Long-term oral administration of amrinone for congestive heart failure: lack of efficacy in a multicenter controlled trial

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ABSTRACT A number of uncontrolled studies have indicated that oral administration of amrinone, a phosphodiesterase inhibitor with potent positive inotropic effects in experimental preparations, may be beneficial in patients with chronic congestive heart failure. The present multicenter trial was designed to prospectively evaluate clinical response and change in exercise tolerance during 12 weeks of amrinone therapy in a double-blind, placebo-controlled protocol. Ninety-nine patients with NYHA functional class 3 or 4 congestive heart failure on digitalis and diuretics, of whom 31 were also receiving captopril, were enrolled. After baseline clinical assessment and determination of exercise tolerance, radionuclide left ventricular ejection fraction, and roentgenographic cardiothoracic ratio, patients were randomly assigned to receive amrinone or placebo, beginning at 1.5 mg/kg tid and increasing to a maximum dosage of 200 mg tid. After 12 weeks of therapy or at the last blinded evaluation in patients who did not complete this protocol, there were no significant differences from baseline values between treatment with amrinone or placebo with regard to symptoms, NYHA functional class, left ventricular ejection fraction, cardiothoracic ratio, frequency and severity of ventricular ectopy, or mortality. Exercise tolerance improved significantly from baseline by 37 ± 10% (mean 163 sec) in patients on amrinone and 35 ± 11% (mean 149 sec) in patients on placebo, but there was no significant difference between treatments. Adverse reactions were significantly more frequent and more severe on amrinone, occurring in 83% of patients and necessitating withdrawal in 34%. Downward adjustment of amrinone dosage because of side effects was responsible for a significantly lower mean total daily dose of 355 vs 505 mg for placebo (p < .001). These findings indicate that oral administration of amrinone is not clinically effective in patients with chronic congestive heart failure, in part because of frequent adverse effects.


IN THE LAST DECADE there has been growing interest in new approaches to drug treatment of refractory congestive heart failure. Early investigations centered on drugs that altered the loading conditions of the left ventricle. More recently, agents possessing positive inotropic activity with chemical structures and mechanisms of action different from those of digitalis glycosides or catecholamines have been investigated.1 Amrinone, a bipyridine derivative,2 was the first of these to undergo extensive clinical evaluation. Short-term therapy with amrinone administered intravenous-

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ly produces marked hemodynamic improvement,3-6 and this preparation is now commercially available. Subsequent descriptions of clinical responses during maintenance oral therapy7-9 were very encouraging. However, later studies yielded mixed results,10-13 and a recently published study in 52 patients who initially exhibited apparent improvement on an oral preparation of amrinone failed to show any differences between those continued on active drug and those withdrawn to placebo.12

This report describes a multicenter prospective trial in which amrinone or placebo was administered to patients continuing on conventional therapy with diuretics and digoxin and, in a subgroup of patients, conventional therapy plus captopril. A randomized, double-blind design with parallel treatment groups was used. Serial clinical assessments, exercise testing, and
noninvasive measurements of cardiac function were made during a 12 week follow-up period to evaluate the efficacy of maintenance doses of amrinone. The results of this trial raise important questions not only about the therapeutic benefit–to–side effect ratio of amrinone administered orally but also about the long-term efficacy of cardiotonic therapy and the design of clinical trials in congestive heart failure.

Methods

Patients. This report comprises 99 patients who were enrolled in 26 centers. Entry criteria included cardiac failure of at least 1 month duration and symptoms consistent with NYHA functional class 3 or 4. In addition, patients were required to be capable of performing treadmill exercise and to remain clinically stable on constant dosages of digitalis and diuretics during an initial baseline phase of at least 1 week. Vasodilators used for the treatment of heart failure, other than captopril, were continued before entry, but seven and five patients continued on prazosin and hydralazine, respectively, for hypertension. These were evenly distributed between the active therapy and placebo groups.

Exclusion criteria included myocardial infarction within 3 months of entry, heart failure resulting from obstructive or restrictive cardiomyopathy, primary valvular disease or acute myocarditis, ejection fraction above 40%, angina pectoris requiring long-term medication or limiting exercise, serious symptomatic arrhythmias or atrial fibrillation with an uncontrolled ventricular response, and significant primary pulmonary, hepatic, renal, or hematologic disease. A further requirement was that exercise testing be limited by heart failure, as manifest by dyspnea or exhaustion.

