(24) (ng ml^{-1} h)	89 ± 32	507 ± 177	313 ± 160	255 ± 46	102 ± 54
CL/*F* (l h^{-1})	12.06 ± 5.84	1.99 ± 0.60	3.81 ± 2.31	3.75 ± 0.68	12.04 ± 7.38
CL_R (l h^{-1})	3.29 ± 0.92	—	0.52 ± 0.13	1.31 ± 0.52	2.27 ± 0.8

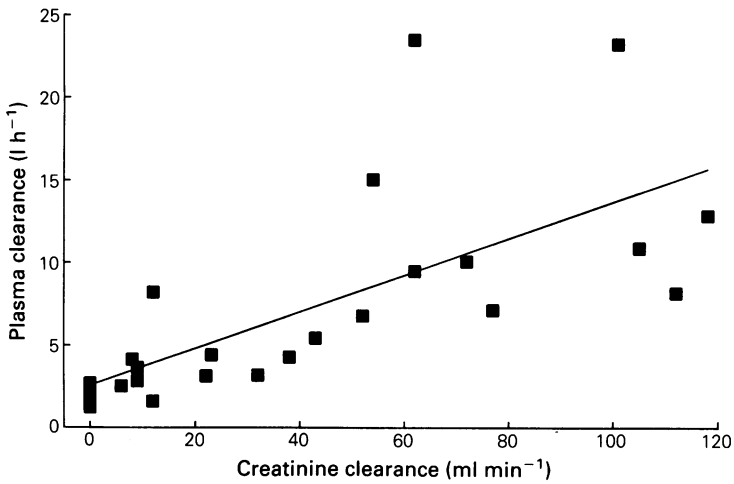

Figure 4 Plasma clearance of cilazaprilat *vs* creatinine clearance. ■ plasma clearance, —— 0.111 · x + 2.57, $r^2 = 0.486$, $P < 0.001$.

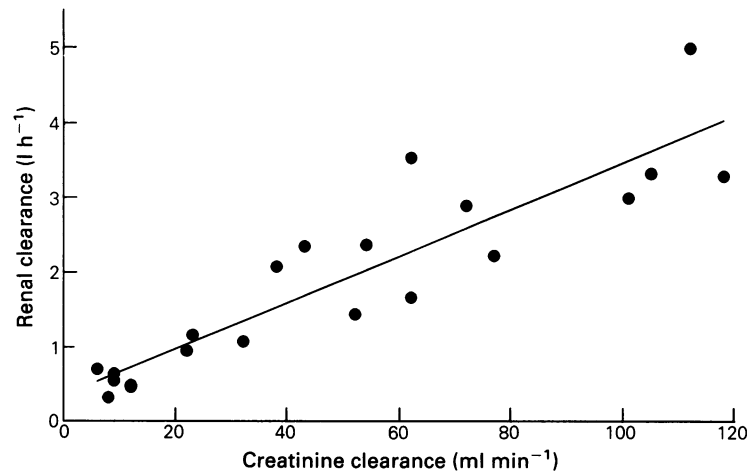

Figure 5 Renal clearance of cilazaprilat *vs* creatinine clearance. • renal clearance, —— 0.0312 · x + 0.349, $r_2 = 0.818$, $P < 0.0001$.

cilazapril. Each session was of 4 h duration. The total recovery of cilazapril in dialysate during the first session averaged 10% of dose and of cilazaprilat 14% of dose. Dialysate recovery of cilazaprilat in the second session averaged 7.2% of dose. Cilazapril was undetectable. Dialysis clearance for cilazapril was 2.4 l h^{-1} and for cilazaprilat 2.2 l h^{-1}.

Discussion

Our pharmacokinetic data in patients with normal renal function were very close to those obtained by Francis *et al.* (1987) in healthy subjects. The relationship between creatinine clearance and cilazapril kinetics in our study was similar to that described by Shionoiri *et al.* (1988) in a smaller number of patients with renal failure.

It is important to note that the changes seen with cilazapril in uraemic patients were similar to those mentioned for other inhibitors of angiotensin converting enzyme. Rommel *et al.* (1980) studied the elimination of a single 100 mg dose of captopril in patients with creatinine clearance ranging from 0 to 566 ml min^{-1}. The relative distribution of captopril and metabolites in blood differed significantly in uraemic patients compared with normal subjects. In renal failure, less unchanged captopril and more metabolites (disulphide conjugates) were found. The rate of urinary excretion decreased with decreasing renal function as the half-life of unchanged captopril and metabolites lengthened markedly at creatinine clearances below 20 ml min^{-1}. A linear relationship was demonstrated between *ke* and CrCL with a very good regression coefficient ($r = 0.957$, $P < 0.001$).

Enalapril maleate resembles cilazapril in that it is a drug which is hydrolyzed *in vivo* to an active metabolite. The influence of renal insufficiency on the serum profiles of enalapril and enalaprilat has also been investigated (Kelly *et al.*, 1986; Lowenthal *et al.*, 1985).

Decreased renal function is associated with increased serum concentration of enalaprilat, increased time to peak concentration, slower decline in serum concentrations and with decreased urinary elimination of the drug (Kelly *et al.*, 1986; Lowenthal *et al.*, 1985). This results in decreased dosage requirements of enalapril maleate. Lisinopril, a lysine analogue of enalaprilic acid, is a new potent angiotensin converting enzyme inhibitor. This drug is excreted unchanged in the urine. In patients with severe renal failure (5–30 ml min^{-1}) the peak concentrations of lisinopril were higher. The declines in serum concentration were slower and the times to peak concentration delayed (Schaik *et al.*, 1987).

These results are clearly important for the use of angiotensin converting enzyme inhibitors in renal impairment. Decreased dosages appear necessary.

Standard doses of cilazapril for the treatment of essential hypertension are 2.5 or 5 mg once daily. Based upon the kinetic results there appears to be little need for alteration of this regimen when creatinine clearance is above 40 ml min^{-1}. When creatinine clearance is below 15 ml min^{-1}, 24 h cilazaprilat concentrations are increased, half-lives are prolonged and inhibition of plasma ACE remains above 90% for at least 24 h. A reduced dosage of 1 mg once a day is indicated for these patients. In patients requiring haemodialysis, drug clearance is very slow. Maintenance doses of 0.5 mg, given after alternate haemodialysis sessions would seem to be appropriate for these patients.

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