Efficacy of enalapril in essential hypertension and its comparison with atenolol

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Summary: The effect of enalapril was evaluated in 67 patients with essential hypertension, and its therapeutic efficacy was compared with atenolol in a placebo run-in, single-blind, cross-over trial. Enalapril significantly reduced blood pressure in all grades of essential hypertension. As monotherapy it 'normalized' blood pressure in 88%, 50% and 25% of patients with mild, moderate and severe hypertension respectively. Optimal dose for most of the patients was 20 to 40 mg/day. Comparison with atenolol revealed almost parallel efficacy of the two drugs, although enalapril produced a significantly greater reduction in systolic blood pressure in patients with mild and moderate hypertension ($P < 0.01$ in each group). No serious side effects were encountered with either drug. Enalapril, therefore, has a potent and slightly superior antihypertensive effect to that of atenolol, and may be used as a 'first-step' drug in the treatment of hypertensive patients.

Introduction

Enalapril is a relatively new, long-acting, non-sulphydryl angiotensin converting enzyme (ACE) inhibitor with a few side effects.^{1,2} In placebo-controlled trials, it has been reported to be effective in controlling blood pressure (BP) in about 50 to 75% patients with mild to moderate hypertension.^{3–5} However, most of the clinical trials have been done with a fixed dose of 20 mg or 40 mg per day. Blood pressure response with increasing doses of enalapril has been correlated by only a few workers,^{6,7} and its optimal dose has not been elucidated. Moreover, only a few studies have been done to evaluate its therapeutic efficacy as a monotherapeutic agent in patients with severe hypertension.⁸

Comparative studies on the antihypertensive effect of enalapril with beta blockers propranolol,^{9,10} metoprolol¹¹ and atenolol^{8,12} have shown these drugs to be of almost similar efficacy. However, the place of enalapril as a 'first-step' antihypertensive drug has not yet been clearly established. We selected atenolol for comparison as it is a conventional first-line antihypertensive drug and because of the limited reports available on the comparative efficacy of the two drugs.^{8,12}

The objective of the present study was two fold: (i) to evaluate the antihypertensive efficacy and tolerance of increasing doses of enalapril in patients with essential hypertension of severity ranging from mild to severe, and to find out its optimal therapeutic dose; and (ii) to compare the efficacy and safety of enalapril with that of atenolol in order to evaluate the place of enalapril as a 'first-step' drug in hypertensive patients.

Materials and methods

The patients

Sixty seven patients with essential hypertension completed the trial. All patients gave informed consent and were randomly selected from the hypertension clinic. Patients with secondary or malignant hypertension, pregnancy, heart failure, heart block, diabetes mellitus, bronchial asthma or peripheral vascular disease and significant renal or hepatic dysfunction were not included in the study. All patients underwent a complete physical examination, chest X-ray, electrocardiogram, blood biochemistry and urine analysis. Depending on diastolic blood pressure (DBP), patients were classified into mild (90–104 mmHg)–25 cases, moderate (105–120 mmHg)–30 cases, and severe hypertension (> 120 mmHg)–12 cases. There

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were 33 males and 34 females, aged 28 to 65 years (48.30 ± 2.34). Average duration of hypertension was 5.7 ± 1.1 years with a range of 1 month to 18 years.

Study design

This was a placebo run-in, single-blind, cross-over study for 8 to 10 weeks with each of enalapril and atenolol. After withdrawal of their previous anti-hypertensive treatment, all patients received placebo (1 tablet daily) for 4 weeks as a 'washout' period. Patients were then randomly assigned to once daily treatment with either enalapril or atenolol. Starting dose of enalapril was 10 mg/day for mild and 20 mg/day for moderate and severe hypertension. Depending on therapeutic response, it was increased at 2-weekly intervals to 20 to 40 to 60 to 80 mg/day unless diastolic BP was reduced below 90 mmHg or the patient developed side effects of the drug. Starting dose of atenolol was 50 mg/day for mild hypertension which was increased to 100 mg/day after 4 weeks if required. Patients with moderate and severe hypertension received a fixed dose of 100 mg/day for 8 weeks or less if diastolic BP was 'normalized'. While crossing-over to the other drug, all patients received an intervening placebo for 4 weeks as washout period. The trial was considered to be complete if diastolic BP was normalized (< 90 mmHg) or after the patient had received the maximum dose of enalapril (80 mg/day) and atenolol (100 mg/day), each for at least 4 weeks.

