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Enalapril in moderate to severe hypertension: a comparison with atenolol

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1 Patients with moderate to severe essential hypertension (mean untreated supine blood pressure 190/112 mm Hg) received once daily enalapril 20–40 mg or atenolol 50–100 mg, supplemented if required by hydrochlorothiazide 25–100 mg, in a randomized observer-blind trial.

2 Both regimens produced a highly significant reduction in supine and standing blood pressure.

3 There was no significant difference in the antihypertensive effects of enalapril and atenolol when they were used as monotherapy. After hydrochlorothiazide was added to patients not achieving 'target' blood pressure, the fall in systolic pressure was significantly greater in the enalapril group than in the atenolol group, despite similar dosage of hydrochlorothiazide in the two groups.

4 At the end of 6 months' treatment, a supine diastolic blood pressure of 90 mm Hg or below was achieved in 74% of patients on enalapril plus hydrochlorothiazide and 56% of patients on atenolol plus hydrocholorothiazide. This difference was not statistically significant.

5 A small rise in plasma urea and creatinine was observed in the enalapril group and a small rise of urea only in the atenolol group. These changes were statistically significant but of uncertain clinical importance.

6 This study confirms that once daily enalapril and atenolol, both alone and in combination with hydrochlorothiazide, are effective drugs in the management of moderate to severe hypertension.

Keywords atenolol enalapril hydrochlorothiazide moderate to severe hypertension once daily treatment

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Introduction

The management of patients with hypertension necessitates life-long drug therapy. β-adrenoceptor blockers and thiazide diuretics are currently the mainstay of therapy, used either alone or in combination, although neither group of drugs is devoid of adverse effects (Medical Research Council Working Party, 1981). New drugs need to be evaluated against these existing standards. We report a study comparing the use of enalapril, a new angiotensin converting enzyme inhibitor, with atenolol, a cardioselective β-adrenoceptor antagonist, as first step therapy for patients with moderate to severe essential hypertension.

Methods

This was an open randomized, parallel group study conducted in five hypertension units in the United Kingdom. Outpatients between the ages of 18 and 75 years were considered if they had a previously documented supine diastolic blood pressure of 110–130 mm Hg.

Patients with any evidence of secondary or accelerated hypertension were excluded from the study as were patients with cardiac failure, angina, recent myocardial infarction or stroke, heart block, valvular heart disease or a resting heart rate of less than 54 beats min^{-1}. Patients were also excluded if they had any other contraindication to receiving atenolol, enalapril or hydrochlorothiazide or had clinically significant hepatic or renal dysfunction. Baseline haematology, biochemistry and urinalysis were within normal limits on entry to the study. Women in whom pregnancy was possible were excluded. Ethics committee approval was granted at each institution and informed consent was obtained from all patients.

At the initial visit, a complete physical examination, chest X-ray and ECG were performed. All antihypertensive therapy was discontinued, according to the manufacturer's recommendations, and patients then received one placebo tablet each morning for 2 weeks or for a shorter period if active treatment was considered to be necessary before this time had elapsed.

At the end of the placebo period, patients whose supine diastolic pressure was in the range 105–130 mm Hg were randomized at each centre to receive either enalapril 20 mg or atenolol 50 mg once daily. The goal of therapy was a supine diastolic blood pressure of 90 mm Hg or below. Patients were seen at two weekly intervals for 12 weeks, then 4 weekly up to 26 weeks. After 4 weeks of active treatment, titration to enalapril 40 mg or atenolol 100 mg was allowed if the supine diastolic blood pressure was still greater than 90 mm Hg. After 8 weeks of treatment, if the supine diastolic blood pressure remained greater than 90 mm Hg, hydrochlorothiazide 25 mg daily was added and could be titrated up to 100 mg at 2 week intervals, if required. If during active therapy the supine diastolic blood pressure increased to above 120 mm Hg it was permitted to increase the dose of the test drugs, or to add hydrochlorothiazide if appropriate, earlier than the proposed 4 weeks. After the 26 week randomized study, patients in the enalapril group were followed for a total of 52 weeks to gain longer term safety data.

