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Enalapril in essential hypertension: a comparative study with propranolol

ENALAPRIL IN HYPERTENSION STUDY GROUP (UK)

1 We report the first comparative study on enalapril maleate, a new angiotensin converting enzyme inhibitor, in patients with uncomplicated mild to moderate essential hypertension. Fifty-four patients were randomly assigned to treatment with enalapril or propranolol for 16 weeks following a placebo run-in-phase. The study was double-blind.

2 Enalapril and propranolol both reduced blood pressure, though the changes were significantly greater with enalapril. Propranolol reduced heart rate, enalapril did not. More patients treated with enalapril were normotensive at the end of the study. Enalapril treatment was associated with a significant reduction in weight. Both drugs raised plasma potassium and urea. No haematological abnormalities occurred with enalapril and there were no reports of rash, taste disturbance or proteinuria. At the end of the trial the mean daily dose of enalapril was 20 mg and that of propranolol was 180 mg.

Keywords enalapril propranolol hypertension

Introduction

Enalapril maleate (MK-421) is a new, orally active angiotensin converting enzyme inhibitor. Its efficacy as an antihypertensive agent in patients with essential hypertension has been demonstrated (Ferguson *et al.*, 1982; Gavras *et al.*, 1981). No data have hitherto been published comparing its efficacy relative to existing therapies. We report the results of a double-blind study comparing enalapril to propranolol as a first-step drug for the treatment of patients with mild to moderate essential hypertension.

Methods

This was a randomised, double-blind, parallel group study conducted in five specialist hypertension units in the United Kingdom. Outpatients, aged between 18 and 60 years, were entered if they had mild to moderate essential hypertension with an untreated supine diastolic blood pressure (phase V) between 95 and 114 mm Hg taken as an average of at least four measurements over a 2-week period.

Evidence of secondary, malignant or accelerated hypertension excluded patients, as did cardiac failure, angina, recent myocardial infarction or stroke, valvular heart disease, second or third degree heart block or a resting heart rate of less than 54 beats/min. Patients were also excluded if they had a contraindication to receiving propranolol, e.g. bronchospasm, diabetes mellitus or abnormal renal or hepatic function.

All patients entering the trial had a haemoglobin level and white cell and platelet counts within the normal range of the respective hospital laboratory. Women who were pregnant or nursing, or in whom pregnancy was possible were excluded. Informed consent was obtained from patients, and the ethics committee of each participating hospital approved the protocol.

At the initial evaluation (week 0) a complete physical examination, chest X-ray, electrocardiogram and fundoscopy were performed.

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All antihypertensive therapy was stopped and placebo tablets, identical in appearance to the study drugs, were then given at a dose of one tablet twice daily for 4 weeks. Patients were seen at 2-weekly intervals throughout the study and only those with an average supine diastolic blood pressure between 95 and 114 mm Hg at the end of the placebo phase entered the active treatment phase.

At the start of the 12-week active treatment phase (weeks 5 to 16), patients were randomly assigned to receive either enalapril 5 mg twice daily or propranolol 40 mg twice daily. Enalapril and propranolol tablets were identical in appearance. Separately balanced randomisation schedules were used for each of the participating clinics. After 4 weeks of active treatment patients whose diastolic blood pressure was greater than 90 mm Hg were given enalapril 10 mg twice daily or propranolol 80 mg twice daily. After 8 weeks on active treatment the doses of the two drugs were increased, if necessary, to 20 mg twice daily or 120 mg twice daily respectively. If during active therapy diastolic pressure rose to above 120 mm Hg then dose titration was allowed earlier than the scheduled 4 weeks. Similarly a decrease in the dosage of test drug was allowed if any non-serious adverse reaction was thought to be dose-related.

If at the end of the 16-week study, diastolic blood pressure was still above 90 mm Hg despite maximal dose levels being used, then hydrochlorothiazide (25 mg) was added in an open manner. This report, however, does not include the follow-up of these patients.

At each visit blood pressure was taken in a standard manner using a random zero sphygmomanometer. After 10 min of rest, supine blood pressure was measured at least three times and the average of the last two measurements which did not differ by more than 5 mm Hg was recorded. After standing for 2 min, blood pressure was again measured. Pulse rate was measured in both the supine and erect positions. Weight was measured at each visit.

At each visit laboratory assessment was performed for haemoglobin and white cell count, urea and electrolytes, plasma creatinine and urinalysis. At weeks 2, 4 and 16, a more detailed assessment was performed and included fasting glucose, uric acid and liver function tests. Throughout the study, adverse reactions were sought by both clinical examination and laboratory investigation and their severity evaluated. Symptoms were elicited by open questioning and all reported symptoms were recorded irrespective of the physician's assessment of the likelihood that the symptom was related to the test drug. Although a β-adrenoceptor blocker was used in the trial a specific questionnaire concentrating on known β-adrenoceptor blocker adverse effects was not employed. Such a questionnaire would be expected to bias the reporting of symptoms against the β-adrenoceptor blocker.

Therapy could be withdrawn at any time during the study at the discretion of the investigating physician. The use of any drug known to have an effect on blood pressure was not allowed.

