The pharmacokinetics of perindopril and its effects on serum angiotensin converting enzyme activity in hypertensive patients with chronic renal failure

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- 1 Perindopril, an orally active angiotensin converting enzyme inhibitor, was given to 23 hypertensive patients with stable chronic renal failure for 15 days. The dose of perindopril was 2 or 4 mg once a day according to the degree of renal failure. The creatinine clearance of the patients ranged from 6 to 67 ml min⁻¹ 1.73 m⁻². The pharmacokinetics of perindopril and perindoprilat, its active metabolite, were studied after acute and chronic administration of perindopril.
- 2 The drug was well tolerated and creatinine clearance was unaltered by treatment.
- 3 In both groups, steady-state was reached within 3 days of chronic treatment.
- 4 After both acute and chronic drug administration renal impairment had no effect on perindopril pharmacokinetics but the pharmacokinetics of perindoprilat were altered significantly. After chronic administration the serum accumulation ratio was 1.81 in patients with mild renal failure and 5.35 in patients with severe renal failure. Chronic administration did not modify the renal clearance of perindoprilat nor its elimination half-life.
- 5 A significant correlation between the renal clearance of perindoprilat and creatinine clearance was observed ($r = 0.87$ first dose, $r = 0.83$ last chronic dose).
- 6 A non-linear relationship between serum perindoprilat concentration and inhibition of angiotensin converting enzyme was described by a modified Hill equation. Values of IC₅₀ were $1.11 \pm 0.07 \mu\text{g l}^{-1}$ (mean $\pm$ s.d.) in patients with severe renal failure and $1.81 \pm 0.20 \mu\text{g l}^{-1}$ in patients with moderate renal failure. Chronic administration increased maximal inhibition and decreased the time to maximal inhibition only in patients with severe renal failure.
- 7 An initial dosage adjustment of perindopril is recommended according to the degree of renal failure.

Keywords perindopril angiotensin-converting enzyme inhibitors
pharmacokinetics kidney failure

Introduction

Perindopril is an orally active angiotensin converting enzyme (ACE) inhibitor developed as an antihypertensive agent for once daily administration (Herpin *et al.*, 1989; Zanchetti & Desché, 1989). It is a mono-ethylester prodrug which requires de-esterification *in vivo* to the active metabolite, perindoprilat (MacFadyen *et al.*, 1990).

Previous studies in healthy volunteers and hypertensive patients have described the pharmacokinetics of

both perindopril and perindoprilat (Devissaguet *et al.*, 1990; Drummer *et al.*, 1987; Lees & Reid, 1987a; MacFadyen *et al.*, 1990). Perindopril, like other ester prodrugs, is mainly cleared by metabolism, whereas perindoprilat is mainly excreted by the kidneys. Since the major route of elimination of perindoprilat is urinary excretion it is anticipated that impaired renal function, often associated with hypertension and fluid overload, would affect the kinetics of perindoprilat.

This study was designed to investigate the disposition kinetics of perindopril and perindoprilat in hypertensive patients with chronic and stable renal failure after both acute and chronic administration of perindopril. The time course of serum ACE inhibition was assessed simultaneously.

Part of the work included in the paper was presented to the British Pharmacological Society in January 1990 (Slovic *et al.*, 1990).

Methods

Subjects

This multicentre study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committees of the participating institutes. Informed consent was obtained from all subjects before the study.

Twenty-three hypertensive patients with chronic and stable renal failure completed the study. They were divided into two groups depending on their degree of renal failure as indicated by creatinine clearance (CL_{Cr}). Endogenous creatinine clearance was calculated from serum creatinine and 24 h urinary creatinine excretion and corrected for standard body surface area (1.73 m^{-2}). Patients with severe renal failure (group A, CL_{Cr} ranging from 6 to $30 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$) received 2 mg perindopril once a day and patients with moderate renal failure (group B, CL_{Cr} ranging from 31 to $67 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$) received 4 mg once a day. Nine male and three female patients aged between 26 and 70 years (mean 51.5 ± 14.6 years) were included in group A, and eight male and three female patients aged between 47 and 75 years (mean 62.1 ± 8.0 years) were included in group B.

