Enalapril in patients with chronic heart failure: a placebo-controlled, randomized, double-blind study


ABSTRACT  A number of studies have shown short-term hemodynamic and symptomatic improvement in patients with congestive heart failure treated with angiotensin converting–enzyme inhibitors. The long-term efficacy of the oral long-acting converting–enzyme inhibitor enalapril remains to be established in controlled studies. We evaluated this drug in 36 patients with New York Heart Association functional class II to III heart failure who were clinically stable on digoxin and diuretic therapy. After baseline assessment of symptoms, exercise capacity, and results of echocardiographic examination and right heart catheterization, patients were randomly assigned to treatment with 5 mg enalapril twice daily (n = 18) or placebo (n = 18) in a double-blind fashion. The two groups had similar clinical, echocardiographic, and hemodynamic characteristics before treatment. After 3 months of treatment, the enalapril group showed a significant improvement as judged by subjective patient impression, functional class, and exercise duration (9.3 ± 5.7 vs 17.6 ± 5.6 min; p < .001). Diuretic dosage was reduced in six patients and increased in one patient, one patient had died and another had been withdrawn from the study. In the placebo group there was no significant change with respect to patient impression, functional class, or exercise duration; diuretic dosage was increased in seven patients and four patients had died. Echocardiographic left ventricular dimensions were significantly reduced and left ventricular shortening fraction significantly increased in the enalapril group but were unchanged in the placebo group. Hemodynamic assessment showed a significant reduction in left ventricular filling pressure from 23 ± 8 to 13 ± 5 mm Hg (p < .005) and an increase in stroke volume index from 25 ± 9 to 33 ± 7 ml/m² (p < .01) in the enalapril group, but no change in the placebo group (left ventricular filling pressure 20 ± 8 to 23 ± 8 mm Hg, NS; stroke volume index 28 ± 9 to 27 ± 8 ml/m², NS). Thus, enalapril is effective in patients with chronic heart failure, providing significant hemodynamic and symptomatic benefit with long-term treatment.


**Methods**

Patient selection. Thirty-six patients with chronic heart failure due to ischemic heart disease or cardiomyopathy and who were in New York Heart Association functional class II or III were included in the study. All patients had clinical and radiologic signs of cardiomegaly and congestive heart failure despite treatment with digoxin and diuretics. Patients with chronic lung disease, primary valvular heart disease, angina, claudication, recent myocardial infarction (within 3 months), or systemic arterial hypertension (systolic blood pressure < 90 mm Hg) were excluded from consideration as were those on other vasodilatory drugs. The study protocol was approved by the Auckland Hospital Ethical Committee and informed consent was obtained from each patient.

Study design. Preliminary assessment was carried out 2 weeks before randomization and commencement of treatment at which time patients underwent a practice treadmill exercise test. Previous medications were continued unchanged and patients entered the study if they were clinically stable at the time of baseline assessment 2 weeks later. At this time another treadmill
exercise test was performed followed by right heart catheterization and echocardiography. Digoxin and diuretic regimens were continued unchanged, with morning drug dosage being given at least 3 hr before assessment. After baseline assessment, patients were randomly assigned to treatment with either 5 mg enalapril twice daily or matching placebo in a double-blind fashion for a 3 month period. All medications were recorded on a card that each patient carried and it was marked at the time of each dosage. Patients were reviewed clinically after 2, 4, and 8 weeks of treatment and all dosages were kept constant. The diuretic dosage, however, was adjusted if necessary because of congestive symptoms and/or signs and change in body weight; the dosage was increased if there was clinical evidence of fluid retention and weight increase and reduced if prerenal azotemia was noted with a decrease in weight. At 3 months patients underwent repeat exercise testing, right heart catheterization, and echocardiographic examination. Again assessment was at least 3 hr after morning drug dosage and was at a time of day similar to that when the baseline assessment was made.

Assessment. Treadmill exercise evaluation was carried out with the use of the Naughton protocol11 with continuous stages of 3 min duration until limiting symptoms of dyspnea or fatigue occurred. In addition to assessment of functional class and treadmill exercise duration, at the end of the study period the subjective impression of the patient was recorded. The patients were asked to specify whether they felt either much better, a little better, no change, a little worse, or much worse while on the trial medication.

