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Initial and Steady State Pharmacokinetics of Cilazapril in Congestive Cardiac Failure

M. N. WISEMAN†, J. E. ELSTOB, R. J. FRANCIS*, A. N. BROWN*, S. RAJAGURU*, J. STEINER* AND D. S. DYMOND

*St Bartholomew's Hospital, London, EC1A 7BE and *Roche Products Ltd, PO Box 8, Welwyn Garden City, Hertfordshire AL7 3AY, UK*

Abstract—Twenty one patients with NYHA class II–III congestive heart failure received single ascending doses of 0·5, 1·25 and 2·5 mg cilazapril daily followed by the minimum effective dose for six weeks. Fifteen patients completed the study, but the data from only 11 were sufficiently complete for kinetic evaluation. The pharmacokinetics of the metabolite, cilazaprilat, after a single dose of 0·5 mg cilazapril were similar to previous observations in healthy volunteers at identical dosage. Repeat administration, however, led to greater accumulation than previously observed in volunteers at the higher dosages of 1·25 or 5 mg given for 8 days. Seven patients experienced adverse events. Four were severe, leading to withdrawal of the patients from the study, but only one event was related to cilazapril. Of the other three, one suffered a myocardial infarction and subsequently died due to worsening congestive heart failure. One other patient was withdrawn with two adverse events probably related to cilazapril. No other deaths occurred amongst the study population, and there were no significant abnormalities in haematology or blood chemistry.

Cilazapril (Ro 31-2848/006) is a novel drug which has been shown to be safe and effective in the treatment of essential hypertension (Sanchez et al 1988) where satisfactory antihypertensive effects were achieved with doses ranging from 0·5 to 10 mg.

Non-specific esterases rapidly hydrolyse the drug to the active metabolite cilazaprilat, which is a potent inhibitor of angiotensin converting enzyme (ACE) (Natoff et al 1985). The pharmacokinetics of cilazapril have been investigated in volunteers (Francis et al 1987; Williams et al 1989) and hypertensive patients (Meredith et al 1989) at dosages within the therapeutic range.

ACE inhibitors now occupy a significant place in the management of congestive heart failure (CHF) (Anon 1985). The only previous report concerning the pharmacokinetics of cilazapril in this condition occurs in the proceedings of a symposium (Rosenthal et al 1989).

The present study was designed to assess the effects of cilazapril in patients with CHF NYHA class II–III, and to determine the drug's pharmacokinetic profile in these patients. Pharmacokinetic and safety aspects only are considered in the present report.

Materials and Methods

Subjects

Twenty one patients were recruited into the study (Table 1). Inclusion criteria were: age 18–65 years, in sinus rhythm, congestive heart failure, NYHA class II–III treated with loop diuretics. Informed written consent was obtained and the study was approved by the hospital's ethics committee. Patients were excluded if they had evidence of primary renal or hepatic disease, or if there was any need for medication other than diuretics or digoxin.

Correspondence: D. S. Dymond, Department of Cardiology, St Bartholomew's Hospital, London EC1A 7BE, UK.
† Current address: The Mt Sinai Heart Institute, Mt Sinai Medical Center, One Mt Sinai Drive, Cleveland, Ohio 44106, USA.

Study design

This was an open pilot study in 21 patients with symptomatic heart failure, using single oral doses of 0·5, 1·25 and 2·5 mg cilazapril on each of three successive days followed by the minimum effective dose daily for a further six weeks.

At entry into the study, the patients were given a standard physical examination and their heart failure was graded. Full blood count, plasma biochemistry, ECG and chest X-ray were performed. There were no significant alterations in any of these parameters during the course of the study.

On study day 1 the patients were catheterized (Swan-Ganz catheter), and a single oral 0·5 mg dose of cilazapril was administered. Clinical assessments and haemodynamic measurements were made at intervals both before drug intake and up to 24 h. Similar procedures were followed on days 2 and 3 after the 1·25 and 2·5 mg doses. From day 4 onwards, patients were treated with the smallest dose that produced a significant reduction in the pulmonary capillary wedge pressure (>5 mm Hg). It was intended to treat patients for six weeks and then readmit for final pharmacokinetic profile and haemodynamic study.

