



ENALAPRIL VERSUS ATENOLOL IN THE TREATMENT OF ESSENTIAL HYPERTENSION: A CROSS-OVER PLACEBO CONTROLLED STUDY

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Abstract

Purpose: This was conducted in an effort to determine efficacy and safety of Enalapril in the management of blood pressure (BP) on different levels of essential hypertension as compared to Atenolol that is a commonly used beta-blocker as a first line treatment of hypertension.

Methods: A cross-over study was performed because it involved 96 patients with essential hypertension in a part placebo-controlled experiment, where they were not aware of the actual study. Patients received a random allocation of Enalapril (10 mg/day, 20 mg/day and up to 80 mg/day in mild, moderate and severe hypertension respectively) or Atenolol (50 mg/day, or up to 100 mg/day in moderate and severe hypertension). BP was taken at two-week intervals and therapeutic changes given as per individual response. During the study side effects were observed. **Findings:** Enalapril was more effective in lowering both the systolic and diastolic BP than Atenolol in all haste of hypertension. The best variation in efficacy was achieved on the patients having severe hypertension where Enalapril provided a more significant fall in the BP. Enalapril had few and non-dose-dependent adverse effects whilst the other drug was shown to be well tolerated. In its turn, atenolol was less effective, though it worked. In conclusion, enalapril is a very powerful and well-tolerated antihypertensive in comparison to Atenolol and might be better than it. It is specifically useful in treating moderate and mild hypertension and it lacks some disadvantages to Atenolol in extreme cases and among people with other complications of the heart such as heart failure or bronchial asthma. Its efficacy in isolated systolic hypertension needs to be studied further as well as its best dosing in case of severe disease.

Keywords: Enalapril, Atenolol, Hypertension, Antihypertensive treatment, Systolic blood pressure, Beta-blockers

Introduction

Enalapril is a comparatively new, long acting, non sulphydryl angiotensin converting enzyme (ACE) inhibitor which has minimal side effects. In studies where placebo controlled, it has been proven successful in management of both blood pressure (BP) and systolic pressure in about 50-75 percent of mild-moderate hypertensive patients. Nevertheless, in the majority of the clinical trials set amount of 20 mg and 40 mg of this daily dose was applied. Very few studies have investigated the correlation of blood pressure response and a difference in dose of enalapril and the optimal dose is unknown. Also, very few studies have been carried out to determine the effectiveness of the drug as monotherapy in severe hypertensive subjects.

Comparative research has shown that enalapril and beta blockers have same efficacy on antihypertension as enalapril has equal efficacy with propranolol, metoprolol and atenolol. Nevertheless, the place of enalapril as an initial or first-line antihypertensive drug is not quite established yet. The selection of Atenolol as the reference was based on the fact that the said drug has been used as a standard first-line agent and that few are the reasons about the drug comparing it to that of the reference.

These were the main aims of the research: (i) to evaluate the ability of enalapril to lower blood pressure of patients with essential hypertension (severity ranging between mild and severe) and to determine the best dose of the drug; (ii) to compare the efficacy and safety of enalapril and atenolol in order to identify the possible role of enalapril as an initial line of medication in patients with hypertension.

Materials and Methods

Patients

Ninety-six patients with essential hypertension were involved with the trial. Patients were recruited by picking them randomly in the hypertension clinic and all of them gave informed consent. The patients who had secondary or malignant hypertension, were pregnant or had heart failure, heart block, diabetes mellitus, bronchial asthma, peripheral vascular disease, or severe renal or hepatic dysfunction were excluded. All of the patients were thoroughly examined physically, examined by X-ray of the chest, electrocardiogram, Blood Biochemistry, Urine Analysis. Depending on diastolic blood pressure (DBP), the patients were divided into mild (90-104 mmHg) - 30 cases, moderate (105-120 mmHg) - 40 cases and severe hypertension cases (>120 mmHg) - 26 cases. There were 45 men and 51 women aged between 28-65 years (means age 48.30 $\pm$ 2.34 years). The mean of the duration of hypertension was 5.7 $\pm$ 1.1 years and had a range of 1 month to 18 years.

Study Design

The current study was placebo-controlled, single-blind, cross-over, carried out in 8-10 weeks and both enalapril and atenolol were administered to each patient. The patients took a placebo (1 tablet/day) during 4 weeks used as a washout period after withdrawing any antihypertensive drugs previously used. The patients then were randomly allocated to be given once daily dose of either enalapril or atenolol. In mild hypertension, enalapril was used as 10 mg/day, but in moderate and severe hypertension, it was used as 20 mg/day. The therapeutic response determined the increase or decrease of the dosage that occurred every two weeks to reach 20, 40, 60, or 80 mg/day, unless the diastolic BP fell below 90 mmHg or side effects occurred. Initial dosage of atenolol was 50 mg/day in the case of mild hypertension and it might be upsurged to 100 mg/day after 4 weeks in case of need. The fixation in the power of 100 mg/day and up to 8 weeks or to the normalization of diastolic BP was applied to patients with moderate and severe hypertension. At the crossover stage to the second drug, there was a washout of 4 weeks with a placebo treatment of all patients.

