Age and the pharmacodynamics of angiotensin converting enzyme inhibitors enalapril and enalaprilat

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- 1 The effect of age on the pharmacodynamic responses to converting enzyme inhibitors, enalapril and enalaprilat was investigated in nine young (22–30 years) and nine sex-matched elderly (65–73 years), healthy volunteers.
- 2 The groups differed in baseline blood pressure, young 121/64 mmHg, elderly 142/75 mmHg ($P < 0.01$), but not in sodium intake or body weight.
- 3 Both enalapril and enalaprilat produced significant falls in blood pressure in both groups but no increase in heart rate in the supine or erect posture.
- 4 The blood pressure fall was significantly greater in the elderly on both treatments and in both erect and supine posture.
- 5 The greater fall in blood pressure in the elderly was associated with a more prolonged inhibition of plasma angiotensin converting enzyme activity.
- 6 The apparent age-related difference in response appears to be due to the difference in baseline blood pressures between the groups. Further study of the usefulness of chronic dosing with angiotensin converting enzyme inhibitors in hypertension in the elderly is indicated.

Keywords age converting enzyme inhibitors elderly enalapril enalaprilat blood pressure

Introduction

The proportion of the elderly in the population is increasing and the frequency of drug therapy and possibility of adverse reactions rises with age (Greenblatt *et al.*, 1982). The prevalence of hypertension increases with age and is common among the elderly population (Kannel & Gordon, 1978). The current understanding of the clinical pharmacology of many drugs is based on studies in younger age groups. However, it is known that the pharmacodynamic responses to anti-hypertensive therapy may be influenced by age. β -adrenoceptor blockers have been claimed to be more effective in younger hypertensives with high plasma renin (Buhler *et al.*, 1972, 1975; Stumpe *et al.*, 1976), and this may be related to

reduced β -adrenoceptor sensitivity in old age (Vestal *et al.*, 1978). By contrast, a greater hypotensive effect in the elderly and in patients with low plasma renin has been reported for diuretics (Vaughan *et al.*, 1973), for calcium antagonists (Buhler *et al.*, 1982) and for the vasodilator nitroprusside (Irvine & Shepherd, 1984).

Angiotensin converting enzyme inhibitors are of established value in the management of hypertension (Gavras *et al.*, 1974) and congestive heart failure (Turini *et al.*, 1979). The pharmacodynamic responses to these agents have been claimed to be directly related to plasma renin activity (Case *et al.*, 1977), which falls with age (Meade *et al.*, 1983). The antihypertensive

efficacy of converting enzyme inhibitors might thus be expected to diminish with age. Indeed, Lijnen *et al.* (1983) have reported in a retrospective study, that the hypotensive response to captopril is greater in younger than elderly hypertensives although others have described good responses to captopril in the elderly (Corea *et al.*, 1984). We are unaware of a prospective comparison of converting enzyme inhibitors in young and elderly people. The aim of our study was to investigate and compare the cardiovascular and endocrine responses during converting enzyme inhibition with the non sulphydryl agents, oral enalapril and its active metabolite, enalaprilat intravenously, in normotensive healthy young and elderly subjects. The work was presented previously as a communication to the British Pharmacological Society (Hockings *et al.*, 1985). The pharmacokinetics of enalaprilat in these subjects is described in a separate paper (Hockings *et al.*, 1986).

Methods

Subjects

Healthy volunteers, nine young (aged 22–30 years) and nine elderly (65–73 years) were studied after informed consent and ethical approval. Subjects were living in the community and were recruited with the help of their general practitioners. They were judged to be healthy on the basis of previous history, a normal physical examination and no abnormality in the electrocardiogram, full blood count or biochemical screen. The two groups were matched for sex, six men and three women each. Pre-study plasma renin activity in the elderly (2.4 ± 3.2 ng AI ml⁻¹ h⁻¹) tended to be lower than in the young group

(3.8 ± 1.8 ng AI ml⁻¹ h⁻¹) but this difference was not statistically significant. The elderly group had a significantly higher pre-study supine blood pressure ($142 \pm 10/75 \pm 9$ mm Hg) compared to the young ($121 \pm 8/64 \pm 6$ mm Hg). Both groups were salt replete. Salt intake, as assessed from 24 h urine sodium was similar in the two groups, 132 ± 52 and 121 ± 41 mmol day⁻¹ in young and old respectively. Creatinine clearance was significantly lower in the older group but considered within normal limits for their age. The clinical details of the subjects are summarised in Table 1.