Blood samples (5 mL) were collected immediately before the first administration of drug on day 0, and then at 0·5, 1, 2, 3, 4, 6, 8, 12 and 24 h after this dose. The same time points were used for samples collected immediately before and following the final dose, which varied between day 36 and day 63. Each sample was collected into a lithium heparin plastic tube, and the plasma separated by centrifugation within 4 h of blood collection. The plasma was divided into two plain plastic collection tubes and stored at −20°C.

Cilazaprilat concentration and ACE activity in plasma were measured by pre-validated radioenzymatic assays in the Pharmacokinetics and Metabolism Department, Roche Products (Welwyn Garden City, UK).

Plasma samples for cilazaprilat were heat-treated to inactivate endogenous ACE and then incubated with a fixed amount of rabbit-lung ACE in the presence of an artificial substrate, [^{14}C]hippuryl-histidyl-leucine. Liberated [^{14}C]hippuric acid was extracted with pentyl acetate and the radioac-

Table 1. Patient demography.

Patient	Age	Sex	Wt (kg)	Ht (cm)	Aetiology	Concomitant medication	Pharmacokinetic data
1	54	M	79	171	IHD	Frusemide Digoxin ISDN Salbutamol	Incomplete
2	46	M	87	177	IHD	Frusemide Amiloride	
3	65	M	61	168	IHD	Frusemide Amiloride	Withdrawn day 14 Severe hypotension
4	55	M	61	175	IHD+HT	Frusemide Amiloride ISDN	Incomplete
5	59	M	63	182	IHD	Frusemide Amiloride	Withdrawn day 1
6	66	M	91	183	IHD	Frusemide Amiloride Metolazone	Incomplete
7	63	M	84	171	IHD	Frusemide Amiloride	Withdrawn day 14 Hypotension
8	59	M	69	171	IHD	Frusemide Amiloride	Incomplete
9	52	M	61	168	IHD	Frusemide Amiloride Digoxin	
10	59	M	74	173	IHD	Frusemide Amiloride	
11	59	M	59	173	IHD	Frusemide Amiloride Aspirin	Withdrawn day 3 Treatment failure
12	58	M	59	160	IHD	Bumeta- mide KCl	
13	53	M	68	172	IHD	Frusemide Amiloride	
14	64	M	75	177	IHD	Frusemide KCl	Withdrawn day 26 Intercurrent MI
15	59	M	75	172	IHD	Frusemide Amiloride Bezafibrate	
16	58	M	86	172	IHD	Bumeta- mide KCl	
17	56	M	72	174	IHD	Frusemide Amiloride	
18	61	M	81	174	IHD	Frusemide Amiloride	Withdrawn day 1 Sepsis
19	67	F	76	170	IHD	Frusemide Amiloride Aspirin	
20	55	M	78	176	IHD+HT	Frusemide Amiloride	
21	55	M	84	176	IHD	Frusemide Triamterene	

Mean (with range): age 57·9 (46–67), wt 73·5 (59–91), height 173 (160–183). IHD: ischaemic heart disease. HT: hypertension. ISDN: isosorbide dinitrite.

tivity determined by liquid scintillation counting. Standards and quality control (QC) samples were processed along with the unknowns and a calibration curve obtained by regression analysis. Concentrations of cilazaprilat were expressed as ng mL^{-1}. Samples for ACE activity were incubated directly with the artificial substrate. Activities of ACE were expressed as units L^{-1} where one unit is defined as that amount of ACE which will cleave 1 μmol of substrate per min at 37°C. For both drug and ACE assays the assay precision was better than 7%.

Individual pharmacokinetic data sets were analysed by "model independent" methods. The peak concentration (C_{max}) and the time to peak (t_{max}) were observed values. The area under the concentration time curve to 24 h (AUC_{24}) was

Table 2. Pharmacokinetic parameters for cilazaprilat.

