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Pharmacokinetics of intravenous cilazaprilat in normal volunteers

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The pharmacokinetics of 1 mg, 2 mg and 4 mg of cilazaprilat administered intravenously were determined in a group of eight volunteers. The fall in plasma concentration was polyphasic. Elimination was predominantly by renal excretion of the unchanged drug. The mean renal clearance values following 1 mg, 2 mg and 4 mg doses were 5.3 ± 0.5, 8.1 ± 0.5, and $9.8 \pm 0.5\ l\ h^{-1}$ and plasma clearances were 7.8 ± 0.5, 10.4 ± 0.5 and $11.8 \pm 0.6\ l\ h^{-1}$, respectively. Thus, plasma and renal clearances were dose dependent. ACE inhibition was greater than 82% for the first 4 h and about 55% at 24 h, after all three doses. There were no significant haemodynamic effects at any dose.

Keywords cilazaprilat pharmacokinetics

Introduction

Cilazaprilat is a new angiotensin converting enzyme inhibitor which is poorly absorbed from the gastrointestinal tract (Natoff *et al.*, 1985). Cilazapril, the monoethyl ester is used for oral treatment and is rapidly absorbed and de-esterified in the liver to the active diacid metabolite cilazaprilat. Few studies have been performed on the intravenous pharmacokinetics of ACE inhibitors (Duchin *et al.*, 1982; Till *et al.*, 1982; Singhvi *et al.*, 1988). The aim of this study was to investigate the pharmacokinetic and pharmacodynamic effects of intravenous cilazaprilat in normal volunteers.

Methods

Eight normal male volunteers aged 24.7 ± 2.5 years (mean ± s.e. mean) gave informed consent. The study protocol was approved by the Ethics Committee of the Queen's University of Belfast. Single intravenous doses of cilazaprilat 1, 2 and 4 mg were given, at weekly intervals, in a dose escalating design with random placebo. Each subject presented fasting, had an intravenous cannula inserted for blood sampling and lay supine for 30 min in a temperature controlled room. The drug or placebo was given intravenously over 2 min into the opposite arm. Blood samples were taken for measurement of cilazaprilat concentrations and ACE inhibition at 0, 5, 10, 15 and 30 min and 1, 2, 4, 6, 8, 12 and 24 h after drug administration. Urine was collected from 0 to 4 h, 4 to 8 h and 8 to 24 h for measurement of cilazaprilat. Heart rate (HR) and supine blood pressure (SBP) were measured at the time intervals as above except that there was no 10 min or 12 h reading. Blood pressure was recorded standing, after 5 min erect, at 0, 30 min, 1, 4, 6, 8 and 24 h. Forearm blood flow and venous capacitance were measured by venous occlusion plethysmography at 30 min, 2, 4, 6, 24 h after drug administration. Cilazaprilat and angiotensin converting enzyme activity were measured by standard radioenzymatic methods (Francis *et al.*, 1987). ACE inhibition was assessed by assuming that the activity in the pre-drug sample was the baseline level which was

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inhibited in subsequent samples taken that day. Individual data sets were analysed by 'compartmental model-independent' pharmacokinetic methods. Cilazaprilat concentrations at peak (C_{max}) and at 24 h ($C(24)$) were observed.

The theoretical initial concentration $C(0)$ was calculated by back-extrapolation from the first two data-points in each profile. The initial volume of distribution was calculated from the dose divided by $C(0)$. Linear regressions of log concentration *vs* time yielded a first phase half-life $t_{½,1}$ from the period 0.5–4 h and a terminal phase half-life $t_{½,2}$ from 6–24 h. The area under the plasma drug concentration *vs* time curve (AUC) was calculated by the trapezoidal method and extrapolated to infinity using the terminal phase half-life. Plasma clearance was derived from dose divided by AUC to infinity and renal clearance from total urinary recovery divided by the corresponding AUC.

Results

The initial volume of distribution of cilazaprilat was between 10 and 12 l. The decline in plasma cilazaprilat concentration after dosing was polyphasic (Figure 1). At 15 min the plasma concentrations were less than 50% of the $C(0)$ values. In the period from 0.5 to 4 h, initial half-lives of around 0.8 h were found. The values of AUC(0,4) were directly proportional to dosage. By 24 h after dosing, the mean plasma drug concentration-time profiles had converged so that $C(24)$ values were similar and not directly proportional to dosage (Table 1).

The plasma clearance of cilazaprilat, calculated from total AUC values, increased significantly with increasing dosage. The total urinary recovery of cilazaprilat averaged 66, 80 and 84% after 1, 2 and 4 mg doses, and hence mean renal clearance values were 5.3 to 9.8 l h^{-1}, and were significantly dependent on dosage. The mean creatinine clearance was 5.16 ± 0.25 l h^{-1} over 24 h after each dose. The renal clearance of unbound cilazaprilat exceeded the creatinine clearance for all doses, suggesting that tubular secretion of cilazaprilat was occurring. ACE inhibition was > 82% for the first 4 h after all doses and inhibition declined gradually to values around 55% for all doses at 24 h.