Study design. Potential candidates were initially entered into a baseline stabilization period lasting 1 to 3 weeks, during which all medications were continued at their previous dosages as far as possible. During the baseline period the patients underwent two treadmill exercise tests at least 1 week and not more than 3 weeks apart. A modified Naughton exercise protocol consisting of consecutive 2 min stages was used.14 The duration of the second test was required to be within 20% of the duration of the initial test, with neither test permitted to exceed 12 min. In addition, a posterior-anterior chest roentgenogram, electrocardiogram, radionuclide ejection fraction, and results of routine laboratory testing were obtained during the baseline period. At six centers, 24 hr ambulatory electrocardiographic monitoring was performed twice during the baseline period for comparison with subsequent studies after 4 and 8 weeks of therapy. Patients who met the exercise testing criteria and exhibited clinical stability were entered into the treatment phase.

Treatment was initiated by adding amrinone or matching placebo to the patients’ previous medical regimens in a randomized double-blind fashion. Amrinone was available in 75, 100, 150, and 200 mg capsules, and the initial dosage was selected to approximate 1.5 mg/kg tid. Clinical evaluations including exercise testing were repeated after 1, 2, 4, 8, and 12 weeks of treatment. The drug dosage was adjusted upward to a maximum of 200 mg tid after 2 weeks if an optimal clinical response or at least a 20% improvement in exercise duration were not seen. Downward adjustment of dosage based on the presence of adverse reactions was also permitted. The ejection fraction was measured at 8 weeks, and the electrocardiogram and chest roentgenogram were taken again at 12 weeks.

Termination of blinded therapy was permitted if, in the opinion of the investigator, a serious adverse reaction to amrinone had occurred or if the patient exhibited significant clinical deterioration. In the latter case, at the investigator’s option, the treatment code could be broken and open-label amrinone therapy could be initiated. All patients were followed in the scheduled manner for the entire 12 weeks regardless of changes in the study drug.

Randomization method and data analysis. Patients were assigned to group 1 if they were not receiving captopril and to group 2 if previous captopril therapy was continued. Randomization was accomplished from a central office and carried out separately for groups 1 and 2. The randomization was further stratified by pretreatment NYHA functional class (3 or 4) and exercise tolerance (below 8 min or 8 to 12 min).

The trial was designed to evaluate changes in symptoms and NYHA classification, exercise tolerance, ejection fraction, cardiothoracic ratio, ventricular ectopy, and adverse reactions. Deaths, withdrawals due to treatment failure, and adverse reactions were also analyzed as trial end points. The significance of changes in quantitative variables measured more than twice were determined by analysis of variance. The two-tailed t test was used to examine changes in variables measured only twice and for the comparison of baseline and last double-blind assessments. The chi square statistic was used to compare treatments with respect to shifts in NYHA class, symptoms, and incidences of adverse reactions.

A preplanned analysis was conducted when one-half of the projected number of patients needed to detect a 2 min difference in exercise response with α = 0.01 and β = 0.1 had completed the protocol.15 This article presents the results of this analysis, after which the overall study was terminated.

Results

Treatment group characteristics. Table 1 lists demographic data and baseline test results for the different treatment groups. There were no significant differences in age, sex distribution, and etiology of heart failure (ischemic or nonischemic) between patients randomized to amrinone and placebo. Baseline NYHA classification and severity of dyspnea and fatigue (rated on a 0 to 4 scale as absent, mild, moderate, severe, or very severe) were similar, as were the pretreatment medications and measurements of exercise time, ejection fraction, and cardiothoracic ratio.

Medication dosing and treatment end points. The mean daily dose of amrinone in patients continuing on treatment was 355 mg, or approximately 1.6 mg/kg tid, which was significantly lower than that of the 505 mg mean dose of placebo (p < .001). Amrinone was maintained at the highest permissible dosage, 200 mg tid, in only 11 patients; lower dosages were used in 41% of the remaining patients because of adverse reactions. In contrast, 29 patients receiving placebo were given 200 mg tid and only 4% patients had their dosage limited by side effects.

