Single dose pharmacokinetics of perindopril and its metabolites in hypertensive patients with various degrees of renal insufficiency

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- 1 Perindopril is a prodrug which is hydrolysed *in vivo* to the active metabolite perindoprilat, an angiotensin-converting enzyme inhibitor. Perindoprilat glucuronide is also found in plasma.
- 2 The pharmacokinetics of perindopril and its metabolites were studied after administration of a single 4 mg dose to hypertensive patients with various degrees of renal failure.
- 3 The absorption and elimination of perindopril were not influenced by the degree of renal failure.
- 4 The mean area under the serum concentration-time curve of the active metabolite perindoprilat increased from 93 ng ml⁻¹ h in subjects with normal renal function to 1106 ng ml⁻¹ h in patients with severe renal failure, whereas its half-life varied from 5.0 to 27.4 h.
- 5 In the same subjects, the mean area under the curve of perindoprilat glucuronide increased from 78 to 513 ng ml⁻¹ h, while its half-life varied from 1.8 h to 7.7 h.
- 6 Perindopril, perindoprilat, and perindoprilat glucuronide were dialysable.
- 7 The extent and duration of serum angiotensin-converting enzyme inhibition was augmented in renal failure. The mean area under the inhibition time curve (extrapolated to infinity) increased from 2490 %·h in subjects with normal renal function to 42241 %·h in patients with severe renal impairment. The half-life of inhibition varied from 12.1 h to 100.4 h. This effect of renal failure on the pharmacodynamics of perindoprilat was more pronounced than its influence on perindoprilat kinetics.
- 8 In view of the important influence of renal impairment on the elimination and action of the active substance perindoprilat, a dosage reduction of perindopril is proposed in patients with renal failure. In dialysis patients administration of perindopril after dialysis is recommended.

Keywords angiotensin-converting enzyme inhibitors hypertension perindopril pharmacokinetics kidney failure chronic

Introduction

Perindopril (S 9490) is an angiotensin-converting enzyme (ACE) inhibitor pro-drug without a sulphydryl group (Vincent *et al.*, 1982). Perindopril is hydrolysed *in vivo* to the active diacid metabolite perindoprilat (S 9780) (Laubie *et al.*, 1984). Minor metabolic pathways lead to glucuronide-conjugates (S 9490 glucuronide and S 9780 glucuronide) (Devissaguet *et al.*, 1990).

Peak plasma concentrations of perindoprilat are

obtained 4 to 8 h after administration of perindopril in healthy and hypertensive subjects, followed by a rapid decline and then by a prolonged terminal phase. This long terminal phase seems to reflect the high affinity of perindoprilat for plasma ACE and can be considered to be relevant to its pharmacodynamics (Devissaguet *et al.*, 1990).

Perindopril is effective in the treatment of hyper-

tension and of congestive heart failure (Luccioni *et al.*, 1988; Thuillez *et al.*, 1987). Since renal failure is often associated with these conditions and since the kidney is the main route of elimination of perindoprilat, this study was designed to investigate the influence of various degrees of renal insufficiency on the pharmacokinetics of perindopril and its main metabolites after a single oral dose. The effect of haemodialysis on serum perindopril and perindoprilat concentrations was also determined in patients with end-stage renal disease.

Methods

Patients

Twenty-six hypertensive patients (8 women and 18 men) participated in the study. They were divided into five groups depending on their renal function as determined by measurement of ^{51}Cr -EDTA clearance and/or creatinine clearance (Table 1). Group 1 patients had normal renal function (clearance greater than $100 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$). Group 2 patients had mild chronic renal failure (clearance $31\text{--}80 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$), group 3 patients had moderate chronic renal failure (clearance $15\text{--}30 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$) and group 4 patients had severe chronic renal failure (clearance less than $15 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$). Group 5 patients had end-stage renal disease and were studied on two occasions, differing only in terms of time interval between dialysis and the administration of perindopril.

All patients were hypertensive (diastolic pressure in supine position between 90 and 125 mm Hg) and there was no history of any recent cardiovascular accident. Patients on ACE inhibitors were excluded. Usual anti-hypertensive treatment was continued throughout the study, since the main objective was to study the pharmacokinetics of perindopril.

Written informed consent was obtained from all patients and the study protocol was approved by the Medical Ethics Committee of the University Hospital of Antwerp.