Right heart catheterization was performed with a balloon-tipped catheter to measure intracardiac pressures and cardiac output by the thermodilution technique. Cardiac output measurements were obtained in triplicate and expressed as cardiac index corrected for body surface area. A precordial electrocardiographic lead was used for recording heart rate and systemic arterial pressure was measured by cuff and mercury column sphygmomanometer. Hemodynamic measurements were made at 30 min intervals until consecutive measurements with less than 10% variation for cardiac output and mean pulmonary capillary wedge pressure were obtained, the last set of measurements being taken as baseline values. A similar procedure was followed for repeat cardiac catheterization at 3 months, again with measurements being made at a time of day similar to that when baseline data were obtained.

Echocardiographic examination was carried out in supine patients with an Electronics for Medicine Model IV Echograph and a 13 mm 2.25 MHz medium-focus transducer. Transducer position, echographic gain, and patient position were adjusted to obtain optimal recordings of left ventricular dimensions in the minor axis.12 In all cases repeat echocardiograms were obtained with the patient in the same position as for the baseline study. Left ventricular end-diastolic dimension was measured at the peak of the R wave of the electrocardiographic QRS complex and the end-systolic dimension at the time of peak anterior motion of the left ventricular posterior wall. Left ventricular shortening fraction was derived from the left ventricular end-diastolic and end-systolic dimensions.13

Statistical analysis. At baseline the two treatment groups were compared to determine independence of clinical characteristics with the chi-square test of homogeneity and for bias of continuous variables with Student’s t test. Values at baseline and 3 months were compared within each group with Student’s t test for paired data. Assuming that the possibility of improvement from a low value was the same as from a higher value of the same variable, the changes from baseline to 3 months were compared with the Mann-Whitney U test for group differences according to treatment. The initial assumption was corroborated by the finding of similar confidence intervals, by the Student’s t test for group differences, for the means and variances of the 3 month values for all the variables that were homogeneous in the two groups at baseline. Test results were considered to be significant if p < .05. Data are presented as mean ± SD.

Results

Patient groups. Eighteen patients were randomly assigned to treatment with enalapril and 18 patients received placebo. The clinical, echocardiographic, and hemodynamic characteristics noted at baseline are listed in tables 1 to 3. All but two patients in the enalapril group were able to exercise on the treadmill, echocardiographic recordings were obtained in all but one patient in the placebo group, and hemodynamic measurements were made in all but one patient in the enalapril group. There were no significant differences between the groups with respect to any of these baseline characteristics or measurements except for treadmill exercise duration, and this difference was of borderline statistical significance. In the enalapril group baseline treadmill exercise duration was 9.2 ± 5.6 min and in the placebo group it was 13.1 ± 6.4 min (p = .05). There were more patients in the enalapril than in the placebo group in whom heart failure was related to ischemic heart disease and fewer with disease of a nonischemic cause, but this difference was not significant.

Clinical response. During the study period there were five deaths, one in the enalapril group and four in the placebo group. All these deaths were sudden and at-

<p>| TABLE 1 |
| Clinical characteristics of patient groups at baseline |</p>
<table>
<thead>
<tr>
<th>Enalapril group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61 ± 9</td>
</tr>
<tr>
<td>Range</td>
<td>41–75</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
</tr>
<tr>
<td>Etiology of heart failure</td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>11</td>
</tr>
<tr>
<td>Nonischemic disease</td>
<td>7</td>
</tr>
<tr>
<td>Duration of symptoms (mo)</td>
<td>31 ± 40</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>15</td>
</tr>
<tr>
<td>II</td>
<td>3</td>
</tr>
<tr>
<td>Digoxin dosage (mg)</td>
<td>0.19 ± 0.12</td>
</tr>
<tr>
<td>Furosemide dosage (mg)</td>
<td>118 ± 66</td>
</tr>
<tr>
<td>Patients on additional diuretic medication</td>
<td>6</td>
</tr>
<tr>
<td>Treadmill exercise duration (min)</td>
<td>9.2 ± 5.6</td>
</tr>
</tbody>
</table>

Enalapril vs placebo, all NS except for treadmill exercise duration (p = .05).
TABLE 2
Radiologic and echocardiographic measurements of patient groups at baseline

