Inotropic therapy for refractory congestive heart failure with oral fenoximone (MDL-17,043): poor long-term results despite early hemodynamic and clinical improvement

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ABSTRACT Thirteen male patients with NYHA class IV congestive heart failure refractory to conventional therapy were treated with oral fenoximone, a new imidazole compound with inotropic and vasodilator effects, for a mean duration of 11 weeks (range 2 to 34). On initial hemodynamic evaluation, the effects of oral fenoximone were comparable to those of the intravenous form and included a significant (p = .0001) increase in cardiac index (mean ± SD) (1.7 ± 0.4 to 3.0 ± 0.7 liters/min/m²) and a significant (p = .0001) but modest decrease in pulmonary capillary wedge pressure (27 ± 6 to 23 ± 6 mm Hg), with only minor overall changes in heart rate and arterial blood pressure. Symptomatic improvement by at least one NYHA class was observed in all patients during the first week of therapy with fenoximone; however, severe and symptomatic congestive heart failure recurred in seven patients within an average of 8 weeks after initiation of therapy, resulting in death in all seven. Of the remaining six patients, two died suddenly at home within 3 weeks of initiation of therapy, one died from ventricular fibrillation in the hospital 7 weeks after initiation of therapy, and two died from noncardiac causes. One patient is currently alive with NYHA class II heart failure 21 weeks after the initiation of therapy. Partial or complete attenuation of hemodynamic efficacy of oral fenoximone during long-term administration was demonstrated during repeat hemodynamic evaluation in six of eight patients. We conclude that despite short-term hemodynamic and clinical benefits, oral fenoximone therapy in patients with NYHA class IV congestive heart failure does not produce sustained clinical or hemodynamic benefit and is associated with a high mortality.


CONTINUED uncertainty about the inotropic efficacy of cardiac glycosides in patients with severe congestive heart failure as well as their limited margin of safety have prompted a search for more potent orally effective inotropic drugs. 1-10 Fenoximone (1,3-dihydro-4-methyl-5-[4-(methylthio)-benzoyl]-2H-imidazole-2-one), an imidazole compound, has recently been shown to produce potent inotropic and vasodilator effects in a number of experimental studies involving normal as well as failing hearts. 8, 9, 11 Preliminary short-term studies of intravenous fenoximone have also demonstrated its potent salutary hemodynamic effects in patients with severe heart failure. 12, 13 In this study we report our experience with the use of intravenous and oral fenoximone therapy in the treatment of 13 patients with NYHA class IV chronic heart failure refractory to conventional therapy.

Patients and methods

We studied 13 male patients with a mean age of 70 years (range 59 to 81) under a protocol approved by our institutional review board. Each patient had clinical evidence of persistent severe congestive heart failure of at least 3 months duration, in spite of long-term digitalis, diuretic, and in many cases, oral vasodilator therapy. The underlying basis for heart failure was ischemic heart disease in 12 patients and idiopathic congestive cardiomyopathy in the remaining patient. All patients were bedridden and severely symptomatic (NYHA functional class IV) at the time of inclusion in the study. The mean prestudy left ventricular ejection fraction as determined by radionuclide ventriculography was 0.19 (range of 0.10 to 0.36). All patients were studied in the coronary care unit. All long-acting cardioactive medications were discontinued 24 to 48 hr before study, except for maintenance digitalis, antirhythmic drugs, and diuretics. Diuretics were withheld on the day of the study. After written
informed consent was obtained, a No. 7F thermodilution Swan-Ganz catheter was inserted via the internal jugular or antecubital approach and positioned in the pulmonary artery under pressure monitoring and fluoroscopic guidance. Pulmonary capillary wedge pressure was used as an indirect index of left ventricular filling pressure. A 20-gauge cannula was inserted percutaneously into the radial artery for continuous monitoring of blood pressure.

All pressures were measured at end-expiration with transducers placed at the midchest level along the fourth intercostal space with patients in the supine or semirecumbent position. Cardiac output was determined by thermodilution.