Table 2 shows the treatment end points. There were no significant differences between amrinone and placebo treatments in the numbers of patients withdrawing because of worsening heart failure (four vs six for the combined groups) or in the number of deaths (two
TABLE 1
Baseline characteristics of the treatment group

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2 (on captopril)</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amrinone</td>
<td>Placebo</td>
<td>Amrinone</td>
</tr>
<tr>
<td>n</td>
<td>32</td>
<td>36</td>
<td>15</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>53 ± 2</td>
<td>57 ± 2</td>
<td>57 ± 4</td>
</tr>
<tr>
<td>Men</td>
<td>28(88)</td>
<td>33(92)</td>
<td>12(80)</td>
</tr>
<tr>
<td>Ischemic cardiomyopathya</td>
<td>18(56)</td>
<td>17(47)</td>
<td>9(60)</td>
</tr>
<tr>
<td>NYHA 3</td>
<td>31(97)</td>
<td>32(89)</td>
<td>12(80)</td>
</tr>
<tr>
<td>NYHA 4</td>
<td>1(3)</td>
<td>4(11)</td>
<td>3(20)</td>
</tr>
<tr>
<td>Dyspnea ratingb</td>
<td>1.9 ± 0.1</td>
<td>2.0 ± 0.1</td>
<td>2.1 ± 0.2</td>
</tr>
<tr>
<td>Fatigue ratingb</td>
<td>2.0 ± 0.1</td>
<td>2.1 ± 0.1</td>
<td>2.3 ± 0.2</td>
</tr>
<tr>
<td>No. on digoxin</td>
<td>31</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>No. on diuretics</td>
<td>32</td>
<td>36</td>
<td>15</td>
</tr>
<tr>
<td>Mean exercise time (sec)</td>
<td>461 ± 31</td>
<td>441 ± 25</td>
<td>398 ± 47</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.19 ± 0.08</td>
<td>0.21 ± 0.10</td>
<td>0.24 ± 0.08</td>
</tr>
<tr>
<td>Cardiac output ratio</td>
<td>0.54 ± 0.06</td>
<td>0.55 ± 0.04</td>
<td>0.56 ± 0.06</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM. Values in parentheses are percentages. No intergroup difference achieved statistical significance.

aPatients whose etiology of congestive heart failure was coronary artery disease and prior myocardial infarction. Remaining patients had congestive heart failure of various etiologies, without significant intergroup differences in distribution.

bDyspnea and fatigue were rated on a scale from 0 to 4 (0 = none, 1 = mild, 2 = moderate, 3 = bad, 4 = very bad).

each). However, 34% of the combined group of 47 patients treated with amrinone and only 2% of the 52 patients receiving placebo withdrew because of adverse reactions (p < .01). This difference was significant in the group 1 patients, and the same trend was apparent in group 2 (p < .10). Because of the large number of dropouts due to adverse reactions, only 57% of the patients on amrinone completed the study compared with 79% of patients on placebo (p < .01).

Clinical evaluation of response. Table 3 shows the mean values for NYHA classification, symptom ratings, and the physicians’ and patients’ overall global assessments of clinical status. Only the pretreatment and final double-blind evaluations are shown because the number of patients declined progressively during the course of the study, particularly in the amrinone group.

Although there was a trend toward improvement with both amrinone and placebo, the changes from baseline to the last blinded visit did not achieve significance for any variable. Furthermore, the responses with amrinone and placebo were essentially identical. When the individual patients’ visit-by-visit changes in NYHA class or symptom scores were evaluated, there were no differences in the number that improved or worsened between the amrinone and placebo groups.

TABLE 2
Treatment outcome

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2 (on captopril)</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amrinone</td>
<td>Placebo</td>
<td>Amrinone</td>
</tr>
<tr>
<td>n</td>
<td>32</td>
<td>36</td>
<td>15</td>
</tr>
<tr>
<td>Withdrawn-worsening CHF</td>
<td>2(6)</td>
<td>6(17)</td>
<td>2(13)</td>
</tr>
<tr>
<td>Withdrawn-adverse reaction</td>
<td>12(38)a</td>
<td>1(3)</td>
<td>4(27)</td>
</tr>
<tr>
<td>Discontinuedb</td>
<td>1(3)</td>
<td>3(8)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Died</td>
<td>2(6)</td>
<td>2(6)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Completed 12 wk</td>
<td>17(53)</td>
<td>25(69)</td>
<td>10(67)</td>
</tr>
</tbody>
</table>

CHF = congestive heart failure.

Values in parentheses are percentages.

