The pharmacokinetics of enalapril in patients with compensated liver cirrhosis

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The possibility of an impaired hepatic de-esterification of enalapril to enalaprilat due to hepatic dysfunction was assessed in seven patients with compensated liver cirrhosis and 10 normal control subjects. The peak serum concentration and time to the peak serum concentration of enalaprilat, as well as the suppression of serum angiotensin converting enzyme activity, following a single oral dose of enalapril maleate (10 mg) were not different in the two groups. The elimination half-life of enalaprilat was related to renal function. The results suggest that hepatic biotransformation of the drug may not be disturbed in a clinically significant manner in patients with moderate hepatic dysfunction due to compensated liver cirrhosis.

Keywords enalapril enalaprilat liver cirrhosis pharmacokinetics

Introduction

Enalapril maleate, a widely used angiotensin converting enzyme (ACE) inhibitor, is a pro-drug the pharmacological activity of which as an ACE inhibitor is dependent on hepatic de-esterification to the active diacid metabolite, enalaprilat (Johnston *et al.*, 1984; Larmour *et al.*, 1985). An earlier *in vitro* study showed that the conversion of enalapril to enalaprilat in liver homogenates from cirrhotic livers was considerably less than in normal liver homogenates (Johnston *et al.*, 1984). However, there has been little information as to whether the presence of hepatic dysfunction due to liver cirrhosis would affect the pharmacokinetics of enalapril in a clinically significant manner (Ohnishi *et al.*, 1989; Todd & Goa, 1989). We, therefore, assessed the pharmacokinetics of enalapril in these patients.

Methods

Seven Japanese male patients with biopsy-proven liver cirrhosis in a clinically compensated stage (one patient with alcoholic cirrhosis and six

with postnecrotic cirrhosis, age 52.5 (9.7) years, γ -globulin 23.6 (3.7) %, serum albumin concentration 41 (5) g l⁻¹, total bile acid 22.7 (13.2) μ mol l⁻¹, % retention of intravenously-infused indocyanine green (ICG) at 15 min 19.5 (6.3) %, all as means and (s.d.)) and 10 normal male volunteers (age 49.8 (13.5) years, γ -globulin 12.0 (1.5) %, serum albumin concentration 43 (6) g l⁻¹, total bile acid 5.2 (1.8) μ mol l⁻¹, ICG retention at 15 min 5.4 (2.5) %) were studied after informed consent had been obtained. The study protocol was reviewed and approved by the local ethics committee. Patients with heart failure or renal failure (i.e., serum creatinine level $\geq$ 130 μ mol l⁻¹) were excluded from the study. No drugs were given for at least 2 weeks before the study. Venous blood was collected at 0, 0.5, 1, 2, 4, 6, 8, 12 and 24 h and 24 h urine sampling was done after a single oral dose of 10 mg enalapril maleate. Venous blood for measurement of serum ACE activity was also obtained at 0 and 4 h after enalapril administration. Blood pressure in the supine position was also monitored before each blood sampling.

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Enalaprilat in serum and urine was measured by radioimmunoassay, and intact enalapril was determined by measuring the difference in enalaprilat concentration before and after total hydrolysis of enalapril to enalaprilat using a rat liver preparation (Hichens *et al.*, 1984; Ishizaki *et al.*, 1988). Serum ACE activity was measured by enzymatic assay (Kelly *et al.*, 1986). Differences in measurements were assessed by Wilcoxon's rank sum test and Wilcoxon's signed-rank test, where appropriate. The correlation between elimination half-life ($t_{1/2}$) of enalaprilat and glomerular filtration rate was analyzed by Spearman's method with calculation of the rank coefficient value (r_s). A P value < 0.05 was considered significant.

Figure 1 Mean ($\pm$ s.e. mean) a) serum enalapril and b) enalaprilat concentration-time plots following a single oral dose of enalapril maleate (10 mg) in seven patients with compensated liver cirrhosis ($\bullet$) and 10 normal control subjects ($\circ$).

