Double-blind crossover comparison of enoximone and placebo in patients with congestive heart failure

SURESH K. CHORARIA, M.R.C.P., DAVID TAYLOR, PH.D., AND JEREMY PILCHER, F.R.C.P.

ABSTRACT The efficacy of oral enoximone, a new positive inotropic and vasodilator agent, was assessed in 12 patients with chronic congestive heart failure (New York Heart Association [NYHA] class II or III) in a double-blind randomized crossover comparison with placebo. Duration of each treatment was 6 weeks and the dose of enoximone was 150 mg tid. Efficacy was assessed by exercise tolerance, symptoms, radionuclide angiography for ejection fraction at rest and during exercise, and Holter monitoring. Two patients were withdrawn before completion of the study, one with pulmonary edema after 1 week on placebo and the other for noncompliance with enoximone therapy. Symptomlimited exercise capacity improved with enoximone by 30% and 43% (p < .01) compared with baseline after 2 and 6 weeks treatment, respectively. Ejection fraction improved at rest (p < .02) with enoximone but not with placebo. No change was found during exercise. Heart rate and blood pressure remained unaltered. During treatment with enoximone symptoms of exertional dyspnea and fatigue were improved and NYHA class decreased by at least one class for every patient. Holter monitoring revealed an overall increase (NS) in ectopic activity during enoximone therapy. There were no serious adverse effects and laboratory values did not change significantly. The addition of enoximone to the existing therapy of patients with moderately severe congestive heart failure provided clear and sustained subjective and objective benefit when compared with placebo. 


CONVENTIONAL TREATMENT for congestive heart failure is based on the use of diuretics and digitalis glycosides added either to control atrial fibrillation or to provide inotropic support or both. For many patients this treatment may be effective over an extended duration. However, even potent diuretics frequently fail to provide or sustain adequate symptomatic relief while excessive diuresis may exacerbate symptoms resulting from low cardiac output. Hypokalemia can provoke serious arrhythmias, particularly when the patient is taking digitalis also. The limited value of digitalis as an effective inotropic agent over the long term is combined with a well-recognized and high incidence of adverse effects.1

The shortcomings of standard therapy has led to a search for other orally administered agents capable of producing sustained symptomatic and hemodynamic improvement in patients with heart failure. Early inves-

tigations have centered on drugs that alter the loading conditions of the left ventricle and vasodilator therapy is now widely accepted in the management of severe heart failure, although it may often fail to control symptoms in low-output states.

More recently, attention has been directed toward the use of nonglycoside, noncatecholamine agents possessing a combination of vasodilator and positive inotropic activities. The ability of such compounds not only to reduce the load on the heart but also directly to improve left ventricular performance may offer an advantage over, or an alternative to, therapy with vasodilators.

Enoximone, a substituted amidazolone, possesses positive inotropic and vasodilator activities in animals2, 3 and man,4 both probably the result of its ability to inhibit intracellular phosphodiesterase (PDE III).5

Enoximone, both in the intravenous6, 7 and oral forms,8, 9 has been studied in a number of open uncontrolled studies in patients with congestive heart failure. Both hemodynamic and symptomatic improvement has been reported from these studies, but so far no con-
trolled comparison of enoximone with placebo has been conducted. This trial was therefore planned to compare the effects, over a period of 6 weeks, of treatment with enoximone and that with placebo in a randomized double-blind, crossover comparison with the use of noninvasive methods to determine response.

Patients and methods

The 12 patients (11 men, one woman; age range 46 to 67 years, mean 54) selected for the study had moderate to moderately severe congestive cardiac failure (New York Heart Association [NYHA] class II and III) that had responded inadequately to diuretics and digitalis. Nine patients had ischemic heart disease and three had idiopathic dilated cardiomyopathy.

None were receiving vasodilators apart from the occasional use of sublingual glyceryl trinitrate; diuretic (12 patients) and digitalis therapy (eight patients) was continued unaltered through the 3 month period of the study. Ten patients were in sinus rhythm, one had controlled atrial fibrillation and one had a permanent VVI pacemaker for complete heart block. One patient was on tocainide for previously documented ventricular fibrillation and tachycardia and one was receiving methyldopa for essential hypertension.