At each visit blood pressure was measured, using Hawksley random zero sphygmomanometers, by observers unaware of the patient's therapy. Measurements were made after 10 min of supine rest and again after 2 min standing. Measurements in the supine position were made three times and the average of the last two measurements, which did not differ by more than 5 mm Hg, was recorded. Diastolic phase V was recorded. Measurements were also made of weight and supine heart rate.

Laboratory assessments were performed at each visit for haematology, urea and electrolytes, serum creatinine and urinalysis. A fuller assessment including uric acid and liver function tests was carried out after 16 and 26 weeks of treatment. Adverse reactions were sought throughout the study by clinical and laboratory examinations as well as by open questioning.

Data analysis

Paired Student's *t*-tests were used to compare changes in blood pressure, pulse rate and other continuous variables from baseline within each treatment group and unpaired *t*-tests were used for between-group comparisons. Chi-squared tests were used to compare the proportion of patients in each group achieving goal blood pressures. Data were examined only after completion of the study. It was anticipated that goal blood pressure might be achieved in 80% of patients in the enalapril group and 60% of patients in the atenolol group. To detect such a difference at the 5% level of significance with 80% power (two-tailed) would require 85 patients in each group. In the event, the recruitment rate would have necessitated an unacceptably prolonged study with all its attendant difficulties and the study was stopped on completion of 94

patients. The results at 26 weeks (goal blood pressure achieved in 74% of enalapril group and 56% of atenolol group) were close to our initial estimate. Because of the limited number of patients, however, the study lacked the power to show that the observed difference in the proportion of patients achieving goal blood pressure was statistically significant.

Results

Ninety-four patients completed the 2 week placebo phase and were randomized to receive enalapril (n = 51) or atenolol (n = 43). This slight imbalance was due to the unequal numbers of patients recruited at each centre and the within centre randomization scheme. Baseline demographic data were similar between the groups. The mean age of patients in the enalapril group was 56 years (range 37–74), compared to mean age of 55.5 years (range 33–68) in the atenolol group. Forty-seven percent of patients in the enalapril group and 45% in the atenolol group had previously been treated with either a diuretic or a β-adrenoceptor blocker prior to the study. Newly diagnosed untreated hypertensives constituted 22% of the enalapril group and 37% of the atenolol group. The mean duration of preceding hypertension was 73.9 months (range 1–384 months) in the enalapril group and 45.9 months (range 0–288 months) in the atenolol group. At entry, electrocardiographic evidence of left ventricular hypertrophy ($SV_1 + RV_5 > 35$ mm) was present in 31% of patients in the enalapril group and 30% of patients in the atenolol group.

Two patients in each group were lost to follow-up. Ten other patients failed to complete the 26 week study for a variety of reasons (Table 4) but the available data from these patients have been included in the analysis.

Blood pressure and pulse rate

Blood pressure and pulse rate data for the two groups throughout the trial are shown in Table 1. Systolic and diastolic pressures fell significantly at each time point relative to week 0, in both treatment groups, in both the supine and erect positions. Diastolic blood pressure was lowered equally in both groups. The reduction in systolic pressure was significantly greater in the enalapril group than in the atenolol group from 8 weeks onwards. Pulse rate was significantly reduced in the atenolol group whereas there was no change in the enalapril group.

At 26 weeks, 34 of 46 patients in the enalapril group (74%) reached the target blood pressure

Table 1 Mean blood pressure (mm Hg) and pulse rate (beats min^{-1}) for all patients (s.d.). Between group comparisons of reduction in systolic blood pressure from week 0 (P values in table) showed a significantly greater effect of enalapril. Between group comparisons of reduction in diastolic blood pressure showed no significant differences. Within group analysis showed that both treatment regimens produced a significant reduction in blood pressure compared to week 0 at subsequent time points ($P < 0.001$). Supine heart rate was significantly reduced at all time points by atenolol ($P < 0.01$)

