Multicenter Trial of Oral Enoximone in Patients With Moderate to Moderately Severe Congestive Heart Failure
Lack of Benefit Compared With Placebo

Barry F. Uretsky, MD, Mariell Jessup, MD, Marvin A. Konstam, MD, G. William Dec, MD, Carl V. Leier, MD, Joseph Benotti, MD, Srinivas Murali, MD, Howard C. Herrmann, MD, and James A. Sandberg, MD, for the Enoximone Multicenter Trial Group

A multicenter double-blind, randomized, placebo-controlled trial of oral enoximone, a phosphodiesterase inhibitor, was conducted in 102 outpatients (50 receiving enoximone and 52 receiving placebo) with moderate to moderately severe congestive heart failure. All were on a long-term regimen of digoxin and diuretics without vasodilators and converting enzyme inhibitors. Symptom score was obtained, and exercise testing was performed monthly for 4 months. There were no differences between groups in symptoms or exercise duration at the end of 4 months. A subgroup undergoing analysis of oxygen consumption with measurement of anaerobic threshold during exercise showed an increase (p<0.05) in anaerobic threshold at 1 month with enoximone (2.7±0.8 ml O2/kg/min) compared with placebo (−0.8±1.2 ml O2/kg/min). This improvement was not sustained at 4 months (0.5±1.7 ml O2/kg/min with enoximone and 0.2±1.5 ml O2/kg/min with placebo). The dropout rate was significantly higher (p<0.02) with enoximone (46%) than with placebo (25%). Adverse effects other than death were slightly, but not significantly, higher with enoximone (32%) than with placebo (22%). During therapy, five deaths occurred in the enoximone group, and none occurred in the placebo group (p<0.05). Two deaths were sudden, two were from progressive congestive heart failure, and one was from acute myocardial infarction. With intention-to-treat analysis and inclusion of patients who were removed from therapy because of lack of study drug effect, 10 deaths occurred in the enoximone group, and three occurred in the placebo group (p<0.05). All five enoximone- and three placebo-treated patients who died after therapy was discontinued died from terminal myocardial failure. This study does not demonstrate improvement in exercise capacity or symptoms with 16 weeks of enoximone therapy compared with placebo in patients with congestive heart failure receiving digoxin and diuretics without vasodilators and does not provide evidence that enoximone is beneficial in the long-term therapy of chronic heart failure. The unexpectedly worse survival rate with enoximone therapy raises concerns about a possible detrimental effect of enoximone in the dose range given in this study. (Circulation 1990;82:774-780)

Application of inotropic therapy is the most direct approach of counteracting the myocardial systolic dysfunction that is often the underlying abnormality in the development of chronic congestive heart failure. Nevertheless, proof of the efficacy of this approach remains incomplete.

Exoximone, an imidazole derivative, has been studied extensively in the syndrome of chronic heart failure.1-8 The compound is a phosphodiesterase inhibitor whose positive inotropic action is mediated through phosphorylation of the calcium channel and sarcoplasmic reticulum to allow for more ambient cytoplasmic calcium availability during actin-myosin interaction.9

Exoximone has been studied in its intravenous and oral preparations. In both forms, it produces marked increases in cardiac performance as measured by

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Address for correspondence: Barry F. Uretsky, MD, 3494 Presbyterian-University Hospital, DeSoto at O’Hara Streets, Pittsburgh, PA 15213.
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cardiac output and stroke work.\textsuperscript{1–8,10} In addition, marked decreases in cardiac filling pressures occur, and in some studies, decreases in systemic blood pressure have been shown.\textsuperscript{1–8,10} It has been observed to exert an inotropic effect in humans as measured by both an increase in the peak rate of rise of left ventricular pressure and a shift to the left of the end-systolic pressure-volume relation.\textsuperscript{4,11} In animals and humans, there is evidence of arterial vasodilation, which may account for a significant percentage of the drug’s effect.\textsuperscript{12}

Enoximone is well absorbed from the gastrointestinal tract.\textsuperscript{13} Hemodynamic effects of oral enoximone have been shown to be sustained for several months.\textsuperscript{13} The present study was undertaken to determine whether enoximone in a randomized, placebo-controlled manner combined with digoxin and diuretics improves symptoms and exercise tolerance in patients with moderate to moderately severe heart failure.

