

Comparison of the pharmacokinetics and pharmacodynamics of oral doses of perindopril in normotensive Chinese and Caucasian volunteers

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- 1 The pharmacokinetics of perindopril and perindoprilat and the hormonal and haemodynamic responses following a single oral dose were studied in 12 Chinese and 10 Caucasian healthy, normotensive volunteers on two occasions. Perindopril was given on the first occasion as a 4 mg dose and then after at least 10 days as a weight-adjusted dose of 4 mg/70 kg. Plasma was sampled for assay of perindopril, perindoprilat, plasma renin activity (PRA), aldosterone, angiotensin I (AI) and ACE activity. Urine was collected for perindopril and perindoprilat assay. A radioimmunoassay technique was used to measure the prodrug and its active metabolite.
- 2 The time to maximum concentration (t_{\max}) for perindopril was shorter for the Chinese group after the 4 mg dose (median 0.5, range 0.5–1.5 h vs median 1.0, 0.5–1.5 h $P < 0.05$) and also tended to be shorter after the weight-adjusted dose (median 0.5, range 0.5–1.0 h vs median 1.0, range 0.5–3.0 h). C_{\max} and AUC tended to be higher after the 4 mg dose in the Chinese group who had a lower body weight than the Caucasians.
- 3 The t_{\max} of perindoprilat tended to be shorter for both doses and there was a tendency towards a higher C_{\max} after the 4 mg dose in the Chinese group but there was no statistically significant difference between the two groups.
- 4 There were no differences in the levels of PRA, plasma AI, plasma aldosterone or the degree of ACE-inhibition for either dose in the two ethnic groups.
- 5 Blood pressure was measured at intervals up to 24 h post-dose in both the supine and standing positions. Perindopril reduced blood pressure acutely with respect to the pre-dose level with good tolerability in both groups.
- 6 The pharmacokinetics of perindopril are essentially the same in Chinese and Caucasians although absorption of the prodrug and conversion to the active metabolite appeared to be more rapid in the Chinese group. However, there were no differences in its hormonal or haemodynamic effects and no alteration of the standard dose of 4 mg appears to be necessary for Chinese subjects.

Keywords perindopril perindoprilat pharmacokinetics Chinese Caucasians

Introduction

Over the past 20 years ethnic differences in drug pharmacokinetics and pharmacodynamics have been receiving increasing attention. The subject is complex and many factors have been shown to be involved,

from dietary influences such as eating charcoal broiled beef [1] to genetic factors affecting plasma protein binding [2]. With the antihypertensive drugs, it has been recognised for many years that

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Negro patients are less responsive to β -adrenoceptor blockers than Caucasians [3] whereas Chinese subjects appear to be more sensitive to propranolol than Caucasians [4]. ACE-inhibitors are becoming increasingly popular in the treatment of hypertension and some ethnic differences have been identified in the response to these drugs. As with the β -adrenoceptor blockers, ACE-inhibitors, especially without co-administration of a diuretic, may be less effective in Negro and Indian hypertensives than in Caucasians [5, 6]. However, there does not appear to have been any direct comparison of the pharmacokinetics or pharmacodynamics of ACE inhibitors in Chinese and Caucasians. The present study was performed to compare the pharmacokinetics and pharmacodynamics of the ACE inhibitor perindopril, in healthy Chinese and Caucasians.

Perindopril is a non-thiol ACE inhibitor that has been studied extensively in Caucasian populations. The ester prodrug is hydrolysed *in vivo* to form an active metabolite, the diacid perindoprilat, which is a potent and long lasting ACE inhibitor.

Methods

Subjects

Ten healthy Caucasian subjects, six males and four females (mean age 30, range 20–40 years; mean weight 72, range 52–94 kg) and twelve Chinese subjects, six males and six females (mean age 25, range 20–41 years; mean weight 59, 48–75 kg) completed the study. The Caucasians were significantly heavier and taller than the Chinese subjects, partly because a larger proportion were male. Both groups were residing in Hong Kong and on their normal diet prior to the study days. No salt restrictions were imposed. All the subjects were healthy, normotensive volunteers who gave their written informed consent and underwent a thorough medical examination, including biochemical investigations and an ECG before being included in the study. Pre-treatment renal function was normal in both groups with mean values for plasma urea, creatinine, sodium and potassium in Chinese and Caucasians, respectively being urea 4.99 and 5.21 mmol l⁻¹, creatinine 81.6 and 86.2 μ mol l⁻¹, and sodium 140 and 139 mmol l⁻¹. No concomitant medications, caffeine, tobacco or alcohol were allowed during the study period. The study was approved by the Chinese University of Hong Kong's Clinical Research Ethics Committee.