The nature of the study was settled as the process was completed either by bringing the diastolic BP to normal (<90 mmHg) or when the patient achieved the maximum dose of both enalapril 80 mg/day and atenolol 100 mg/day within 4 weeks. Each patient was brought to the clinic once every 2 weeks and more often in a case of emergency. The blood pressure was recorded and the side effects noted at every visit. Blood pressure was measured in all occasions after every 10 minutes relaxation in the same position occupied by the patient. The right arm was measured with the help of a random zero mercury sphygmomanometer at the time range of 16:00 to 18:00 h. Systolic and diastolic blood pressure were determined by using first and fifth Korotkoff sounds respectively. A response to therapy was recorded as lowering of diastolic BP by above 10 mmHg or a DBP of less than 90 mmHg. BP that was restored to less than 90mmHg was defined as normotension or normalization of BP.

Statistical Analysis

Mean BP was determined by adding diastolic BP to the one third of the variation between systolic BP and diastolic BP. All the data are reported as mean values + standard error of the mean (s.e.m.). With the use of paired t-test, statistical comparisons concerning antihypertensive effects of enalapril and atenolol were done. P-value of less than 0.05 was regarded as statistically significant and less than 0.01 was highly significant. The severe, the moderate and the mild groups had the following power of the test: SBP 0.5-0.6, 0.6-0.7 and 0.3-0.4 respectively; DBP 0.1-0.0, <0.1 and 0.3-0.4 respectively and MBP 0.8-0.9, 0.3-0.4 and 0.3-0.4 respectively.

Result

Table 1 reveals the relative effect of Enalapril and Atenolol, when used on patients with mild, moderate and severe essential hypertension on their blood pressure. Other details in the data are their systolic, diastolic and mean blood pressures (BP) and the percentage of change in systolic blood pressure-diastolic blood pressure (SBP/DBP) before and after the intake of either drug. The values are presented as means of standard error of 96 patients broken down to various hypertension classes.

In mild hypertension (32 patients), Enalapril caused a significant lowering of systolic and diastolic BP, both systolic BP decreased significantly, the value of systolic BP reducing to 139.8 ± 2.6 mmHg (B) against 161.9 ± 3.5 mmHg (A) and that of diastolic BP declining to 87.0 ± 1.0 mmHg (B) against 105.0 ± 1.0 mmHg (A). This therapy led to the 13/15 percent change in SBP/DBP. Atenolol showed a tiny but different reduction of the systolic BP, starting at 159.0 ± 3.0 mmHg (A) to 146.0 ± 2.8 mmHg (B) and a larger reduction in diastolic BP (103.0 ± 1.0 mmHg to 87.5 ± 4.8 mmHg). The rate of SBP/DBP diminution was 8/15 at the percentage.

In moderate case of hypertension (40 patients) Enalapril caused the drop of systolic BP 179.5 mmHg (A) to 153.5 (B) and the fall of diastolic BP 110.5 (A) to 95.0 (B). There was a decrease in the mean BP of 128.0 ± 4.3 mmHg (A) to 114.5 ± 2.6 mmHg (B) leading to a decrease of 13/14 in SBP/DBP. The effect of atenolol was more severe when it lowered the systolic BP with values of 184.0 ± 4.3 mmHg (A) to 162.0 ± 3.6 (B) and diastolic BP that decreased to 109.5 ± 1.3 mmHg and 95.5 ± 1.2 mmHg, respectively. Such a treatment resulted in 12/13 decrease in SBP/DBP.

On severe hypertension (24 patients), Enalapril demonstrated significant systolic BP to range up to 203.5 ± 6.0 mmHg (A) to 172.5 ± 5.8 mmHg (B) and diastolic BP lowered down to 126.0 ± 1.2 mmHg (A) to 106.0 ± 3.8 mmHg (B). BP reduced by 16/16 percent to 128.0 ± 4.1 mmHg (B) compared with 151.5 mmHg ± 2.3 (A) BP and this made a significant difference because the SBP was lower in the same way that the DBP was lower. Atenolol lowered systolic BP (A) 193.5 ± 5.3 mmHg and (B) 180.0 ± 4.8 mmHg and the diastolic BP (A) 119.0 ± 2.4 mmHg and (B) 109.0 ± 2.9 mmHg. There was a reduction in average BP of the form 144.0 ± 3.0 mmHg (A) to 134.0 ± 3.3 mmHg (B), with a decrease of 7/12 SBP/DBP.