ACE inhibitors and diuretics were withdrawn 2 weeks before the start of the study. All other antihypertensive drugs (calcium antagonists, β -adrenoceptor antagonists, α -adrenoceptor antagonists) were continued throughout the study, as necessary. In group A, all patients were hypertensive as defined by a diastolic blood pressure of $\geq 95 \text{ mm Hg}$ except two who were well controlled by their associated antihypertensive therapy (nifedipine 20 mg twice daily and nifedipine 40 mg twice daily associated with labetalol 200 mg twice daily and prazosin 1 mg twice daily).

In group B, 6 of the 11 were hypertensive, the others were well controlled by atenolol (50 mg once daily associated with nifedipine 10 mg four times daily or 20 mg twice daily, atenolol 100 mg once daily). Patients with unstable or malignant hypertension or secondary hypertension except if it is due to nephropathy, patients with bilateral renal artery stenosis or arterial stenosis of a single kidney, patients with a medical history of heart failure and hepatic disease were excluded as were patients who had received a drug in the course of development in the previous month. Patients were not allowed to drink alcohol and xanthine beverages or to smoke more than 10 cigarettes per day during the periods of blood sampling.

Study design

Perindopril (2 mg or 4 mg tablets of Coversyl[®], Lab. Servier, France) was given in the morning with 100 ml tap water after an overnight fast. During the periods of blood sampling, light standard meals were given at least 2 h after administration of the drug.

Patients were selected for entry following a pre-study evaluation. Blood sampling for pharmacokinetic studies was performed following an acute administration of perindopril and after 15 days of chronic administration.

During each pharmacokinetic session, samples of venous blood (6 ml) were collected in dry tubes for the measurement of serum perindopril and perindoprilat concentrations and ACE inhibition before and at 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120 and 168 h after perindopril administration. In addition, during the chronic administration period, four blood samples were drawn for the measurement of trough drug concentrations (C_{min}) before administration of perindopril.

During the study sessions urine was collected in 4 h fractions for the first 12 h after drug administration, then from the 12th to the 24th and then in 24 h fractions from 24 h to 168 h after administration.

Blood pressure and heart rate were monitored regularly for tolerance and any side-effects were noted.

Analytical methods

Serum and urine samples were frozen at -20°C until assay. Perindopril and perindoprilat concentrations in both serum and urine were measured by specific radioimmunoassay. Because of the cross-reactivity of a glucuronide metabolite with the active metabolite, a chromatographic step (anion-exchange chromatography) was carried out prior to the r.i.a. in order to separate perindopril, perindoprilat and the immunoreactive metabolite. After chromatography perindoprilat was measured directly, whereas perindopril was determined after quantitative alkaline hydrolysis to perindoprilat (Doucet *et al.*, 1990). The limit of determinations of the method in plasma and urine samples was 0.5 ng ml^{-1} . The intra-assay coefficient of variation was $\leq 10.8\%$ and the inter-assay coefficient of variation was $\leq 10.4\%$, both on the exploitable part of the calibration curve ($B/T > 10\%$).

Serum ACE activity was measured by a method derived from that described by Cushman & Cheung (1983) using [^{14}C]-hippuryl-L-histidyl-L-leucine (HHL) as the substrate.

Pharmacokinetic analysis

Peak serum concentration (C_{max}), time to reach the peak (t_{max}), trough serum concentration (C_{min}) and the cumulative amount excreted in urine (A_e), were obtained directly from the individual data. The curve fitting was performed for each subject with the ELSMOS software using the log-linear regression method (Francis, 1984).