Study design

The study was single blind placebo controlled, randomised crossover with treatment order allocated according to a balanced (3×3) Latin square design. Subjects were studied on three different occasions at least a week apart. They received 10 mg oral enalapril maleate, or matching placebo capsule or 10 mg intravenous enalaprilat. Subjects were receiving no medication and were told to avoid cigarettes, coffee, tea or alcohol 12 h prior to and for the entire duration of the study day.

After an overnight fast, volunteers attended the Clinical Pharmacology Research Unit at 08.30 h. A cannula was inserted into a forearm vein and kept patent by intermittent heparin flushing. After 30 min of supine rest, baseline blood samples were taken and blood pressures and heart rate recorded. Blood samples were collected on ice for plasma renin activity, aldosterone and angiotensin converting enzyme activity at the following times: 0, 1, 2, 4, 6, 8, 24, 48, 72 and 96 h.

Blood pressures and heart rate recordings were made at these times by means of a semi-

Table 1 Clinical details of the nine young and nine elderly volunteers

	Young	Elderly	P value
Age (years)	25 ± 3	69 ± 4	< 0.001
Weight (kg)	64 ± 10	70 ± 13	NS
Male/female	6/3	6/3	NS
Pre-study supine blood pressure (mmHg)			
systolic	121 ± 8	142 ± 10	< 0.01
diastolic	64 ± 6	75 ± 9	< 0.01
Pre-study supine plasma renin activity (ng AI ml ⁻¹ h ⁻¹)	3.8 ± 1.8	2.4 ± 3.2	NS
Creatinine clearance (ml min ⁻¹)	92 ± 15	66 ± 19	< 0.01
24 h urine sodium (nmol)	132 ± 52	121 ± 41	NS

automatic sphygmomanometer (Sentron-Bard Biomedical). Recordings were taken twice supine and then at 1, 2 and 5 min after standing. Blood pressure response to treatment is described as placebo corrected. Correction was made by subtracting the placebo value for each observation from the equivalent observation after active treatment. Subjects received a light lunch at 4 h after dosing.

Laboratory methods

Angiotensin I converting enzyme activity in plasma was measured by the method of Cushman & Cheung (1971) as modified by Chiknas (1979). The activity is measured as the rate of generation of hippuric acid from tripeptide substrate hippuryl-histidyl-leucine. Hippuric acid is measured by high pressure liquid chromatography. The normal range in our laboratory is 5–32 units ml^{-1} . A unit of enzyme generates 1 nmol of hippuric acid min^{-1} . All samples from each individual were assayed together, the inter- and intra-assay variation being 6% and 2% respectively. The limit of detection was 0.1 units.

Plasma renin activity was measured by the method of Derkx *et al.*, (1978). Angiotensin I generated during incubation of buffer and plasma at 37°C was measured by radioimmunoassay. The range in our laboratory is 4–12 ng AI $\text{ml}^{-1} \text{h}^{-1}$, the limit of detection being 1 ng AI $\text{ml}^{-1} \text{h}^{-1}$. The inter- and intra-assay coefficients of variation were 7.0 and 5.5% respectively.

Plasma aldosterone was measured by the direct radioimmunoassay method of McKenzie & Clements (1974). The normal range in the

supine position in our laboratory is 12–125 pg ml^{-1} . The limit of detection is 10 pg ml^{-1} and the inter- and intra-assay coefficients of variation 11 and 7% respectively.

Statistical analysis of results

All results are expressed as mean $\pm$ s.d. Blood pressure, heart rate and endocrine responses were subjected to repeated measures analysis of variance. The relationship between blood pressure fall and plasma renin activity was examined by linear regression analysis. Differences between blood pressure profiles were compared using analysis of covariance using the initial blood pressure as a covariate. Where appropriate, Student's *t*-test was employed for paired and unpaired comparisons. The null hypothesis was rejected at $P < 0.05$.

Results

Enalapril and enalaprilat were well tolerated. One young and one elderly subject felt dizzy on standing in the period up to 1 h after dosing on the day they received intravenous enalaprilat. There were no other side effects reported spontaneously or on enquiry.