<table>
<thead>
<tr>
<th></th>
<th>Enalapril group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-ray results (cardiothoracic ratio)</td>
<td>0.56 ± 0.03</td>
<td>0.58 ± 0.06</td>
</tr>
<tr>
<td>Echocardiographic results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic dimension (mm)</td>
<td>66 ± 6</td>
<td>70 ± 11</td>
</tr>
<tr>
<td>LV end-systolic dimension (mm)</td>
<td>60 ± 7</td>
<td>63 ± 10</td>
</tr>
<tr>
<td>LV fractional shortening (%)</td>
<td>10.9 ± 4.2</td>
<td>10.8 ± 2.4</td>
</tr>
</tbody>
</table>

Enalapril vs placebo, all NS.
LV = left ventricular.

tributed to a cardiac cause. One patient in the enalapril group was withdrawn from the study after 8 weeks. This patient sustained a foot injury, developed infective and ischemic complications, and required peripheral vascular surgery necessitating her withdrawal from the study.

Diuretic dosage was increased in one patient in the enalapril group and reduced in six others. In two patients furosemide dosage was reduced and in two spironolactone dosage was reduced. In another two patients in whom weight loss and azotemia were noted spironolactone therapy was stopped. In the placebo group diuretic dosage was increased in seven patients. These changes in dosage were significantly different in the two groups (p < .002).

Functional class improved in all but two of the patients in the enalapril group examined at 3 months, whereas in the placebo group, in two patients it was improved, in two it worsened, and the remainder stayed in the same functional class (p < .001; figure 1). Similarly, treadmill exercise duration improved in the enalapril group from 9.3 ± 5.7 to 17.6 ± 5.6 min (p < .001), whereas in the placebo group it remained unchanged (13.9 ± 7.6 to 13.7 ± 7.2 min, NS). The change in treadmill exercise duration in the enalapril group was significant when compared with the placebo group (p < .005). The results for individual patients are shown in figure 2. Twelve patients in the enalapril group improved their exercise duration by more than one stage (3 min), two patients improved by between 2 and 3 min, and one patient showed no change. Only four patients in the placebo group improved by more than one stage, two patients improved by between 2

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and 3 min, two had a slight reduction, and six a reduction of more than one stage. All 16 patients in the enalapril group said they felt much better while on the trial medication and this subjective impression was significantly different from that in the placebo group; three patients on placebo felt much better, five a little better, and the remainder reported that they felt unchanged or worse (p < .001; figure 3).

Echocardiography. Echocardiographic evaluation showed a reduction in left ventricular dimensions and an increase in fractional shortening in the enalapril group whereas in the placebo group there was the opposite tendency, the changes from baseline to 3 months being significantly different between the groups (figure 4). In the enalapril group left ventricular end-diastolic dimension was reduced from 66 ± 6 to 63 ± 9 mm (p < .005), left ventricular end-systolic dimension was reduced from 60 ± 6 to 56 ± 7 mm (p < .0001), and fractional shortening increased from 10.6 ± 3.5% to 14.5 ± 5.0% (p < .005).

Hemodynamic measurements. The data obtained in the 15 patients in the enalapril group and the 14 patients in the placebo group studied at baseline and 3 months are shown in table 4. There were no significant hemodynamic changes in the placebo group; cardiac, stroke volume, and stroke work indexes declined slightly and ventricular filling pressures remained elevated. In the enalapril group there was a slight but insignificant reduction in mean arterial pressure, but systemic vascular resistance was significantly reduced and cardiac, stroke volume, and stroke work indexes were all significantly increased by approximately 25%. Ventricular filling pressures were significantly reduced, the mean pulmonary capillary wedge pressure becoming normal in the majority of patients despite reduction of diuretic dosage in some patients. The comparative

FIGURE 3. Patients' subjective impressions after 3 months treatment. The patients in the enalapril group all specified feeling much better, whereas the patients in the placebo group had varied impressions, and the impression was significantly different in the two groups.

FIGURE 4. Echocardiographic evaluation at baseline and 3 months. Left ventricular end-diastolic dimension (LVEDD) and left ventricular end-systolic dimension (LVESD) were significantly reduced and left ventricular fractional shortening (% shortening) significantly increased in the enalapril group. The opposite tendency was observed in the placebo group and the changes were significantly different in the two groups.
changes from baseline were significant between the groups for systemic vascular resistance; cardiac stroke volume, and stroke work indexes; and mean pulmonary capillary wedge and right atrial pressures.

