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Humoral effects of perindopril in essential hypertension

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Perindopril is a new orally active non-sulphur containing inhibitor of angiotensin converting enzyme (ACE) with enzyme inhibition being due to perindoprilat, the active diacid [1, 2]. Previous work in patients with essential hypertension has demonstrated significant reductions in blood pressure with doses of 4–8 mg/day over a 1 month period [3, 4]. We have now investigated the effects of perindopril in essential hypertension not only on blood pressure but also on the activity of the renin-angiotensin-aldosterone system as well as on plasma atrial natriuretic peptide (ANP).

This study was approved by the local Ethical Committee, informed consent was obtained in every case and was carried out in 12 patients with uncomplicated essential hypertension. There was a 2 week run- in period followed by a 2- week placebo observation phase, all patients were then randomised to a 1 month cross over treatment period on 2 mg or 8 mg perindopril per day. At the end of the placebo and at the end of each treatment period measurements were taken at 2, 4, 6 and 24 h after taking the last tablet.

Blood pressure and heart rate were measured with standardised ultrasound sphygmomanometer techniques. Blood was taken with the patient sitting upright for 10 min for plasma renin activity (PRA), aldosterone and ANP [5]. Plasma levels of perindopril and perindoprilat were measured by radioimmunoassay after separation on Dowex AGI × 2 ion exchange chromatography. Plasma ACE activity was measured as described [6] using hippuryl histidyl leucine as the substrate. Statistical analysis was by analysis of variance with repeated measures and with paired t-tests. Results are given as means with (SEM).

Plasma levels of perindopril were dose -dependent, highest at 2 h after the oral dose and declined rapidly thereafter; by contrast, plasma level of perindoprilat increased rapidly and remained elevated up to 6 h after the oral dose. After perindopril there was marked dose and time-dependent (ANOVA $P < 0.0001$) inhibition of converting enzyme activity with maximal inhibition 4–6 h after perindopril well in agreement with the levels of perindoprilat (Table).

As found with other ACE inhibitors, administration of perindopril was associated with time-dependent increases in PRA with highest levels at 4 h after perindopril for both doses (ANOVA $P < 0.005$), by contrast, there were reductions in plasma aldosterone (Fig. 1). There were no effects on plasma ANP.

During the placebo period, average blood pressures (supine) ranged from 159–163/98–106 mm Hg. After perindopril there were significant time-dependent changes for both doses of perindopril (ANOVA $P = 0.015$) with blood pressures being lower at 4 h than at 24 h after perindopril (4 h: 148 (4.4) 96 (2.6) for the 2 mg and 142 (5.3) 91 (3.4) mm Hg for the 8 mg dose; 24 h: 155 (4.7) 102 (3.6) for the 2 mg and 154 (4.7) 97 (3.8) mm Hg for the 8 mg dose respectively). Although there was a trend for lower blood pressures with the higher dose of 8 mg there was no overall statistically significant dose-

Table 1. Plasma concentrations of perindopril, perindoprilat and angiotensin converting enzyme in patients with essential hypertension

	Time (h) after placebo/perindopril			
	2	4	6	24
Perindopril (ng/ml)				
2 mg dose	17.9 (1.4)	5.7 (0.5)	3.0 (3.0)	1.0 (0.2)
8 mg dose	76.9 (10.4)	27.1 (4.2)	12.6 (2.0)	1.4 (0.3)
Perindoprilat (ng/ml)				
2 mg dose	6.2 (1.3)	6.4 (0.1)	5.2 (0.3)	1.3 (0.2)
8 mg dose	22.1 (4.6)	24.6 (2.6)	20.8 (2.2)	2.4 (0.3)
ACE activity (mU/ml)				
Placebo	12.2 (1.2)	11.8 (1.1)	11.6 (1.0)	11.8 (1.2)
2 mg dose	2.9 (0.3)	2.4 (0.2)	2.7 (0.3)	5.6 (0.4)
8 mg dose	1.6 (0.3)	1.0 (0.2)	1.2 (0.2)	4.4 (0.5)

(means with (SEM); $n = 12$); measurements were taken at 2, 4, 6 and 24 h after the last dose of placebo/perindopril

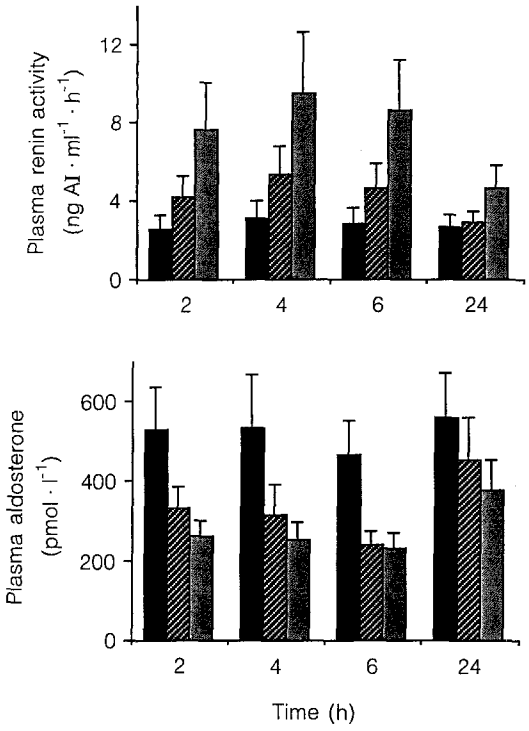

Fig. 1 a, b. Plasma renin activity (**a**) and plasma aldosterone (**b**) in 12 patients with essential hypertension on placebo (■) and after 2 mg (▨) or 8 mg (▨) perindopril. Measurements were taken at 2, 4, 6 and 24 h after the last dose of placebo/perindopril. All values are means with SEM

effect. There were no significant effects in both supine or standing heart rate.

In conclusion, perindopril was an effective inhibitor of ACE activity in patients with essential hypertension. The inhibition was closely related to the plasma levels of the perindopril metabolite perindoprilat and was associated with increases in PRA but not plasma aldosterone. The present study also demonstrates reductions in blood pressure but these were not associated with corresponding changes in heart rate and this is consistent with the possibility that converting enzyme inhibitors in general increase parasympathomimetic activity [2].

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