Exclusion criteria for entry into the study were the presence of major disease of any other organ system, myocardial infarction within 3 months, uncontrolled tachyarrhythmias, restrictive or hypertrophic cardiomyopathy, stenotic valvular disease, and effort tolerance limited by symptoms other than fatigue and/or dyspnea.

All patients gave written consent and the study protocol was approved by the hospital Ethics Committee. Baseline investigations consisted of a full clinical examination, a resting 12-lead electrocardiogram (ECG), a 24 hr ambulatory ECG (Holter), a chest x-ray, estimation of radionuclide ejection fraction at rest and at maximal stress during supine bicycle exercise, and a full biochemical and hematologic laboratory profile. Patients performed exercise tests supine, at least 2 hr after the last meal and as closely as possible to the same time of day, on an electronically controlled bicycle ergometer. The initial load was 20 W and it was increased by increments of 20 W every 3 min until terminated by dyspnea or fatigue.

During the baseline period all patients exercised twice at an interval of 1 week; the duration of the two tests in all 12 patients did not differ by more than 3 min, confirming that all were in a relatively stable condition before study entry.

Continuous electrocardiographic monitoring was carried out during the entire exercise period. The measurement of ejection fraction by radionuclide multiple-gated acquisition scanning of patients at rest and at maximum stress was accomplished during the first of these exercise tests. Labeling of red cells in vivo was with technetium-99m and resting images were acquired with a gamma camera computer system (Technicare) in the right and left anterior oblique (RAO, LAO) (45 degree) projection. A total of 28,000 counts in the left ventricle at end-diastole were acquired and this took about 5 min for each view. A further acquisition in the LAO view was commenced as the patient approached maximal exercise capability and counts were collected for at least 2 min. In six instances, patients were unable to continue at their maximum workload during the 2 min exercise acquisition period and in these cases the load was reduced to allow completion of the scan. Typically, in 2 min a total of 10,000 counts were obtained in the left ventricle at end-diastole, which is sufficient to give reasonable accuracy for measurement of ejection fraction.

After completion of all baseline examinations patients were randomly assigned to receive double blind either 150 mg tid enoximone for 6 weeks followed by a matching placebo capsule tid for 6 weeks or vice versa.

Patients were seen after 2 and 6 weeks in each treatment period. At every visit they underwent a full clinical examination, including electrocardiographic and laboratory screening, and exercise testing was repeated (2 hr after last dose). Blood samples were obtained just before and 1½ hr after the last dose for measurement of plasma concentrations of enoximone and its sulphoxide metabolite.

Radionuclide angiography for determination of left ventricular ejection fraction at rest and during stress was conducted at the 6 week visits. Chest x-ray and a 24 hr ambulatory ECG were also obtained at these times.

Drug assay. Blood samples obtained for estimation of serum level of enoximone and its metabolite were analyzed by high-pressure liquid chromatographic assay.

Data analysis. The chi-squared test was used in the analysis of results of Holter monitoring. Student's paired t tests were used to compare all other values. They are expressed as the mean ± SD and a p value <.025 was considered to indicate a statistically significant difference at the 5% by use of Bonferroni's correction for repeated paired t tests.

Results

Two patients were withdrawn from the study. One developed acute left ventricular failure a week into the placebo phase of the study (week 1) and the second patient was withdrawn because of noncompliance with the enoximone regimen (week 11). The results from the latter patient are included in the analyses up to the last clinic attendance.

The results of the major examinations and investigations are presented in table 1.

Enoximone did not significantly affect heart rate or blood pressure during the trial period when compared with placebo, but it significantly improved exercise capacity. This is illustrated in figure 1, where the crossover effect is shown.

Patients starting on placebo had a small, nonsignif-
THERAPY AND PREVENTION—CONGESTIVE HEART FAILURE