The variation in hemodynamic response for individual patients is shown in figure 5. Ten patients in the enalapril group had an increase in stroke volume index of more than 5 ml/m², together with a reduction in mean pulmonary capillary wedge pressure of more than 5 mm Hg. In four of these patients diuretic dosage had been reduced and in one patient there had been an increase. No patient in the placebo group showed similar hemodynamic improvement. Four patients in the placebo group showed hemodynamic deterioration, as evidenced by a reduction in stroke volume index of more than 5 ml/m² or an increase in pulmonary capillary wedge pressure of more than 5 mm Hg. Two patients in the enalapril group had reductions in stroke volume index and mean pulmonary capillary wedge pressure was unchanged in both.

Changes in treadmill exercise duration for individual patients were correlated with changes in cardiac index and mean pulmonary capillary wedge pressure, as shown in figures 6 and 7. In the enalapril group most patients had improved treadmill exercise duration and hemodynamics whereas in the placebo group most showed no change or a deterioration.

Side effects. There were no major side effects observed during the study period. No patient experienced symptoms of hypotension and the blood pressure reduction that was observed in the enalapril group was not significant. There were no significant changes in serum levels of urea, creatinine, or electrolytes in the

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enalapril group. However, in two patients resolution of congestive symptoms and signs and weight loss were associated with the increase of serum urea with return to baseline values after withdrawal of spironolactone. In a third patient, serum potassium level rose above normal and returned to within the normal range after reduction of spironolactone. There was no significant hematologic change or proteinuria in any patient. Three patients in the enalapril group experienced minor skin itch or rash. One patient complained of intermittent moderate facial itch without rash that occurred from the fourth week of treatment. Another patient complained of intermittent slight itch involving the hands and lower limbs without rash from the seventh week of treatment. A third patient experienced a macular erythematous nonirritant rash on the trunk and arms that appeared during the first week of treatment and remained thereafter.

Discussion

Vasodilating drugs are now widely used in the treatment of chronic heart failure and the effects of various nonparenteral agents have been assessed, including oral and topical nitrates, 14,15 hydralazine, 16,17 prazosin, 18-22 and captopril. 1-5 The hemodynamic and symptomatic benefits of the angiotensin converting–enzyme inhibitor captopril have been well established in a number of studies and recently evidence of efficacy has been obtained from controlled studies. 6,7 Enalapril is a new long-acting ethyl ester converting–enzyme inhibitor that is deesterified to an active metabolite. 8 It has a more gradual onset of effect and prolonged duration of action than captopril. 9 Thus, there may be less of a tendency to sudden hypotension and dosage requirements can be less frequent. In addition enalapril does not contain a sulphydryl group, which may be associated with some of the adverse effects of captopril. 10 Hence, theoretically there may be less potential for toxicity. Preliminary assessment of enalapril in open pilot studies has demonstrated short-term hemodynamic improvement in small groups of patients with heart failure. 23-25 Our study provides definite evidence of hemodynamic and symptomatic benefit from enalapril in patients with chronic heart failure during a placebo-controlled randomized trial.

The patient groups had comparable baseline clinical and hemodynamic characteristics except with respect to treadmill exercise duration. Although the difference between the enalapril and placebo groups was of borderline statistical significance, it is possible that the enalapril group, being more limited, had greater potential for subsequent improvement. Alternately, if exercise capacity was related to severity of heart failure and prognosis, poorer progress might have been expected in this group. However, the groups were well matched in all other respects and unequivocal improvement after enalapril treatment was shown by various methods of assessment, all of which were consistent for the group. Furthermore, changes in exercise duration correlated well with changes in cardiac index and mean pulmonary capillary wedge pressure. The clinical stability of the patient population studied was evident from the lack of change in the placebo group during the study period.

