Beneficial effects of intermittent home administration of the inotrope/vasodilator milrinone in patients with end-stage congestive heart failure: A preliminary study

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Background End-stage congestive heart failure (CHF) is associated with a high mortality rate and is often refractory to standard medical treatment. Although parenteral inotropes have been beneficial in hospitalized patients, their use in outpatients has been limited by toxicity and tachyphylaxis.

Methods and Results To determine whether patients with end-stage CHF could safely tolerate intermittent outpatient inotropic therapy and demonstrate both symptomatic and functional improvement with these agents, we studied the effects of low-dose, intermittent home infusions of the inotrope/vasodilator milrinone in 10 patients with end-stage CHF. After showing hemodynamic improvement with milrinone while hospitalized, central lines were placed and patients were given the drug at home with small portable infusion pumps, starting at 3 days a week for 6 hours at a time over a 3-month period. Patients tolerated the drug well, with no deaths and a fourfold decrease in hospitalizations during the study. Arrhythmias were minimal and angina decreased in two patients. Mean total, physical, and emotional scores on the Minnesota Living with Heart Failure Questionnaire reflected a general trend of symptomatic improvement throughout the infusion period. The mean number of reported hours of improvement after infusion progressively increased throughout the study, producing a mean of 25 hours of postinfusion improvement during the final week (p < 0.01). Repeat hemodynamic study at the end of the 3-month period showed trends toward improvement in cardiac function.

Conclusions This is the first study to demonstrate safety, efficacy, hemodynamic, and functional improvement in patients receiving low-dose, intermittent outpatient milrinone therapy. We believe this improvement partly relates to a "training" effect on the heart or peripheral muscles and circulation. These promising results suggest that given appropriately, inotropes have an important therapeutic role in the outpatient treatment of end-stage CHF. (Am Heart J 1998;135:121-9.)

Despite recent improvements in the treatment of congestive heart failure (CHF), the annual mortality rate of patients with end-stage disease (New York Heart Association class III-IV) continues to be high, ranging from 20% to 50%. Although cardiac transplantation is a viable option in qualified patients, the prolonged waiting period is associated with a high mortality rate. Thus there is a continuing need to investigate therapeutic modalities that might benefit these patients in terms of decreasing the frequency of hospitalization and providing symptomatic relief without contributing to excess mortality rate.

Although the short-term use of parenteral inotrope administration in intensive care units is generally thought to be beneficial in decompensated heart failure, attempts to use these agents in outpatients have met with considerable difficulties. Problems such as tachyphylaxis and increased morbidity and mortality rates have prevented the widespread use of inotropic therapy in outpatients. Experience in our own and other laboratories has shown that prolonged, continuous sympathetic exposure contributes to arrhythmias, ischemia, β-adrenergic receptor downregulation, and abnormalities of the immune system, all of which may contribute to worsened left ventricular dysfunction and increased mortality rate. To lessen these deleterious effects, consideration has been given to intermittent rather than continuous administration of these inotropes.

To investigate this hypothesis, we chose the bipyridine derivative milrinone for its combined inotropic,
vasodilating, and dromotropic effects\textsuperscript{12-14} as well as its proven success in hospitalized patients with decompen-
sated CHF.\textsuperscript{10-11} Ten patients with late-stage CHF who had been receiving maximal outpatient medical therapy were enrolled in a 3-month open-label pilot study. These patients received intermittent outpatient milri-
none infusions to determine the safety and tolerability of intermittent infusions given at home and to assess the effects of this therapy on symptoms and hemody-
namics. We also wanted to assess the possible training effects of an increasing cumulative dose of milrinone, as demonstrated by progressively longer periods of postinfusion symptomatic improvement.

**Methods**

**Patients**

Patients with late-stage CHF who continued to have symptoms at rest despite maximal outpatient medical therapy were screened. Each prospective subject signed an informed consent for 3 days of inpatient milrinone infusion under close monitoring in the intensive care unit. Patients who demonstrated hemodynamic and symptomatic improvement without adverse side effects were offered participation in the study. All patients considered for the study had symptoms at rest or with minimal exertion.

Ten patients were selected for participation in the home milrinone infusion study (Table I). Nine were male and one was female. The age of our study patients ranged from 36 to 81 years, with a mean age of 61 ± 5 years. Each patient had had dilated cardiomyopathy with CHF for at least 3 years, the cause of which was either idiopathic or ischemic heart disease. The mean baseline radionuclide ejection fraction (RNEF) of the study patients was 20% ± 1.6%. Three patients were potential transplant candidates, and the remaining seven were considered to have end-stage CHF in need of palliation.