Study protocol

Perindopril was administered as the *tert*-butylamine salt in a single oral dose of 4 mg to the patients when fasting.

Blood samples were taken in dry tubes. After centrifugation, serum was separated in two fractions and

frozen at -18°C pending analysis. In group 1, samples were drawn before and then 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96 and 120 h after administration. In groups 2, 3, 4 and 5, additional samples were drawn at 144 and 168 h after administration.

Group 5 patients underwent a 4 h dialysis 24 h after the administration of perindopril in study period A. Haemodialysis was performed by means of a AK10 monitor (Gambro, Lund, Sweden) using a cuprophane 1 m^2 dialyser Lundia 03H (Gambro, Lund, Sweden). The blood flow through the dialyser was held constant at 200 ml min^{-1} . During dialysis, samples for drug assay were obtained simultaneously from the inflow and outflow of the extracorporeal blood circuit at the start of dialysis and after 1, 2, 3 and 4 h (i.e. 24, 25, 26, 27 and 28 h after administration).

In study period B group 5 patients received the drug 2 h prior to dialysis. Samples were drawn before and then 0.5, 1, 1.5, 2, 7, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, 120, 144 and 168 h after drug administration. In addition, during dialysis samples were obtained from the inflow and outflow at the start of dialysis and after 1, 2, 3 and 4 h (i.e. 2, 3, 4, 5 and 6 h after administration).

Samples for measurement of serum ACE activity were taken before and 2, 4, 8, 12, 24, 48, 72 and 96 h after administration in the five groups. Additionally, samples were obtained at 120, 144 and 168 h in groups 2, 3, 4 and 5.

In group 1, 2, 3 and 4, a urine sample was collected before administration and then all urine was collected during the following periods: 0–4, 4–8, 8–12, 12–24, 24–48, 48–72, 72–96, 96–120, 120–144 and 144–168 h after administration (urine in the patients of group 1 was collected only until 120 h). In group 5 urine collections were based upon when the patients excreted urine. Times after administration were carefully recorded. Samples were stored at -20°C until analysis.

Analytical methods

Prior to analysis, perindopril, perindoprilat and perindoprilat glucuronide were separated by chromatography on a Dowex AG-1X2 column (Biorad, Richmond, CA). Perindoprilat and its glucuronide were measured directly by a specific radioimmunoassay (Doucet *et al.*, 1990), with a sensitivity of 0.5 ng ml^{-1} and an interassay variability of $< 20\%$ at the lowest concentration. Perindopril was first converted to perindoprilat by alkaline hydrolysis. Serum ACE activity was measured using the method described by Neels *et al.* (1984).

Table 1 Clinical characteristics of patients (mean $\pm$ s.e. mean)

Group	n	Age (years)	Creatinine clearance ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)	^{51}Cr -EDTA clearance ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)	SBP/DBP (mm Hg)
1	6	29.0 ± 1.0	134.7 ± 7.8	N.D.	$136 \pm 3/83 \pm 3$
2	6	43.8 ± 5.3	62.3 ± 8.0	51.7 ± 7.3	$138 \pm 9/92 \pm 8$
3	6	51.0 ± 3.7	23.1 ± 3.0	20.8 ± 2.3	$144 \pm 10/95 \pm 9$
4	4	54.0 ± 9.4	9.6 ± 0.9	7.8 ± 1.5	$146 \pm 8/88 \pm 7$
5	4	39.3 ± 8.1	4.1 ± 1.2	4.0 ± 0.8	$143 \pm 11/84 \pm 10$

N.D.: Not determined.

Pharmacokinetic analysis

Peak serum concentration ($C_{\max}$) and time to $C_{\max}$ ($t_{\max}$) were obtained from the experimental values of the individual profiles.

The half-lives were calculated as $t_{1/2,i} = \ln 2 / \lambda_i$, where λ_i was the rate constant of the i th phase of the concentration-time curve calculated by a standard linear regression method.

The area under the serum concentration-time curve $AUC(0,t)$ from time 0 until the final measurable concentration $C(t)$ was calculated using the log/linear trapezoidal method and extrapolated to infinity (AUC) using the apparent terminal half-life.