All patients attended the clinic at 2-weekly intervals, and earlier if required. At each visit blood pressure was measured and side effects objectively enquired. All blood pressure measurements were made uniformly after rest for at least 10 minutes, in the sitting position, in the right arm, using a random zero mercury sphygmomanometer almost at the same time (between 16.00 and 18.00 h) on each visit. The first and fifth Korotkoff sounds were used to determine systolic and diastolic BP respectively. 'Response' to therapy refers to a reduction in diastolic BP of > 10 mmHg or to < 90 mmHg, and 'normotension' or 'normalization' of BP refers to diastolic BP < 90 mmHg.

Statistical analysis

Mean BP was calculated as diastolic BP plus one third of systolic minus diastolic BP. All data are shown as mean $\pm$ standard error of mean (s.e.m.) values. Statistical analysis to compare the anti-hypertensive effect of enalapril and atenolol included 't' test applied to paired comparison.¹³ A *P* value of < 0.05 was considered as significant and *P* value of < 0.01 as highly significant.

The power of the test for the mild, moderate and severe groups was SBP 0.5–0.6, 0.6–0.7 and 0.3–0.4, DBP 0.1–0, < 0.1 , 0.3–0.4 and 0.1–0.2, and MBP 0.8–0.9, 0.3–0.4, 0.3–0.4 respectively.

Results

Relation to severity of hypertension

Response to enalapril treatment was noticed in all patients with mild, 20(66.6%) with moderate and 7(58.3%) patients with severe hypertension; whereas 'normalization' of BP was achieved in 22(88%) with mild, 15(50%) with moderate and 3(25%) patients with severe hypertension. The dose of enalapril required to 'normalize' the BP was 10 mg in 5, 20 mg in 22, 40 mg in 17 and 60 mg in 6 patients. Increasing the dose further to 80 mg/day, however, did not produce any additional beneficial effect.

Response to atenolol treatment occurred in all patients with mild, 26(86.6%) with moderate and 7(58.3%) patients with severe hypertension, blood pressure was 'normalized' in 23(92%), 13(43.3%) and 2(16.6%) patients respectively. The dose of atenolol required to 'normalize' BP was 50 mg in 12 and 100 mg in 26 patients.

Effect on entire patient group

There was a significant reduction in mean $\pm$ s.e.m. values of systolic, diastolic and mean BP in all grades of hypertension with both drugs as compared to placebo (Table I). The magnitude of reduction in BP was slightly greater with enalapril (13 to 16%) as compared to atenolol (7 to 15%). Comparison of their antihypertensive effect revealed no significant difference in diastolic BP but reduction in systolic BP was significantly greater with enalapril than atenolol in both mild and moderate hypertension groups ($P < 0.01$ in each group) as shown in Figures 1 and 2. In patients with severe hypertension, the fall in BP was relatively more with enalapril than atenolol but the difference was statistically insignificant.

The pulse rate for the entire group of 67 patients before and after enalapril treatment was 75.5 ± 1.6 and 76.4 ± 1.7 ($P =$ not significant), whereas with atenolol treatment it decreased from 76.2 ± 1.8 to 66.8 ± 1.5 ($P < 0.001$).

Side effects

On enalapril treatment 2 patients each had headache and somnolence and 1 had dizziness whereas with atenolol there was dizziness in 2 and heart failure in 1 patient.