	First dose					Last dose			
Patient	C_{max} (ng mL^{-1})	t_{max} (h)	AUC_{24} (μg h L^{-1})	$t_{\frac{1}{2}}$ (μg h L^{-1})		C_{max} (ng mL^{-1})	t_{max} (h)	AUC_{24} (μg h L^{-1})	$t_{\frac{1}{2}}$ (h)
	(0·5 mg cilazapril)					(0·5 mg cilazapril)			
2	8·8	1·0	47	4·5		13	1·0	98	5·0
10	7·3	2·0	49	4·5		12	3·0	77	2·5
16	5·5	1·0	39	4·2		8	3·0	74	5·2
17	6·5	2·0	61	9·2		13	2·0	146	4·9
					Mean	11	2·3	98	4·4
					% s.d.	23	43	34	29
						(1·25 mg cilazapril)			
9	9·4	2·0	76	nc		40	3·0	253	2·7
12	3·3	3·0	29	nc		28	3·0	189	3·0
					Mean	34	3·0	221	2·8
						(2·5 mg cilazapril)			
13	4·5	2·0	52	5·7		37	3·0	338	4·1
15	3·8	4·0	37	nc		45	2·0	265	2·9
19	6·7	3·0	55	6·7		69	2·0	400	2·5
20	5·4	2·0	40	4·3		45	3·0	245	3·0
21	5·7	3·0	47	2·1		36	3·0	258	2·8
Mean	6·1	2·3	48	51		46	2·6	301	3·1
% s.d.	32	40	26	41		29	21	22	21

C_{max}, t_{max}—peak and time of peak concentration; AUC_{24}—24 h area under curve; $t_{\frac{1}{2}}$—half-life post-peak up to 8 h; nc—not calculable.

calculated by the trapezoidal rule assuming an exponential change between adjacent points. Half-life in the interval one point post-peak to 8 h was estimated by weighted linear regression of the log-transformed data.

Among the pharmacodynamic parameters, AO was the activity in each patient before the first dose of cilazapril. All values for ACE inhibition were derived by reference of post-dose ACE activity to the appropriate AO value.

Peak inhibition (I_{max}), the time to peak (t_{Imax}), the inhibition at 24 h (I_{24}) and the inhibition immediately before the last dose (IO) were obtained directly from the analytical data.

Protocol deviations and withdrawals

Twenty one patients were recruited into the study, but six were withdrawn before the last day of dosing: of these, two became pyrexial during the initial three day catheter study, two developed significant hypotension and one had an intercurrent myocardial infarction during the six weeks out of hospital phase; one did not respond to the drug.

Of the remaining 15 patients, data from 11 could be fully evaluated with respect to drug plasma concentration data. In four patients (1, 4, 6 and 8) pharmacokinetic data were excluded because of incomplete collection of plasma samples.

Statistical analysis

Last and first dose data were compared by two-tailed paired *t*-test, and the different treatment groups by two-tailed *t*-test comparison of means.

Results

No cilazaprilat was detectable in any plasma sample before the first cilazapril dose. The mean plasma level of cilazaprilat in the 11 fully evaluated patients over a 24 h period following first and last doses is shown in Fig. 1. Pharmacokinetic parameters are presented in Table 2. Plasma concentrations after the first dose of 0·5 mg increased rapidly, to a peak between 1 and 3 h after drug administration. The mean time of peak was 2·3 h, and the mean peak concentration 6·1 mg mL^{-1}. Post-peak, plasma concentrations declined with a mean half-life up to 8 h of 5·1 h. Between 8 and 24 h the rate of decline was slower, such that at 24 h the mean plasma concentration was 1·1 ng mL^{-1}. The mean AUC_{24} was 48 μg h L^{-1}.