Design

Prior to selection, all volunteers underwent a thorough medical examination, including a complete medical history, an electrocardiogram, blood pressure (BP) and heart rate (HR) measurement, both supine and standing, and a clinical examination. Blood was taken for a variety of haematological and biochemical investigations. A 24 h urine collection was

made for measurement of electrolytes and renal function. Those subjects who met the inclusion criteria commenced the study within 14 days, following an overnight fast. On the first study day, the subject received a standard 4 mg dose in capsule form with 100 ml of water, whilst on Day 14, a weight-adjusted, 4 mg/70 kg dose was given through a combination of small dosage capsules (0.5 mg, 1 and 2 mg). A standard light lunch was served after a delay of at least 3 h post-dosing. The evening meal was also light.

Blood samples were collected for plasma perindopril, perindoprilat and ACE-activity before administration and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96 and 120 h after perindopril administration. For the assay of aldosterone, PRA and AI concentrations, blood samples were collected before and at 2, 4, 6, 8, 12, 24, 48, 72, 96 and 120 h after drug administration. After sampling, the blood was immediately centrifuged at 3000 rev min⁻¹ for 10 min. The plasma was then separated and frozen at -20°C prior to assay.

Urine was collected into bottles containing 2 g of boric acid as a preservative. Samples were collected over the following time periods: 0, 0–4, 4–8, 8–12, 12–24, 48–72, 72–96 and 96–120 h. After mixing and volume measurement, a 10 ml aliquot was frozen at -20°C prior to analysis of perindopril and perindoprilat concentrations.

BP and HR were measured with a Dinamap Accutor automatic sphygmomanometer at the following times: 0, 4, 6, 8, 12, 24, 48, 72, 96 and 120 h in both the supine and standing positions.

All the volunteers were recruited over a 6 month period and samples were stored and assayed together.

Sample analysis

Perindopril and perindoprilat were assayed in plasma and urine by radioimmunoassay (r.i.a.). The immunogen was raised using the lysine derivative of perindoprilat conjugated to bovine serum albumin. As the immunogen showed no affinity for perindopril, a hydrolysis step was required in the preparation of the samples. After chromatographic separation of perindopril, perindoprilat and perindoprilat glucuronide, hydrolysis of perindopril was performed by alkaline saponification using a Dowex AG 1 \times 2 anion exchange column. The radioligand was prepared by iodination of the *p*-hydroxyphenyl derivative of the lysine analogue of perindoprilat. The quantification limit of the method was 0.5 ng ml⁻¹. The intra- and inter-assay coefficients of variation were both < 6%. The method is described in detail by Van Den Berg *et al.* [7].

Plasma ACE-activity was measured using a method derived from the spectrometric assay described by Cushman & Cheung [8] which uses [¹⁴C]-hippuryl-L-histidyl-L-leucine as the substrate [7].

Aldosterone was measured by r.i.a. with [¹²⁵I]-aldosterone (Kit: SB-ALDO 2, International CIS-BP 32-91192 Gif sur Yvette, France). The quantification limit was 15 pg ml⁻¹.

Plasma renin-activity and angiotensin I were

measured by r.i.a. with [125 I]-AI (Kit: SB-REN-2, International CIS-BP 32-91192 Gif sur Yvette, France). AI was assayed at 37°C and PRA was calculated as $(\text{ng } 37^\circ\text{C} - \text{ng } 4^\circ\text{C}) \times 1.12 \div \text{time of incubation}$, and expressed as $\text{ng ml}^{-1} \text{ h}^{-1}$. The quantification limit was 0.2 ng ml^{-1} of AI.

Plasma protein binding was determined at 37°C with tritiated perindopril and perindoprilat by an equilibrium dialysis technique using Dianorm R apparatus, and based on the method described by Bree *et al.* [9].

Pharmacokinetic analysis

Curve fitting was performed for each subject by an extended least squares regression analysis for each subject using the SIPHAR software (Version 4.0; Simed, 1991). The data were fitted to a two compartment model with first order absorption, using the following equation:

$$Ct = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} - (C_1 + C_2) e^{-k_a t}$$

where Ct equals the plasma concentration of perindopril at time t , and C_1 and C_2 are the coefficients of the initial and terminal declining phases respectively. The exponentials λ_1 , λ_2 and k_a are the rate constants of the respective phases. The maximum plasma concentration (C_{max}) and time to reach the maximum (t_{max}) were obtained directly from the individual data. The area under the curve (AUC(t)) was calculated from 0 to the last measurable drug concentration (C_p) by the trapezoidal method and extrapolated to infinity (AUC) using the slope of the terminal phase. The half-life ($t_{1/2}$) of each phase was calculated by the standard equation: $t_{1/2} = 0.693/\lambda$, where λ is the rate constant (slope) of that phase. Mean residence time (MRT) was calculated as:

$$\Sigma \text{Coefficient (i) / Exponential (i)}^2$$

where i corresponds to each phase – the absorption, alpha and beta phases. The total plasma clearance (CL) was calculated by the ratio: dose/AUC.