*p < .01 amrinone vs placebo.

bPatients withdrew for stated reasons unrelated to therapy. Note: Two group 1 amrinone patients and one group 2 amrinone patient withdrew due to worsening CHF and adverse reactions; these are listed in both categories.
Quantitative measurements of efficacy. By design, exercise tolerance was chosen to be the primary objective measurement of efficacy. Because the number of patients decreased over time and because patients who withdrew (whether because of lack of efficacy or adverse reactions) exhibited less improvement, the most valuable comparison is the results of the final blinded test. This showed 29% and 55% improvement over baseline in patients on amrinone in groups 1 and 2, respectively (weighted mean 37 ± 10% or 163 sec), and a comparable 21% and 64% improvement in patients on placebo (weighted mean 35 ± 11% or 149 sec). Importantly, the magnitude of change in exercise time in patients on amrinone was not different from that in patients on placebo at any point. Figure 1 plots the mean values for exercise duration for the subset of patients who completed the 12 week double-blind period (27/47 on amrinone and 41/52 on placebo). Again, a progressive and significant improvement was present on both treatments, but no difference between treatments was seen.

Table 4 presents the radionuclide ejection fraction values and cardiothoracic ratios. No significant changes occurred between the baseline and the final blinded measurements on either treatment. Forty-one patients, including 18 treated with amrinone and 23 receiving placebo, underwent ambulatory electrocardiographic monitoring. These findings are also shown in table 4. There were no significant differences in the number of single ventricular premature depolarizations, couplets, or runs of three or more between the baseline periods and treatment periods. Furthermore, there were no differences in the numbers of patients

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Clinical evaluation of response</th>
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<tbody>
<tr>
<td></td>
<td>Group 1</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
</tr>
<tr>
<td>Amrinone</td>
<td>3.0 ± 0.03</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.1 ± 0.05</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
</tr>
<tr>
<td>Amrinone</td>
<td>1.9 ± 0.1</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.0 ± 0.1</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Amrinone</td>
<td>1.9 ± 0.1</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.1 ± 0.1</td>
</tr>
<tr>
<td>Patient global</td>
<td></td>
</tr>
<tr>
<td>Amrinone</td>
<td>1.8 ± 0.1</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.8 ± 0.1</td>
</tr>
<tr>
<td>MD global</td>
<td></td>
</tr>
<tr>
<td>Amrinone</td>
<td>2.0 ± 0.1</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.0 ± 0.1</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SE. Symptoms and global symptom status were rated from 0 to 4 as described in table 1. No significant differences between amrinone and placebo were present.
exhibiting higher grades of ectopy during treatment by the Lown classification. On blinded qualitative analysis of the ambulatory electrocardiograms, 12 of 18 patients on amrinone and 16 of 23 patients on placebo were considered to have no change or decreasing ectopy during treatment. Two and four patients on amrinone had moderate or marked increases, respectively, compared with four and three on placebo. Again, these differences were not significant. Three subjects, one on placebo and two on amrinone, exhibited a marked increase in runs of ventricular premature depolarizations, but no patient experienced symptomatic arrhythmias during monitoring. Figure 2 plots the frequency of runs of ventricular premature beats on treatment compared with baseline.

**Adverse reactions.** Overall, there were 53 adverse reactions recorded in 24 of the 52 patients on placebo. These were generally rated mild or moderate, the most common category being gastrointestinal complaints, and only one patient was withdrawn because of a presumed adverse reaction. A total of 127 adverse reactions were noted in 38 of the 47 patients receiving amrinone; 83% of the adverse reactions were considered moderate or severe and necessitated withdrawal in 16 patients (34%). The most frequent problems were gastrointestinal complaints (usually nausea, vomiting, and/or diarrhea) in 49%, liver function abnormalities in 14%, thrombocytopenia (platelet counts below 100,000/μl) in 16%, and a syndrome of fatigue, malaise and fever in 16%. Most adverse reactions in patients on amrinone occurred as the dose was increased.