**Initial infusion**

Before hospitalization for initial infusion of milrinone, each patient performed a 6-minute walk test and had an echocar-
diogram, a 24-hour period of Holter monitoring, and an RNEF. The patients also filled out the Minnesota Living with Heart Failure Questionnaire. The patients were then brought into the intensive care unit where Swan-Ganz catheterization was performed to determine baseline cardiac output, systemic vascular resistance, mixed venous oxygen saturation, and pulmonary arterial wedge pressure (PAWP). After hemody-

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\text{Table I. Initial patient characteristics and hemodynamic parameters}
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<table>
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<tr>
<th>Age (y)</th>
<th>Cause</th>
<th>RNEF (%)</th>
<th>Initial CO (L/min)</th>
<th>Max CO (L/min)</th>
<th>Max CO (mm Hg)</th>
<th>Initial PAWP (mm Hg)</th>
<th>Min PAWP (mm Hg)</th>
<th>Initial MVO2 (%)</th>
<th>Initial MVO2 (%)</th>
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<td>Mean ± SEM</td>
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<td>53.4 ± 2.6</td>
<td>65.2 ± 1.8</td>
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CO, Cardiac output.
flush the catheter and hookup system and unhook the infusion. Materials were provided for patients to record their blood pressure, pulse, temperature, and weight. Each patient was provided an event monitor (Instromedix, Portland, Ore.). This lap recorder telephonically transmitted the patients’ electrocardiogram to the cardiac home nursing service, which in turn relayed appropriate information to a physician. These monitors were worn by all patients and routinely used during infusion days and emergently if symptoms occurred. The nursing service also provided a 24-hour on-call nurse.

Milrinone was administered by portable CADD plus infusion pumps (Sims-Deltec Inc., Milwaukee, Wis.). The infusion pumps were battery operated (9-volt), programmable for total volume to be delivered (milliliters per hour) and total amount given, and had the capability to run intermittently or continuously. These small (8” × 3” × 1”), lightweight (2-pound) pumps were worn in a fanny pack around the patient’s waist, which allowed them to ambulate and perform daily activities (Fig. 1). The dose of milrinone (0.375 to 0.75 µg/kg/min) was based on hemodynamic values obtained during the preceding hospitalization. Initially, milrinone was infused over a 6-hour period on 3 nonconsecutive days of the week (Table II).

The home infusions were continued for 3 months. The patients returned at 4 and 12 weeks for another 6-minute walk test and at 12 weeks for repeat Holter monitoring and RNEF. Holter monitors were looked at subjectively with a substantial chance of error. At the end of the 3-month home infusion period, nine patients had repeat invasive hemodynamic assessment. Milrinone was discontinued in most patients at that time; however, four patients requested to continue receiving the drug for an additional period. These patients were tapered off after several months (Table II).

Physiologic and metabolic parameters such as electrolyte levels, renal function, liver function, coagulation, weight, and hydration/nutritional status were assessed weekly for the first 4 weeks, then monthly for the duration of the study unless additional monitoring was clinically indicated.

Data collection and analysis
Each patient was evaluated during the infusion period with a number of parameters, including quality of life and cardiac function, as well as day-to-day physiologic parameters such as blood pressure, heart rate, and the presence or absence of arrhythmias. For the purposes of this study, quality of life was centered on the individual’s ability to perform routine activities of daily living. Specific components were evaluated by the 6-minute exercise walk test and the New York Heart Association functional class. The Minnesota Living with Heart Failure Questionnaire was administered to each patient before his or her initial infusion, 4 weeks into the home infusion period, and at the end of the infusion period (12 weeks). This questionnaire is a patient self-assessment measure developed to evaluate the therapeutic response to interventions for heart failure.15 Questions were answered based on a six-point response format ranging from 0 (not applicable) to 5 (very much affecting one’s life). Total scores were calculated by adding the responses to all 21 items to quanti-
tate a patient’s perceived disability caused by heart failure. Additionally two groups of questions that have previously been shown to be highly interrelated were evaluated. These questions evaluated the physical and emotional dimensions of a patient’s disability related to heart failure. Changes from baseline total, physical, and emotional score were calculated for each patient at baseline, 4 weeks, and 12 weeks.

Paired t tests were used to evaluate the significance of changes of RNEF, hemodynamics, and the Minnesota Living with Heart Failure Questionnaire. Repeated measures of analysis of variance were done to evaluate the results of the 6-minute walk test.

Results

Hospital infusions

Three patients initially screened showed either no sustained effects of milrinone (one patient) or adverse effects, including tachycardia (one patient) and arrhythmia (one patient).

The data from the initial hospitalizations for milrinone infusion are summarized in Table I. The mean cardiac output increased from 4.1 ± 0.4 L/min at baseline to a maximum of 5.5 ± 0.3 L/min (p < 0.001). Mean PAWP decreased from 23.8 ± 2.6 mm Hg to 15.2 ± 1.7 mm Hg (p = 0.002), and mixed venous oxygen saturation increased from 53.4 ± 2.6 to a maximum of 65.2 ± 1.8 (p < 0.001).

