Antihypertensive effect of single doses of enalapril in hypertensive patients treated with bendrofluazide

J. WEBSTER, D. NEWNHAM, O. J. ROBB & J. C. PETRIE

Department of Therapeutics and Clinical Pharmacology, University of Aberdeen, Foresterhill, Aberdeen AB9 2ZB

- 1 This study was designed to investigate the validity of the then current recommendations for initiation of therapy with enalapril in hypertensive patients on treatment with a diuretic.
- 2 Enalapril in single doses of 10 and 20 mg was given to 13 hypertensive patients on treatment with bendrofluazide 5 mg daily in a randomised, crossover, placebo controlled study.
- 3 The mean maximal reduction in blood pressure was similar with both doses (35/20 mmHg supine, 38/20 mmHg standing), occurred on average within 6 h of tablet ingestion, and was not accompanied by any significant change in heart rate.
- 4 Three patients experienced symptomatic hypotension. In one patient this was incapacitating after 10 mg and precluded exposure to 20 mg.
- 5 This study shows that in hypertensive patients receiving treatment with diuretics, the addition of enalapril should be undertaken with caution. An optimal starting dose of enalapril in such patients remains to be confirmed.

Keywords enalapril bendrofluazide hypertension initial dose effects

Introduction

Enalapril is an angiotensin converting enzyme (ACE) inhibitor that has recently been approved in the United Kingdom for general use in the treatment of hypertension and heart failure. As with captopril the antihypertensive effect may be augmented by the addition of therapy with diuretics. The addition of hydrochlorothiazide to enalapril increased the antihypertensive effect in both mild (Enalapril study group, 1984) and moderate to severe (Webster *et al.*, 1986) hypertension, without evidence of severe symptomatic or postural hypotension. However, the reverse procedure—the addition of captopril to patients already on diuretic therapy—may cause profound hypotension (Hodsman *et al.*, 1983; Kramer *et al.*, 1982). Patients susceptible to profound hypotension may be salt depleted and highly dependent on activation of their renin-angiotensin-aldosterone system to maintain their electrolyte homeostasis and blood pressure. Symptomatic hypotension has recently also been

recognised in hypertensive patients when enalapril is added to diuretic therapy, as reported by our group in a case report arising within the present study (Webster *et al.*, 1985). A similar effect has recently been reported in patients with heart failure (Cleland *et al.*, 1985).

Prior to our alerting case report, initial dose ranging studies with enalapril in hypertension had suggested that a daily dose of at least 10 mg might be necessary to achieve blood pressure control in most patients (Bergstrand *et al.*, 1985). The maximal response to 10 mg and 20 mg was similar but the duration of effects was longer after the higher dosage (Gavras *et al.*, 1981). Our study was designed to investigate further the initial response to enalapril in hypertensive patients receiving diuretic therapy in view of the extensive co-prescription of these drugs.

The aim of the present study was to compare the initial blood pressure response to a single 10 mg dose of enalapril with that to a single dose of

20 mg enalapril and with that to a single dose of placebo in patients on bendrofluazide for hypertension. These were the doses recommended for routine use at the time of the design and conduct phase of the study.

Methods

Patients with hypertension were formally invited to participate in the study if their supine diastolic blood pressure was between 95–115 mm Hg (phase V) after at least 4 weeks on monotherapy with bendrofluazide 5 mg daily. Patient exclusion criteria included accelerated hypertension, severe symptomatic ischaemic heart disease, hepatic dysfunction identified either clinically or by significant abnormalities of routine liver function tests, renal impairment defined as a serum creatinine of greater than $150 \mu\text{mol l}^{-1}$, women of reproductive potential and any condition requiring concomitant medication during the study.

Suitable patients underwent a full clinical examination and had investigations performed including urinalysis, routine biochemistry, haematology, chest X-ray, 12-lead electrocardiography and urinary catecholamines.

All patients remained on bendrofluazide 5 mg daily throughout the study, which was designed as a randomised double-blind, three way cross-over protocol. The randomised treatments, of identical appearance, were enalapril 10 mg and 20 mg and placebo, each given as a single dose. Study treatments were separated by a minimum of 7 days and a maximum of 12 days. On each of the three study days, patients attended the clinical laboratory after taking their morning bendrofluazide with a light breakfast and were allowed to lie supine for 20 min. Blood pressure was then measured in duplicate (phase V diastolic) using a Hawksley random zero sphygmomanometer. Heart rate was measured from the radial pulse over 30 s. A venous blood sample was withdrawn for measurement of routine biochemistry, plasma aldosterone concentration and plasma renin activity. Blood pressure and heart rate measurements were then repeated after the patient had been standing for 2 min.

After the test tablet was administered with 100 ml water, blood pressure and heart rate measurements were repeated after 5 min supine and 2 min standing at 30 min intervals until 4 h and again at 6, 8, 12 and 24 h.

Measurements were also made of body weight 24 h urine volume and 24 h urinary electrolytes on each study day. Plasma aldosterone concentration and plasma renin activity were measured by radioimmunoassay (Sorin Biomedica).