	Enalapril					*Atenolol*		
Week	n	*Systolic*	*Diastolic*	*Pulse*	P	n	*Systolic*	*Diastolic*	*Pulse*
Supine									
−2	51	186 (24)	105 (10)	77 (12)		43	187 (24)	109 (11)	77 (11)
0	51	195 (18)	112 (9)	82 (14)		43	189 (21)	112 (8)	83 (13)
2	51	172 (29)	101 (10)	83 (11)	< 0.1	43	173 (26)	103 (10)	73 (13)
4	51	171 (28)	99 (12)	82 (12)	> 0.2	43	172 (24)	97 (10)	70 (11)
6	51	163 (27)	96 (12)	81 (14)	0.1	43	171 (24)	97 (10)	71 (12)
8	51	158 (26)	92 (12)	81 (13)	< 0.01	43	165 (20)	93 (8)	71 (9)
12	49	151 (23)	88 (10)	81 (12)	< 0.02	39	159 (21)	89 (9)	72 (13)
16	49	147 (18)	87 (9)	79 (11)	< 0.01	38	160 (18)	90 (6)	70 (8)
26	46	146 (24)	87 (11)	78 (10)	< 0.01	34	157 (21)	91 (7)	69 (12)
39	40	143 (23)	88 (10)	79 (11)					
52	41	145 (21)	88 (11)	76 (10)					
Erect									
0	51	190 (19)	114 (10)			43	183 (23)	113 (8)	
2	49	170 (26)	104 (12)		< 0.2	43	169 (23)	104 (11)	
8	51	153 (27)	94 (15)		< 0.01	43	158 (21)	94 (8)	
16	49	144 (17)	89 (9)		< 0.05	38	151 (19)	91 (8)	
26	46	142 (22)	88 (12)		< 0.01	34	151 (20)	92 (8)	

Table 2 Number (%) of patients in enalapril groups in whom goal blood pressure (supine diastolic 90 mm Hg or below) was achieved. Chi-squared tests showed no significant differences between enalapril and atenolol at 8,16, or 26 weeks

	Week					
	8		*16*		*26*	
	Enalapril n *(%)*	*Atenolol* n *(%)*	*Enalapril* n *(%)*	*Atenolol* n *(%)*	*Enalapril* n *(%)*	*Atenolol* n *(%)*
Controlled	25 (49)	16 (37)	31 (63)	25 (66)	34 (74)	19 (56)
Not controlled	26 (51)	27 (63)	18 (37)	13 (34)	12 (26)	15 (44)
Hydrochlorothiazide added	23 (45)	14 (33)	35 (71)	30 (79)	33 (73)	33 (77)
Total	51	43	49	38	46	34

Table 3 Doses of enalapril and atenolol, and supplementation by hydrochlorothiazide in the two treatment groups throughout the study. Results show the treatments being administered at each of the study visits

	Weeks								
	2	*4*	*6*	*8*	*10*	*12*	*16*	*20*	*26*
Enalapril									
< 20 mg	—	—	1	1	1	2	2	2	2
20 mg	50	46	16	15	15	13	12	12	11
40 mg	1	5	34	35	35	36	35	35	35
Withdrawn	—	—	—	—	—	—	2	2	3
Hydrochlorothiazide									
0	51	51	47	28	21	18	16	14	14
25 mg	—	—	2	18	14	17	17	16	14
50 mg	—	—	2	4	14	11	10	12	13
100 mg	—	—	—	1	2	5	6	7	7
Withdrawn	—	—	—	—	—	—	2	2	3
Atenolol									
50 mg	43	38	15	12	9	8	8	7	6
100 mg	—	5	28	31	34	34	31	31	29
Withdrawn	—	—	—	—	—	1	4	5	8
Hydrochlorothiazide									
0	43	43	38	29	18	14	13	11	10
25 mg	—	—	2	9	17	14	11	12	11
50 mg	—	—	3	3	5	9	6	7	7
100 mg	—	—	—	2	3	5	9	8	7
Withdrawn	—	—	—	—	0	1	4	5	8

level compared with 19 of 34 (56%) in the atenolol group (Table 2). This difference was not statistically significant—($P > 0.1$), but the study did not have the power to establish a difference of less than 20%.