**Analyses by subgroup.** To determine whether selected subsets of patients exhibited a beneficial response not seen in the overall group, the exercise tolerance results and clinical evaluations were examined in relation to age, etiology of heart failure, baseline symptoms, initial clinical classification, and pretreatment exercise tolerance. It was not possible to compare the results in different centers, since individual institutions did not enroll an adequate number of subjects. Patients with ischemic heart disease showed less improvement in exercise time (23% on placebo, 27% on amrinone) than those with nonischemic cardiomyopathy (45% on placebo, 53% on amrinone), but the changes with amrinone and placebo were comparable in both groups. Patients who were initially more limited (exercise time

**TABLE 4**

Ejection fraction, cardiothoracic ratio, and ambulatory electrocardiographic findings

<table>
<thead>
<tr>
<th></th>
<th>Amrinone</th>
<th></th>
<th>Placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Treatment</td>
<td>Baseline</td>
<td>Treatment</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.20 ± 0.08</td>
<td>0.22 ± 0.09</td>
<td>0.23 ± 0.11</td>
<td>0.23 ± 0.10</td>
</tr>
<tr>
<td>Cardiothoracic ratio</td>
<td>0.55 ± 0.06</td>
<td>0.54 ± 0.05</td>
<td>0.55 ± 0.06</td>
<td>0.50 ± 0.07</td>
</tr>
<tr>
<td>VPDs/hr(^a)</td>
<td>7.7 ± 1.4</td>
<td>8.9 ± 1.6</td>
<td>8.6 ± 1.2</td>
<td>9.3 ± 1.5</td>
</tr>
<tr>
<td>VPD pairs/hr(^a)</td>
<td>1.5 ± 0.3</td>
<td>2.1 ± 0.6</td>
<td>1.9 ± 0.3</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>VPD runs/hr(^a)</td>
<td>0.8 ± 0.1</td>
<td>1.2 ± 0.3</td>
<td>0.9 ± 0.1</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>Lown 4B or above</td>
<td>14/18</td>
<td>13/18</td>
<td>16/23</td>
<td>18/23</td>
</tr>
</tbody>
</table>

\(^a\)Because of nonnormal distribution of these variables, these values are expressed as a square root transformation. Quantitative and nonparametric analyses of the raw data also failed to show significant differences.

**FIGURE 2.** Mean number of 3 beat or longer runs of ventricular premature depolarizations (VPDs) per hour before and during treatment. The horizontal axis is the mean of two baseline 24 hr periods and the vertical axis indicates the worst of the two on therapy examinations. The line of identity is shown for reference. Two points off of the vertical axis are shown with their values in parentheses. Three patients, one on placebo and two on amrinone, exhibited a marked increase.
of 8 min or less) showed a 42% increase on placebo and 51% on amrinone, compared with 22% and 20%, respectively, in those who exercised from 8 to 12 min before treatment. This, in part, reflects the shorter pretreatment time; moreover, the response to amrinone and placebo were again similar. The same trends toward greater exercise tolerance changes in more ill patients were noted when the patients were stratified by symptom ratings as well, but no advantage of amrinone therapy was detectable.

Discussion

Background and outcome. The development of a new generation of cardiotoxic drugs, of which amrinone is thus far the best studied and most widely used, has engendered considerable interest.17-18 The positive inotropic effects of amrinone have been demonstrated in experimental preparations5, 19 and, to the extent possible, in patients,3 although some workers have questioned these findings.20, 21 Initial results of uncontrolled hemodynamic studies3-6 and short-term clinical observations7, 8 suggested that amrinone is remarkably effective. Two groups have also reported improvement in exercise tolerance, both acutely and during maintenance therapy.5, 9, 13, 22, 23 However, a recently published amrinone withdrawal study with negative results raised concern about clinical benefit of amrinone therapy.12

Since the expectations of uncontrolled studies frequently are not verified in controlled ones, the present multicenter trial was designed to prospectively examine the clinical and exercise tolerance responses to amrinone administered orally with a randomized, double-blind, placebo-controlled parallel design. Despite the many previous enthusiastic reports, significant efficacy of the study drug was not demonstrated. Thus, although oral administration of amrinone was associated with symptomatic improvement in many patients and a significant increase in exercise tolerance, as has been reported in uncontrolled studies, these beneficial responses were of no greater magnitude than those in the placebo-treated patients. Two issues require further discussion: first, whether a beneficial effect of amrinone could have been missed in this trial, and second, why amrinone failed to be effective despite previously reported short-term hemodynamic improvement.