No significant changes were observed in the haemodynamic measurements when compared with placebo. For example, with the 4 mg dose there were no significant differences in standing heart rate (89.5 ± 3.8 and 91.6 ± 3.7 beats min^{-1}) standing mean arterial blood pressure (84.2 ± 3.2 and 81.3 ± 3.1 mm Hg) or forearm

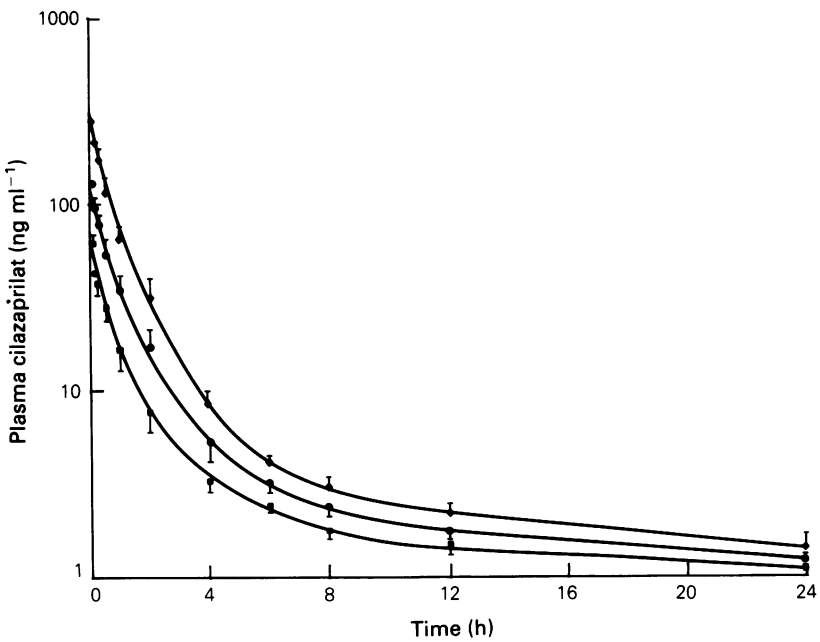

Figure 1 Plasma concentration of cilazaprilat (mean ± s.d.) after i.v. injection of (◆) 4 mg, (●) 2 mg and (■) 1 mg.

Table 1 Pharmacokinetic parameters after single intravenous doses of cilazaprilat to eight volunteers (mean ± s.e. mean)

Parameter (units)	*Dose* 1 mg	2 mg	4 mg
C_{max} (ng ml^{-1})	62.3 ± 3.0	138.7 ± 13.6	305.5 ± 18.2
$C(24)$ (ng ml^{-1})	1.04 ± 0.08	1.2 ± 0.03	1.4 ± 0.13
CL (l h^{-1})*	7.8 ± 0.5	10.4 ± 0.5	11.8 ± 0.6
CL_R (l h^{-1})*	5.3 ± 0.5	8.1 ± 0.5	9.8 ± 0.5
$t_{½,1}$ (h)	0.8 ± 0.08	0.76 ± 0.03	0.79 ± 0.02
$t_{½,2}$ (h)	21.5 ± 4.6	15.2 ± 0.9	17.7 ± 5.1
V_1 (l)	11.8 ± 0.7	10.7 ± 1.3	10.1 ± 0.8
$C(0)$ (ng ml^{-1})	80.8 ± 4.8	188.6 ± 19.6	385.6 ± 29.1
AUC(0,24) (ng ml^{-1} h)	123.2 ± 10.2	182.6 ± 8.2	323.5 ± 18.8
AUC(0,4) (ng ml^{-1} h)	56.5 ± 2.5	118.0 ± 8.8	231.1 ± 12.6

* Mean values for each dose differ significantly ($P < 0.05$) from each other by analysis of variance.

blood flow (2.6 ± 0.6 and 2.4 ± 0.4 ml 100 ml^{-1} min^{-1}) 30 min after placebo and drug administration, respectively. Plasma ACE inhibition was 100% 30 min after drug administration.

Discussion

In this study no change in blood pressure and heart rate was recorded after acute dosing with intravenous cilazaprilat. The effects of ACE inhibitors on blood pressure in previous studies of healthy volunteers have been variable (Fasanella d'Amore *et al.*, 1987; Till *et al.*, 1982) and may reflect differences in sodium balance.

The plasma concentration-time curve for cilazaprilat is similar in shape to that for enalaprilat and captopril (Ulm *et al.*, 1982; Duchin *et al.*, 1982). The initial volume of distribution of cilazaprilat was close to the volume of extracellular fluids. There was a rapid initial fall up to 15 min after dosing which indicated some form of drug distribution. The log-linear decline from 0.5 to 4 h could be explained by rapid excretion of free drug and the slower decline after 6 h by gradual excretion of the drug following release from its bound form. Plasma and renal clearances increased with increasing dosage, probably because the binding to ACE was saturated and so there was more free drug available for rapid excretion.

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