Data analysis

Paired Student's *t*-tests were used to compare blood pressure, pulse rate and other continuous variables within each treatment group and unpaired *t*-tests were used for between group comparisons. Chi-squared tests were used to compare frequency distributions with respect to blood pressure control and the incidence of adverse reactions.

The changes in study variables between the end of the placebo period and the end of the trial are based only on patients contributing valid data at the given time points. No substitutions have been made for missing data. Thus, reported mean differences in the results tables cannot be deduced by simple subtraction of week 16 data from week 4 data, due to differing numbers of patients at each of these time points.

Results

Fifty-four patients completed the evaluation

Table 1 Patient baseline data

	Enalapril (n = *28*)	*Propranolol* (n = *26*)
Age (years) mean	49.1	50.5
range	26–61	32–65
Males (%)	64	38
Mean duration of known hypertension (years)	6.2	4.1
Previously treated for hypertension (%)	43	42
Weight (kg) (mean ± s.d.)	80.6 ± 16.3	73.2 ± 12.0

period (weeks 0–4) and were allocated randomly to enalapril (n = 28) or propranolol (n = 26) treatment. The two groups were well matched with regard to baseline characteristics as shown in Table 1.

Blood pressure and pulse rate

Table 2 details the blood pressure and pulse rate data for the two groups at the end of the baseline placebo period (week 4) and after 12 weeks of active therapy (week 16). In both treatment groups systolic and diastolic pressures fell significantly in both the supine and erect positions. Pulse rate fell significantly in the propranolol group but there was no change in the enalapril treated patients. Enalapril reduced blood pressure significantly further than did propranolol to the extent of 7/4 mm Hg in the supine position and 11/7 mm Hg in the erect position ($P < 0.001$). More patients on enalapril were controlled at a level of 90 mm Hg or below (17 enalapril, 13 propranolol) and more patients in the propranolol group had final diastolic pressures above 95 mm Hg (eight propranolol, four enalapril). This difference in distribution was not statistically significant. At week 16 the mean daily dose of enalapril being taken was 20 mg compared to 180 mg of propranolol.

Weight

Although the weights of the two groups were significantly different initially, by the end of the trial mean weight had increased significantly in those receiving propranolol (+ 0.9 kg ± 1.6, $P < 0.05$) and had decreased significantly in those on enalapril (−1.4 kg ± 2.0, $P < 0.01$). The difference in weight change between the two groups was also significant ($P < 0.001$).

Biochemistry and haematology

Table 3 documents the changes in biochemical variables during the trial. Both drugs raised plasma potassium significantly, this being more prominent with enalapril. Plasma urea rose slightly and similarly on both drugs, whereas creatinine rose to a greater extent on propranolol. Neither drug significantly altered fasting blood sugar, liver function tests or plasma uric acid. There were no clinically significant haematological abnormalities with either therapy and in particular white cell counts were unaffected. Proteinuria did not occur in any patient.

Adverse reactions

Eight patients (28.6%) in the enalapril and 11

Table 2 Blood pressure and pulse rate data for the two groups at the end of the baseline placebo period (week 4) and after 12 weeks of active therapy (week 16)

		Enalapril				*Propranolol*				*Between group difference*
		Week 4 n = 28	*Week 16* n = 26	*4–16* n = 26	*Within group difference* P	*Week 4* n = 26	*Week 16* n = 24	*4–16* n = 24	*Within group difference* P	P
Supine systolic (mm Hg)	Mean	165.0	140.5	−24.8	< 0.001	169.4	152.9	−17.8	< 0.001	< 0.001
	s.d.	18.1	17.8	18.1		17.5	20.2	14.1		
Supine diastolic (mm Hg)	Mean	101.5	86.4	−15.0	< 0.001	102.8	91.2	−11.3	< 0.01	< 0.001
	s.d.	5.6	11.2	9.8		6.1	8.7	6.0		
Supine pulse rate (beats/min)	Mean	78.8	75.9	−2.1	NS	83.5	60.7	−23.5	< 0.01	< 0.01
	s.d.	11.9	9.6	12.1		11.7	6.6	11.4		
Erect systolic (mm Hg)	Mean	165.1	133.9	−31.4	< 0.001	164.6	145.9	−20.5	< 0.01	< 0.001
	s.d.	22.3	17.1	20.6		22.3	17.1	20.6		
Erect diastolic (mm Hg)	Mean	109.7	90.9	−19.6	< 0.001	107.3	94.5	−12.4	< 0.01	< 0.001
	s.d.	8.9	10.4	8.4		12.6	9.1	13.7		
Erect pulse rate (beats/min)	Mean	86.7	86.5	+0.1	NS	89.1	64.6	−25.1	< 0.01	< 0.01
	s.d.	12.9	12.8	12.6		14.8	7.6	15.4		

Table 3 Changes in plasma potassium, plasma urea, plasma creatinine and fasting blood sugar