The following parameters were calculated according to classical equations:

$AUC(0,t)$ = area under the serum drug concentration-time curve from 0 to the last measurable concentration,

calculated using the linear trapezoidal rule,

$t_{(1/2,i)}$ = half-life estimated by $0.693/\lambda_i$ where λ_i is the slope of the regression line of the i^{th} phase of the $\ln$ drug concentration-time curve ($t_{1/2,ur}$: calculated from urinary data),

R_{ac} = the accumulation ratio was estimated from:

$$R_{ac} = \frac{\text{AUC}(0,24) \text{ last chronic dose}}{\text{AUC}(0,24) \text{ initial dose}}$$

CL_R = the renal clearance of perindopril and perindoprilat calculated from the slope of the regression line of the following function:

$Ae(0,t) = CL_R \cdot \text{AUC}(0,t) + \text{intercept}$ (where $Ae(t)$ is the cumulative amount of perindopril or perindoprilat excreted in urine at time t and $\text{AUC}(0,t)$ the area under the serum concentration time curve between 0 and t).

ACE activity analysis

Assuming that the serum ACE activity measured at time 0 (just before the first dose) represented 0% inhibition, the percentage inhibition of ACE was calculated at each time from:

% inhibition

$$= \frac{\text{ACE activity at time 0} - \text{ACE activity at time } t}{\text{ACE activity at time 0}} \times 100$$

The maximum percentage of inhibition ($I_{\max}$), the time taken to reach this maximum ($t_{I\max}$) and residual inhibition 24 h after administration (I_{24}) were recorded for each subject.

To evaluate the relationship between serum perindoprilat concentration and ACE inhibition, sets of pooled values of patients receiving 2 mg or 4 mg perindopril after the last chronic administration were fitted by the following Hill function using non-linear least squares regression:

$$I = \frac{I_{\max} \times C^s}{(C_{50}^s + C^s)}$$

where $I_{\max}$ is the maximum percentage inhibition, C is the serum diacid concentration, C_{50} is that value which yields 50% inhibition and s is the sigmoidicity parameter of the inhibitory effect-drug concentration curve.

Statistical analysis

Between groups and between period comparisons of pharmacokinetic parameters and ACE-inhibition data were performed by analysis of variance followed by *post-hoc t*-test when there was a significant global effect.

$t_{\max}$ and $t_{I\max}$ were compared using a Wilcoxon *t*-test for inter-period comparisons and a Mann-Whitney *t*-test for inter-group comparisons.

Results

Perindopril pharmacokinetics

The mean pharmacokinetic parameters obtained in the two groups after the initial dose and the last chronic dose of perindopril are summarised in Table 1.

Peak serum concentrations of perindopril were reached within 1 h in both groups and were 55 ± 19 and $111 \pm 29 \mu\text{g l}^{-1}$ in group A (2 mg) and group B (4 mg), respectively.

$t_{\max}$ and $C_{\max}$ values observed after the first dose were not statistically different from those observed after the last chronic dose. During the chronic dose period, $C_{\min}$ was constant at about $1 \mu\text{g l}^{-1}$ in both groups by the third treatment day, and the accumulation ratios were 1.05 and 1.19 for group A and group B, respectively.

Perindopril was rapidly excreted in the urine; the excretion was essentially complete within 24 h in both groups and the amounts excreted were not different in the two periods. Moreover, the daily excretion observed during the chronic dose study remained similar even though the percentage of dose excreted was higher in group B (4 mg) than in group A (2 mg).

The elimination half-lives of perindopril estimated from serum and urine data were similar and were not altered after chronic administration. Given the observed half-life and the dosing schedule, no significant accumulation occurred, as demonstrated by the accumulation ratio and $C_{\min}$ values in both groups.

Perindoprilat pharmacokinetics

The mean serum perindoprilat concentration-time curves in the two groups after the initial dose and the last chronic

Table 1 Pharmacokinetic parameters (mean $\pm$ s.d., * median (range)) describing the fate of perindopril in groups A (2 mg) and B (4 mg) after an acute dose and the last chronic dose of perindopril