Table 1 Antihypertensive effect of enalapril and atenolol in different grades of essential hypertension

Groups	No. of patients	Systolic BP		Diastolic BP		Mean BP		% reduction in SBP/DBP
		A	B	A	B	A	B	
Mild hypertension	25							
On enalapril		160.9 ± 3.2	138.8 ± 2.4*	104.5 ± 2.3	86.6 ± 0.9*	121.6 ± 1.1	103.9 ± 1.0*	13/15
On atenolol		158.6 ± 2.7	145.4 ± 2.7*	102.5 ± 0.7	87.1 ± 4.6**	121.5 ± 1.1	112.8 ± 1.2***	8/15
Moderate hypertension	30							
On enalapril		178.3 ± 3.9	152.7 ± 4.2*	110.2 ± 0.9	94.5 ± 1.8*	127.6 ± 4.2	113.9 ± 2.5***	13/14
On atenolol		183.0 ± 4.1	161.5 ± 3.3*	109.3 ± 1.2	94.9 ± 1.1	133.7 ± 1.9	117.7 ± 1.7*	12/13
Severe hypertension	12							
On enalapril		202.8 ± 5.9	171.2 ± 5.6†	125.3 ± 1.1	105.1 ± 3.7†	150.8 ± 2.2	127.2 ± 4.0†	16/16
On atenolol		192.5 ± 5.1	179.2 ± 4.7	118.3 ± 2.5	108.8 ± 2.8†	143.1 ± 2.9	133.2 ± 3.2	7/12
All patients	67							
On enalapril		176.2 ± 2.9	150.8 ± 2.7*	110.7 ± 1.4	93.4 ± 1.4*	129.5 ± 2.3	112.5 ± 1.7*	14/15
On atenolol		175.5 ± 2.9	158.6 ± 2.5*	108.3 ± 1.2	90.4 ± 1.3*	130.8 ± 1.5	118.6 ± 1.6*	9/12

Values are given as mean ± s.e.m.; P values: * < 0.001, ** < 0.002, *** < 0.005, † < 0.01. A – placebo; B – active treatment.

Figure 1 Comparison of blood pressure response to enalapril (●) and atenolol (▲) in 25 patients with mild hypertension.

Figure 2 Comparison of blood pressure response to enalapril (●) and atenolol (▲) in 30 patients with moderate hypertension.

Discussion

The study was properly designed to minimize the influence of bias or natural variability of results by wash-out periods, taking BP measurements in uniform situations using a random zero mercury sphygmomanometer and adopting clearly defined criteria. A placebo run-in washout period of more than 4 weeks was considered undesirable because

of the attendant risks of uncontrolled hypertension.

Our results of enalapril therapy in patients with mild to moderate hypertension are comparable to those reported earlier.³⁻⁵ Enalapril alone failed to control BP in a majority of the patients with severe hypertension. The optimal dose of enalapril for most of the patients, who achieved normalization of BP, was 20 mg to 40 mg/day. A smaller dose (10 mg/day) was effective in only a few patients with mild hypertension, and increasing the dose to 60 mg/day benefited only a few patients. Only a few previous studies^{6,7} have compared the BP response with different doses of enalapril administered.

Comparative studies of enalapril with beta blockers in patients with mild to moderate hypertension have revealed it to be as effective as propranolol,^{9,10} metoprolol¹¹ and atenolol.^{8,12} In the present study, comparison of enalapril and atenolol revealed almost parallel efficacy of the 2 drugs in all grades of hypertension, although the per cent reduction in BP with enalapril was superior to atenolol. Moreover, reduction in systolic BP was more marked with enalapril than atenolol in patients with both mild and moderate hypertension ($P < 0.01$ in each group). Similar findings have been reported by other workers.^{8,12} The greater reduction in systolic BP with enalapril compared with atenolol appears clinically important as there is now greater evidence to suggest that

increased systolic rather than diastolic BP is predictor of cardiovascular morbidity.^{14,15} Moreover, it may prove to be a useful drug for the treatment of isolated systolic hypertension. Further study is required in this direction.