Haemodialysis clearance was calculated as:

$$CL_{HD} = Q \frac{C_i - C_o}{C_i} + Q_{uf} \frac{C_o}{C_i}$$

where C_i and C_o are the drug concentrations respectively at the inflow and outflow of the dialyser, Q = bloodflow $\times$ (1 - haematocrit) is the plasma flow through the dialyser, Q_{uf} is the ultrafiltration flow-rate, calculated as:

$$Q_{uf} = \frac{W_s - W_e + W_{fl}}{\text{dialysis time}}$$

where W_s and W_e are the weight of the patients at the start and end of dialysis and W_{fl} the weight of the fluid administered to the patient during dialysis.

Renal clearance (CL_R) was calculated from $Ae(t)/AUC(0,t)$, where $Ae(t)$ is the cumulative amount excreted in the urine at time t and $AUC(0,t)$ is the area under the concentration time curve from time 0 to t ; t being the last experimental time common to urine and serum data.

The percentage inhibition of serum ACE activity was calculated at each time after perindopril administration from the ratio $100X$ (ACE activity before intake) - (ACE activity at time t)/(ACE activity before intake). Maximum inhibition ($I_{\max}$) and time taken to reach this maximum ($It_{\max}$) were obtained by inspection of the individual data. The half-life of ACE inhibition ($It_{1/2}$) and the area under the percentage inhibition time curve $IAUC(t)$ and $IAUC(\infty)$ was calculated using the same methods as for the drug kinetics.

Statistics

Group results are expressed as mean $\pm$ s.e. mean, with the exception of values of $t_{\max}$, where the median and range of experimental values were used. The means of pharmacokinetic and pharmacodynamic variables (except for $C_{\max}$ and $It_{\max}$) between groups of patients were compared by one-way analysis of variance, and if significant, followed by multiple comparison using the Newman-Keuls test (Winer, 1971). Haemodialysis clearance in group 5 (period A and B) was compared by a two-way analysis of variance. The Kruskal-Wallis test was used to compare $C_{\max}$ and $t_{\max}$ between different groups, and if significant, followed by a multiple comparison test (Daniel, 1978). Finally, correlations between serum half-life, $AUC(0,t)$ and the renal clearances of

perindopril, perindoprilat and perindoprilat conjugate and creatinine clearance were assessed.

Results

The clinical characteristics of the patients who participated in the study are shown in Table 1. The blood pressure values shown are those taken immediately before the administration of the study drug. In many patients current antihypertensive therapy was continued because of ethical reasons.

The mean serum concentrations of perindopril are shown for groups 1 to 4 in Figure 1a. The absorption of perindopril was rapid irrespective of the degree of renal failure. The mean maximum concentration and mean

Figure 1 Mean serum concentrations of perindopril (a), perindoprilat (b) and perindoprilat glucuronide (c) after a single oral dose of 4 mg perindopril in subjects with normal renal function (group 1, Δ), and with mild (group 2, $\blacktriangle$), moderate (group 3, $\square$), and severe (group 4 $\blacksquare$) renal failure.

Table 2 Pharmacokinetic parameters (mean $\pm$ s.e. mean, except * median and range) describing the fate of a 4 mg oral dose of perindopril in five groups of four subjects with varying renal function