Derived hemodynamic variables were calculated as follows:

Cardiac index (CI) (liters/min/m²) = cardiac output (CO)/body surface area (BSA)

Stroke volume index (SVI) (ml/beat/m²) = CI/heart rate (HR)

Stroke work index (SWI) (gm-m/m²) = [mean arterial pressure (MAP) − pulmonary capillary wedge pressure (PCW)]

Systemic vascular resistance (SVR) (dynes-sec-cm⁻⁵) = MAP − mean right atrial pressure (RAP) × 80

Pulmonary vascular resistance (PVR) (dynes-sec-cm⁻⁵) = mean pulmonary arterial pressure (MPA) − PCW × 80

CO

Study protocol

Administration of intravenous fenoximone. On the day of the study, baseline hemodynamic measurements were repeated at 15 min intervals until a steady state was ensured, with less than 10% variability between two consecutive measurements. In all patients such hemodynamic stability was demonstrated with two to three consecutive baseline measurements.

Fenoximone in doses of 0.5 mg/kg per dose was subsequently administered slowly, every 15 to 20 min, through a central venous line, with hemodynamic measurements obtained immediately before and after each dose. Once a plateau in cardiac output increment was achieved or a cumulative total dose of 4 mg/kg was administered, no further drug was given and hemodynamic response was monitored for at least the next 6 hr.

Oral fenoximone. The following day, after adequate washout of the effects of intravenous fenoximone, serum baseline hemodynamic measurements were again performed to ensure a steady state. Oral fenoximone was subsequently administered, beginning with a dose of 2 mg/kg; the dose was increased by 1 to 2 mg/kg every 2 hr, with hemodynamic measurements 30 min, 1 hr, and 2 hr after each dose. Administration of fenoximone was stopped once peak hemodynamic effect was achieved, defined in all patients by a plateau in the increment of cardiac output. Patients were subsequently placed on maintenance oral therapy, every 6 to 8 hr, with the peak dose derived as described above.

Long-term administration of fenoximone and follow-up. All patients were evaluated daily until discharge from the hospital and weekly for the first month after discharge. Subsequent outpatient evaluation was performed every 2 to 4 weeks by the same investigators and included a standard history and physical examination as well as a series of appropriate laboratory tests.

Follow-up hemodynamic evaluation. Repeat hemodynamic evaluation was performed in eight patients 1 to 28 weeks (average 8) after the initiation of drug therapy. Plasma levels of fenoximone and its major metabolite were determined 2 to 4 hr after the maintenance dose in six patients. The hemodynamic response to intravenous fenoximone was redetermined in four patients at follow-up.

Statistical analysis. All data are expressed as mean ± SD. The data were analyzed with a two-factor analysis of variance with repeated measures on both factors. The two factors were (1) route of drug with two levels (1 = intravenous fenoximone, 2 = oral fenoximone) and (2) time of measurement with two levels (1 = control, 2 = peak). The p values presented are from tests on the main effects of these two factors when the interaction was not significant. Whenever the interaction was significant, separate analyses were conducted with the Tukey test at the p < .05 level of significance. The serial measurements of hemodynamic variables over time were examined by an analysis of variance for repeated measurements.

Results

Short-term hemodynamic effects of intravenous and oral fenoximone. Detailed data are summarized in table 1. The peak cumulative dose of intravenous fenoximone ranged from 1 to 3 mg/kg (mean 2.2), whereas the peak cumulative dose of oral fenoximone ranged from 1.7 to 19 mg/kg (mean 6.5). Peak doses were determined by attainment of a plateau in cardiac output in all 13 patients. Both intravenous and oral fenoximone produced significant (p = .0001) and comparable changes in cardiac index (+84% vs +72%; p = NS), stroke volume index (+70% vs +59%; p = NS), stroke work index (+79% vs +65%; p = NS), pulmonary capillary wedge pressure (−27% vs −15%; p = NS), and systemic vascular resistance (−46% vs −39%; p = NS). Neither form of the drug produced a significant overall change in mean arterial pressure. However, both the intravenous and the oral preparations produced a comparable small but significant (p = .02) increase in heart rate (+4% vs +6%; p = NS). As shown in figure 1, both intravenous and oral fenoximone produced prompt and significant (p < .05) alterations in cardiac index and pulmonary capillary wedge pressure, which persisted for up to 6 hr after the peak dose.