The cumulative amount of compound excreted in the urine at time t (Ae_t) was expressed in mg or as a percentage of the dose administered. The renal clearance (CL_R) was calculated from the ratio of $Ae_t/\text{AUC}(t)$, the time t corresponding to the duration of the collection period.

Perindopril plasma concentrations were analysed between 0–12 h after which time they were considered to be negligible (see discussion). Perindoprilat was analysed from 0 to the last measurable concentration.

Statistical analysis

Inter-group comparisons were made for parametric parameters with Student's unpaired t -test and for non-parametric parameters (e.g. t_{max} and $t_{1/2}$) with the Mann-Whitney U test. Intra-group comparisons between the doses were made with the paired Student's t -test and the non-parametric equivalent, the Wilcoxon Signed Rank test. In addition, a one-way analysis of variance with repeated measures

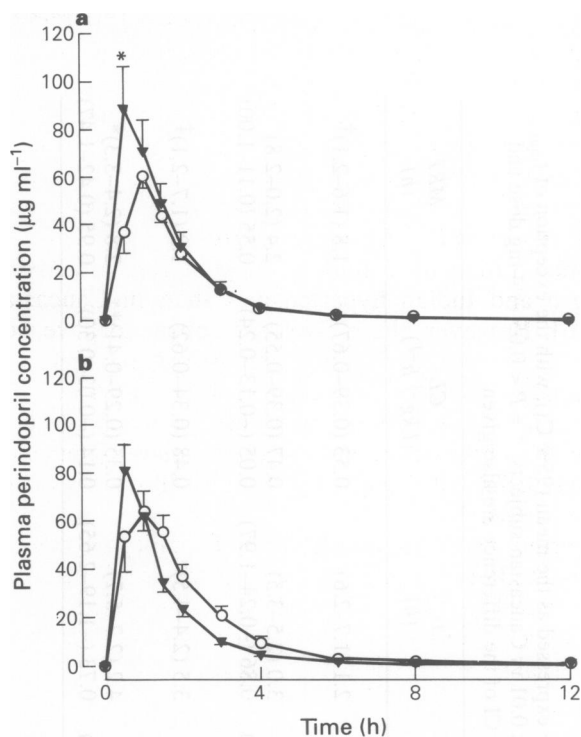


Figure 1 Mean plasma perindopril concentrations vs time in 12 Chinese (\blacktriangledown) and 10 Caucasians (\circ) after a) perindopril 4 mg and b) perindopril 4 mg/70 kg, * = $P < 0.05$ vs Caucasian subjects.

(repeated measures ANOVA) was performed on all the data for blood pressure and heart rate. Significant results were corrected for multiple comparisons using the Bonferroni Procedure. Both SigmaStat (Jandel Scientific, 1992) and the S-Stat (Simed, 1991) software packages were used to perform the statistical analyses. The level of statistical significance chosen for all comparisons was $P < 0.05$. Results are expressed as mean \pm s.e. mean or 95% confidence intervals (CI). Where appropriate, the difference between the means of the two groups and the CI of the difference are also given. Non-parametric data are given as the median plus the range. The study had a power of 0.8 to detect a difference of 1.2 standard deviations between the groups when alpha equals 0.05.

Results

Perindopril pharmacokinetics

Mean plasma concentrations vs time are presented in Figure 1. Mean pharmacokinetic parameters are presented in Table 1.

After administration of the drug, the plasma concentrations had peaked by 1 h and subsequently declined rapidly with a biphasic elimination phase, allowing calculation of absorption, alpha and beta half-lives. Elimination of perindopril occurred so quickly that 8 h after the 4 mg dose the mean plasma concentration represented only 2.1% of the peak concentration in Caucasians, and 1.5% in Chinese. By 12 h the concentrations were down to 0.7% and 0.4%

Table 1 Perindopril pharmacokinetic variables in Chinese and Caucasians. The data are expressed as the mean (95% CI), with the exception of t_{\max} and C_{\max} which are given as median (range); † = $P < 0.05$ vs Caucasian subjects; ‡ = $P < 0.01$ vs Caucasian subjects; * = $P < 0.05$ vs 4 mg dose and ** = $P < 0.01$ vs 4 mg dose. The difference between the means of the two groups and the CI of the difference are also given