**Methods**

Seven centers participated in this trial (see Appendix). One hundred two patients were randomized to therapy after providing written, informed consent. All patients had moderate to moderately severe heart failure (New York Heart Association functional class II or III). Congestive heart failure was due to ischemic heart disease, hypertensive heart disease but without significant hypertension at the time of the study, idiopathic dilated cardiomyopathy, or end-stage valvular disease but without any active valvular lesions. Patients were required to exercise to maximal effort and to complete at least 3 minutes but no more than 16 minutes of exercise by using a modified Naughton multistage protocol with 2-minute stages.\textsuperscript{14} Dyspnea and fatigue were the only exercise limiting factors accepted that did not exclude patients from study.

Five centers analyzed oxygen consumption during the exercise study. In these centers, inclusion criteria were maximal oxygen consumption of at least 10 ml O\textsubscript{2}/min/kg during exercise and a baseline ejection fraction less than 40% by radionuclide ventriculography. Exclusion criteria were the use of vasodilators (converting enzyme inhibitors, hydralazine, prazosin, or long-acting nitrates); women of childbearing potential; cardiomyopathy secondary to restrictive, hypertrophic, or stenotic valvular disease; a recent myocardial infarction within 3 months; symptomatic ventricular arrhythmias; angina pectoris requiring more than 5 tablets of nitroglycerin/wk; renal insufficiency defined as a serum creatinine level greater than 3 mg%; evidence of severe pulmonary, hepatic, hematologic, or neurological disease; or patients who had taken an experimental drug within 4 weeks of the study. Patients were permitted to take antiarrhythmic agents, anticoagulants, and potassium supplements as necessary. Furthermore, long-term digoxin or diuretic therapy was required for entrance into the study.

**Study Design**

The baseline phase of the trial lasted 2–6 weeks and consisted of at least three visits 7–10 days apart. All patients were maintained on optimal doses of diuretics or digoxin. On the initial visit, a complete history, physical examination, and laboratory evaluation were obtained. The latter included analysis of complete blood count, electrolytes, glucose, blood urea nitrogen, creatinine, uric acid, total protein, albumin, digoxin level, glutamic pyruvate transaminase, glutamic oxalate transaminase, alkaline phosphatase, total bilirubin, phosphorous, calcium, urinalysis, electrocardiogram, and chest radiogram. Exercise tests were performed on each visit to determine patient eligibility. For a patient to be eligible, the final two tests had to be at least 3 minutes in length and within 2 minutes of each other. Patients with an exercise duration variability greater than 2 minutes on the final two tests were tested a fourth time. Patients who had an exercise duration less than 3 minutes or greater than 16 minutes or a variability greater than 2 minutes on the final two tests were dropped from the study. An average of the final two determinations of exercise duration was considered as baseline. Dyspnea and extreme fatigue were endpoints in determining exercise duration. Patients who stopped exercising for other reasons were dropped from the study.

After the baseline phase, all patients were randomized to receive oral enoximone or placebo. Patients were stratified into two groups based on body weight: less than 62.5 kg or 62.5 kg or more. The patients weighing less than 62.5 kg received 50 mg enoximone three times a day, which could be titrated to 100 mg three times a day during the 16-week study. Patients weighing 62.5 kg or more received 75 mg enoximone three times a day at the beginning, which could be titrated to 150 mg three times a day. After 4 weeks of the lower-dose regimen, the doses were increased to the higher levels unless the investigator deemed it inadvisable.

A patient was considered a dropout and not continued on the study drug if intravenous diuretics or increases in oral diuretics were required that lasted more than 7 days. If the patient was dropped from the double-blind phase, the patient was not allowed to receive enoximone in an unblinded manner for the remainder of the 16-week study but was followed up with the same methods as if receiving the study drug.