	Group A		Group B	
	First dose	Last dose	First dose	Last dose
$C_{\max}$ ($\mu\text{g l}^{-1}$)	55 ± 19	53 ± 11	111 ± 29	108 ± 32
$t_{\max}$ (h)*	1 (1–1)	1 (1–2)	1 (1–1)	1 (1–1)
$t_{1/2,1}$ (h)	1.4 ± 0.5	1.3 ± 0.4	1.3 ± 0.4	1.4 ± 0.3
$\text{AUC}(0,24)$ ($\mu\text{g l}^{-1} \text{ h}$)	153 ± 88	158 ± 49	274 ± 88	296 ± 91
$\text{AUC}(0,t)$ ($\mu\text{g l}^{-1} \text{ h}$)	223 ± 5.7	265 ± 67	363 ± 94	451 ± 115
R_{ac} *	—	1.05 (0.71–1.86)	—	1.19 (0.82–1.39)
$C_{\min}$ ($\mu\text{g l}^{-1}$)	—	0.93 ± 0.28	—	1.31 ± 0.88
Ae (% dose)	4.4 ± 3.1	3.6 ± 3.0	10.3 ± 4.7	13.2 ± 5.3
$t_{1/2,ur,1}$ (h)	1.9 ± 0.6	2.1 ± 0.6	1.9 ± 0.3	2.1 ± 0.6

dose are shown in Figure 1 and mean pharmacokinetic parameters are listed in Table 2.

Peak serum perindoprilat concentrations were reached within 12 h in group A (2 mg) and 6 h in group B (4 mg) after the first dose. After the last chronic dose $t_{\max}$ was similar in both groups; median values were 4 h or 6h.

In group A $t_{\max}$ was significantly shorter ($P < 0.01$) and $C_{\max}$ and AUC significantly greater ($P < 0.001$) after chronic administration. In group B, $t_{\max}$ was also significantly shorter ($P = 0.0156$) with a significant increase in $C_{\max}$ ($P < 0.001$) and AUC(0,24) ($P < 0.001$).

Serum perindoprilat concentration-time curves were similar in both groups, showing a biphasic decay. The initial half-life was about 12 h in group A and 8 h in group B after acute administration and was not modified by chronic administration. The terminal elimination half-life was difficult to calculate because of the low concentrations near the assay limit. A median value of about 98 h was derived for group A and 85 h for group B after the first dose. These values were not significantly modified after the last chronic dose.

During the chronic dose period, $C_{\min}$ stabilized at about $9 \mu\text{g l}^{-1}$ in group A and about $6 \mu\text{g l}^{-1}$ in group B. This steady state was reached within the third day of treatment in both groups. The accumulation ratio was 5.35 and 1.81 for groups A and B, respectively.

Urinary excretion of perindoprilat was slower than that of perindopril, excretion being complete between 96 and 120 h after administration. The amount excreted, expressed as a percentage of administered dose, was dependent on renal function. Thus, in group A only 7.6% of the dose was excreted vs 16.5% for group B. In contrast, after chronic administration, excretion of the diacid was significantly increased in both groups ($P < 0.001$, Figure 2). Renal clearance was not influenced by chronic administration.

There was a highly significant correlation between the renal clearance of perindoprilat and creatinine clearance ($r = 0.87$ first dose, $r = 0.83$ last chronic dose) (Figure 3).

ACE activity

Figure 4 shows the time course of changes in percentage inhibition of serum ACE following acute and chronic administration of perindopril.

After acute administration, ACE activity was inhibited rapidly (50% inhibition at 1 h post-dose), a mean peak inhibition of $81\% \pm 9.6$ was reached at 12 h in group A and a mean peak of $89\% \pm 7.8$ was reached at 6 h in group B. Twenty-four hours after the initial dose mean inhibition was $76\% \pm 11$ relative to baseline in both

Figure 1 Serum concentrations of perindoprilat after acute and chronic dosing of perindopril in group A (2 mg) and group B (4 mg).