In all patients (96 patients) Enalapril decreased systolic BP by 26.0 (+3.2/95 = 177.5) mmHg (A) to 130.0 (-2.8/95 = 151.5) mmHg (B) with a reduction in diastolic BP by 17.4 (+1.5/95 = 111.0)

mmHg (A) to 76.4 (-1.5/95 = 93.6 There was a decrease in mean BP with a reading of 130.5 +/- 2.5 mmHg (A) to 113.5 +/- 1.8 mmHg (B), which translates into a 14/15 reduction in SBP/DBP. The systolic BP was dropped to 159.0 mmHg to 176.0 mmHg (A) and diastolic BP was reduced to 90.5 mmHg to 110.5 mmHg (A) by atenolol. The average BP decreased by 9/12 of the SBP/DBP noted as 131.5 +/- 1.4 mmHg (A) to 119.0 +/- 1.7 mmHg (B).

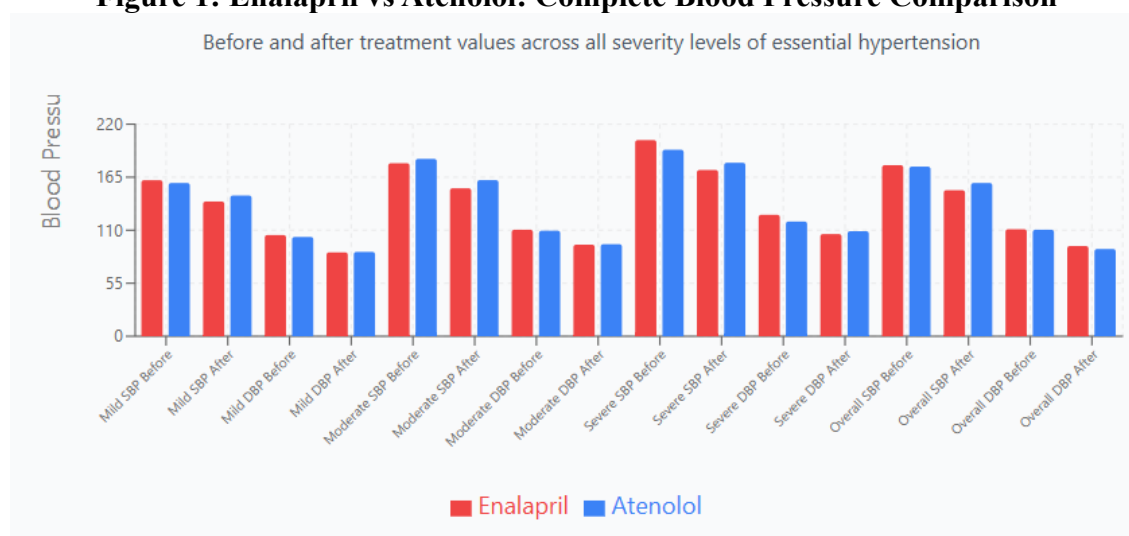
To sum up, in all degrees of hypertension the values of both systolic and diastolic blood pressure were reduced most after Enalapril, the percentage reduction in SBP/DBP being greatest when the case is of severe hypertension. Although it is effective, Atenolol showed a relatively less decrease in BP, as compared to Enalapril, especially in the severe cases. There was less percentage of SBP/DBP reduction as compared to Enalapril in the mild and moderate hypertension groups.

Table 1 shows clearly the unequivocal difference in the effect of Enalapril and Atenolol in basic hypertension control in different dosages and could be of worth in forming clinical decisions in use of antihypertensive drugs.

Table 1: Contrast of Enalapril with Atenolol Antihypertensive in Various Levels of Essential Hypertension

Groups	No. of patients	Systolic BP (A) ± S.E.	Systolic BP (B) ± S.E.	Diastolic BP (A) ± S.E.	Diastolic BP (B) ± S.E.	Mean BP (A) ± S.E.	Mean BP (B) ± S.E.	% Reduction in SBP/DBP
Mild hypertension	32	161.9 ± 3.5	139.8 ± 2.6	105.0 ± 1.0	87.0 ± 1.0	122.0 ± 1.2	104.5 ± 1.2	13/15
		159.0 ± 3.0	146.0 ± 2.8	103.0 ± 1.0	87.5 ± 4.8	122.0 ± 1.2	113.0 ± 1.3	8/15
Moderate hypertension	40	179.5 ± 4.0	153.5 ± 4.3	110.5 ± 1.0	95.0 ± 1.9	128.0 ± 4.3	114.5 ± 2.6	13/14
		184.0 ± 4.3	162.0 ± 3.6	109.5 ± 1.3	95.5 ± 1.2	134.0 ± 2.0	118.0 ± 1.8	12/13
Severe hypertension	24	203.5 ± 6.0	172.5 ± 5.8	126.0 ± 1.2	106.0 ± 3.8	151.5 ± 2.3	128.0 ± 4.1	16/16
		193.5 ± 5.3	180.0 ± 4.8	119.0 ± 2.4	109.0 ± 2.9	144.0 ± 3.0	134.0 ± 3.3	7/12
All patients	96	177.5 ± 3.2	151.5 ± 2.8	111.0 ± 1.5	93.6 ± 1.5	130.5 ± 2.5	113.5 ± 1.8	14/15
		176.0 ± 3.0	159.0 ± 2.6	110.5 ± 1.3	90.5 ± 1.4	131.5 ± 1.4	119.0 ± 1.7	9/12