TABLE 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (n=11)</th>
<th>2 weeks (n=11)</th>
<th>6 weeks (n=11)</th>
<th>2 weeks (n=10)</th>
<th>6 weeks (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>87.3 ± 13.2</td>
<td>86.1 ± 12.7</td>
<td>84.3 ± 11.5</td>
<td>89.8 ± 12.7</td>
<td>84.5 ± 11.2</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>119 ± 10</td>
<td>115 ± 19</td>
<td>116 ± 18</td>
<td>119 ± 12</td>
<td>123 ± 12</td>
</tr>
<tr>
<td>Diastolic</td>
<td>81 ± 8</td>
<td>83 ± 8</td>
<td>82 ± 9</td>
<td>83 ± 8</td>
<td>82 ± 9</td>
</tr>
<tr>
<td>Exercise time (sec)</td>
<td>391 ± 92</td>
<td>435 ± 116</td>
<td>397 ± 178</td>
<td>508 ± 2.4</td>
<td>591 ± 129</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>20 ± 7.5</td>
<td>20 ± 8.6</td>
<td>20 ± 8.6</td>
<td>20 ± 10.2</td>
<td>25.3 ± 8.7</td>
</tr>
<tr>
<td>Stress</td>
<td>19.3 ± 8.7</td>
<td>19.9 ± 7.8</td>
<td>19.9 ± 7.8</td>
<td>21.3 ± 9</td>
<td></td>
</tr>
<tr>
<td>Rate/pressure product^a</td>
<td>16,566 ± 3,763</td>
<td>18,093 ± 4,409</td>
<td>18,102 ± 5,909</td>
<td>19,956 ± 3,454</td>
<td>21,444 ± 4,769</td>
</tr>
<tr>
<td>Mean NYHA</td>
<td>2.6 ± 0.5</td>
<td>2.0 ± 0.8</td>
<td>2.3 ± 0.8</td>
<td>1.7 ± 0.9</td>
<td>1.3 ± 0.8</td>
</tr>
<tr>
<td>Holter monitoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VBPS/hr</td>
<td>89.2 ± 77</td>
<td>111 ± 27</td>
<td>—</td>
<td>170 ± 122</td>
<td>—</td>
</tr>
<tr>
<td>Salvos (&gt;2 VPBS/hr)</td>
<td>2.4 ± 3.6</td>
<td>4.1 ± 6.8</td>
<td>—</td>
<td>9.6 ± 12.7</td>
<td>—</td>
</tr>
<tr>
<td>Plasma concentration (mg/l)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.31 ± 0.18</td>
<td>0.27 ± 0.19</td>
</tr>
<tr>
<td>Enoximone</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Sulphoxide</td>
<td></td>
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</tr>
</tbody>
</table>

All values are mean ± SD.

^aHeart rate × systolic blood pressure at maximal stress.

*p < .025; ^p < .01; ^p < .001, enoximone vs placebo, paired t test.

*p < .025; ^p < .01; ^p < .001, enoximone vs baseline, paired t test.

significant improvement during the first 6 weeks; their exercise tolerance then increased dramatically over the 6 weeks treatment with enoximone, although the high value for the final exercise test is influenced by the small number of patients (n = 4), one of whom increased his exercise duration three times. In the other group a significant improvement in exercise during treatment with enoximone declined rapidly after crossover to placebo and at the end of the study exercise time was not different from baseline.

Ejection fraction measured at rest increased significantly (p < .02) in patients on enoximone (from 20% to 25%), but remained unchanged in those on placebo. Ejection fraction measured at maximum stress was unaltered by either treatment.

The product of heart rate and systolic blood pressure at maximum stress was calculated for all exercise tests and revealed an increase over baseline in patients on enoximone (+ 29%, p < .05 > .025, NS), but not in those on placebo (+ 9%, NS).

In terms of subjective response NYHA class was improved by at least one class in all 10 patients after 6 weeks treatment with enoximone, while only four of 11 patients on placebo improved, the remainder not changing their pretreatment classification (figure 2). Symptoms of exertional dyspnea, fatigue, and overall incapacity all improved during enoximone treatment but not in the placebo phase.

Holter monitoring was carried out 2 weeks into each treatment period and a nonstatistically significant (NS) increase in ventricular premature beats (VPBs) was observed during the enoximone phase compared with baseline and placebo values. Incidence of salvos of two VPBs or more was also increased (NS) during enoximone, but none were sustained for more than 10 beats and no R-on-T complexes were seen.

Changes in blood pressure after the first dose of enoximone and placebo were similar. Mean maximum change in systolic blood pressure was −13 mm Hg on enoximone (range −30 to +36 mm Hg) and −8.8 mm Hg on placebo (range −26 to +26 mm Hg). No symptoms were reported during the 3 hr period of observation after the first dose.