Results

The mean serum concentration-time data for enalapril and enalaprilat after the oral dosing of enalapril maleate are shown in Figure 1. Higher peak serum concentrations (C_{max}) and greater areas under the concentration-time curve (AUC) of enalapril were observed in the patients than in the control subjects. The $t_{1/2}$ of enalapril was slightly longer in the patients (Table 1), but the difference did not reach a statistically significant level. The C_{max} and time to the peak concentration of enalaprilat and urinary recovery ratio of enalaprilat/total drug (enalapril plus enalaprilat) were not different in the two groups (Table 1). The $t_{1/2}$ of enalaprilat was slightly prolonged in the patients (Table 1), and there was a significant correlation ($r_s = -0.688$, $P < 0.01$) between the $t_{1/2}$ of enalaprilat and the glomerular filtration rate. Serum ACE activity was reduced from 16.8 (5.2) to 3.2 (2.6) i.u. l⁻¹ in the patients and from 11.1 (3.1) to 1.5 (0.6) i.u. l⁻¹ in the control subjects. The fall in serum ACE activity was similar in the patients (82.8 (7.5) %) and the controls (86.4 (3.7) %). Diastolic blood pressure decreased significantly at 4 and 6 h both in the patients (Δ mm Hg: 7.4 (6.3) at 2 h and 15.0 (6.8) at 4 h postdose) and control subjects (Δ mm Hg: 12.6 (9.4) at 2 h and 7.2 (8.8) at 4 h postdose) as compared with the respective predose levels. The systolic blood pressure and heart rate remained unaltered in both groups.

Discussion

Although we cannot exclude the possibility of a type 2 statistical error because of the small number of patients (e.g., the powers $[1-\beta]$ to detect statistical difference in the $t_{1/2}$ were 0.80 for enalaprilat and 0.1 for enalapril), the results suggest that the hepatic biotransformation of enalapril to enalaprilat may not be impaired to a clinically significant extent in patients with compensated liver cirrhosis. This suggestion is supported by the observation of significant and similar suppression of serum ACE activity in both groups.

Earlier and higher C_{max} values of enalapril observed in the patients may reflect porto-caval shunting and a lowered first-pass metabolism. The difference in the $t_{1/2}$ of enalaprilat between the two groups can be explained by a decreased renal elimination of enalaprilat as a result of diminished kidney function in the patients (GFR: 72.0 (6.3) ml min⁻¹ in the patients and 114.0 (19.9) ml min⁻¹ in the control subjects).

Table 1 Pharmacokinetic parameters for enalapril and enalaprilat after an oral dose of enalapril (10 mg) in seven patients with liver cirrhosis and 10 normal subjects

<i>Kinetic parameters</i>	<i>Enalapril</i>		<i>Enalaprilat</i>	
	<i>Controls</i>	<i>Patients</i>	<i>Controls</i>	<i>Patients</i>
Observed peak serum concentration (ng ml ⁻¹)	65.8 [17.7] (39.2–93.9)	110.1 [44.4] ^a (55.7–159.2)	43.6 [20.8] (16.1–89.5)	36.8 [13.4] (13.6–51.3)
Time to peak serum concentration (h)	1.0 [0.3] (0.5–2.0)	0.7 [0.5] (0.5–2.0)	3.9 [0.9] (2.0–6.0)	3.8 [1.0] (2.0–4.0)
Apparent elimination <i>t</i> _{1/2} (h)	0.78 [0.41] (0.44–1.65)	0.84 [0.45] (0.61–1.25)	4.87 [0.66] (3.53–5.67)	6.52 [1.86] ^a (5.31–9.97)
AUC (ng ml ⁻¹ h)	112.2 [33.2] (76.7–177.7)	176.1 [70.2] ^a (98.0–276.1)	369.7 [101.5] (191.1–537.0)	381.2 [162.9] (220.3–657.1)
Renal clearance (ml min ⁻¹)	263.4 [83.8] (146.0–447.9)	230.0 [80.1] (108.5–242.6)	127.9 [30.3] (108.5–196.1)	105.6 [30.1] (76.3–151.6)
Urinary recovery ratio/total drug	—	—	0.62 [0.06] (0.53–0.70)	0.52 [0.15] (0.33–0.70)

Data are given as the mean [s.d.] and (range). AUC = area under the serum concentration-time curve from zero to infinity; Total drug = enalapril plus enalaprilat. ^a *P* < 0.05 from controls.

Enalaprilat is known to be eliminated primarily by renal excretion (Ulm *et al.*, 1982), and renal impairment is associated with decreased excretion of the drug (Fruncillo *et al.*, 1987; Kelly *et al.*, 1986).

Recently, Ohnishi *et al.* (1989) reported decreased $C_{\max}$ and AUC values for enalaprilat in

patients with liver cirrhosis. The reason for the discordant observations between Ohnishi's study and ours might lie in different grades of hepatic impairment in the studied patients.

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