Table 2 Pharmacokinetic parameters (mean $\pm$ s.d., * median (range)) describing the fate of perindoprilat in groups A (2 mg) and B (4 mg) after an acute dose and the last chronic dose of perindopril

	Group A		Group B	
	First dose	Last dose	First dose	Last dose
$C_{\max}$ ($\mu\text{g l}^{-1}$)	3.6 ± 2.0	18.3 ± 5.1	10.1 ± 5.3	21.1 ± 12.6
$t_{\max}$ (h)*	12 (8–24)	6 (3–12)	6 (4–8)	4 (2–8)
$t_{1/2,1}$ (h)	12.1 ± 5.4	10.4 ± 3.1	7.7 ± 2.5	7.1 ± 1.2
$t_{1/2,2}$ (h)*	98.3 (51.5–149)	79.9 (47.4–130)	85.2 (45.8–249)	85.8 (41.4–158)
AUC(0,24) ($\mu\text{g l}^{-1} \text{h}$)	58 ± 31	333 ± 114	149 ± 77	286 ± 142
AUC(0,t) ($\mu\text{g l}^{-1} \text{h}$)	181 ± 58	637 ± 340	268 ± 107	483 ± 201
$R_{ac} 24^*$	—	5.35 (2.98–13.59)	—	1.81 (1.44–3.04)
A_e (% dose)	7.6 ± 4.2	28.5 ± 10.5	16.5 ± 6.7	28.4 ± 8.3
$t_{1/2,ur,1}$ (h)	9.9 ± 4.0	9.0 ± 2.8	5.2 ± 1.4	6.0 ± 1.3
CL_R (ml min^{-1})	11.9 ± 7.2	13.5 ± 7.4	31.7 ± 9.3	35.8 ± 10.4

Figure 2 Cumulative urinary excretion of perindopril following acute (a) and chronic (b) administration of perindopril in group A (□) and in group B (●).

Figure 3 Relationship between cumulative renal clearance of perindopril and creatinine clearance (CL_{Cr}) in hypertensive patients with altered renal function.

groups, and at 96 h ACE inhibition was slightly higher in group A (47% vs 40%).

During the chronic administration period, the trough percentage inhibition stabilized within 3 days of treatment in both groups. After the final repeated dose, peak inhibition of ACE was reached at 5 h ($92\% \pm 5.4$) and 3 h ($90\% \pm 5.3$) in group A and B, respectively. Inhibition 24 h after the last chronic dose was $86\% \pm 9.0$ and $69\% \pm 15$ in groups A and B, respectively.

In group A I_{max} was significantly higher ($P < 0.001$) and t_{Imax} significantly shorter ($P < 0.0010$) after chronic administration. In group B I_{max} was not significantly different ($P = 0.401$) but t_{Imax} was significantly shorter after the last chronic administration ($P < 0.010$).

There was a non-linear relationship between serum perindoprilat concentration and inhibition of ACE, which could be described by a modified Hill equation (Figure 5). Using the relation calculated with pooled data obtained after the last chronic administration the IC_{50} value was $1.11 \pm 0.07 \mu g l^{-1}$ in group A ($s = 1.34 \pm 0.15$) and $1.81 \pm 0.20 \mu g l^{-1}$ in group B ($s = 1.08 \pm 0.11$).

Tolerability

Only minor side effects were reported and renal function did not change during the study. In group A mean creatinine clearance was $16.6 \pm 6.4 ml min^{-1} 1.73 m^{-2}$ at inclusion and $17.4 \pm 9.8 ml min^{-1} 1.73 m^{-2}$ after chronic treatment with perindopril; in group B mean creatinine clearance was $47.9 \pm 13.0 ml min^{-1} 1.73 m^{-2}$ at inclusion and $52.6 \pm 20.8 ml min^{-1} 1.73 m^{-2}$ after chronic treatment.

Figure 4 Time-course of serum ACE inhibition (expressed as percentage) after acute and chronic dosing of perindopril in group A (2 mg, □) and group B (4 mg, ●).

Figure 5 Relationship between serum concentration of perindoprilat and percentage inhibition of ACE following the last chronic administration of perindopril in group A (2 mg, $\square$) and group B (4 mg, $\bullet$).

Discussion

The main aim of this study was to examine the influence of renal insufficiency on the disposition of perindopril and its active metabolite and on serum ACE inhibition after both acute and chronic administrations of perindopril.