While significant hemodynamic and symptomatic improvement was clearly demonstrated in the group receiving enalapril, there was wide individual variation in hemodynamic response within the group. The majority showed significant hemodynamic improvement, but in a few cases hemodynamic measurements were not significantly improved and this was inconsistent with the symptomatic improvement noted. We did not attempt to assess regional circulation or obtain hemodynamic measurements during exercise, which may have explained some of this disparity. Such additional complementary studies are required to confirm the hemodynamic benefits of enalapril and allow a better understanding of mechanisms that our study was not designed to investigate.

The subjective patient impression recorded cannot be reliably quantitated or validated and in some cases was disparate with other measures of improvement, which demonstrates the difficulty of accurately assessing change in such patients and the importance of controlled studies. Several enalapril-treated patients reported feeling very much better in nonspecific terms such as improved general well-being, improved men-
toral function, energy, and appetite, but had relatively minor changes in other, more objective, measures of improvement. This again emphasizes the limitations of the methods of assessment available and the need to study mechanisms of improvement further. The need for careful control and a number of different methods of assessment is exemplified by the case of the single patient in the placebo group who improved from functional class III to I, showed similar improvement in treadmill exercise performance, and yet showed no hemodynamic changes.

The relatively low and fixed dosage of enalapril used in this study was chosen for reasons of safety within a double-blind study. There is evidence that 5 mg twice daily may be insufficient for complete angiotensin converting–enzyme inhibition in some patients, who may require 10 mg twice daily or more. Thus, greater improvement may have been produced in some patients had the dose been titrated according to clinical response. The delayed onset and prolonged duration of action and difficulty in detecting a peak response to enalapril make the determination of an optimale dose difficult in a short-term hemodynamic study. Nevertheless, the dosage used in this study produced hemodynamic improvement in the group and in the majority of individual patients. Because of the delayed diuretic effect and reduced diuretic requirements of some patients, increases in enalapril dosage should probably be made only after judging the response to treatment over some weeks. From our study it seems that only a minority of patients will require a higher dosage than that used, but further studies are required to determine optimal dosage.

There were no major side effects observed. However, diuretic requirements were reduced in six patients and in two of these weight loss was associated with prerenal azotemia that necessitated cessation of spironolactone therapy. In a third patient hyperkalemia responded to reduction of spironolactone dosage. Thus, patients’ clinical states, body weights, and serum biochemistries should be closely monitored during the first few months of treatment and the diuretic dosage should be adjusted appropriately. In particular, spironolactone may need to be withdrawn; the need to continue therapy with an aldosterone antagonist along with an angiotensin converting–enzyme inhibitor (which causes blockade of aldosterone production) should be questioned and patients on this combination should be followed closely. In our experience with captopril we have generally found it possible to stop spironolactone at the time of commencing dosing with the converting–enzyme inhibitor, continuing patients on a combination of captopril and furosemide without spironolactone or potassium supplements. The occurrence of minor skin rash and irritation in three patients suggests that enalapril, like captopril, may have a tendency to cause this side effect. The more serious side effects of proteinuria and agranulocytosis reported for captopril and associated with the sulfhydryl group have not been observed after low-dose captopril in patients with heart failure and were not observed in this study.

Although, like captopril, enalapril has both arterial and venodilating properties, it does appear that the effect of preload and reduction of elevated ventricular filling pressures is greater than on cardiac output. Angiotensin II appears to have relatively little direct effect on the venous bed and it has been suggested that, for captopril, indirect effects on other vasoactive substances such as bradykinin, catecholamines, and prostaglandins are relevant. In addition, the diuretic effect of angiotensin converting–enzyme inhibition achieved through aldosterone blockade would obviously contribute to preload reduction. Overdiuresis with excessive preload reduction may compromise cardiac output and offset the increase achieved through arterial dilatation.

In summary this study establishes the efficacy and safety of enalapril in the treatment of patients with chronic heart failure. Further complementary studies are required to elucidate the mechanisms of action, determine optimal dosage, and study effects of the drug on long-term patient survival.

We acknowledge the assistance of Mr. Ken McGrath in preparing the illustrations and Miss Robyn Cliffe in preparing the manuscript. The interest of Dr. W. M. Smeeton and Mrs. Margaret Relph and the support of Merck, Sharp & Dohme Limited is also acknowledged.

References

CIRCULATION
D N Sharpe, J Murphy, R Coxon and S F Hannan

Circulation. 1984;70:271-278
doi: 10.1161/01.CIR.70.2.271

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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