The pharmacokinetics of perindopril in patients with liver cirrhosis

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Perindopril is a non-sulphydryl angiotensin converting enzyme (ACE) inhibitor which requires hydrolysis to its active metabolite, perindoprilat, to produce its effects. Ten cirrhotic patients with mild to severe disease were studied after oral administration of a single 8 mg dose of perindopril as its *tert*-butylamine salt. Compared with a historical control group of young healthy volunteers receiving the same single oral dose of perindopril, mean AUC values of the prodrug perindopril were double in patients with liver cirrhosis (602 ± 294 s.d. ng ml⁻¹ h vs 266 ± 70 s.d. ng ml⁻¹ h) whereas the mean AUC of perindoprilat was found to be similar (134 ± 139 ng ml⁻¹ h vs 120 ± 29 ng ml⁻¹ h). The partial metabolic clearance of perindopril to perindoprilat was much lower in the cirrhotics (26 ± 12 ml min⁻¹ vs 58 ± 22 ml min⁻¹). The maximum inhibition of plasma ACE activity measured in the cirrhotic patients ($87.5 \pm 5.1\%$) was comparable with that previously reported with perindopril in patients with mild hepatic impairment as well as in patients with essential hypertension. We suggest that liver cirrhosis may be associated with impaired deesterification of perindopril to its active metabolite perindoprilat but that no dosage adjustment of perindopril is required in cirrhotic patients.

Keywords perindopril angiotensin converting enzyme inhibition liver cirrhosis

Introduction

Perindopril is a non-sulphydryl prodrug angiotensin converting enzyme (ACE) inhibitor requiring conversion to its active metabolite, perindoprilat, by hydrolysis in the liver. Perindopril also undergoes glucuronidation and further hydrolysis to yield perindoprilat glucuronide (PGL), a compound which does not inhibit ACE activity. However, perindoprilat does not appear to be directly conjugated to form perindoprilat glucuronide (Grislain *et al.*, 1990).

The pharmacokinetics and pharmacodynamics of perindopril, have previously been studied in young and elderly healthy subjects (Bussien *et al.*, 1986; Lecocq *et al.*, 1990; Lees *et al.*, 1988; Lees & Reid, 1987a, b; Richer *et al.*, 1987) as well as in patients with essential hypertension (Lees & Reid, 1987c). A recent study suggested that severe hepatic insufficiency was associated with a decrease in the deesterification of enalapril, another prodrug ACE inhibitor, to its active metabolite enalaprilat (Ohnishi *et al.*, 1989). However, moderate hepatic impairment may have little effect on the disposition kinetics of enalapril (Baba *et al.*, 1990) and perindopril (Tsai *et al.*, 1989). We, therefore, examined the disposition kinetics of perindopril and its metabolites in patients with liver cirrhosis.

Methods

Subjects

Ten patients (seven males and three females, 40 to 70 years of age) with liver cirrhosis were studied after informed consent was obtained. The study design was approved by the Ethics Committee at Saint-Antoine University Hospital. These patients had mild to severe liver cirrhosis (Pugh score: 5 to 11). All but two had a biopsy-proven liver cirrhosis. There were nine patients with alcoholic cirrhosis and one patient with post-hepatic cirrhosis. One patient had hepatic encephalopathy and moderate ascites was present in four patients. All were normotensive and had normal renal function, except patient 1 who had mild renal insufficiency with a plasma creatinine concentration of $148 \mu\text{mol l}^{-1}$. Five patients were receiving other drugs (spironolactone and meprobamate; phloroglucinol and chlorazepate; paracetamol, dextropropoxyphene and ferrous fumarate; spironolactone; triazolam, lorazepam and folic acid).

Study design

Patients were studied after an overnight fast. A single oral dose of 8 mg perindopril as its *tert*-butylamine salt

(two tablets of 4 mg) was administered at 09.00 h with 100 ml tap water after a catheter was inserted into an antecubital vein for blood sampling. Heparinized plasma samples and urine were collected up to 96 h after drug intake. Aliquots were frozen at -20°C until analyzed.

Laboratory methods

Perindopril, perindoprilat and PGL were assayed in plasma and urine as described previously (Doucet *et al.*, 1990). Plasma ACE activity was determined using [^{14}C]-hippuryl-histidyl-leucine as a substrate for ACE (Ryan *et al.*, 1977).

Data analysis

Pharmacokinetic analysis The areas under the plasma concentration vs time curves (AUC) of perindopril, perindoprilat and PGL were calculated using the log-linear method up to the last plasma concentration (Chiou, 1978). No extrapolation was made to infinity because drug concentrations were undetectable or close to assay sensitivity at 96 h. Partial metabolic clearance (CL_m) of perindopril to perindoprilat or PGL was calculated from $\text{CL}_o \times (Ae/\text{dose})$, where CL_o is the oral clearance of perindopril calculated from $\text{dose}/\text{AUC}(0,96\text{ h})$, Ae is the urinary recovery of the metabolite over 96 h and dose is the dose of oral perindopril (6.667 mg perindopril in 8 mg perindopril tert-butylamine salt) expressed in molar units (Breimer, 1983). Fractional cumulative urinary recovery of perindopril, perindoprilat and PGL were calculated separately as $(Ae/\text{dose}) \times 100$,

where Ae is the total amount of each compound excreted in urine over 96 h and dose is the amount of perindopril base administered. Both terms of this ratio were expressed in molar units. Total urinary recovery of perindopril and its metabolites was calculated as $[(Ae_{\text{perindopril}} + Ae_{\text{perindoprilat}} + Ae_{\text{PGL}})/\text{dose}] \times 100$. Finally, renal clearances (CL_R) of perindopril, perindoprilat and PGL were calculated from $Ae/\text{AUC}(0,96\text{ h})$.