Figure 1: Enalapril vs Atenolol: Complete Blood Pressure Comparison



Discussion

The investigation was carefully planned to reduce the effect of prejudice and the inherent variation of the outcome by providing suitable wash-out intervals, consistent conditions of measurement of BP and by a random zero mercury sphygmomanometer. Clearly defined evaluation criteria of BP were taken up. The washout period with a placebo of more than 4 weeks was not preferred since this period presents the risk of uncontrolled hypertension over this duration.

We come up with the same results on utilizing enalapril in treatment of patients with mild to moderate high blood pressure as we did in earlier reports. However, enalapril did not work as well in patients with severe hypertension as among most of the patients. Most of the patients were treated

at an optimal dose of 20 to 40 mg /day in order to normalize their BP. There were too minimal cases in which a lower dose of 10 mg/day effectively benefited the patient with mild hypertension and a greater dose of 60 mg/day did produce to lesser benefits to the few patients. There are few previous publications that directly compared the BP change with varied amount of enalapril.

Comparing the enalapril with beta blockers in mild to moderate hypertensive conditions in patients, a number of studies have revealed that enalapril was as effective as propranolol, metoprolol and atenolol. In the present research, analogy of enalapril and atenolol showed that they were almost similar in terms of efficacy at all levels of hypertension. Nevertheless, the percentage change of BP with enalapril was higher than that of atenolol. In addition, enalapril had caused a much greater decrease in systolic BP than atenolol in mildly or moderately hypertensive patients ($P<0.01$) ($P<0.01$ and $P<0.01$). Previous studies have the same outcomes.

Although there is no large difference between reducing systolic BP with enalapril and atenolol in terms of clinical importance, such a consequence is relevant since the recent studies indicate that higher systolic BP but not diastolic BP is a better indicator of cardiovascular morbidity. Besides, enalapril can be especially effective in the management process of isolated systolic hypertension; and more studies should be conducted to investigate its capabilities in relation to this type of hypertension.

In this research, the side effects of enalapril were considered as light and non life threatening and had no relationship with the dose taken. The reported side effects (10 cases out of 1000 to 1000 cases) include headache, dizziness, fatigue, diarrhea, skin rash, nausea, disturbance of the taste and, as a rare exception, hypotension. Such side effects were mostly adverse but temporary.

Conclusively, enalapril displayed good antihypertensive results culminating in regulation of BP in most patients with mild to moderate hypertension upon usage of 20 to 40 mg/day. It was tolerated well and showed at least equal and probably better efficacy with atenolol. As well enalapril lacks the restrictions of the beta blocker in disorders like heart failure, heart block, bronchial asthma, diabetes mellitus and peripheral vascular disease. Consequently, enalapril is effective, proven, safe and reliable first-line agent as an antihypertensive in management of hypertension.

Conclusion

To sum up, with regard to lowering blood pressure level, it is proved that Enalapril has remarkable and steady positive effect as it reduces blood pressure level to a great extent in cases of essential hypertension, be it mild or severe. The most successful outcome that was found was that the drug controlled both systolic and diastolic blood pressure at a range of 20-40 mg/day. Enalapril was compared to Atenolol in the reduction of systolic blood pressure and the study revealed that enalapril was more superior in reducing systolic blood pressure in patients with mild to moderate hypertension to justify its usefulness in the management of hypertension. Moreover, it was established that Enalapril was highly tolerated with minimum side effects that were not serious and not dose related.

Atenolol also proved to be effective in antihypertension but not as effective as Enalapril, especially in severe cases of hypertension. Also, it is seen that Enalapril has a terrific advantage over the beta blockers as it does not have restrictions in diseases that involve heart failure, heart block, bronchial asthma, diabetes mellitus and peripheral vascular disease.

Based on the results of this study, enalapril proves itself to be a safe, consistent and also possibly better first-line anti-hypertensive medicine than atenolol in patients having essential hypertension. It is a powerful substitute to people with hypertension, mostly those with mild to moderate types of the condition and could as well provide advantages as regards to the treatment of isolated systolic hypertension. There should be further studies concerning the duration of effects and correct dosing of Enalapril for severe cases.

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