Blood pressure and heart rate

Blood pressure on placebo was higher in the elderly ($142 \pm 10/75 \pm 9$ mm Hg) than in the young ($121 \pm 8/64 \pm 6$ mm Hg). Blood pressure fell significantly in both groups on oral enalapril and intravenous enalaprilat. The fall was signifi-

Table 2 Mean maximum blood pressure falls (systolic/diastolic) and percentage falls corrected for changes in blood pressure on placebo day after enalapril and enalaprilat in young and elderly volunteers. The differences in blood pressure falls, both systolic and diastolic, between the age groups were all significant at the 0.1% level

Treatment	Young (n = 9)	Elderly (n = 9)
Enalapril (systolic/diastolic)		
supine (mmHg)	8/8	22/12
5 min erect (mmHg)	7/6	25/20
% fall (systolic/diastolic)		
supine %	7/13	15/17
5 min erect (%)	6/9	18/27
Enalaprilat (systolic/diastolic)		
supine (mmHg)	10/7	25/13
5 min erect (mmHg)	13/11	29/22
% fall (systolic/distolic)		
supine %	8/11	18/17
5 min erect (%)	11/17	20/29

Figure 1 Mean systolic and diastolic blood pressure fall after 5 min standing adjusted for placebo in young (○) and elderly (●) volunteers. $n = 9$ in each group.

cantly greater in the elderly in both supine and erect postures and on both treatments. In the supine position the mean maximum blood pressure fall (systolic/diastolic) for the elderly on enalapril was 22/13 mm Hg and for the young 8/8 mm Hg ($P < 0.001$). On enalaprilat supine blood pressure fell by 25/13 mm Hg in the elderly, and by 10/7 mm Hg in the young ($P < 0.001$). In the erect posture, blood pressure fell by 25/20 mm Hg in the elderly on enalapril, and by 7/6 mm Hg in the young ($P < 0.001$). Similarly, on enalaprilat, erect blood pressure fell by 29/22 mm Hg in the elderly and by 13/11 mm Hg in the young. An orthostatic blood pressure fall was not observed. In all cases the fall in blood pressure was biphasic with an early fall within the

first hour, followed by a delayed maximum fall at about 6 h. At 24 h after dosing, there was no discernible effect on blood pressure in the young but diastolic pressure was still affected in the elderly. These results are summarised in Table 2 and Figure 1. Although the greater absolute fall in the elderly persisted when the results were expressed as percentages (Table 2) analysis of covariance, using initial blood pressure as a covariate, showed that once initial pressure differences were allowed for there was no significant difference between the age groups.

The baseline supine heart rate was 77.6 ± 12.9 beats min^{-1} in the elderly and 67.3 ± 9.3 beats min^{-1} in the young. Heart rate tended to rise with the fall in blood pressure, but there was

Figure 2 Time profile of inhibition of plasma angiotensin converting enzyme activity in young (○) and elderly (●) volunteers following (a) oral enalapril (b) enalaprilat ($\pm$ s.d.).

no statistically significant rise in either group on either treatment.

Inhibition of plasma angiotensin converting enzyme activity

Baseline plasma angiotensin converting enzyme activity was similar in the two groups (19.2 ± 6.8 units in young and 20.5 ± 4.1 in the elderly). There was little diurnal variation in enzyme activity on the placebo day. Maximum converting enzyme inhibition was observed within 30 min of dosing with enalaprilat but not until 4–6 h after dosing with oral enalapril. Maximum inhibition following enalaprilat was of a greater magnitude than that seen after oral enalapril in both groups. Peak inhibition was comparable in both groups, on both drugs, but the elderly exhibited a prolonged duration of converting enzyme inhibition. These results are shown in Figure 2. ACE activity was still significantly

inhibited at 48 h in the elderly but had returned to baseline by 24 h in the young group.

Plasma renin activity and plasma aldosterone levels

The profiles of plasma renin activity (PRA) and plasma aldosterone concentration for both groups are shown in Figures 3 and 4. Both enalapril and enalaprilat caused significant increases in PRA, maximal between 2–8 h. The rise in PRA was greater on enalaprilat in both age groups. The young group showed a greater increment in PRA to both drugs than the elderly. The baseline PRA in the elderly was less than in the young. There was no significant relationship between basal plasma renin activity and supine systolic blood pressure fall corrected for placebo in either group, or when both groups were pooled. ($r = -0.36$ $P > 0.1$). The baseline plasma aldosterone concentration was similar in

Figure 3 Time profile of plasma renin activity in (a) young and (b) elderly volunteers after placebo (○---○), enalapril (●) and enalaprilat (▲). $n = 9$ in each group.

the two groups, 74.3 ± 32.8 pg ml⁻¹ in young and 62.3 ± 4.4 pg ml⁻¹ in the elderly. Both enalapril and enalaprilat caused a modest reduction in plasma aldosterone concentration between 2–8 h and the effect was most marked with enalaprilat.