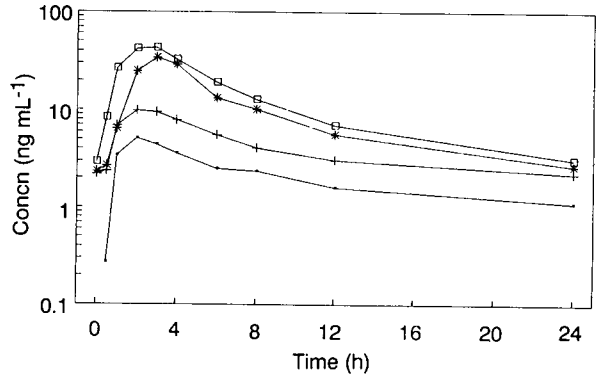

FIG. 1. ●—first dose (0·5 mg cilazapril, n = 11); + last dose (0·5 mg cilazapril daily, n = 4); * last dose (1·25 mg daily, n = 2), □ last dose (2·5 mg daily, n = 5).

Individual variation was up to threefold in peak and 24 h concentrations, but less than twofold in AUC.

In the multiple-dose phase of the study, four patients received 0·5 mg cilazapril once-daily for 8 weeks, 2 patients 1·25 mg and 5 patients 2·5 mg.

After the last dose, cilazaprilat plasma concentrations increased rapidly, to a peak between 1 and 3 h after drug administration. The mean times to peak were 2·3, 3·0 and

Table 3. Plasma ACE inhibition parameters.

	First dose					Last dose		
Patient	AO (units L^{-1})	I_{max} (%)	t_{Imax} (h)	I_{24} (%)		I_{max} (%)	t_{Imax} (h)	I_{24} (%)
	(0·5 mg cilazapril)					(0·5 mg cilazapril)		
2	23	92	1·0	60		92	1·0	48
10	18	92	2·0	73		91	3·0	55
16	19	87	2·0	57		88	3·0	47
17	29	88	2·0	66		89	2·0	71
					Mean	90	2·3	55
					% s.d.	2	43	16
						(1·25 mg cilazapril)		
						97	3·0	76
9	38	97	4·0	70		97	3·0	73
12	24	83	4·0	60	Mean	97	3·0	74
						(2·5 mg cilazapril)		
13	25	76	4·0	65		96	4·0	77
15	25	83	4·0	56		98	2·0	52
19	14	88	3·0	65		99	2·0	67
20	19	86	2·0	61		98	2·0	62
21	14	84	3·0	58		97	3·0	58
Mean	23	87	2·8	63	Mean	98	2·6	63
% s.d.	31	7	38	8	% s.d.	1	34	13

AO—pre-treatment plasma ACE activity; I_{max}, t_{Imax}—peak and time of peak inhibition; I_{24}—inhibition at 24 h.

2·6 h for the 0·5, 1·25 and 2·5 mg treatment groups and the corresponding mean peak concentrations 11, 34 and 46 ng mL^{-1}, respectively. Mean half-lives up to 8 h were 4·4, 2·8 and 3·1 h, and mean 24 h plasma concentrations 2·2, 2·7 and 3·1 ng mL^{-1}, respectively. Mean AUC_{24} values were 98, 221 and 301 $\mu g\ h\ L^{-1}$, respectively. Variation was twofold or less for all parameters for each treatment group.

Comparison of the multiple-dose data for the 0·5 mg treatment group with the first-dose data for the same patients showed that the peak and the 24 h cilazaprilat concentrations were 61 and 94% higher, respectively. AUC_{24} was 101% higher. All these changes except the 24 h concentration were statistically significant.

Comparison of the multiple-dose data for the 1·25 and 2·5 mg treatment groups with those for the 0·5 mg group showed that the mean peak cilazaprilat concentrations were three- and fourfold higher, respectively and AUC_{24} values were two- and threefold higher.