Possible confounding factors. One factor that may have made it more difficult to detect a response to amrinone is the significant improvement demonstrated by the placebo groups. For example, patients in groups 1 and 2 given placebo increased their exercise tolerance by 21% and 64%, respectively. This magnitude of improvement on placebo exceeded the trivial change (+0.4%) observed in a recent multicenter trial of captopril, which used the same exercise protocol.24 In this regard, there were three important differences in study design between the present trial and the captopril study. In the latter study, single-blind placebo therapy was instituted during the baseline stabilization period for a minimum of 2 weeks before the initial exercise tests, and a minimum exercise time of 3 min was required. In the present study, placebo was not given during the pretreatment period, and there was no minimum exercise time. The trend toward an increase in the mean exercise duration between the two baseline tests (figure 1) is therefore noteworthy. The increase in exercise tolerance in the patients continuing on captopril (group 2), whether given amrinone or placebo, was particularly striking and was significantly greater than that seen in group 1 (p < .05). The greater improvement in group 2 patients may have represented a further response to captopril, since maximum improvement in exercise tolerance with captopril may take many months to occur.25 Therefore it would seem advisable for future studies to administer placebo during any stabilization phase, to lengthen the pretreatment observation period, to employ minimum exercise criteria, and to avoid concomitant vasodilator therapy.

Nonetheless, these factors should have affected both placebo and amrinone groups comparably, and the sample size was adequate to detect beneficial treatment responses to amrinone in the major measurements if they were present. Although enrollment was discontinued after the preliminary analysis, this study was sufficiently sensitive to detect a 2 min (26%) difference in exercise tolerance response between patients on amrinone and placebo at \( \alpha = .05 \) with a power of .88 (\( \beta = .12 \)) in group 1 and a power greater than .90 (\( \beta < .10 \)) in the combined groups. Similarly, the power for detecting a 0.5 class difference in NYHA functional class response between the amrinone and placebo treatments was .90. Previous therapeutic trials with similar or smaller numbers of subjects with the same efficacy measures in comparable patients have yielded positive results.24-30

Other important questions concern whether the optimal patient population and efficacy measurements were used. The great majority of the patients entered were in NYHA class 3. Although patients with milder symptoms may have had greater myocardial reserve and provided a more stable control group, the degree of improvement was lower in patients with fewer pretreatment symptoms and better exercise tolerance. On
the other hand, although the initial favorable studies with amrinone tended to include more class 4 patients, controlled studies and exercise testing are more difficult in this group. In addition, there was no tendency toward greater improvement on amrinone than on placebo even in the most symptomatic subjects. Patients with ischemic cardiomyopathy exhibited less improvement than those with primary myocardial disease. Nonetheless, there was no trend toward greater improvement with amrinone than placebo in patients with nonischemic cardiomyopathy.

The choice of efficacy measurements in patients with chronic congestive heart failure is limited. Most therapeutic trials in patients with heart failure have used similar exercise protocols and assessed maximum exercise capacity. Since patients with heart failure rarely perform maximum exercise, it might be more accurate physiologically to measure duration of exercise at a submaximal load. Nonetheless, previous trials have been able to demonstrate significant differences between treated and placebo groups with other drugs by these same measurements.24, 26-30 Hemodynamic measurements were not performed in this trial and may have been helpful in understanding the lack of clinical response to amrinone, but the frequent discordance between these measurements and both clinical and exercise assessments suggests that hemodynamic measurements themselves are inadequate outcome assessments.

Possible explanations for negative results. Assuming that the negative results are accurate, it becomes essential to consider the discrepancy between these findings and the many published positive reports with amrinone. One possible explanation derives from the most significant difference between the amrinone and placebo groups, namely the very high incidence of adverse reactions. Eighty-three percent of subjects receiving amrinone reported at least one potential adverse effect, an average of 2.7 per treated patient, and 34% of the patients withdrew for this reason. Previous investigators had described all of the major side effects encountered and had suggested that therapy might be limited by toxicity,10-12, 31-33 but nonetheless this high incidence in a more stable population was unexpected. Of particular importance is that in addition to causing many withdrawals, these adverse reactions limited the dosage of amrinone that could be administered. Forty-one percent of patients receiving amrinone as compared with only 4% of patients receiving placebo (p < .01) required a downward dosage adjustment because of side effects, and the mean daily dosage of amrinone (355 mg) was considerably lower than the 505 mg received by the placebo group. These findings raise the possibility that oral administration of amrinone may have been more effective if it had been possible to use higher dosages.34 However, previous positive studies have used similar oral dosages of amrinone, and two groups have reported increased exercise tolerance ascribed to amrinone at the same dosage as used in the present trial.13, 21 Furthermore, patients receiving the higher dosages of amrinone in this study showed no greater degree of improvement than those on lower dosages.