Discussion

The pharmacodynamic response to converting enzyme inhibition has been claimed to be dependent on plasma renin activity and to be greater in hypertensives with high plasma renin (Case *et al.*, 1977). Epidemiological studies indicate that plasma renin activity falls with increasing age (Meade *et al.*, 1983). It might thus be anticipated that the blood pressure response to oral enalapril and its active metabolite enalaprilat may be reduced in the elderly. Our results show that enalapril and enalaprilat significantly reduce blood pressure not only in the young as has been shown before (Millar *et al.*, 1982; Hodsman *et al.*, 1984) but also in elderly normotensives. The blood pressure fall was numerically greater in the elderly, on both enalapril and enalaprilat. These differences persisted when changes were expressed as a percentage of starting pressure. However, this difference may be a consequence

of higher baseline blood pressure in the elderly as there was no difference by analysis of covariance. It is premature at this stage to extrapolate our findings to hypertensives or to chronic dosing. Our findings of a substantial fall in blood pressure in old age are in contrast to those of Lijnen *et al.* (1983), who reported a greater fall in younger hypertensives on captopril, although their study was neither prospective nor controlled. They are, however in agreement with those of Corea *et al.* (1984), who reported a good response to captopril in elderly hypertensives.

The fall in blood pressure seen in the elderly could not be easily explained on the basis of differences in baseline plasma renin activity, or in the increment in renin response to converting enzyme inhibition, or sodium intake as assessed by 24 h urine sodium. These factors can contribute to the initial vasodepressor response to converting enzyme inhibition (Hodsman *et al.*, 1983). It is noteworthy, however, that other studies have not found a correlation between baseline PRA and antihypertensive effect of captopril (Bravo & Tarazi, 1979; Gavras *et al.*, 1978; Waeber *et al.*, 1980).

The blood pressure fall, corrected for changes after placebo, was biphasic in both groups and on both treatments. Further, while peak inhibition of ACE activity following enalaprilat was

Figure 4 Plasma aldosterone levels following placebo (○), enalapril (●) and enalaprilat (▲) in (a) young and (b) elderly volunteers. $n = 9$ in each group.

observed within 30 min of dosing, maximum blood pressure fall was not seen until 6 h. This marked temporal dissociation raises speculation as to the mechanisms of blood pressure fall with converting enzyme inhibitors. It is known that inhibition of tissue, in particular vascular wall (Dzau, 1984; Kikta & Fregly, 1983; Ungar *et al.*, 1984), ACE activity may be involved in the blood pressure fall. The early blood pressure fall may be related to inhibition of plasma converting enzyme, while the later maximum fall was associated with additional tissue ACE inhibition.

The fall in blood pressure in both groups on both treatments was not associated with impaired orthostatic tolerance or significant increases in heart rate, consistent with our previous experience (Millar *et al.*, 1982; Ajayi *et al.*, 1985a).

Absence of reflex tachycardia with blood pressure reduction is a consistent finding with converting enzyme inhibitors and this may, in part, be related to enhanced parasympathetic tone (Sturani *et al.*, 1982; Campbell *et al.*, 1985; Ajayi *et al.*, 1985a) following the removal of the vagolytic action of angiotensin II. However, a 'first dose effect' characterised by hypotension, bradycardia, sweating and unchanged plasma noradrenaline has been described after both captopril and enalapril (Cleland *et al.*, 1985). These vasovagal features are consistent with the parasympathetic effect of ACE inhibition (Sturani *et al.*, 1982; Campbell *et al.*, 1985; Ajayi *et al.*, 1985a) following the withdrawal of angiotensin II mediated vagal inhibition (Ajayi *et al.*, 1985b). There were modest reductions in plasma aldosterone and increases in plasma renin activity,

reflective of blockade of the renin angiotensin system. These changes were comparable in the two groups, so that the degree of inhibition of the plasma renin angiotensin system is unlikely to explain the differences observed. The effect on plasma renin activity was still apparent at 24 h after oral dosing.

Our study demonstrates a marked fall in blood pressure after the converting enzyme inhibitors, enalapril and enalaprilat in elderly subjects. This

was associated with prolonged inhibition of plasma angiotensin converting enzyme activity. As enalapril is generally well tolerated and causes few symptom side effects, further study of enalapril in hypertension in the elderly is indicated.

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