At week 8 hydrochlorothiazide had been added to 23 patients (45%) in the enalapril group and 14 patients (33%) in the atenolol group (Table 3). At 26 weeks, 14 patients remained on enalapril alone (27%) and 10 patients on atenolol alone (23%). The mean dosage requirement of all patients was 37 mg enalapril and 49 mg hydrochlorothiazide, or 92 mg atenolol plus 53 mg hydrochlorothiazide.

Fifty-two weeks treatment in the enalapril group

Forty-one patients (22 males, 19 females: mean age 57.2 years) completed the 26 week study and were followed until 52 weeks. The decreases in blood pressure seen at 26 weeks in these patients were maintained for the remainder of the follow up period. In addition, pulse rate fell slightly and there was a small reduction in weight (2.2 kg).

Three patients had the dose of hydrochlorothiazide reduced with no loss of blood pressure control. In a further seven patients hydrochlorothiazide was changed to comparable doses of Moduretic (hydrochlorothiazide 50 mg and

Table 4 Results of laboratory investigations

Week	*Enalapril* n	*0*	*8*	*16*	*26*	*Atenolol* n	*0*	*8*	*16*	*26*
Haemoglobin ($g\ dl^{-1}$)	41	14.7	14.4	14.2	14.2	32	14.8	14.7	14.9	14.9
White blood cells ($\times 10^9\ l^{-1}$)	41	6.9	6.8	6.7	6.6	32	6.9	7.0	7.0	6.7
Serum Na ($mmol\ l^{-1}$)	41	141	141	141	140	29	141	141	141	142
Serum K ($mmol\ l^{-1}$)	39	4.1	4.0	4.1	4.1	28	4.0	4.0	4.0	3.9
Serum urea ($mmol\ l^{-1}$)	40	5.4	5.8*	6.7**	6.7**	30	4.9	5.5**	5.8**	5.4**
Serum creatinine ($\mu mol\ l^{-1}$)	40	101	105	109**	110*	30	97	97	97	98

Significant changes from week 0: * $P < 0.05$; ** $P < 0.01$

amiloride 25 mg). One patient had labetalol 200 mg added. Of the 41 patients followed to 12 months, seven were controlled on enalapril alone, while the others required hydrochlorothiazide in dosages from 25 to 100 mg.

Haematology and biochemistry results at 52 weeks showed no change from 26 weeks.

Biochemistry and haematology

Results of laboratory investigations are summarized in Table 4. Between group comparison of serum creatinine results showed significantly higher values at 16 and 26 weeks in the enalapril/hydrochlorothiazide group ($P < 0.05$). The increase from baseline was significantly greater at 16 weeks in the enalapril group ($P < 0.05$). Blood urea rose marginally in both drug groups from 8 weeks onwards ($P < 0.01$), although between group comparisons showed a significant difference in absolute values between the groups only at 26 weeks ($P < 0.01$). Neither drug altered fasting blood glucose, liver function tests or serum urate. White blood cell counts were unchanged in both groups and there was no occurrence of proteinuria.

One patient in each group developed hyperkalaemia (potassium $> 6.0\ mmol\ l^{-1}$). Three patients in the atenolol/hydrochlorothiazide group developed hypokalaemia (potassium $< 3.0\ mmol\ l^{-1}$).

Adverse reactions

The total number of adverse experiences was similar in the two groups, with 21 patients in the enalapril group and 24 patients in the atenolol group reporting at least one symptom. The nature of the reports and the reasons for patients failing to complete 26 weeks in the study are indicated in Table 5. One patient died in the atenolol group after a perforated peptic ulcer. Two patients were withdrawn because therapy was ineffective: one from the enalapril group at 10 weeks (supine blood pressure 140/110 mm Hg) and one from the atenolol group at 10 weeks (supine blood pressure 215/134 mm Hg).