ANOVA was used to analyse differences in baseline blood pressure and heart rate, differences in maximum changes in blood pressure from baseline and differences in biochemical investigation results. Time, order and treatment interactions were examined, using orthogonal contrasts.

The study was approved by the Aberdeen Joint Ethics Committee. All patients gave informed written consent.

Results

Some characteristics of the patients recruited are shown in Table 1. Thirteen patients were recruited, of whom twelve completed each phase of the study. The available data from the one patient who completed only two out of the three study visits are included in the overall analysis. Recruitment was discontinued after 13 patients because of concern about hypotension at these doses.

Blood pressure

The mean (s.e. mean) baseline supine blood pressures at visits 1, 2, and 3 were 172/101 (8/2); 163/96 (5/2) and 158/96 (5/3) respectively. The corresponding mean (s.e. mean) baseline standing blood pressures at visits 1, 2, and 3 were 157/97 (7/2), 148/92 (5/3) and 147/84 (6/4). The spontaneous change in blood pressure with time was statistically significant ($P < 0.001$). To allow for these anticipated changes in baseline blood pressure, analysis of drug effects was based on changes from baseline. The mean decreases in blood pressure (0–6 h) were not significantly different for visits 1, 2 and 3, showing that there were no significant linear relationships with time.

The mean changes in supine and standing blood pressure from baseline are shown in Figures 1 and 2. In these patients on bendrofluazide both doses of enalapril reduced blood pressure, compared with placebo. There was no important difference between the 10 and 20 mg doses. The maximum decrease in blood pressure occurred between 4 and 8 h after 10 mg and 20 mg enalapril. Twenty-four hours post dosing there was a consistent trend for the antihypertensive effect of enalapril 20 mg to persist longer than that of enalapril 10 mg although the separation was small and not statistically significant.

The mean maximal changes in blood pressures are shown in Table 2. There was no significant difference between 10 mg and 20 mg enalapril in the maximal changes in either supine or standing blood pressures. Both doses were significantly different from placebo ($P < 0.01$).

Table 1 Characteristics of patients. Blood pressure is the supine recording at the pre-trial screening assessment after at least 4 weeks therapy with bendrofluazide. Patients experiencing adverse effects during the study are identified by their treatment sequence and by a brief comment on the individual adverse effects. The fall in standing blood pressure after 10 mg enalapril at 6 h compared with baseline is shown for each patient.

Sex	Age (years)	Weight (kg)	Creatinine ($\mu\text{mol l}^{-1}$)	BP (mmHg)		Duration of hypertension (years)	Time on bendrofluazide (months)	Treatment sequence	Adverse experiences	Comments	Fall in standing BP at 6 h after 10 mg enalapril (mm Hg)		
1	F	62	68.5	87	166	96	21	—	115	E20 E10 P	nausea/vomiting 12 h after E20	possibly drug related	34/11
2	F	61	65.0	75	210	96	11	—	43	E10 P E20	legs 'wobbly' on standing after E10	definite drug induced hypotension	59/24
3	F	47	57.2	59	186	114	9	—	5	P E10 —	dizzy, nauseated unable to stand after E10	definite drug induced hypotension	66/50
4	M	74	80.0	150	162	96	7	—	84				21/0
5	F	64	57.6	107	230	104	4	—	2				20/11
6	F	59	78.0	77	170	104	7	—	84	E10 E20 P	mild headache 4 h after E10	uncertain if drug related	5/6
7	M	35	71.0	93	152	104	1	6	2				24/12
8	F	56	77.0	74	220	106	—	5	2				29/12
9	M	26	90.0	82	160	96	—	7	2				28/23
10	M	26	69.0	93	164	97	—	4	2				28/11
11	M	62	84.0	100	181	113	9	—	36	E20 P E10	dizzy, heart racing after E20, dizzy mild headache, tired after E10.	definite drug induced hypotension	60/39
12	F	60	62.0	72	214	108	24	—	2				49/13
13	M	41	89.6	80	189	113	—	6	4				5/7

Figure 1 Change in supine blood pressure at intervals from baseline. Points are means for systolic, placebo (□), enalapril 10 mg (△), enalapril 20 mg (○) and diastolic, placebo (■), enalapril 10 mg (▲), enalapril 20 mg (●). Representative bars for s.e. mean are shown at 6 h.

Figure 2 Change in standing blood pressure at intervals from baseline. Points are means for systolic, placebo (□), enalapril 10 mg (△), enalapril 20 mg (○) and diastolic placebo (■), enalapril 10 mg (▲), enalapril 20 mg (●). Representative bars for s.e. mean are shown at 6 h.

Heart rate

No major or consistent changes in mean supine or standing heart rate were observed (Figure 3), and there were no significant differences between the three test agents.

Biochemistry

The mean results are shown in Table 3. There

were no significant differences between visits or treatment phases in results for 24 h urinary volume and electrolytes, plasma aldosterone concentration, and plasma renin activity.

