Br. J. clin. Pharmac. (1992), **34**, 366–369

Effect of alacepril on blood pressure and neurohumoral factors at rest and during dynamic exercise in patients with essential hypertension

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We assessed blood pressure and neurohumoral factors at rest and during exercise in 10 patients with essential hypertension before and after treatment with the new angiotensin converting enzyme inhibitor, alacepril (25–50 mg day^{-1}). Alacepril significantly lowered mean blood pressure at rest and at the same exercise load as before treatment without affecting heart rate response. The response of plasma renin activity, plasma aldosterone, and plasma adrenaline were not changed by alacepril, but increase of plasma angiotensin II and plasma noradrenaline during exercise were significantly attenuated after alacepril treatment (ANOVA, $P = 0.04$, both). The change in mean blood pressure during exercise was positively correlated with the decrease in plasma angiotensin II ($r = 0.65$, $P < 0.05$). These results demonstrated that alacepril was effective in essential hypertension both at rest and during exercise, suggesting that the antihypertensive effect during exercise might be related to the decrease in pressor hormones, especially in plasma angiotensin II.

Keywords alacepril angiotensin converting enzyme inhibitor renin-angiotensin-aldosterone system exercise test essential hypertension

Introduction

Alacepril was developed in Japan as a new angiotensin converting enzyme inhibitor characterized by long lasting antihypertensive activity (Kono, 1983). Alacepril is metabolized to captopril via a metabolite desacetyl-alacepril. It was reported that the duration of the antihypertensive effect lasted 1.5–2.0 times as long as that of captopril (Takeyama *et al.*, 1985) and accordingly, it was effective in hypertensive patients with once or twice daily administration (Ikeda *et al.*, 1985). The longer action of alacepril as compared with captopril might relate to the metabolite, desacetylalacepril which reported to have sympatho-inhibitory activity (Minato *et al.*, 1989).

Although its antihypertensive activity was well documented and the effects of renin-angiotensin system at resting state have been reported (Iimura *et al.*, 1986), the influences of alacepril on exercise-induced changes of blood pressure (BP), renin-angiotensin system and sympathetic nervous activity still remain to be assessed. In this study we investigated the effects of alacepril on BP and neurohumoral factors both at rest and during dynamic exercise.

Method

Ten hypertensive patients were enrolled in this study. They consisted of five males and five females, mean age of 54 (range 39–65 years), with essential hypertension in WHO classes I or II. They met the criteria of systolic BP > 160 mmHg, and/or diastolic BP > 95 mmHg at the last two visits prior to the study. Secondary hypertension was excluded by clinical examination, routine blood and urine analysis and hormonal examinations. Serum creatinine concentrations of all patients were within normal limits. All patients gave written informed consent.

The exercise test was performed using treadmill (Marquett CASE 12) by modified Bruce protocol. Electrocardiogram was continuously monitored, while BP was measured by cuff technique at rest, 1 min interval during and post exercise. The criteria for stopping exercise were i) achievement of 85% of predicted maximum HR, ii) leg fatigue or shortness of breath, iii) SBP ≧ 260 mmHg or DBP ≧ 130 mmHg. An intravenous cannula was inserted into a forearm vein. Blood sampling was carried out for determination of plasma renin activity (PRA), plasma angiotensin II(AII), plasma aldosterone (PA), plasma noradrenaline (NA) and plasma adrenaline

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(A) at rest (30 min of bed rest) and immediately after exercise. PA level was also determined at 5 and 10 min postexercise. After taking alacepril at a dose of 25–50 mg/day (twice daily) for 2–4 weeks, patients underwent the same test at the same time of the day as the first test. PRA was measured by r.i.a. with γ-Coat Renin Kit (Ogihara *et al.*, 1980), AII by r.i.a. with PEG method (Morimoto *et al.*, 1983), and PA by Aldosterone-r.i.a. kit II (Ogihara *et al.*, 1977). Plasma NA and A were assayed by h.p.l.c. with THI method (Yui *et al.*, 1980). Normal values at rest were as follows: PRA 0.5–2.0 ng ml^{-1} h^{-1}, AII < 25 pg ml^{-1}, PA 47–131 pg ml^{-1}, NA 60–450 pg ml^{-1}, A < 120 pg ml^{-1}.