The primary efficacy variables for evaluating enoximone included change in the duration of exercise and symptoms as measured by the patient’s overall feeling of impairment, physician’s global evaluation of impairment, patient’s daily activity scale, and New York Heart Association functional classification. Other measured variables included severity of symptoms of dyspnea and fatigue, number of hospitalizations, change in radionuclide ejection fraction, drop-out rate, and adverse events. Efficacy evaluations were performed at 4, 8, 12, and 16 weeks, and the
primary efficacy evaluation was performed at 16 weeks. In patients who were dropped from the double-blind study, the final evaluation performed while the patient was on the study drug was considered for endpoint analysis.

Statistical Analysis

Standard linear regression models that incorporated investigators, treatments, and investigator-treatment interaction as sources of variation were used to analyze changes from baseline in exercise duration and ejection fraction. Extended Mantel-Haenszel tests were used for the analysis of categorical variables. Fisher's exact test and the $\chi^2$ test were used for analysis of adverse events and dropouts, including mortality at 4 months.

Table 1. Patient Characteristics: Enoximone Multicenter Trial

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Treatment group</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Enoximone</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>50</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>62±1</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>38/12</td>
</tr>
<tr>
<td>Race (W/B)</td>
<td>45/5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79±2</td>
</tr>
<tr>
<td>CHF duration (mo)</td>
<td>40±8</td>
</tr>
<tr>
<td>NYHA (II/III)</td>
<td>15/35</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>21±1</td>
</tr>
<tr>
<td>ICM/NICM</td>
<td>27/23</td>
</tr>
<tr>
<td>Cardiomegaly* (%)</td>
<td>82</td>
</tr>
<tr>
<td>Cardiothoracic ratio*</td>
<td>0.56</td>
</tr>
</tbody>
</table>

* Determination by chest radiography.

Results

There were 50 patients in the enoximone group and 52 in the placebo group. Demographic and clinical characteristics were similar between the two groups (Table 1). The mean enoximone dose was 4.2±2 mg/kg/day, 1.4±0.1 mg/kg/dose, or 330±16 mg/day.

There were no differences between groups in the major end points of the study. The change in exercise duration was similar between the two groups with no significant differences at any time point (Figure 1). Furthermore, responses were not significantly different when patients were analyzed by etiology of heart failure, namely between patients with nonischemic and ischemic cardiomyopathy. However, there was a significant improvement ($p<0.05$) in exercise duration for the enoximone group at 4 and 12 weeks and for the placebo group at 12 weeks compared with their own baseline values.

In the subgroup of 59 patients (five centers) who underwent oxygen consumption evaluation during exercise testing, a trend toward improvement in maximal oxygen uptake at 1 month with enoximone was observed (enoximone group, +1.5±0.7; placebo, −0.0±0.7 ml/kg/min; $p=0.14$). This trend was not apparent at 8 weeks. Because of a statistically significant lack of consistency of the treatment difference in maximal oxygen consumption across centers at 12 and 16 weeks, data across centers could not be pooled at these time points. There was an initial improvement ($p<0.05$) in anaerobic threshold with enoximone at 4 weeks compared with placebo, but this difference was not apparent by 16 weeks (Figure 2).

Symptom scores for dyspnea, fatigue, overall functional impairment, and New York Heart Association class were similar in both groups during treatment (Figure 3). There was no significant change in left
ventricular ejection fraction in either group at 4 months. The dropout rate was significantly higher (p<0.05) in the enoximone group than in the placebo group (46% enoximone, 25% placebo). Lack of clinical improvement or worsening heart failure or dyspnea caused discontinuation of enoximone in 13 patients and of placebo in 11 patients. Adverse effects necessitated discontinuation of enoximone in four patients and of placebo in two patients. Other patients were dropped from the study because of a combination of the lack of effect with symptoms or death. Overall adverse effects were similar in the placebo and enoximone groups (Table 2) except for the incidence of diarrhea, which was 2% in the placebo group and 20% in the enoximone group (p<0.01), and palpitations, which occurred in five patients in the enoximone group and one patient in the placebo group (p=0.12). At the end of the 4-month study period, there were five deaths (10%) in the enoximone group and no deaths in the placebo group (p<0.05). Two deaths were sudden, two were from progressive congestive heart failure, and one was from acute myocardial infarction. With intention-to-treat analysis, there were 10 deaths in patients assigned to enoximone (20%), whereas there were three deaths (6%) in the patients assigned to placebo (p<0.05). All deaths in both patient groups assigned to, but not receiving, study drug at the time of death (placebo, three patients; enoximone, five patients) were due to terminal myocardial failure.