Clinical follow-up (figure 2). All patients showed marked symptomatic improvement (by at least one or two NYHA classes) during the first week of drug therapy as reflected by an improved sense of well being and ability to ambulate with minimal or no symptoms. However, seven of 13 patients (54%) developed recurrence of symptoms of severe heart failure (NYHA class IV) between 1 and 28 weeks (average 8) after initiation of drug therapy, with six requiring readmission to the coronary care unit for intensive therapy. All six of these patients subsequently died, five from intractable heart failure and one from pneumonia and concomitant pulmonary fibrosis, both documented at autopsy. Of the remaining seven patients, one died at home of intractable heart failure 10 weeks after initi-
TABLE 1
Summary of short-term hemodynamic effects of fenoximone in patients with refractory heart failure

<table>
<thead>
<tr>
<th></th>
<th>IV fenoximone</th>
<th>Oral fenoximone</th>
<th>p value</th>
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<tbody>
<tr>
<td></td>
<td>Ctl</td>
<td>Peak</td>
<td>Ctl</td>
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<tr>
<td></td>
<td>Ctl vs peak</td>
<td>Oral Ctl vs peak</td>
<td>Ctl vs Ctl</td>
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<tr>
<td>HR (beats/min)</td>
<td>87 ± 15</td>
<td>89 ± 15</td>
<td>84 ± 11</td>
</tr>
<tr>
<td>AP (mm Hg)</td>
<td>79 ± 11</td>
<td>74 ± 14</td>
<td>80 ± 6</td>
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<tr>
<td>PA (mm Hg)</td>
<td>41 ± 7</td>
<td>33 ± 8</td>
<td>39 ± 8</td>
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<tr>
<td>PCW (mm Hg)</td>
<td>30 ± 5</td>
<td>22 ± 5</td>
<td>27 ± 6</td>
</tr>
<tr>
<td>RA (mm Hg)</td>
<td>13 ± 4</td>
<td>7 ± 3</td>
<td>12 ± 4</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>1.7 ± 0.3</td>
<td>3.0 ± 0.4</td>
<td>1.7 ± 0.4</td>
</tr>
<tr>
<td>SVI (ml/beat/m²)</td>
<td>20 ± 7</td>
<td>35 ± 8</td>
<td>22 ± 7</td>
</tr>
<tr>
<td>SWI (gm-m/m²)</td>
<td>14 ± 7</td>
<td>24 ± 9</td>
<td>16 ± 8</td>
</tr>
<tr>
<td>PVR (dyne-sec-cm⁻⁵)</td>
<td>306 ± 77</td>
<td>155 ± 63</td>
<td>312 ± 102</td>
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</table>

Data are expressed as mean ± SD.

HR = heart rate; AP = mean arterial pressure; PA = mean pulmonary artery pressure; PCW = mean pulmonary capillary wedge pressure; RA = mean right atrial pressure; CI = cardiac index; SWI = stroke work index; SVI = stroke volume index; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; IV = intravenous; Ctl = control.

The administration of drug therapy, one died in renal failure superimposed on recurrent intractable heart failure 12 weeks after initiation of therapy, and one died from a rupture of a suprarenal aneurysm of the abdominal aorta 2 weeks after initiation of drug therapy. The only survivor (patient 12) among these 13 is currently alive, with NYHA class II heart failure 21 weeks into drug therapy.