	C_{\max} (mg l ⁻¹)	t_{\max} (h)	AUC (mg l ⁻¹ h)	$t_{1/2,1}$ (h)	$t_{1/2,z}$ (h)	CL (l kg ⁻¹ h ⁻¹)	MRT (h)
<i>Chinese subjects, Perindopril 4 mg (n = 12)</i>							
Mean (95% CI):	86 (43–238)	0.5 (0.5–1.5)	159 (109–209)	0.52 (0.46–0.58)	2.1 (1.7–2.6)	0.53 (0.39–0.67)	1.8 (1.6–2.1)†
<i>Caucasian subjects, Perindopril 4 mg (n = 10)</i>							
Mean (95% CI):	59 (45–105)	1.0 (0.5–1.5)	124 (110–138)	0.65 (0.53–0.77)	3.0 (2.5–3.5)	0.47 (0.39–0.55)	2.4 (2.0–2.8)
Difference (CI):	—	—	35 (25–95)	0.12 (–0.02–0.26)	0.86 (–0.24–1.97)	0.05 (–0.13–0.24)	0.55 (0.11–1.00)
<i>Chinese subjects, Perindopril 4 mg/70 kg (n = 12 for C_{\max} and t_{\max} otherwise n = 11)</i>							
Mean (95% CI):	94 (39–127)	0.5 (0.5–1.0)	141 (108–174)	0.66 (0.54–0.78)	3.5 (2.4–4.5)*	0.48 (0.34–0.62)	1.9 (1.7–2.1)‡
<i>Caucasian subjects, Perindopril 4 mg/70 kg (n = 10)</i>							
Mean (95% CI):	69 (45–135)	1.0 (0.5–3.0)	172 (138–206)**	0.69 (0.64–0.74)	4.2 (2.7–5.7)	0.35 (0.29–0.41)**	2.8 (2.4–3.3)*
Difference (CI):	—	—	31 (–20–82)	0.03 (–0.13–0.20)	0.73 (–1.19–2.65)	0.14 (–0.03–0.30)	0.95 (0.42–1.47)

of the peak in Chinese and Caucasians respectively. The pattern was similar when the dose was adjusted for weight, in Caucasians the plasma concentration was at 2.6% of the peak at 8 h and 1.0% at 12 h. In Chinese it was at 0.9% at 8 h and 0.6% at 12 h post-dose.

The plasma concentration vs time curves were similar in Chinese and Caucasians. However, the Chinese exhibited a significantly shorter t_{\max} after the 4 mg dose (median 0.5, range 0.5–1.5, vs median 1.0, range 0.5–1.5, $P < 0.05$) and there was still a tendency towards a shorter t_{\max} after the 4 mg/70 kg dose (median 0.5, range 0.5–1.0 vs median 1.0, range 0.5–3.0). C_{\max} tended to be higher in the Chinese subjects when the dose was not adjusted for weight (median 85.9, range 43.1–238 vs median 58.6, range 45.0–105), however this difference did not reach significance.

AUC(t) and AUC were similar between the groups after both doses. However, the Caucasians showed a significant increase in both parameters after the weight-adjusted dose (AUC(t): 122 ± 7 vs 167 ± 17 , $P < 0.05$; AUC: 124 ± 7 vs 172 ± 17 , $P < 0.01$).

The half-life of the absorption phase ($t_{1/2,ab}$) was significantly shorter in the Chinese subjects after both doses, particularly so after the weight-adjusted dose ($P < 0.01$). The half-lives of the λ_1 phase ($t_{1/2,1}$) and λ_z ($t_{1/2,z}$) phases did not differ significantly between the groups, although there was a tendency towards a longer $t_{1/2,z}$ in the Caucasians, particularly after the weight-adjusted dose. The Chinese exhibited significantly longer $t_{1/2,z}$ after the weight-adjusted dose, in comparison with their 4 mg values. The MRT was also longer in Caucasians, the difference being significant after both doses, but more so after the adjusted dose ($P < 0.01$).

Clearance (CL) did not demonstrate an ethnic difference between the two groups, but there was a substantial decrease in the CL value in Caucasians when the dose was adjusted for weight ($P < 0.01$).