Side effects of enalapril were mild and trivial in the present study, and were unrelated to its dose. Its reported side effects were 0.5 to 5% and included headache, dizziness, fatigue, diarrhoea, skin rash, nausea, taste disturbance and, rarely, symptomatic hypotension.^{1,2,6}

In conclusion, enalapril was found to possess potent antihypertensive effect. It controlled BP in the majority of patients with mild to moderate hypertension at a dose of 20 to 40 mg/day. It was well tolerated, and has a parallel or slightly superior antihypertensive effect as compared to atenolol. Moreover, it has no limitations to its use with beta blockers as observed in conditions such as heart failure, heart block, bronchial asthma, diabetes mellitus and peripheral vascular disease. Enalapril is, therefore, clearly an effective and safe alternative first-line drug in the 'stepped-care' approach to the treatment of hypertension.

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References

- McFate, S.W., Kulaga, S.F., Moncloa, F., Pingaoni, R. & Walker, J.F. Overall tolerance and safety of enalapril. *J Hypertens* 1984, 2(Suppl 2): 113-117.
- Moncloa, F., Sromovsky, J.A., Walker, J.F. & Davies, R.D. Enalapril in hypertension and congestive heart failure. Overall review of efficacy and safety. *Drugs* 1985, 30(Suppl 1): 82-89.
- Lund-Johansen, P. & Omvik, P. Long-term haemodynamic effects of enalapril (alone and in combination with hydrochlorothiazide) at rest and during exercise in essential hypertension. *J Hypertens* 1984, 2(Suppl 2): 49-56.
- Sassano, P., Chatellier, G., Alhenc-Gelas, F., Carvol, P. & Menard, J. Antihypertensive effect of enalapril as first-step treatment of mild and moderate uncomplicated essential hypertension. *Am J Med* 1984, 7: 18-22.
- Fouad, F.M., Tarazi, R.C., Bravo, E.L. & Textor, S.C. Haemodynamic and antihypertensive effects of the new oral angiotensin-converting-enzyme inhibitor MK-421 (enalapril). *Hypertension* 1984, 6: 167-174.
- Davies, R.O., Irvin, J.D., Kramsch, D.K., Walker, J.P. & Moncloa, F. Enalapril worldwide experiences. *Am J Med* 1984, 77: 23-35.
- Bergstrand, R., Herlitz, H., Johansson, S. *et al.* Effective dose range of enalapril in mild to moderate essential hypertension. *Br J Clin Pharmacol* 1985, 19: 605-611.
- Arr, S.M., Burgees, J., Cooper, W.D. *et al.* A comparative study of enalapril and atenolol in moderate to severe hypertension. *Br J Clin Pharmacol* 1984, 18: 290-292.
- Simon, A.C., Levenson, J.A., Bouthier, J., Manrek, B. & Safar, M.E. Comparison of oral MK-421 and propranolol and their effects on arterial and venous vessels of the forearm. *Am J Cardiol* 1984, 53: 781-785.
- Enalapril in Hypertension Study Group (UK). Enalapril in essential hypertension: A comparative study with propranolol. *Br J Clin Pharmacol* 1984, 18: 51-56.
- O'Connor, D.T., Mosley, C.A., Cervenka, J. & Bernstein, K.N. Contrasting haemodynamic responses to the angiotensin enzyme inhibitor enalapril and the beta-andrenergic antagonist metoprolol in essential hypertension. *J Hypertens* 1984, 2(Suppl 2): 89-92.
- Helgeland, A., Strommen, R., Hagelund, C.H. & Tretli, S. Enalapril, atenolol and hydrochlorothiazide in mild to moderate essential hypertension. A comparative multicentre study in general practice in Norway. *Lancet* 1986, i: 872-875.
- Bradford Hill, A. *Principles of Medical Statistics*, 9th edition. The Lancet Limited, London, 1971, pp. 141-151.
- Kannel, W.B., Dawber, T.R. & McGee, D.L. Prospectives of systolic hypertension. *Circulation* 1981, 61: 1179-1182.
- Lichtenstein, M.J., Shipley, M.J. & Rose, G. Systolic and diastolic blood pressure as predictors of coronary heart disease mortality in Whitehall study. *Br Med J* 1985, 29: 243-245.