Follow-up hemodynamic evaluation (table 2). Of the eight patients undergoing repeat hemodynamic evaluation, six were readmitted 1 to 28 weeks after initiation of drug therapy because of recurrence of symptoms of severe NYHA class IV heart failure, whereas the remaining two patients were admitted 6 to 10 weeks after onset of drug therapy on an elective basis. Both of these patients had improved symptomatically to NYHA class II at the time of reevaluation. For the group, the average stroke volume index of 21 ± 7 ml/beat/m² at follow-up while on oral therapy was comparable (p = NS) to the predrug control value of 20 ± 5 ml/beat/m² and was significantly lower (p = .001) than the short-term postdrug value of 33 ± 5 ml/beat/m². Similarly, the average pulmonary capillary wedge pressure of 28 ± 9 mm Hg at follow-up was comparable (p = NS) to the predrug control value of 28 ± 6 mm Hg. Challenge with intravenous fenoximone at a dose higher than the one used during the short-term phase of the study failed to increase the stroke volume index to levels achieved during the short-term phase in three of four patients.

Adverse effects. All 13 patients experienced various degrees of nausea, anorexia, vomiting, diarrhea,
which generally required symptomatic therapy. Although ventricular ectopic beats and short runs of self-terminating ventricular tachycardia were observed at various times during the course of therapy in all patients, a cause-and-effect relationship is difficult to establish because ventricular arrhythmias of a similar nature were present in all patients before fenoximone therapy. None of the patients developed any clinical evidence of myocardial ischemia or infarction.

Discussion

Conventional therapy of severe chronic heart failure with digitalis and potent diuretics often produces unsatisfactory clinical results necessitating the use of additional unloading therapy with vasodilators. Although vasodilators represent a substantial advance in the therapy of severe heart failure, a significant number of patients receiving these agents either fail to show a sustained clinical benefit or develop intolerable side effects. Thus, in recent years newer and more potent orally effective inotropic drugs, working as sympathomimetic agents or by hitherto poorly understood mechanisms, have been evaluated in the therapy of refractory heart failure.

Fenoximone is a new nonsympathomimetic, non-glycoside inotropic drug that has been shown to possess significant direct inotropic and vasodilator effects in isolated preparations, intact normal animals, and experimental preparations of heart failure.

Short-term hemodynamic effects of intravenous and oral fenoximone. In this study, short-term intravenous administration of fenoximone resulted in striking hemodynamic effects as reflected by an 84% increase in cardiac index and a 27% decrease in pulmonary capillary wedge pressure, with only minimal changes in heart rate and systemic blood pressure. Peak hemodynamic effects were observed at an average cumulative dose of 2.2 mg/kg, with the effects lasting at least 6 hr. Our results differ from those of Uretsky et al., who, while observing comparable increases in cardiac output, reported greater decreases in pulmonary capillary wedge pressure (−48%) and systemic arterial pressure (−19%). However, these differences could be explained by the greater vasodilator effects produced by the larger doses (mean dose 5.8 mg/kg) used in their study. Our study further demonstrates that orally administered fenoximone likewise produces significant short-term hemodynamic effects comparable to those resulting from intravenous administration. Thus a 72% increase in cardiac index and a 15% decrease in pulmo-

<table>
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<td>Follow-up hemodynamic data on eight patients</td>
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<table>
<thead>
<tr>
<th>Patient</th>
<th>SVI (ml/beat/m²)</th>
<th>PCW (mm Hg)</th>
<th>Left ventricular ejection fraction</th>
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<tr>
<td></td>
<td>Ctl Short-term FU</td>
<td>Ctl Short-term FU</td>
<td>Ctl FU</td>
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<tr>
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<td>26</td>
<td>34 14</td>
<td>24 24 28</td>
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<tr>
<td>Mean</td>
<td>20</td>
<td>33 21</td>
<td>28 24 28</td>
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<tr>
<td>± SD</td>
<td>5</td>
<td>5 7</td>
<td>6 4 9</td>
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| p value | Ctl vs short-term <.001 | Ctl vs FU NS | FU NS |