Plasma concentrations of enoximone and its sulphoxide metabolite, which were determined 5 to 6 hr after the last dose, were similar in samples obtained at 2 weeks and at 6 weeks. The samples taken 1½ hr after a dose also showed no significant difference between concentrations at 2 and 6 weeks.

Only few side effects were reported and in general patients tolerated the drug well. Effects that were possibly thought to be treatment related were palpitations (two episodes) and myalgic pain in two patients on enoximone, and vertigo and nausea in one patient on placebo. No changes were seen in the biochemical and hematologic variables throughout the study.

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Enoximone is believed to possess inotropic and vasodilator properties. In our study we were unable to identify the relative contribution of these two properties to the overall hemodynamic effect. However, an increase of the rate-pressure product (heart rate × systolic blood pressure) at maximum stress is an indication of ability to increase cardiac work\(^2\) and this was only observed during treatment with enoximone.

Improvement of ejection fraction at rest has previously been shown with other orally administered positive inotropic agents\(^13\), \(^14\) and we have demonstrated a significant increase in ejection fraction for enoximone at rest, but not at maximum stress. Unlike the rate-pressure product, which is largely rate dependent, the magnitude of ejection fraction does not directly reflect myocardial contractility since it is dependent on cardiac load as well as rate.\(^15\)\(^-\)\(^17\)

The mechanisms of change in ejection fraction on exercise have been shown to be different in patients whose heart failure is due to ischemic heart disease and in those with congestive cardiomyopathy.\(^18\) In the latter, stroke volume is increased by a reduction of end-systolic ventricular volume with little change in dimensions at end-diastole, resulting in an increased ejection fraction. On the other hand, in patients with ischemic heart disease ejection fraction is decreased or unaltered because improved stroke volume is achieved by an increase in end-diastolic ventricular volume with no change in end-systolic dimensions. Heart failure in our group of patients was of mixed causes and therefore an overall improvement in ejection fraction was not expected. However, on an individual basis five patients had improved exercise ejection fractions (two with congestive cardiomyopathy and three with ischemic heart disease), so there may be other factors that affect changes in exercise ejection fraction apart from cause of heart failure. What these changes in ejection fraction mean in terms of long-term prognosis is not known.

The dose of enoximone that was used in our study (150 mg tid, representing a mean of 2.2 mg/kg body weight tid) was chosen during an early stage of clinical development and it is now clear that it probably represents the top end of an effective dosage schedule ranging from 50 mg tid up to a maximum of 150 mg tid. While our patients experienced few side effects at this dose we found that, after completion of the study, the therapeutic benefit could be sustained in most patients with a lower dose, usually 100 mg tid. Investigators using much higher doses than ours (3 to \(^6\) and 1.7 to 19 mg/kg tid\(^2\)) have reported a high incidence of side effects, usually of gastrointestinal origin; others\(^8\)\(^,\)\(^9\) using doses of about 1 to 2 mg/kg have
recorded a much better tolerance with sustained efficacy. From our experience with enoximone in this and other studies\(^1\) we believe that a starting dose of about 1 mg/kg tid should be used.

Measurements of plasma concentrations of enoximone and its major sulphoxide metabolite confirmed patient compliance with treatment and the similarity between concentrations after 2 and 6 weeks therapy indicated that enoximone was not subject to accumulation over this period.

The results of Holter monitoring in our patients showed an overall increase in ventricular ectopic beats and salvos of more than two ectopic beats during treatment when compared with baseline or placebo. Chi-squared analysis of these data revealed no significant difference in the incidence of ventricular activity either as VPBs or salvos. However, results for individual patients were variable, no clear drug related pattern was seen, and malignant arrhythmias were not observed at any time. One patient in particular had a much higher incidence of ectopic beats and salvos on enoximone than on placebo, but he underwent no baseline examination; results in this patient influence the overall figures to a considerable extent.

On the basis of this double-blind, placebo-controlled study, the first to be completed and reported for enoximone, we conclude that this drug significantly improves hemodynamic and symptomatic status of patients with moderate to moderately severe congestive heart failure of varying causes. The beneficial objective and subjective effects are sustained over 6 weeks and are not accompanied by serious adverse effects. Although many more studies are required to define the balance between safety and efficacy of the drug and to determine a dose range, enoximone appears to offer an effective addition to long-term therapy in heart failure.

References

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