Discussion
These data do not provide evidence that enoximone, a hemodynamically potent phosphodiesterase inhibitor, improves exercise tolerance and symptoms beyond that achieved by digoxin and diuretics in patients with moderate to moderately severe congestive heart failure during a 16-week period. The reason for this lack of efficacy is not evident. These negative findings may not be generalizable to other phosphodiesterase inhibitors, other enoximone dose regimens, or other patient populations. The present study resembles previous investigations of amrinone, the first oral phosphodiesterase inhibitor tested for long-term management of patients with heart failure.15,16 Two multicenter trials failed to demonstrate any improvement in exercise duration and symptoms. One explanation for the lack of efficacy for amrinone was that it produced multiple adverse effects that yielded a high dropout rate and limited the dose that could be administered. In the present study, such adverse side effects were uncommon. The inability of patients to tolerate protocol doses of the drug is, therefore, unlikely to explain the lack of efficacy noted in the present trial.

That the enoximone dose in this study was too high must also be considered. Such a situation may be likened to studying digoxin at doses above the therapeutic range and observing dropouts from side effects such as nausea, vomiting, palpitations, increased ventricular arrhythmias, abnormal color vision, and, most importantly, death. We consider the possibility of an excessive dose unlikely if clinical effects are related to hemodynamic activity of the drug. The hemodynamic effects of the dose used (approximately 1–1.5 mg/kg/dose) is intermediate on the dose-response curve17; a lower dose would likely have minimized the hemodynamic effects in the resting state. On the other hand, a low dose with only minor hemodynamic effects may improve exercise performance. Evidence for this comes from our results at 4 weeks when a trend toward improved exercise duration and a significant improvement in anaerobic threshold were observed. By design, a lower dose of enoximone was given relative to the subsequent 12 weeks. This hypothesis is supported by preliminary data from a double-blind trial that showed 50 mg, but not 100 mg, improved 4- and 8-week exercise performance compared with placebo.18 The side-effect profile was also acceptable, with a similar incidence in the enoximone and placebo groups. Although lower doses, hypothetically, could have produced improved clinical effects, no empiric
data or theoretical considerations presently support such a contention.

A lack of improvement in the enoximone group compared with the placebo group may be due to a marked improvement in exercise tolerance in patients receiving placebo. This possibility accounts for the protocol design that required the investigators to perform at least three exercise tests at baseline, using the average of the final two tests with the requirement that they be within 120 seconds of each other to be considered a "stable" baseline. Under these conditions, there was a small improvement in exercise performance at 16 weeks in the placebo group, similar in magnitude to that observed in studies in which efficacy has been demonstrated for other agents such as converting enzyme inhibitors and isosorbide dinitrate.\textsuperscript{19,20} The minimal improvement over time in the placebo group, therefore, seems unlikely to have obscured a therapeutic effect of enoximone in this study.

Another confounding aspect of this study is the less than complete testing at 16 weeks in both groups. Not all patients performed exercise tests at each time point throughout the 16 weeks. Could this have obscured a therapeutic effect of enoximone? This appears unlikely because the dropout rate was higher with enoximone than with placebo and a similar number of patients were reported to have no clinical effect or worsened heart failure. Although it is theoretically possible that one group was favored by the incomplete data, there are no data to support this speculation. It should be noted that incompleteness of data collection using exercise testing as a primary end point has been a universal problem in controlled heart failure studies, including those with a positive outcome for the active agent.\textsuperscript{20,21}

Recently, another phosphodiesterase inhibitor, milrinone, a compound structurally related to amrinone but with an improved side-effect profile, was shown to be effective in improving symptoms and exercise tolerance compared with placebo.\textsuperscript{20} In that study, patients on diuretic therapy were randomized to receive either the phosphodiesterase inhibitor milrinone alone, digoxin alone, milrinone and

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**Table 2. Enoximone Multicenter Trial: Adverse Events Occurring in More Than 5% of Patients**

<table>
<thead>
<tr>
<th>Adverse event (n)</th>
<th>Placebo (n=52)</th>
<th>Enoximone (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsened heart failure</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>10*</td>
</tr>
<tr>
<td>Chest pain</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