The total amount of unchanged drug excreted in the urine represented $18.6 \pm 5.4\%$ and $21.0 \pm 6.1\%$ of the dose after 4 mg and 4 mg/70 kg respectively in the Chinese group and $18.3 \pm 5.8\%$ and $18.7 \pm 3.2\%$ respectively in the Caucasian group. There were no statistical differences between the two groups. In both Chinese and Caucasians, perindopril was almost completely excreted within the initial 8 h period.

Perindoprilat pharmacokinetics

Mean plasma concentrations vs time are presented in Figure 2. The mean pharmacokinetic parameters for both Chinese and Caucasians after each dose are shown in Table 2. Conversion of perindopril to perindoprilat was rapid, with perindoprilat first appearing in the plasma within 30 min of perindopril administration. Subsequently, it decayed in a multi-exponential manner with three distinct phases being detectable. As with the prodrug, it was possible to calculate a half-life for the absorption phase and also the two elimination phases. Although not reaching statistical significance, the plasma concentrations of perindoprilat in Chinese subjects were higher than in

Table 2 Perindoprilat pharmacokinetic variables in Chinese and Caucasians. The data are expressed as the mean (95% CI), with the exception of t_{max} and C_{max} which are given as median (range); † = $P < 0.05$ vs Caucasian subjects; ‡ = $P < 0.01$ vs Caucasian subjects; * = $P < 0.05$ vs 4 mg dose. The difference between the means of the two groups and the CI of the difference are also given

	C_{max} ($mg\ l^{-1}$)	t_{max} (h)	AUC ($mg\ l^{-1}\ h$)	$t_{1/2,1}$ (h)	$t_{1/2,z}$ (h)	CL ($l\ kg^{-1}\ h^{-1}$)	MRT (h)
Chinese subjects, Perindopril 4 mg (n = 12 for C_{max} and t_{max} otherwise n = 11)	Mean (95% CI): 3.6 (2.0–13.0)	4.0 (3.0–8.0)	119 (95–144)	4.4 (3.5–5.3)	43 (30–56)†	0.63 (0.53–0.73)‡	48 (34–62)†
Caucasian subjects, Perindopril 4 mg (n = 10 for C_{max} and t_{max} otherwise n = 7)	Mean (95% CI): 2.7 (1.9–8.2)	7.0 (3.0–12.0)	132 (119–145)	5.4 (3.3–7.5)	63 (55–71)	0.42 (0.36–0.48)	78 (64–92)
Difference (CI):	—	—	14 (–21–49)	0.98 (0.76–1.20)	20 (0.75–39)	0.21 (0.08–0.34)	30 (7–53)
Chinese subjects, Perindopril 4 mg/70 kg (n = 12 for C_{max} and t_{max} otherwise n = 10)	Mean (95% CI): 3.8 (1.6–8.9)	4.0 (1.5–8.0)	126 (102–150)	5.3 (3.9–6.8)	63 (52–75)*	0.49 (0.11–0.57)*	74 (58–90)*
Caucasian subjects, Perindopril 4 mg/70 kg (n = 10 for C_{max} and t_{max} otherwise n = 7)	Mean (95% CI): 3.8 (1.5–8.2)	7.0 (1.5–12)	142 (118–166)	6.5 (3.2–9.8)	64 (47–82)*	0.40 (0.34–0.46)*	68 (51–84)
Difference (CI):	—	—	16 (–22–54)	1.20 (–2.30–4.71)	1.06 (–20–22)	0.09 (–0.02–0.20)	6 (–9–32)

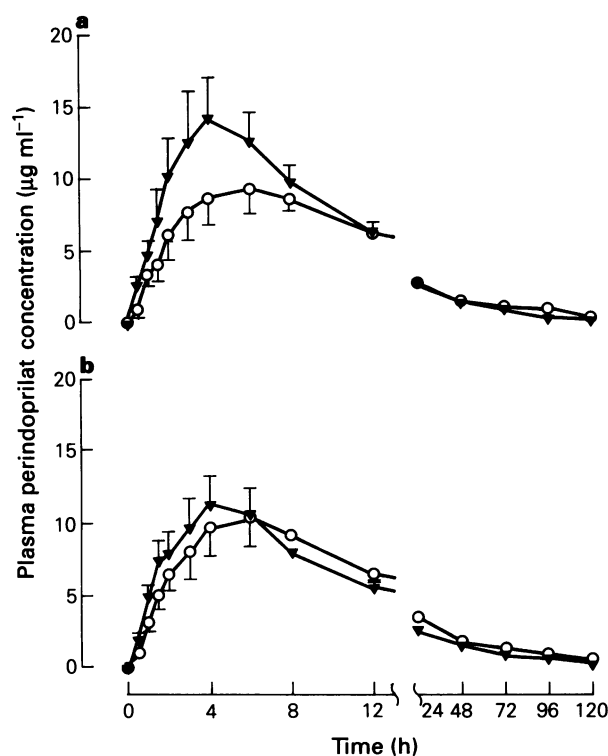


Figure 2 Mean plasma perindoprilat concentrations vs time in 12 Chinese (▼) and 10 Caucasians (○) after a) perindopril 4 mg and b) perindopril 4 mg/70 kg.

