Efficacy of enalapril in essential hypertension and its comparison with atenolol

M. El Mangoush, N.K. Singh, S. Kumar, A. Basha, B.S. Gupta¹, Y.K. Bolya and A. Gamati

Departments of Medicine and ¹Community Medicine, Hawai Hospital, Arab Medical University, Benghazi, Libya.

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 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 atenolol⁸,¹² 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

Correspondence: M. El Mangoush, M.D., F.R.C.P., P.O. Box 2583, Benghazi, Libya
Accepted: 21 September 1989
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 antihypertensive 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 ± standard error of mean (s.e.m.) values. Statistical analysis to compare the antihypertensive effect of enalapril and atenolol included ‘t’ test applied to paired comparison. 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 ± s.e.m. values of systolic, diastolic and mean BP in all grades of hypertension with both drugs as compared to placebo (Table 1). 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.
Discussion

The study was properly designed to minimize the influence of bias or natural variability in 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 subgroups. A placebo run-in washout period of more than 4 weeks was considered undesirable because

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

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of patients</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
<th>Mean BP</th>
<th>% reduction in SBP/DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Mild hypertension</td>
<td>25</td>
<td>160.9 ± 3.2</td>
<td>138.8 ± 2.4*</td>
<td>104.5 ± 2.3</td>
<td>86.6 ± 0.9*</td>
</tr>
<tr>
<td>On enalapril</td>
<td></td>
<td>160.9 ± 3.2</td>
<td>138.8 ± 2.4*</td>
<td>104.5 ± 2.3</td>
<td>86.6 ± 0.9*</td>
</tr>
<tr>
<td>On atenolol</td>
<td></td>
<td>158.6 ± 2.7</td>
<td>145.4 ± 2.7*</td>
<td>102.5 ± 0.7</td>
<td>87.1 ± 4.6**</td>
</tr>
<tr>
<td>Moderate hypertension</td>
<td>30</td>
<td>178.3 ± 3.9</td>
<td>152.7 ± 4.2*</td>
<td>110.2 ± 0.9</td>
<td>94.5 ± 1.8*</td>
</tr>
<tr>
<td>On enalapril</td>
<td></td>
<td>183.0 ± 4.1</td>
<td>161.5 ± 3.3*</td>
<td>109.3 ± 1.2</td>
<td>94.9 ± 1.1</td>
</tr>
<tr>
<td>On atenolol</td>
<td></td>
<td>202.8 ± 5.9</td>
<td>171.2 ± 5.6†</td>
<td>125.3 ± 1.1</td>
<td>105.1 ± 3.7†</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>12</td>
<td>192.5 ± 5.1</td>
<td>179.2 ± 4.7</td>
<td>118.3 ± 2.5</td>
<td>108.8 ± 2.8†</td>
</tr>
<tr>
<td>All patients</td>
<td>67</td>
<td>176.2 ± 2.9</td>
<td>150.8 ± 2.7*</td>
<td>110.7 ± 1.4</td>
<td>93.4 ± 1.4*</td>
</tr>
<tr>
<td>On enalapril</td>
<td></td>
<td>176.2 ± 2.9</td>
<td>150.8 ± 2.7*</td>
<td>110.7 ± 1.4</td>
<td>93.4 ± 1.4*</td>
</tr>
<tr>
<td>On atenolol</td>
<td></td>
<td>175.5 ± 2.9</td>
<td>158.6 ± 2.5*</td>
<td>108.3 ± 1.2</td>
<td>90.4 ± 1.3*</td>
</tr>
</tbody>
</table>

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.

M. E. MANGOUSSH et al.
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. 