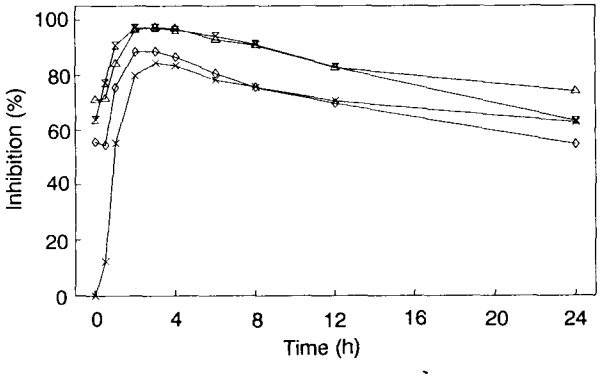

FIG. 2. x first dose (0·5 mg cilazapril, n = 11); ◇ last dose (0·5 mg cilazapril daily, n = 4); △ last dose (1·25 mg daily, n = 2), ▽ last dose (2·5 mg daily, n = 5).

Mean plasma ACE inhibition profiles are shown in Fig. 2 and parameter values in Table 3. The mean plasma ACE activity before the first dose was 22·6 units L^{-1}. Plasma ACE activity in the 11 patients after the first dose of 0·5 mg cilazapril declined rapidly, to a peak inhibition between 1 and 4 h after drug administration. The mean time to peak was 2·8 h, with inhibition subsequently declining gradually.

In the multiple-dose phase of the study, the mean plasma ACE inhibition profiles were similar to the first dose profiles, except that predose inhibition ranged from 55 to 71%. The maximum inhibition was close to 100% for the two higher dose groups.

Discussion

Kinetic parameter values obtained in the present study in cardiac failure patients following the first 0·5 mg oral dose of cilazapril, generally were similar to those observed in fasted, healthy young volunteers receiving identical doses (Massarella et al 1989). This was true for time of peak concentration (2·3 h for congestive heart failure patients vs 1·8 h for healthy young volunteers), peak concentration value (6·1 ng mL^{-1} vs 5·4 ng mL^{-1}), and AUC_{24} (48 $\mu g\ h\ L^{-1}$ as against 42 $\mu g\ h\ L^{-1}$). These data suggest that cardiac failure does not have a major influence on the pharmacokinetics of cilazaprilat.

The changes in parameter values for cilazaprilat seen on repeat administration of cilazapril at 0·5 mg daily for 6 weeks (61, 94 and 101% increases in peak, trough and area, respectively) were greater than those observed at steady state in young, healthy volunteers given the higher dosages of 1·25 or 5 mg daily for 8 days (< 25% change in 4 h or trough concentrations) (Nussberger et al 1987) but the disparate nature of the studies precludes drawing any meaningful conclusions. The combination of congestive heart failure and age, with their attendant decreases in cardiac output, organ

perfusion and renal function, may, however, contribute to lower clearance and hence greater carry-over from one dosage to the next, particularly as the elimination of cilazaprilat is known to be exclusively renal (Williams et al 1989).

The difficulties associated with interpretation of ACE inhibitor kinetic data by "model independent" methods have been commented on previously (Dickstein et al 1987). They relate to the non-linear binding of these drugs to plasma ACE during the terminal phase. In the context of the present study, the very low dosage (0·5 mg) of cilazapril administered initially leads to a situation where plasma concentrations could largely reflect bound drug, and AUC consequently becomes insensitive to any alterations there might be in free-drug clearance. This situation prevents good estimation of steady-state concentrations from first-dose data. Whilst, theoretically, application of suitable model-dependent techniques to interpretation of the data might appear attractive, in practice this is not feasible when there is no distinct region in which unbound drug dominates.

Four severe adverse events occurred, one of which (an asymptomatic hypotension with cilazapril 2·5 mg) was regarded as being probably related to the drug and forced withdrawal of patients from the study. Co-medication with a high dosage of frusemide may have exacerbated the fall in blood pressure. One case of hypotension classified as moderate was also regarded as probably related to the drug and forced a withdrawal from the study.

Conclusions

The pharmacokinetics of cilazaprilat in cardiac failure patients after a single dose of 0·5 mg cilazapril are similar to previous observations in healthy volunteers at identical dosage. Repeat administration, however, leads to greater drug exposure than previously observed in volunteers given the higher dosages of 1·25 or 5 mg.

Adverse effects related to the drug were not unexpected as they occurred in patients on high doses of diuretics.

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