A three-way, mixed-model analysis of variance (Sokal & Rohlf, 1969) was used for the data analysis. The group (G) and time (T) were the two fixed factors, while the individual subjects were the random factor. The group, the first fixed factor consisted of two levels (before medication and after medication). The time, second fixed factor consisted of six levels (R, EX1, EX2, PK, P0, P5) for mean BP, four levels (R, P0, P5, P10) for PA, and two levels (R, P0) for PRA, AII, NA and A (see abbreviation for Table 1). Student's *t*-test was applied to test for further differences between means. Linear regression analysis was used to determine the correlation between variables. Results were expressed as mean ± s.e. mean. *P* values less than 0.05 were considered significant.

Results

Exercise lasted for 7.4 ± 0.9 min before the treatment and 8.5 ± 0.9 min after alacepril treatment, without significant difference. In both exercise tests, exercise was discontinued by achievement of target HR in five patients, complaint of leg fatigue or shortness of breath in three and BP rise in two. There was a significant difference in mean BP between before treatment and after treatment of alacepril (ANOVA, $P = 0.02$; group). Alacepril lowered mean BP at rest (118 ± 9 → 106 ± 4 mmHg, $P < 0.05$), and at the same load of exercise during alacepril therapy (147 ± 5 → 135 ± 5 mmHg, $P < 0.05$). HR responses (rest: 65 ± 2 → 62 ± 4 beats min^{-1}, peak: 135 ± 3 → 134 ± 4 beats min^{-1}) were not different after alacepril treatment.

The response of PRA, PA, and A during exercise were not different after alacepril treatment ($P > 0.05$; group, time, G × T). However, there were significant differences between before treatment and after treatment of alacepril in the responses of AII and NA during exercise (both $P < 0.05$; G × T). These results showed

Table 1 Effects of alacepril on mean blood pressure and neurohumoral factors at rest and during exercise in patients with essential hypertension

		Control	*Alacepril*	*Source of variance*	P *value*	F *ratio*
Mean BP (mmHg)	R	118 ± 9	106 ± 4	G	0.022	7.60
	EX1	125 ± 6	126 ± 4	T	0.000	22.74
	EX2	141 ± 4	129 ± 6	G × T	0.134	1.79
	PK	147 ± 5	139 ± 6			
	P0	143 ± 3	131 ± 5			
	P5	119 ± 4	114 ± 4			
	Same level	147 ± 5	135 ± 5			
PRA (ng ml^{-1} h^{-1})	R	1.27 ± 0.28	1.31 ± 0.52	G	0.811	0.66
	P0	2.27 ± 0.61	2.59 ± 1.07	T	0.091	3.58
				G × T	0.635	0.24
AII (pg ml^{-1})	R	15.9 ± 1.9	12.7 ± 2.0	G	0.071	4.19
	P0	25.5 ± 7.8	17.4 ± 7.8	T	0.407	0.75
				G × T	0.040	5.73
PA (pg ml^{-1})	R	52.6 ± 8.4	45.7 ± 7.8	G	0.187	2.03
	P0	91.4 ± 13.0	77.4 ± 9.5	T	0.000	17.25
	P5	99.0 ± 12.7	64.7 ± 9.1	G × T	0.368	1.10
	P10	89.7 ± 11.7	61.1 ± 8.0			
NA (pg ml^{-1})	R	127 ± 16	129 ± 19	G	0.099	3.39
	P0	687 ± 102	577 ± 83	T	0.0002	37.99
				G × T	0.042	5.61
A (pg ml^{-1})	R	26 ± 5	27 ± 4	G	0.446	0.63
	P0	78 ± 18	67 ± 11	T	0.005	13.56
				G × T	0.357	0.94

Mean BP: mean blood pressure, PRA: plasma renin activity, AII: plasma angiotensin II, PA: plasma aldosterone, NA: plasma noradrenaline, A: plasma adrenaline, R: rest, EX1: exercise stage 1, EX2: exercise stage 2, PK: peak exercise, P0: immediately after exercise, P5: 5 min postexercise, P10: 10 min postexercise, Same level: at the same load of exercise, G: group, T: time. Values are mean ± s.e. mean.