Analysis of ACE inhibition For each plasma sample, the percentage of ACE inhibition relative to activity before drug administration was calculated as $[1 - (\text{ACE}_{\text{drug}}/\text{ACE}_{\text{baseline}})] \times 100$, where ACE_{drug} is the ACE activity measured in each sample and $\text{ACE}_{\text{baseline}}$ is the activity measured in samples before drug administration. The maximum inhibition of the plasma ACE activity and the time of its occurrence were noted directly from the data.

Results

Results are expressed as mean $\pm$ s.d. The pharmacokinetic parameters of perindopril, perindoprilat and PGL are summarized in Table 1. In five of the ten cirrhotic patients, urine collection was incomplete. Thus, reliable urinary data were available only in five patients (Table 1). The maximum inhibition of plasma ACE activity was $88 \pm 5\%$ and was achieved after 5 h. Twenty-four hours after perindopril administration, the mean inhibition of plasma ACE activity was $59 \pm 9\%$.

Table 1 a) Pharmacokinetic data of perindopril, perindoprilat and PGL

Patient	AUC (ng ml $^{-1}$ h)			Perindoprilat CL_m (ml min $^{-1}$)	PGL CL_m (ml min $^{-1}$)
	Perindopril	Perindoprilat	PGL		
1	1199	496	813	—	—
2	354	74	224	36	38
3	582	46	101	—	—
4	193	39	259	37	132
5	655	30	174	8	13
6	385	125	170	28	21
7	543	81	218	—	—
8	440	120	85	21	33
9	867	110	105	—	—
10	807	221	132	—	—
Mean $\pm$ s.d.	602 $\pm$ 294	134 $\pm$ 139	228 $\pm$ 213	26 $\pm$ 12	48 $\pm$ 48

b) Urinary data

Patient	Urinary recovery (%)			Total urinary recovery (%)	Renal clearance (ml min $^{-1}$)		
	Perindopril	Perindoprilat	PGL		Perindopril	Perindoprilat	PGL
1	—	—	—	—	—	—	—
2	15	11	12	38	46	158	85
3	—	—	—	—	—	—	—
4	13	6	23	42	75	169	139
5	15	5	8	29	26	169	69
6	8	10	7	25	23	79	67
7	—	—	—	—	—	—	—
8	49	8	13	71	123	72	243
9	—	—	—	—	—	—	—
10	—	—	—	—	—	—	—
Mean $\pm$ s.d.	20 $\pm$ 16.5	8 $\pm$ 2.5	13 $\pm$ 6	41 $\pm$ 18	59 $\pm$ 42	130 $\pm$ 50	121 $\pm$ 75

Discussion

In a previous study using the same dose of oral perindopril, study design and drug assay in young healthy volunteers (Devissaguet *et al.*, 1990), the mean AUC of perindoprilat was found to be similar to that observed in our cirrhotic patients ($120 \pm 29 \text{ ng ml}^{-1} \text{ h}$ vs $134 \pm 139 \text{ ng ml}^{-1} \text{ h}$). This suggests that the bioavailability of perindoprilat was not altered in the cirrhotic patients. However, AUC values of the prodrug perindopril were twice as high in patients with liver cirrhosis ($602 \pm 294 \text{ ng ml}^{-1} \text{ h}$ vs $266 \pm 70 \text{ ng ml}^{-1} \text{ h}$). This difference could be explained either by intra- and extra-hepatic shunting resulting in a decrease of first-pass metabolism and/or by a decrease in the activity of hepatic esterases. The partial metabolic clearance of perindopril to perindoprilat appears to be greatly impaired in the five cirrhotic patients with available urinary data relative to that in normal subjects ($26 \pm 12 \text{ ml min}^{-1}$ vs $58 \pm 22 \text{ ml min}^{-1}$). This suggests that liver cirrhosis may be associated with impaired deesterification of perindopril to perindoprilat. In contrast, ageing has been associated with an increased conversion of perindopril into perindoprilat as well as a decreased renal clearance of perindoprilat, both contributing to an increased bioavailability of perindoprilat after oral perindopril (Lees *et al.*, 1988). Our cirrhotic patients were older than the healthy volunteers studied by Devissaguet *et al.* (1990) (six males and six females, 23 to 36 years of age) but the renal

clearance of perindoprilat was similar in both groups ($129 \pm 49 \text{ ml min}^{-1}$ vs $115 \pm 31 \text{ ml min}^{-1}$). The decrease in partial metabolic clearance of perindopril to perindoprilat in our older group of patients with liver cirrhosis compared with the healthy volunteers studied by Devissaguet *et al.* (1990) may, therefore, have been minimized in the present study. On the other hand, an additional influence of portocaval shunting or the effects of concomitant therapy taken by half of the patients cannot be excluded.

Finally, in contrast with our results, a previous study has shown that mild liver cirrhosis had no influence on perindopril disposition (Tsai *et al.*, 1989). The reason for this discrepancy is unclear. A more severe hepatic dysfunction could explain the decrease in the deesterification of perindopril to perindoprilat observed in some of our patients. However, the finding that the maximum inhibition of plasma ACE activity in our group of cirrhotics (87%) was similar to that reported with perindopril in cirrhotic patients with mild hepatic impairment (89%, Tsai *et al.*, 1989) as well as in patients with essential hypertension (80%, Lees & Reid, 1987c) suggests that, overall, no dosage adjustment of perindopril is required in patients with liver cirrhosis.

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