Caucasians, and the concentration-time profiles did not converge until about 24 h post-dose. However, when the dose was adjusted for weight, these differences were much smaller (see Figure 2). The t_{max} for perindoprilat were similar in both races. $AUC_{(t)}$ and AUC showed no difference between races or doses. Both $t_{1/2,ab}$ and $t_{1/2,1}$ were comparable in the two groups. The $t_{1/2,z}$ was significantly longer in the Caucasian volunteers when the dose was not adjusted for weight, but this difference was not evident after the weight adjustment. As would be expected, the derived parameter, MRT showed the same disparity. Both $t_{1/2,z}$ and MRT were statistically different between doses for the Chinese group. The difference in plasma CL was highly significant between the races, but once again, only when the dose was not adjusted for weight ($P < 0.001$).

The total amount of perindoprilat excreted in the urine represented $14.7 \pm 1.5\%$ after the 4 mg dose and $15.0 \pm 1.6\%$ after the weight-adjusted dose in the Chinese group. In the Caucasian group, $13.5 \pm 4.1\%$ and $13.9 \pm 1.58\%$ of the 4 mg and the 4 mg/70 kg doses respectively were excreted as perindoprilat.

At the end of the initial 24 h period, the amount of perindoprilat excreted in the urine represented at least 73% of the total dose excreted. There was no statistical difference in any of the urinary parameters between the two groups.

Pharmacodynamic results

Angiotensin converting enzyme inhibition Figure 3 shows ACE-inhibition vs perindoprilat concentrations in Chinese and Caucasians after both doses. A dose-response relationship was noted in Chinese subjects

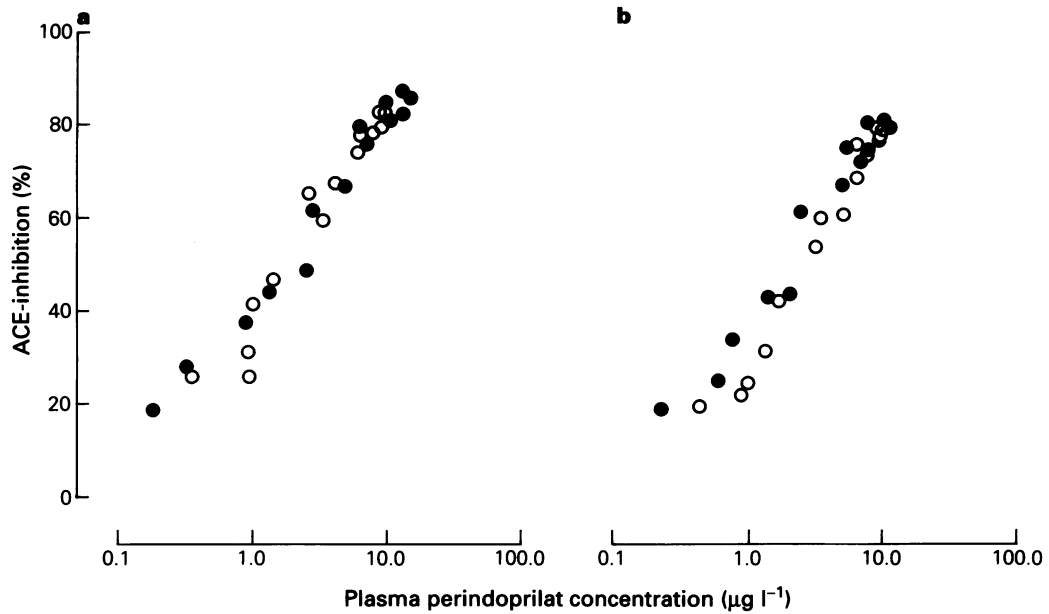


Figure 3 Mean percentage ACE-inhibition plotted against mean plasma perindoprilat concentrations in 12 Chinese (▼) and 10 Caucasians (○) after a) perindopril 4 mg and b) perindopril 4 mg/70 kg.

who achieved 88% inhibition after a 4 mg dose and 84% after the smaller weight-adjusted dose. Regardless of dose, I_{max} was reached within 6 h of administration in the Caucasian group and 5 h in the Chinese group.