A previous single oral dose study of perindopril in patients with renal insufficiency showed a marked influence of renal failure on the pharmacokinetics of perindoprilat (Verpooten *et al.*, 1991). This was manifest in serum drug concentrations (increased), urinary excretion (slowed) and ACE inhibition (increased). In this preliminary study the creatinine clearance of the patients varied widely ($94\text{--}1.4\text{ ml min}^{-1}$). Consequently in the present study, the dosage of perindopril was adjusted to the degree of renal failure. Group A patients with severe renal failure received 2 mg perindopril once a day and group B patients with moderate renal failure received 4 mg once a day.

With respect to historical data obtained from healthy volunteers (Devissaguet *et al.*, 1990) and hypertensive patients with normal renal function (Drummer *et al.*, 1987), renal failure was found to have no effects on the disposition of the parent drug after acute and chronic dosing. In this study, given the dosing interval and the calculated half-life of perindopril, accumulation was neither expected nor observed. Steady state was reached rapidly irrespective of renal function.

In contrast, renal function was found to have a marked influence on the kinetics of perindoprilat. With respect to historical data an increase in values of $C_{\max}$ and AUC were observed. The initial half-life was prolonged with no change in the terminal half-life.

Both groups of patients reached steady state within the first three days of chronic administration and no change in terminal half-life was observed after chronic

administration. These results show that the terminal phase which is attributed to the binding circulation ACE did not cause any delay in reaching a steady state for the active metabolite.

After chronic administration in patients with moderate renal failure (group B) an accumulation ratio of 1.81 was observed. This value is similar to that found in hypertensive patients (Drummer *et al.*, 1987) even though circulating concentrations of the active metabolite were markedly increased and its half-life was prolonged. In group A (patients with severe renal failure) the accumulation ratio increased to 5.35 even though steady state was reached within 3 days. As noted previously (Verpooten *et al.*, 1991), there was a significant correlation between the renal clearance of perindoprilat and creatinine clearance.

In both groups of patients a steady state of ACE-inhibition was achieved within 3 days with a maximal inhibition of about 90% after chronic dosing. The inhibition 24 h after both acute and chronic doses was increased in both groups comparing with a 50% value measured in hypertensive patients (Lees & Reid, 1987b).

Many other ACE inhibitors, either directly acting compounds such as captopril (Giudicelli *et al.*, 1984) and lisinopril (Jackson *et al.*, 1988) or active metabolites of prodrugs such as enalaprilat (Kelly *et al.*, 1986; Lowenthal *et al.*, 1985), ramiprilat (Aurell *et al.*, 1987; Debusmann *et al.*, 1987), cilazaprilat (Shionoiri *et al.*, 1988), alaceprilat (Onoyama *et al.*, 1986) and pentoprilat (Rakhit *et al.*, 1988), as well as the active metabolites of delapril (Onoyama *et al.*, 1988) are mainly cleared by the kidney. Thus, impaired renal function results in higher circulating concentrations of the active drugs, and increased extent and duration of ACE inhibition. Benazeprilat, the active metabolite of benazepril is only partially eliminated by the kidney. However, the finding that renal failure prolongs the duration of plasma ACE inhibition in patients with renal insufficiency suggests that dose adjustment is necessary in patients with severe renal failure (Kaiser *et al.*, 1989; Salvetti, 1990). Spiraprilat, the active metabolite of spirapril, is mainly eliminated by the liver and dose adjustment should not be required in patients with renal failure (Salvetti, 1990).

These drugs are now widely prescribed in patients with hypertension of renal origin or hypertension in the presence of renal impairment and in patients with heart failure often associated with renal insufficiency.

In the case of perindopril, in spite of increased AUC and $C_{\max}$ values of the active metabolite and a slower elimination associated with increased ACE inhibition, the drug was well tolerated on chronic administration. However, a lower dose should be considered in patients with renal failure. A dose of 2 mg perindopril once a day is recommended at the start of treatment for patients with moderate renal failure and 2 mg every second day for patients with severe renal failure.

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