It is also possible that a short-term beneficial response to amrinone is not sustained during long-term oral therapy. Such a loss of efficacy could result from a loss of myocardial responsiveness to inotropic stimulation,35 increased activity of opposing neurohumoral mechanisms producing vasoconstriction and volume expansion,36 or progressive deterioration of myocardial function.22, 23 Amrinone’s mechanism of action remains uncertain. Most, although not all, experimental data support its cardiotonic potential,2, 19, 20 but these findings do not necessarily indicate that this effect is present or, more importantly, is sustained during long-term therapy in the failing heart. Indeed, the present study and the variable results in controlled trials of long-term digoxin therapy37-39 raise some doubt as to whether a clinically important degree of long-term exogenous inotropic stimulation is achievable in many individuals. It should be noted that all patients in this study were receiving digoxin, possibly limiting the potential for an additional inotropic response, although digoxin was also used concomitantly in previous positive studies.

Previously published data also suggest that amrinone produces much of its hemodynamic benefit by acting as a vasodilator.21 Frequent occurrence of tolerance during long-term vasodilator therapy has been described, and this may explain the lack of long-term efficacy of amrinone.36 Previous studies have raised the question of whether long-term amrinone therapy might itself be adversely affecting the myocardium.22, 23, 40 The present trial provides no indication of deterioration of cardiac function on the dosages of amrinone administered, since there were no negative differences between the amrinone- and placebo-treated patients in clinical status, exercise tolerance, ejection fraction, or survival. The results of ambulatory monitoring also failed to indicate any worsening of arrhythmias during treatment.

Implications. The outcome of this trial indicates that during long-term administration, amrinone does not possess a therapeutic-to-toxic ratio that would make it
a clinically useful oral agent, although short-term intravenous treatment with amrinone has been effective. These results have further important implications. They suggest that even strikingly beneficial short-term hemodynamic responses, such as those seen in earlier amrinone studies, may not be translated into long-term clinical improvement. This phenomenon has also been demonstrated previously with some vasodilators. A number of newer positive inotropic agents are now under investigation, including milrinone, a more potent congener of amrinone with a more benign side-effect profile. Although initial studies with these medications have been favorable, the present trial, which failed to demonstrate a beneficial response in any subset of patients, raises some concern about the long-term efficacy of drug therapy directed toward improving myocardial contractility. In any case, these findings indicate the necessity of withholding judgment about the efficacy of any drug until well-designed controlled trials are completed.

Appendix
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References
14. Patterson JA, Naughton J, Pietras RJ, Gunnar RM: Treadmill exer-
cise in assessment of the functional capacity of patients with cardi-
ac disease. Am J Cardiol 30: 757, 1972
18. Braunwald E, Colucci WS: Evaluating the efficacy of new inotro-
19. Endoh M, Yamashita S, Taira N: Positive inotropic effect of amri-
one in relation to cyclic nucleotide metabolism in the canine ventricular muscle. J Pharmacol Exp Ther 221: 775, 1982
21. Wilmshurst PT, Thompson DS, Jenkins BS, Cottart DJ, Webb-
32. Dunkman B, Wilen MM, Franciosa JA: Adverse effects of long-
33. Wilmshurst PT, Webb-Peploe MM: Side effects of amrinone ther-

40. Packer M, Medina N, Yushak M: Hemodynamic and clinical limi-
42. Maskin CS, Sinoway L, Chadwick B, Sonnenblick EH, LeJemtel TH: Sustained hemodynamic and clinical effects of a new cardio-
44. Uretsky BF, Generalovich T, Reddy PS, Spangenberg RB, Fol-
45. Thormann J, Schlepper M, Kramer W, Gottwick M, Kindler M: Effects of AR-L 115 BS (Sulmazol), a cardiotoxic agent, in coro-
nary artery disease: improved ventricular wall motion, increased pump function and abolition of pacing-induced ischemia. J Am Coll Cardiol 2: 332, 1983
Long-term oral administration of amrinone for congestive heart failure: lack of efficacy in a multicenter controlled trial.

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