Angiotensin I (AI) The expected increase in AI levels with ACE-inhibition was not seen in Caucasian subjects and did not achieve significance in Chinese subjects. The results showed wide intra-subject variation with no significant difference between the two groups.

Aldosterone and plasma renin activity (PRA) Plasma aldosterone concentrations were clearly reduced in both groups by 8 h post-dose but had returned to baseline levels by 48 h, regardless of the dose given. The PRA data showed wide intra-subject variation making conclusions difficult. A slight rise was seen in Chinese subjects after the 4 mg dose but otherwise no distinct pattern was discernible.

Plasma protein binding Human plasma albumin (HPA) concentrations were measured in the pre-dose plasma samples collected prior to dosing. The results are shown in Table 3. Levels of HPA were almost identical in the two races, as were the percentages of both perindopril and perindoprilat bound to albumin.

Table 3 Human plasma albumin (HPA) concentrations, perindopril (P) and perindoprilat (Pt) plasma binding levels in Chinese and Caucasians given as mean values with 95% confidence intervals

	HPA ($g\ l^{-1}$)	P binding (%)	Pt binding (%)
Chinese	43 (40–46)	73 (70–77)	18 (14–23)
Caucasians	41 (32–50)	74 (71–78)	19 (15–23)

Blood pressure and heart rate Mean systolic blood pressure, diastolic blood pressure and heart rate in the supine position are shown in Figure 4. The maximum reductions in SBP and DBP compared with the pre-dose levels were seen at between 4 and 6 h in both groups, regardless of dose. However, after the weight adjusted dose, no significant fall was seen in the

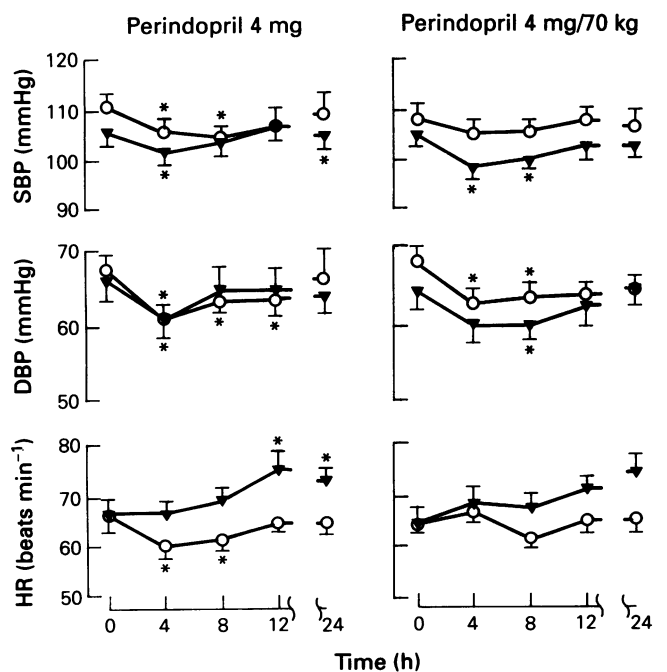


Figure 4 Mean supine systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) in 12 Chinese (▼) and 10 Caucasians (○) after perindopril 4 mg and perindopril 4 mg/70 kg, * = $P < 0.05$ vs baseline values.

Caucasian SBP, although the values for the Chinese group were significantly reduced at 4 and 8 h. DBP was significantly reduced at 4 h and 8 h in the Caucasian subjects and at 8 h in the Chinese.

HR was significantly raised in the Chinese subjects at 12 and 24 h after the 4 mg dose of perindopril, however this trend was no longer significant after the weight-adjusted dose. Caucasians showed a significant reduction in HR at 4 and 8 h.

There were no significant differences between the two groups in either BP or HR response.

In the standing position there was no effect on SBP in either group, regardless of dose. No effect on DBP was seen after the 4 mg dose but there was a tendency towards a reduction in both groups after the weight-adjusted dose, although this was only significant in the Caucasian group at 4 h and 24 h. No effect was seen on HR in the standing position.

Clinical tolerability

Perindopril was well tolerated throughout the study. Only one Chinese subject reported any ill effects and that was dizziness commencing 48 h post-dose and persisting until the following morning. However, her blood pressure had returned to its pre-treatment level by the onset of this symptom. Blood pressure and heart rate stayed within normal limits for every subject throughout the study period.