Home infusions: Toleration of milrinone

Table II summarizes the data accrued during the 3-month outpatient infusion period. Four of the 10 patients remained receiving the initial milrinone dosing schedule of 6-hour infusions 3 days a week; the remaining patients were titrated upward until either symptomatic improvement was seen or they reached dosing intervals of 12-hour infusions 5 days a week. Repeat Holter monitoring during week 12 revealed an increase in arrhythmias in only one patient, an increase in premature ventricular contractions but no sustained ventricular arrhythmias. There was no increase in angina in any of the patients. Two patients reported a decrease in angina. In one of these patients, upon cessation of infusion, unstable angina developed and coronary angioplasty was performed. The number of patient hospitalizations decreased from 18 during the 3 months before the study to four during the home infusion period (Fig. 2 and Table II). Only one of the patient hospitalizations that occurred during the infusion period was for a CHF exacerbation. One other patient, who claimed no significant improvement halfway through the protocol, stopped taking the drug and entered the hospital as a top priority transplant.
patient. His data were still used as ‘intention to treat’ in the analysis. He subsequently died while awaiting cardiac transplantation. Three other patients died in the 6 months after discontinuation of milrinone infusion. Two of these patients died from severe, unremitting heart failure, and the third from complications related to diabetes mellitus. Of the six remaining patients, all except one appeared to lose the beneficial effects of milrinone within 3 months of discontinuation.

**Home infusion: Functional changes**

Fig. 3 depicts the results of the 6-minute walk test. There was a general trend toward improvement. The mean distance walked increased from 830 ± 140 feet to 945 ± 132 feet during week 4 of the infusion period and finally to 1060 ± 129 feet by week 12 ($p = 0.195$) by repeated measures analysis of variance. Eight of the 10 patients improved their walking times by the end of the infusion period.

Fig. 4 shows the results of the Minnesota Living with Heart Failure Questionnaire. Questions were answered on a six-point scale, and total scores were calculated by adding together the points for each of the questionnaire’s 21 items. In addition to total score, physical and emotional components of the questionnaire were independently analyzed. The mean total score for all patients improved from 75.6 ± 4.6 before milrinone infusions to 69.4 ± 5.7 at 4 weeks ($p < 0.05$). The mean total scores continued to improve between the fourth week and the end of the infusion period (week 12), again resulting in a significant improvement over baseline ($p < 0.05$). The mean physical scores for all patients also improved between baseline testing (mean = 30.4 ± 1.7) and week 4 of the infusion period (mean = 26.1 ± 2.4) ($p = 0.06$). The mean physical scores continued to improve between the fourth and twelfth weeks, resulting in a significant improvement over baseline ($p = 0.007$). Finally, the mean emotional scores for all patients were analyzed and again showed a general trend of improvement between the initial responses and responses during weeks 4 ($p = 0.18$) and 12 of the milrinone infusion period ($p = 0.25$).

At the end of the infusion period, nine patients returned to the intensive care unit for hemodynamic monitoring. Fig. 5 displays the results of these studies. As a group these patients showed a significant improvement in cardiac output ($p = 0.03$) over baseline values, with a general trend toward improvement in mixed venous saturation ($p = 0.10$) and PAWP ($p = 0.11$). More than half the patients showed significant improvement in all these parameters. Although there was a general trend toward a slightly increasing ejection fraction at the end of the infusion period ($p = 0.30$), three patients showed markedly improved RNEF values, >5% over baseline, after the milrinone infusions.
Figure 4

Bar graphs showing results of Minnesota Living with Heart Failure Questionnaire for all study patients. Questions were answered based on six-point response format ranging from 0 (not applicable) to 5 (very much affecting one’s life). Total scores were calculated by adding responses to all 21 items to quantitate patient’s perceived disability from heart failure. Values are given as mean ± SD. Two-tailed t tests are labeled *p < 0.05 and **p < 0.01.

Figure 5

Graphs showing patients’ hemodynamic improvement on repeat Swan-Ganz monitoring at end of milrinone infusion period. Means ± SD are also displayed. Cardiac output is displayed in liters per minute, mixed venous saturation (MV O₂) as percentages, PAWP in millimeters of mercury, and RNEF as percentages. Data were analyzed with two-tailed t tests.
In an attempt to correlate initial hemodynamic response with clinical response during the infusion period, as measured by patients’ mean total score on the Minnesota Living with Heart Failure Questionnaire during week 12 of the infusion period. Strong positive correlation was found with a correlation coefficient of 0.73 ($p < 0.05$).