\*p<0.05 placebo vs. enoximone group.
digoxin, or two placebo preparations. Milrinone or digoxin alone was more effective than placebo in improving symptoms and exercise tolerance during a 12-week period. The combination of digoxin and milrinone was no more effective than each agent alone. In the present investigation, digoxin was given with the phosphodiesterase inhibitor enoximone, and thus, the cumulative data suggest that the addition of a phosphodiesterase inhibitor to digoxin, a sodium-potassium ATPase pump inhibitor, does not have additive clinical benefits.

In the subgroup of patients in which oxygen consumption was measured during exercise, anaerobic threshold was improved at 1 month of enoximone therapy with a trend to improvement in maximal oxygen consumption. These data suggest that enoximone allows for improved skeletal blood flow to support aerobic metabolism during submaximal exercise. Enoximone has been shown to increase limb blood flow at rest. Thus, it seems reasonable that increased submaximal exercise results before development of anaerobic metabolism. These data resemble the short-term results with milrinone and would again point to a common effect of phosphodiesterase inhibitors. The lack of continued improvement in this parameter may be due to the relatively small number of patients studied at 16 weeks or an intrinsic limitation of the drug itself.

An unexpected finding of this study was the higher mortality in the enoximone group at the end of 16 weeks. In this context, it is worthwhile to note that this study was not designed as a mortality trial and the differences might have occurred solely by chance. Nevertheless, concern exists that increased mortality may be a problem in some patient subsets treated with agents that increase cyclic AMP either through β-receptor stimulation or phosphodiesterase inhibition. In a preliminary report on outpatient dobutamine therapy, the incidence of death was higher with intravenous dobutamine (p=0.08) than with placebo. Unpublished data on another phosphodiesterase inhibitor, imazodan, showed that in a randomized, placebo-controlled trial, the death rate was higher in patients receiving the phosphodiesterase inhibitor than in those receiving placebo. Finally, in the recent milrinone trial, the death rate was somewhat higher in milrinone-treated patients (p=0.064) than in the nonmilrinone-treated patients. Of note, when differences in randomization factors, particularly ejection fraction, between milrinone and nonmilrinone groups were adjusted, the differences in mortality were not apparent. The present study does not allow for firm conclusions regarding the effect of enoximone on mortality, but it does raise concern in this regard.

In summary, this study does not provide support for long-term use of oral enoximone to improve symptoms and exercise tolerance in patients with moderate-to-moderately severe heart failure. Further studies are required to determine the place of oral enoximone in the outpatient treatment of chronic congestive heart failure.

Appendix

Clinical Sites
Massachusetts General Hospital, Harvard University, Boston. Principal Investigator: G. William Dec, MD. Co-Investigators: Howard C. Herrmann, MD, and Michael Fifer, MD. Nurse Coordinator: Judith Scheer, RN, MPH.

Ohio State University, Columbus. Principal Investigator: Carl V. Leier, MD. Co-Investigator: Philip F. Binkley, MD. Nurse Coordinator: Patricia Huss-Randolph, RN.

Temple University, Philadelphia. Principal Investigator: Mariell Jessup, MD. Nurse Coordinators: Judianne Samaha, RN, and Susan Ulrich, RN.

New England Medical Center Hospitals, Tufts University, Boston. Principal Investigator: Marvin A. Konstam, MD. Co-Investigators: Eric J. Eichhorn, MD, Theresa M. Palabrica, MD, and David M. Brill, MD. Nurse Coordinators: Tami T. Martin, RN, and Cindy K. Lane, RN.

University of Massachusetts, Worcester. Principal Investigator: Joseph Benotti, MD.


Lehigh Valley Medical Center, Allentown, Penn. Principal Investigator: James A. Sandberg, MD. Nurse Coordinator: Lisa Fegely, RN.

Data Center
Merrell Dow Research Laboratories, Cincinnati, Ohio. Director, Clinical Cardiovascular Research: Tel Bekele, MD. Statistician: George Dirnberger.

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congestive heart failure  
enoximone  
phosphodiesterase inhibition  
cardiotonic agents

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