Discussion

This study does not reveal any clinically relevant ethnic differences in the pharmacokinetics or pharmacodynamics of perindopril or perindoprilat between Chinese and Caucasians. The tendency for higher C_{\max} and $AUC(t)$ values in the Chinese after the 4 mg dose can be explained by their lower body weight as this difference was no longer seen after the weight-adjusted dose. The only significant difference between the groups that emerged was the shorter t_{\max} of perindopril in Chinese subjects following the 4 mg dose (median 0.5, range 0.5–1.5 vs median 1.0, range 0.5–1.50, $P < 0.05$). After a weight-adjusted dose the t_{\max} tended to be shorter, but the difference did not reach significance (median 0.5, range 0.5–1.0 vs median 1.0, range 0.5–3.0). However, differences in the observed t_{\max} levels may be distorted because blood samples were only taken at 30 min intervals over the first 2 h. Despite this, the data suggest that perindopril is absorbed slightly faster in Chinese subjects, which could be related to more rapid gastric emptying. The t_{\max} for perindoprilat also tended to be shorter in the Chinese group which would again be compatible with more rapid absorption of the parent drug, allowing earlier conversion to the active product. Whether these findings represent a genuine ethnic difference is uncertain, but they appear to have little effect on the pharmacodynamic responses. In Chinese, levels of circulating α_1 -acid glycoprotein are 25% lower than in Caucasians and this has been implicated in higher plasma concentrations of, and

sometimes increased sensitivity to, certain basic drugs in this racial group [2, 10]. Neither perindopril nor perindoprilat are basic drugs and so are mainly bound to albumin, the levels of which were found to be virtually the same in the two groups (see Table 3).

The small effect of a single dose of perindopril on blood pressure in both groups is in accordance with that reported in other studies conducted on healthy volunteers [11–14]. However, the significant rise in heart rate seen in Chinese subjects at 12 h and persisting at 24 h after a 4 mg dose is an interesting finding. Studies in healthy volunteers generally show no effect on heart rate in response to ACE-inhibition, although one study has demonstrated a rise in healthy Caucasians after 4 mg of perindopril [15].

The pharmacokinetics of perindopril and perindoprilat in plasma proved difficult to fit to standard compartmental models. The terminal elimination half-life of perindopril is generally reported as between 1.5 and 3 h [12, 16, 17]. However, the terminal elimination phase is characterised by extremely low concentrations of the parent drug representing a tiny fraction of the original dose and sometimes leading to the calculation of an unrealistically long $t_{1/2z}$, perhaps due to analytical artifacts [18]. By 12 h the concentration of perindopril in plasma was 0.7% of the peak concentration in Chinese and 0.4% in Caucasians and for many of the subjects, the last measurable perindopril concentration was at 12 h. It therefore seemed justifiable to report the perindopril concentrations only between 0 and 12 h.

In both groups of subjects, free plasma perindoprilat was eliminated in under 7 h, but there was a prolonged terminal elimination phase in excess of 40 h. This phenomenon is probably due to saturable binding to ACE [19, 20]. Mathematical models have been published which better describe the pharmacokinetics of ACE-inhibitors after repeated administration and relate plasma concentration to ACE-inhibition [21, 22]. These models make an excellent attempt to characterise a complicated pharmacokinetic process, which is over-simplified by a standard two-compartment model. However, the application of a complex 'physiologically realistic' model did not seem warranted for a single dose study, as the pharmacokinetics in this situation are essentially linear.

The only pharmacokinetic parameters for perindopril or perindoprilat that differed from others published elsewhere were the cumulative urinary excretion and the renal clearance. The renal clearance of perindopril is higher and the renal clearance of perindoprilat is lower in both the Chinese and the Caucasian group than has previously been reported [12, 18]. There is no obvious reason for this difference. Poorer compliance with sample collection in our subjects is not a valid explanation as this would result in a lower renal clearance.

As perindopril was developed in Europe, information relating to its pharmacokinetics and pharmacodynamics has been gathered mostly from Caucasian populations. This is the case with a great many therapeutic agents, despite the evidence now accumulating about racial differences in drug metabolism. Unfortu-

nately, many authors do not take pharmacanthropology into account and fail to mention the ethnic background of their sample population when reporting their findings.

The present study suggests that the minor differences in pharmacokinetics between healthy Chinese and Caucasian volunteers have no significant effects on the pharmacodynamics of perindopril. We conclude that no adjustment of the standard 4 mg dose is

necessary for Chinese subjects. However, a reduction may be required for patients of very low body weight, i.e. less than 50 kg, and such individuals are more frequently found in Asian populations.

The authors are grateful to Dr C. Arts for the measurement of perindopril and perindoprilat and also to Dr J.P. Tillement and Dr F. Bree for the plasma protein binding analysis.

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(Received 15 June 1994,
accepted 23 November 1994)