Adverse effects

One patient completed the placebo phase but developed severe hypotension 90 min after enalapril 10 mg and did not proceed with the 20 mg

Table 2 Maximum decrease in blood pressure from baseline. Results are shown as mean (s.e. mean).

	n	Placebo 13	Enalapril 10 mg 13	Enalapril 20 mg 12
<i>Supine</i>				
Systolic		17.8 (4.1)	34.7 (5.9)	35.8 (5.5)
Diastolic		10.5 (2.9)	22.7 (3.4)	20.7 (2.8)
<i>Standing</i>				
Systolic		16.7 (3.5)	40.8 (6.2)	36.0 (5.0)
Diastolic		9.9 (2.7)	23.5 (3.8)	18.9 (2.7)

n = number of patients completing each treatment phase.

Figure 3 Change in heart rate at intervals from baseline. Points are means in supine position after placebo (□), enalapril 10 mg (Δ), enalapril 20 mg (○) and in standing position after placebo (■), enalapril 10 mg (▲), enalapril 20 mg (●). Representative bars for s.e. mean are shown at 6 h.**Table 3** Biochemical measurements. Results are shown as mean (s.e. mean).

	n	Placebo 13	Enalapril 10 mg 13	Enalapril 20 mg 12
24 h urine volume (ml)		1420 (128)	1430 (164)	1314 (122)
24 h urine sodium (mmol)		109 (10)	115 (15)	120 (16)
24 h urine potassium (mmol)		40 (6)	34 (3)	33 (3)
Plasma aldosterone (pg ml ⁻¹)		256 (12)	248 (19)	230 (15)
Plasma renin activity (ng ml ⁻¹ h ⁻¹)		4.2 (1.2)	4.7 (1.1)	3.8 (0.9)

n = number of patients completing each treatment phase.

phase. Two weeks later this patient was given 5 mg enalapril in open fashion. Her blood pressure responses to enalapril have been reported previously (Webster *et al.*, 1985). Four other patients experienced adverse symptoms which may have been caused by enalapril (Table 1).

Discussion

This study shows that in hypertensive patients on treatment with bendrofluazide 5 mg once daily, enalapril produces a substantial hypotensive response when given in single doses of 10 mg and

20 mg. The maximum effect occurred within 6 h of treatment and in one patient was severe and incapacitating. The effects of the two enalapril doses were indistinguishable in this study in terms of maximal changes in blood pressure.

The reduction in blood pressure was not accompanied by any significant change in heart rate. The lack of reflex tachycardia in the presence of a fall in blood pressure is consistent with the increased parasympathomimetic activity of angiotensin converting enzyme inhibitors (Ajayi *et al.*, 1985). Excessive parasympathomimetic activity may contribute to syncope after the first dose of captopril (Cleland *et al.*, 1984) and enalapril (Cleland *et al.*, 1985) in patients with heart failure. None of our patients experienced excessive slowing of heart rate.

The patient who suffered the most severe hypotensive response in this study had the highest level of plasma renin activity ($11 \text{ nmol l}^{-1} \text{ h}^{-1}$, $14.3 \text{ ng ml}^{-1} \text{ h}^{-1}$). This suggests she may have been particularly responsive to the natriuretic effect of bendrofluazide and may as a result have been more sensitive to the effects of ACE inhibitors. However, although this may partly explain the hypotensive response in this one patient, none of the other biochemical investigations offered an explanation for the changes in blood pressure. It has been suggested that enalapril may produce a greater fall in blood pressure in elderly subjects, associated with a more prolonged inhibition of plasma angiotensin converting enzyme activity (Hockings *et al.*, 1985). We observed no clear relationship between age and maximum fall in blood pressure. It has recently been reported that severe hypotension may occur when enalapril is added to diuretics in heart failure (Cleland *et al.*, 1985). This may partly reflect the higher doses of potent loop diuretics used and partly the precarious

haemodynamic status of such patients. Patients with uncomplicated hypertension may be better able to compensate for hypotension which may then remain asymptomatic. The dose of diuretic used in our study was quite modest; many patients are treated for hypertension with higher doses and more potent diuretics. It may be anticipated that severe hypotension would be more likely in such patients. This has important implications for the introduction of enalapril in the management of hypertension in both hospital and general practice. The Committee of Safety of Medicines has recently drawn attention to adverse reactions to enalapril, including 25 reports and four deaths attributable to hypotension (Committee on Safety of Medicines, 1986).

Shortly after termination of this study the U.K. Data Sheet for enalapril was amended to recommend lower starting doses in patients on diuretic therapy. Further studies have been planned to investigate these lower initial doses of enalapril added to a diuretic as the use of a smaller initial dose of enalapril may not avoid occasional, but potentially hazardous, hypotensive responses. Previous dose response studies with captopril (Ferguson *et al.*, 1977) and enalapril (Gavras *et al.*, 1981) also suggest that although the duration of antihypertensive effect may decrease as the dose is reduced the maximal response may not change. We recommend that practitioners exercise the greatest caution in the initiation of ACE inhibitor therapy in patients on concurrent diuretics. We suggest that such patients be observed closely after the initial dose.

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