		Plasma potassium (mmol/l)			*Plasma urea (mmol/l)*			*Plasma creatinine (μmol/l)*			*Fasting blood sugar (mmol/l)*		
		Week 2	*Week 16*	*2–16*	*Week 2*	*Week 16*	*2–16*	*Week 2*	*Week 16*	*2–16*	*Week 2*	*Week 16*	*2–16*
Enalapril	*n*	26	22	21	23	22	20	25	23	21	21	19	13
	Mean	3.90	4.41	+0.47*	4.82	5.49	+0.56*	89.5	90.8	+2.8	5.05	4.77	+0.12
	s.d.	0.38	0.84	0.86	1.12	1.2ℓ	1.11	17.1	19.6	14.1	0.91	0.74	0.84
Propranolol	*n*	26	23	22	25	23	22	26	23	22	23	21	19
	Mean	3.96	4.18	+0.23*	4.62	5.27	+0.59**	85.6	90.4	+5.6**	4.89	4.81	−0.22**
	s.d.	0.35	0.52	0.48	1.09	1.42	0.85	17.8	18.4	7.6	0.74	0.73	0.83
Between group difference	*P*	<0.05		<0.001	<0.05		NS	<0.01		<0.01	<0.05		<0.01

* $P < 0.05$, ** $P < 0.01$

patients (42.3%) in the propranolol-treated group reported at least one adverse symptom during the study. Their nature is detailed in Table 4. The total number of adverse experiences did not differ between the two groups but significantly more of the reports in the propranolol-treated group were evaluated as possibly, probably or definitely related to therapy compared to the enalapril-treated group; propranolol 13 of the 16 reports (81%), enalapril four out of 11 reports (36%) ($\chi^2 = 5.63$, $P < 0.05$).

A further two patients in each treatment group failed to complete the 16-week trial. One patient in the enalapril group reported a series of symptoms including nose bleeds, depression, insomnia and a painful right toe; one other patient in the enalapril group emigrated during the study. In the propranolol group one patient had an influenza illness, and a tablet dispensing error precipitated the withdrawal of one other propranolol patient.

Discussion

This study has demonstrated that enalapril effectively lowered blood pressure to a significantly greater degree than did propranolol over a 3-month treatment period and more patients reached normotension on enalapril than on propranolol, in the doses used in this study. One could speculate that using higher doses of propranolol may have altered the results of the trial but the dose range used was that most closely reflecting current practice with respect to this drug (Bai *et al.*, 1982).

The blood pressure reduction achieved by enalapril was not accompanied by a reflex tachycardia as seen with certain other drugs having a vasodilator component to their action, e.g. hydralazine, diuretics. Lack of reflex tachycardia has previously been reported with enalapril and may be the result of activation of vagal parasympathetic tone (Millar *et al.*, 1982). The changes in blood pressure that occur on standing were not influenced by enalapril in our study. Postural hypotension occurred in one patient in each treatment group.

The lack of prominent side-effects with enalapril in this study is encouraging, though the population was relatively small. In particular there were no reports of rash or taste disturbance. Abnormal white cell counts were not seen with enalapril in this trial though most of the instances of captopril-induced neutropenia and agranulocytosis have occurred in patients with multisystem diseases who were taking more than one drug (Heel *et al.*, 1980). No patient developed proteinuria during the trial.

Table 4 Number of adverse symptom reports during active treatment period

	Enalapril	*Propranolol*
Tiredness, lethargy, drowsy	2	4
Headache	2	0
Sweating	2	0
Nausea	1	2
Dizziness, lightheaded	2	0
Postural hypotension	1	1
Paraesthesiae	0	2
Dry cough	1	0
Depression	0	1
Chest pain	0	1
Others	0	5
	11 in 8 patients	16 in 11 patients

The biochemical effects that occurred with enalapril in this study reflect its pharmacological actions. As an inhibitor of angiotensin converting enzyme it blocks the production of aldosterone and hence has diuretic effects. This was demonstrated by the significant weight reduction and small increase in plasma urea. The rise in plasma potassium was probably a result of removal of aldosterone control of distal renal tubular sodium/potassium exchange. This increase in plasma potassium may be of more importance in the presence of impaired renal function, particularly as enalapril is excreted by the kidney (Ulm *et al.*, 1982) and may thus tend to accumulate if glomerular filtration is markedly reduced.

Enalapril maleate is rapidly and well absorbed when given orally (Ulm *et al.*, 1982) and absorption is unaffected by food (Ferguson *et al.*, 1983). It is itself inactive requiring hydrolysis to enalaprilic acid (Tocco *et al.*, 1982) and peak drug levels of the active metabolite occur at 3 to 4 h after a single oral dose (Biollaz *et al.*, 1982). The duration of action of a single oral dose of enalapril, as measured by converting enzyme inhibition, is greater than 24 h (Brunner *et al.*, 1981). Elevation of plasma renin and angiotensin I, together with suppression of angiotensin II and aldosterone occur over a similar time period and are matched by the duration of the antihypertensive effect (Jackson *et al.*, 1982).

In conclusion, enalapril has been shown to be an effective blood pressure lowering agent, at least as effective as propranolol, and in this short study no significant unexpected clinical, haematological or biochemical abnormalities were noted. If these findings are substantiated in other trials, enalapril may play a useful role in the management of essential hypertension.

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