Group	Perindopril				Perindoprilat				Perindoprilat glucuronide			
	C_{max} (ng ml ⁻¹)	t_{max} * (h)	AUC(0,t) (ng ml ⁻¹ h)	$t_{1/2,z}$ (h)	C_{max} (ng ml ⁻¹)	t_{max} * (h)	AUC(0,t) (ng ml ⁻¹ h)	$t_{1/2,1}$ (h)	C_{max} (ng ml ⁻¹)	t_{max} * (h)	AUC(0,t) (ng ml ⁻¹ h)	$t_{1/2,z}$ (h)
1	105 $\pm$ 19	0.75 (0.5'1.5)	182 $\pm$ 36	0.9 $\pm$ 0.1	8.5 $\pm$ 2.6	2.25 (0.5'8.0)	93 $\pm$ 14	5.0 $\pm$ 0.8	30.1 $\pm$ 4.7	1.25 (1.0'2.0)	78 $\pm$ 12	1.8 $\pm$ 0.2
2	93 $\pm$ 12	1.25 (0.6'2.1)	210 $\pm$ 23	1.4 $\pm$ 0.2	12.6 $\pm$ 3.6	3.55 (1.5'10.0)	217 $\pm$ 39	6.1 $\pm$ 1.4	28.3 $\pm$ 6.0	1.9 (1.5'2.1)	119 $\pm$ 29	2.8 $\pm$ 0.4
3	133 $\pm$ 18	0.80 (0.5'1.5)	302 $\pm$ 55	1.6 $\pm$ 0.2	19.5 $\pm$ 3.5	5.55 (2.1'10.0)	398 $\pm$ 99	13.3 $\pm$ 2.8	35.2 $\pm$ 7.2	2.25 (1.1'3.0)	266 $\pm$ 60	4.7 $\pm$ 0.4
4	153 $\pm$ 10	0.70 (0.5'1.0)	448 $\pm$ 151	0.7 $\pm$ 0.1	32.6 $\pm$ 10.7	12.00 (10.0'16.0)	1106 $\pm$ 248	27.4 $\pm$ 1.5	51.1 $\pm$ 5.7	3.25 (1.0'4.0)	513 $\pm$ 82	7.7 $\pm$ 0.7
5A	95 $\pm$ 12	1.25 (0.5'1.5)	248 $\pm$ 35	1.6 $\pm$ 0.2	30.1 $\pm$ 5.5	11.00 (4.0'20.0)	361 $\pm$ 46	31.0 $\pm$ 4.9	39.1 $\pm$ 3.1	3.50 (2.5'4.0)	405 $\pm$ 36	7.8 $\pm$ 0.5

time to reach this concentration did not vary significantly between the groups (Table 2).

The half-life of perindopril was not dependent on renal function ($r = 0.08$; NS). The AUC(0,t) of perindopril tended to increase in relation to renal failure, but this was not statistically significant ($r = 0.25$; NS). Since the sampling period greatly exceeded the half-life of the compound, the total AUC of perindopril was almost identical to its AUC(0,t) value.

The urinary excretion of perindopril decreased in relation to the degree of renal failure. The renal clearance (CL_R) of perindopril was correlated with creatinine clearance (CL_{Cr}): CL_R = 0.23 CL_{Cr} + 2.37 ($r = 0.861$, $P < 0.001$).

In dialysis patients the mean maximum concentration of perindopril, the time to reach this concentration and the area under curve did not differ significantly from the other groups. Only in study period B in which perindopril was administered prior to dialysis, was it possible to calculate perindopril haemodialysis clearance (Table 3).

The mean serum concentrations of perindoprilat in groups 1 to 4 are shown in Figure 1b. There was a significant ($P < 0.05$) difference between group 1 and 4 in the time to reach maximum concentration (Table 2). The mean maximum serum concentrations were significantly ($P < 0.05$) higher in groups 4 and 5A than in group 1. The difference between groups 2 and 4 was also significant ($P < 0.05$).

Since the sampling period was prolonged in the patients with renal failure, the area under curve of perindoprilat AUC(0,t) represented more than 90% of the total AUC. Statistical comparison of the mean AUC(0,t) revealed significant differences between group 1 and group 4 ($P < 0.01$) and 5A ($P < 0.05$), between group 2 and group 4 ($P < 0.01$) and between group 3 and group 4 ($P < 0.05$). Consequently, AUC(0,t) correlated with creatinine clearance ($r = 0.40$, $P < 0.05$).

The initial decline in perindoprilat concentrations corresponded to the main half-life ($t_{1/2,1}$); indeed about 60 to 70% of the experimental AUC was associated with

this phase. Thus, $t_{1/2,1}$ of perindoprilat increased significantly with declining renal function when compared between groups (Table 2) and it correlated significantly with creatinine clearance ($r = 0.41$, $P < 0.05$).

The renal clearance of perindoprilat was significantly correlated with renal function: CL_R = 0.55 CL_{Cr} + 1.97 ($r = 0.94$, $P < 0.001$). Calculation of the dialysis clearance of perindoprilat was possible in both study periods in group 5 and gave similar results (Table 3).