SVI = stroke volume index; PCW = pulmonary capillary wedge pressure; Ctl = predrug control; short-term = postdrug value in initial evaluation; FU = follow-up value on repeat evaluation performed between 1 and 22 weeks after initial evaluation.
nary capillary wedge pressure produced by oral fenoximone in our patients was comparable to the effects produced by the intravenous drug. The average peak oral dose of 6.5 mg/kg was significantly larger than the corresponding peak intravenous dose, consistent with the limited (about 30%) bioavailability of orally administered fenoximone. In general, hemodynamic effects of the oral drug were observed within 1 hr of administration, peaked at 2 to 3 hr, and tended to persist for at least 6 to 8 hr. Sustained hemodynamic effects were generally observed during the 48 to 72 hr of repeated oral administration of peak oral dose without evidence of rapid attenuation of effect.

Early and long-term clinical results. Early clinical improvement, as reflected by a decline in NYHA classification by one or two grades, an improved sense of well being, ability to ambulate with minimal or no difficulty, improved diuresis, and decline in elevated blood urea nitrogen, was observed during the first week of oral therapy in all 13 patients. During this period frequent analysis of rhythm strips revealed frequent ventricular ectopy, but none of the patients developed symptomatic ventricular tachycardia. Despite beneficial early results, seven patients (54%) developed signs and symptoms of recurrent severe congestive heart failure while on continuous oral therapy and in spite of an upward adjustment of dosage of diuretics. In five of these patients, follow-up hemodynamic evaluation while on an unchanged oral dose demonstrated complete attenuation of the hemodynamic effect; there was partial attenuation of the change in stroke volume index in the sixth patient. These effects were noted despite the presence of high blood levels of fenoximone and its major metabolite in the plasma 2 to 4 hr after the oral dose, which is evidence against poor gastrointestinal absorption as an explanation for attenuation of effect. Rechallenge with the intravenous drug failed to produce a hemodynamic response comparable to that produced by a lower intravenous dose during short-term administration. Partial attenuation of hemodynamic response was also documented in an additional patient who was reevaluated electively 6 weeks after the onset of oral therapy despite symptomatic improvement to NYHA class II status. Only one patient showed persistent hemodynamic effects on continued oral drug therapy when electively reevaluated 10 weeks after the onset of therapy. The exact mechanisms responsible for the attenuation in hemodynamic response observed in this study remain to be determined.

Of additional concern to us is the high mortality experienced by our patients over a period of follow-up of less than 1 year from the onset of oral fenoximone therapy. Although 12 of 13 (92%) patients died, 10 deaths were clearly related to cardiac causes, whereas noncardiac problems (rupture of suprarenal abdominal aortic aneurysms and pneumonia with interstitial lung disease) were responsible for the deaths of two patients. Interestingly, sudden death was observed in only three of 10 patients dying of cardiac causes, whereas the remaining seven patients died from intractable heart failure. Considering the cardiac mortality of 10 out of 13 (77%) patients observed in this cohort, our results are consistent with the 1 year mortality of 64% in patients with NYHA class IV heart failure reported in a study of natural history of heart failure in coronary artery disease by Califf et al. The high mortality observed in this study probably reflects an unaltered natural history, although we cannot rule out the possibility that accelerated myocardial dysfunction and/or worsening of cardiac arrhythmias could have resulted from the drug therapy and contributed to the observed mortality. Since all patients were severely symptomatic despite the use of oral vasodilators for several months before inclusion in the protocol, it is highly unlikely that withdrawal of such therapy was responsible for the adverse clinical outcome observed in this study. Adverse noncardiac side-effects were essentially limited to gastrointestinal intolerance, which was observed in nearly all patients.

Thus despite early salutary hemodynamic and clinical results, long-term oral fenoximone therapy in patients with severe NYHA class IV congestive heart failure failed to produce sustained clinical or hemodynamic benefits and had no effect on survival.

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References
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