**Graph showing correlation between initial hemodynamic response, as measured by change in PAWP, and clinical response during infusion period, as measured by patients’ mean total score on Minnesota Living with Heart Failure Questionnaire during week 12 of infusion period.**

**Discussion**

Because inotropes have been useful therapeutic agents for CHF exacerbations for more than a decade, attempts have been made to institute their use on an outpatient basis. The majority of these trials have used the synthetic $\beta$-1 agonist dobutamine. Although studies have shown improvement in cardiac index, New York Heart Association functional class and systemic vascular resistance, the initial excitement over the potential use of these drugs in an outpatients basis has considerably waned because of problems with mortality and morbidity rates and tolerance the drug effects.

As with dobutamine, parenteral milrinone has been shown to be a highly effective therapy for hospitalized patients with decompensated CHF. Some studies indicate that intravenous milrinone may have some advantages over dobutamine. In one randomized trial comparing intravenous milrinone with dobutamine, in 82 patients with severe heart failure milrinone reduced heart rate more than dobutamine and slightly decreased mean arterial pressure, whereas dobutamine did not, and decreased pulmonary capillary wedge pressure earlier and more dramatically than dobutamine.

It was our belief that a combination of an inotrope and vasodilator could be effective in the outpatient
setting if it was given in a controlled fashion using an intermittent dosing schedule. This regimen might obviate drug-induced tachyphylaxis as well as the catecholamine-induced deleterious effects such as arrhythmias, ischemia, and continued deterioration of left ventricular function. The current study was undertaken in an attempt to demonstrate whether patients with end-stage CHF could safely tolerate home infusions while displaying some measure of either symptomatic, functional, or hemodynamic improvement.

Every patient who tolerated 3 days of milrinone in the hospital tolerated 3 months of home infusions. There were no deaths during the infusion period, which, considering the severity of illness of these patients (four deaths in the subsequent 6 months after termination of milrinone) suggests at least the possibility of a survival-enhancing capability. There is, of course, no way to know this without a contemporaneous control group. The well-documented arrhythmogenicity of milrinone caused little difficulty in this study. Only one patient had an increase in arrhythmias (increased premature ventricular contractions) on repeat Holter monitoring during the infusion period. A small number of patients reported a decrease in angina while receiving milrinone, and no patients reported increased angina during the infusion period. These low complication rates may be in part related to the careful scrutiny with which all study patients were monitored in the intensive care unit during the initial infusions. Additionally, some of the decrease in hospitalizations may be attributable to the excellent home nursing care that study patients received.

The beneficial effects of milrinone demonstrated in this study are presumed to be multifactorial in origin. Milrinone has been shown to have both vasodilating and inotropic activity. Additionally, we believe that for the first time we have shown that a “training effect” occurs with the intermittent dosing regimen. The mean number of reported hours of improvement after a given daily dose progressively increased throughout the infusion period, usually starting between 2 to 4 weeks after initiation of the drug. It was beyond the scope of this study to determine whether this training effect reflected improved central hemodynamics or peripheral vascular muscle function. Nevertheless, it is well known that in response to adrenergic states such as sustained exercise a number of adaptations take place in skeletal muscle. These changes include mobilization of energy substrates, augmentation in the oxidative capacity of these tissues, and improvement in tissue perfusion through the recruitment of additional capillary surface area. It is possible that the increased cyclic adenosine monophosphate levels caused by milrinone result in similar changes in cardiac muscle when the drug is used for sustained periods of time. One study involving patients with severe heart failure described structural changes in myocardial mitochondria after the administration of dobutamine, implying that some of the beneficial effects of this inotrope occur at the cellular level. Similar changes in myocardial cells may take place after prolonged administration of milrinone and therefore partially account for the progressive period of improvement seen after each infusion.

Limitations
We acknowledge the inherent weakness of an open-labeled study. We consider this a preliminary study in which patients with end-stage CHF would be treated with intermittent dosing of a carefully prescribed dose of milrinone to examine whether beneficial effects could be ascertained and toxicity avoided. The excellent home nursing care all study patients received certainly accounted for some of the symptomatic improvement and marked decrease in hospitalizations. Nevertheless, our results warrant further study in a double-blinded fashion.

Summary
In the 10 patients we studied with end-stage CHF, intermittent home milrinone infusions were well tolerated and there was some evidence the treatment resulted in symptomatic, hemodynamic, and functional improvement and decreased hospitalizations. These effects may be partially related to a training effect on cardiac or peripheral muscle in addition to the drug’s previously recognized inotropic and vasodilating activity. The promising results of this pilot study suggest that a larger controlled study of outpatient intermittent milrinone versus another inotrope such as dobutamine would be of value. That study is currently being undertaken.

We thank Steven Carter for technological support and Dr. Ralph Shabetai for his continued encouragement and support.

References
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