Mean serum concentrations of perindoprilat glucuronide are shown in Figure 1c. The appearance of this metabolite was rapid. Its maximum serum concentration and the time to reach this maximum were not significantly different among the different groups (Table 2). Significant correlations with renal function were observed for the AUC(0,t) of perindoprilat glucuronide ($r = 0.51$, $P < 0.01$), its serum half-life ($r = 0.66$, $P < 0.005$) and its renal clearance (CL_R = 0.53 CL_{Cr} + 13.96; $r = 0.76$, $P < 0.005$). The dialysis clearance of perindoprilat glucuronide is given in Table 3.

Figure 2 shows the changes in angiotensin-converting enzyme (ACE) inhibition with time in groups 1 to 4. The time to obtain maximal ACE inhibition (I_{max}) tended to increase in relation to the degree of renal failure (Table 4), although only I_{max} of group 1 was significantly different ($P < 0.05$) from those of groups 3 and 5A. The maximal degree of ACE inhibition (I_{max}) showed the

Figure 2 Mean percentage of inhibition of serum angiotensin-converting enzyme (ACE) activity after a single oral dose of 4 mg perindopril in subjects with normal renal function (group 1, Δ), and with mild (group 2, $\blacktriangle$), moderate (group 3, $\square$), and severe (group 4, $\blacksquare$) renal failure.

Table 3 Haemodialysis clearance (mean $\pm$ s.e. mean)

Group 5 Period	CL _{HD} (ml min ⁻¹)		Perindoprilat glucuronide
	Perindopril	Perindoprilat	
A		67.9 $\pm$ 11.2	57.1 $\pm$ 12.6
B	52.0 $\pm$ 8.3	66.5 $\pm$ 9.5	71.7 $\pm$ 9.5

Q_B = 200 ml min⁻¹.

Table 4 Pharmacodynamic parameters describing the inhibition of serum ACE activity after a 4 mg oral dose of perindopril

Group	$I_{\max}$ (%)	$t_{\max}$ (h)	$IAUC_{96}$ (% h)	$IAUC_{\infty}$ (% h)	$t_{1/2}$ (h)
1	66.2 ± 7.4	30 ± 1.0	1647 ± 368	2490 ± 472	12.1
2	74.0 ± 3.9	11.3 ± 2.8	3079 ± 439	12178 ± 3855	80.4
3	83.8 ± 3.2	22.0 ± 5.7	4662 ± 268	49816 ± 34755	137.6
4	90.2 ± 2.6	12.5 ± 4.5	5480 ± 375	42241 ± 25962	100.4
5A	82.4 ± 9.2	43.0 ± 17.2	4545 ± 1568	*	*
5B	80.9 ± 2.7	16.0 ± 10.7	3554 ± 780	*	*

$I_{\max}$: maximum % of inhibition of serum ACE activity

$t_{\max}$: time to reach $I_{\max}$

$IAUC_{96}$: area under inhibition-to-time curve until 96 h after dosing

$IAUC_{\infty}$: area under inhibition-to-time curve until infinity

$t_{1/2}$: half-life of inhibition of serum ACE activity

* : calculation not possible owing to dialysis effects.

same trend, but the differences between groups were not statistically significant ($P = 0.059$).

The area under the curve of inhibition of ACE activity ($IAUC_{96}$) increased significantly ($P < 0.01$) with declining renal function and, therefore, inversely correlated with creatinine clearance ($r = 0.82$, $P < 0.001$). It is important to note that there was a considerable increase in the duration of ACE inhibition in mild renal failure. The correlations between $t_{1/2}$ and $IAUC_{\infty}$ values and creatinine clearance did not reach statistical significance ($r = 0.30$ and $r = 0.10$). The values of the pharmacodynamic parameters in dialysis patients were difficult to interpret, because they were influenced by the removal of active product during dialysis.

A moderate decrease in blood pressure was observed in all groups. A few minor side-effects (i.e. mild headache slight weakness) were noted in some patients. There was no additional impairment of renal function following the administration of perindopril.

Discussion

The single dose pharmacokinetics of perindopril were studied after its oral administration to hypertensive patients with normal renal function and with different degrees of renal failure.

The absorption of the pro-drug perindopril was rapid irrespective of renal function. We observed a small, but statistically significant, increase of AUC with decreasing renal function, possibly related to the fact that the renal clearance of perindopril is only 10% of the total plasma clearance (Devissaguet *et al.*, 1990).