Discussion

This study shows that both enalapril and atenolol are effective treatments for moderate to severe essential hypertension when given once daily over a 6 month period. The antihypertensive effect of both drugs was augmented by the addition of hydrochlorothiazide. The antihypertensive effect of enalapril was apparent 2 weeks after starting therapy and was sustained in patients followed for 12 months. More patients in the enalapril group achieved goal blood pressures than in the atenolol group but this difference was not statistically significant. The mean daily dose of enalapril (37 mg) was relatively high and the addition of hydrochlorothiazide was necessary in two thirds of this group in attempting to achieve 'goal' blood pressure.

The two drugs were comparable in their effect on diastolic pressure, but the reduction in systolic pressure was significantly greater in the enalapril group from 8 weeks onward. The greater reduction in systolic pressure in the enalapril group was achieved without evidence of postural hypotension. A small difference between enalapril and atenolol was apparent, though not statistically significant, at 2 and 4 weeks, when all

Table 5 Number of adverse reports during 6 month's active treatment period

	Enalapril	*Atenolol*
Dizziness, lightheadedness	5	4
Tiredness, lethargy, drowsiness	4	2
Headache	3	3
Abnormalities of cardiac rhythm	2	3
Intercurrent infections	2	4
Nausea, diarrhoea, abdominal discomfort	2	1
Postural hypotension	2	2
Rash	1	2
Breathlessness	1	0
Gout	0	1
Cold hands	0	1
Aches and pains	1	0
Chest pain	0	1
Perforated peptic ulcer (fatal)	0	1
Abnormal laboratory values (clinically significant)	3	7
Total	26	31
Patients	21	24
Reasons for failure to complete 26 weeks' study treatment		
Lost to follow up	2	2
Perforated peptic ulcer (fatal)	0	1
Myocardial infarction	0	1
Abnormal cardiac rhythm	1	1
Hypokalaemia	0	3
Hyperkalaemia	1	0
Therapy ineffective	1	1
Total	5	9

patients were on monotherapy, and widened slightly as the study progressed. The mean dose of hydrochlorothiazide used was similar in the two groups by 26 weeks although there was a tendency for the diuretic to be added earlier in the enalapril group. It is possible that the differences in systolic pressure achieved represent a true enalapril effect although a more likely explanation may be that the addition of hydrochlorothiazide led to an enhanced effect in the enalapril group. A similar pattern has previously been noted in comparison with propranolol in mild hypertenstion (Enalapril in Hypertension Study Group (UK), 1984). The long term clinical advantage of a greater reduction in systolic blood pressure is uncertain although current evidence suggests that diastolic blood pressure achieved during treatment may influence both morbidity and mortality (The Australian Therapeutic Trial in Mild Hypertension, 1980).

A rise in urea occurred in both groups and may reflect the introduction of hydrochlorothiazide. A small rise in creatinine in the enalapril/hydrochlorothiazide group was also noted at 16 and 26 weeks and reflected a general trend rather than a large rise in a few patients. Although statistically significant, these changes are of uncertain clinical importance. Long term follow up would be of interest.

The design of our study requires comment. It was felt that a placebo control group was inappropriate in a 6 month study in these patients, many of whom had severe hypertension. The levels of blood pressure reduction achieved must be viewed accordingly and some allowance made for changes with time and regression to the mean. The baseline pressures in this study showed a tendency to rise during the initial 2 week placebo run-in period, reflecting withdrawal of previous therapy in many patients, and we believe that subsequent changes in blood pressure largely reflect the introduction of effective therapy in the form of either enalapril or atenolol.

Atenolol is one of the most widely prescribed 'standard' antihypertensive drugs in the United Kingdom and has been extensively evaluated in many formal studies. The mean reduction in

supine blood pressure at 26 weeks in the enalapril group was 49/22 mm Hg and in the atenolol group 31/21 mm Hg. It is of interest to compare these with the mean reduction in supine blood pressure of 33/22 mm Hg achieved by the combination of atenolol and bendrofluazide (Petrie *et al.*, 1975), and of 23/16 mm Hg achieved by treatment with atenolol alone (Jeffers *et al.*, 1977) in double blind placebo controlled studies. These comparisons suggest that our study produced a true estimate of the comparative antihypertensive effects of enalapril and atenolol used in combination with hydrochlorothiazide.

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