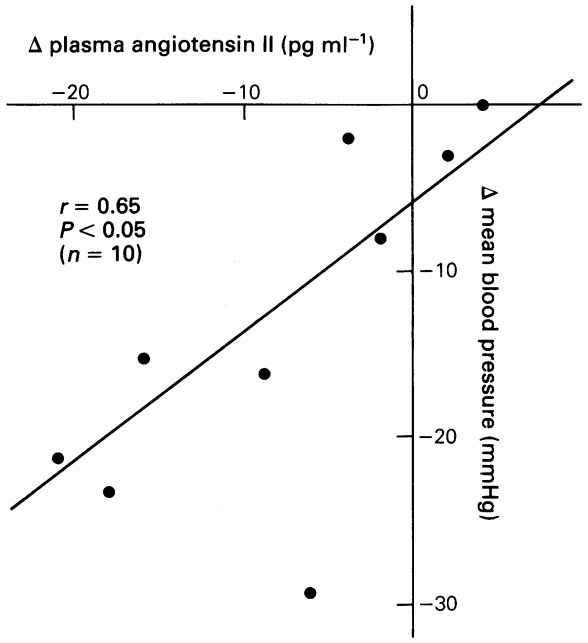

Figure 1 Relationship between change in mean blood pressure (Δ mean blood pressure) during exercise under alacepril treatment and change in plasma angiotensin II concentration (Δ angiotensin II) immediately after exercise in patients with essential hypertension.

that alacepril treatment significantly attenuated the exercise-induced increase in AII and NA levels (Table 1).

The change in mean BP (difference between the BP of peak exercise before treatment and that of the same load of exercise during treatment) was correlated positively with the decrease in AII immediately after exercise ($r = 0.65$, $P < 0.05$) (Figure 1). While no significant correlations were found between the change in mean BP and the changes in AII at rest, in NA immediately after exercise or pretreatment value of PRA.

Discussion

The present study showed that alacepril 25–50 mg/day effectively attenuated BP both at rest and at the same load of exercise without affecting HR response. The results were in agreement with the former observations using ACE inhibitors, captopril (Fagard *et al.*, 1982) and enalapril (Lund-Johansen & Omvik, 1984). Our findings suggested that alacepril is effective in patients with essential hypertension during their submaximal physical activity.

The antihypertensive mechanism of ACE inhibitors is still not yet clarified entirely, but it is generally accepted that ACE inhibitors exert their antihypertensive activity by the consequences of suppression of the renin-angiotensin system and potentiation of the kallikrein-kinin system (Murthy *et al.*, 1987). Moreover, the decrease in the sympathetic activity resulting from the inhibition of AII also played a role for its antihypertensive effect (Philipp *et al.*, 1987). Cerasola *et al.* (1987) reported that enalapril lowered BP, inhibited ACE activity and decreased AII with significant decrease of plasma NA in hypertensives. Morioka *et al.* (1983) demonstrated that enalapril lowered exercise BP with attenuation of the exercised-induced rise of plasma NA in patients with hypertension. We found in this study that the treatment with alacepril significantly attenuated the exercise-induced increase in plasma level of AII and NA. These hormones are important endogenous pressor substances which regulate arterial pressure during exercise. The findings of decreased pressor hormones with a fall in BP after alacepril suggested that the attenuation of these hormones might relate to the BP decrease during exercise. The positive correlation between the decrease in exercise BP and the decrease in AII (Figure 1) further indicated the close correlation between antihypertensive effect of alacepril and the inhibition of AII during exercise.

Although there have been some controversies concerning the effects of ACE inhibitors on sympathetic activity (Crozier *et al.*, 1989), a number of reports (Cerasola *et al.*, 1987; Morioka *et al.*, 1983; Weinberger, 1982) supported the hypothesis that the ACE inhibitor decreased sympathetic activity. This interaction might possibly be interpreted by the known actions of AII on the sympathetic nervous system. They included the inhibition of reuptake of NA (Khairallah, 1972), direct stimulation, both biosynthesis (Roth, 1972) and release of NA (Zimmerman *et al.*, 1972) at nerve endings. Inhibition of AII could therefore exert influence on the synthesis, release and reuptake of NA, resulting in inhibitory effects on sympathetic activity. In our study, exercise duration after alacepril turned out to be slightly longer and sympathetic activity might be more augmented as the workload increased. However, exercise-induced increase in plasma NA level was attenuated by alacepril treatment. Alacepril is metabolised to captopril via desacetyl-alacepril, a metabolite of alacepril (Matsumoto *et al.*, 1986). Minato *et al.* (1989) reported that the metabolite itself possessed sympatho-inhibitory activity. Therefore it was possible that the decrease in NA might be caused by sympatho-inhibitory action of this metabolite in addition to the influence of decreased level of AII on sympathetic activity.

In conclusion, alacepril was effective in patients with essential hypertension both at rest and during exercise and its antihypertensive effect during exercise might be related to the decrease in pressor hormones, especially in AII caused by ACE inhibition.

We would like to thank Dr Don W. Wallick for his help with the statistical analysis.

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(Received 27 January 1992, accepted 18 May 1992)