The conversion of perindopril to the active diacid metabolite, perindoprilat, is probably not affected by renal failure. The delayed appearance of the maximum concentration of perindoprilat and the higher concentrations are most likely the result of diminished renal excretion of this hydrophilic compound in renal impairment. Indeed, the elimination kinetics of perindoprilat were significantly influenced by renal failure. A 12-fold increase in AUC was observed in patients with severe renal failure in comparison with subjects with normal renal function, while the main half-life of perindoprilat showed a sixfold increase. The high renal clearance of perindoprilat confirms the importance of the kidney in

the excretion of the active metabolite. Furthermore, decreasing renal function was associated with an increase in AUC and serum half-life of the inactive metabolite perindoprilat glucuronide.

Assuming that each dose in a multiple dosing regimen is administered in the post-distribution phase of the preceding dose, an accumulation ratio (R_{α}) can be defined indicating the degree of drug accumulation between the first dose and steady state (De Vane & Jusko, 1982):

$$R_{\alpha} = \frac{1}{1 - e^{-\lambda_1 t}}$$

where t equals the dosage interval (h) and λ_1 is the first-order elimination rate constant (h^{-1}). Using this equation, the data of this study and an assumed dosing interval of 24 h, the accumulation ratio of perindoprilat would be 1.0 in subjects with normal renal function, 1.1 in patients with mild renal failure, 1.4 in patients with moderate renal failure, 2.2 in patients with severe renal failure, and 2.4 in patients with end-stage renal failure. The accumulation ratio of the metabolite perindoprilat glucuronide would be close to 1 in all groups.

Therefore, because of the accumulation of the active compound a dosage reduction in renal failure seems necessary. In view of the low accumulation factor of perindoprilat glucuronide the absence of any clinical effect of this metabolite after multiple dosing is anticipated.

Perindopril and its active metabolite are dialysable. Therefore, the drug should be administered to dialysis patients after dialysis. In the event of overdose with perindopril in renal failure patients, haemodialysis may be an appropriate treatment in view of the prolonged half-life of the active compound perindoprilat in these patients.

The extent and duration of serum converting enzyme inhibition after a single dose of perindopril increased with the degree of renal failure. However, this increase did not parallel the change in the pharmacokinetics of perindoprilat. Thus, in mild renal failure the 'half-life' of ACE inhibition increased 7-fold, while the serum half-life of perindoprilat increased by only 20%. There have been few reports on the duration of ACE inhibition in patients with renal failure. Only one has reported an

inverse relationship between creatinine clearance and time at more than 90% ACE inhibition after quinapril administration (Begg *et al.*, 1989). We can only speculate on the mechanisms involved in this disproportionate increase in ACE inhibition in renal failure. If the relationship between serum perindoprilat concentrations and ACE inhibition is described by the Hill equation, it is conceivable that in patients with renal failure the serum concentrations of perindoprilat would be well above the IC_{50} values, leading to an apparent increase in pharmacodynamic 'half-life'. Alternatively, renal impairment could enhance tissue accumulation of the enzyme inhibitor. Since perindoprilat has a strong affinity for the enzyme, continuous release of small quantities of the inhibitor from these tissue stores could be responsible for prolonged enzyme inhibition.

The pharmacokinetics of perindopril and its metabolites are comparable to those of the other pro-drug ACE inhibitors enalapril (Kelly *et al.*, 1986; Lowenthal *et al.*, 1985) and ramipril (Debusmann *et al.*, 1987). The kinetics of lisinopril, an enalaprilat derivative, are similar

to those of perindoprilat (van Schaik *et al.*, 1987). Renal excretion is the major route of elimination of captopril consistent with an increased plasma half-life in patients with renal failure (Duchin *et al.*, 1984). There are also indications that the active metabolites of captopril accumulate in renal failure and cause prolonged duration of plasma ACE inhibition and blood pressure reduction (Giudicelli *et al.*, 1984).

In the elderly, the pharmacokinetics and pharmacodynamics of perindopril are altered (Lees *et al.*, 1988). This finding can probably be attributed to the decrease in kidney function frequently observed in this population (Elseviers *et al.*, 1987).

In conclusion, initial dose reduction of perindopril is recommended in patients with renal impairment. The effects of multiple dosing in patients with renal failure is currently under investigation (Slovick *et al.*, 1990).

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