Amrinone Therapy in Patients with Heart Failure*
Lack of Improvement in Functional Capacity and Left Ventricular Function at Rest and During Exercise
Donald L. Johnston, M.D.; Dennis P. Humen, M.D.; and William J. Kostuk, M.D.

Short-term amrinone therapy has been shown to exert beneficial hemodynamic effects in patients with heart failure. To determine whether this improvement persists longer, the effects of maximally tolerated doses of amrinone on exercise duration, oxygen consumption, and left ventricular function and volumes were examined during maintenance therapy. After four weeks of amrinone therapy, 75 to 150 mg three times a day (mean 292 ± 70 mg daily), treadmill exercise duration, maximal oxygen consumption, and functional class were unchanged from control values. Radionuclide-derived ejection fraction and end-diastolic and end-systolic volumes were not altered at rest or during maximal supine exercise. Similarly, significant changes in echocardiographic end-systolic and end-diastolic dimensions did not occur. This lack of clinical benefit on functional capacity and left ventricular function, together with frequent adverse reactions, will limit the application of amrinone in the treatment of heart failure. These findings are relevant to the investigation of amrinone-like derivations presently being studied for the treatment of heart failure. Before their release, these agents will require careful evaluation and demonstration of a therapeutic action during maintenance therapy, together with a low incidence of adverse reactions.

Amrinone, a bipyridine derivative, has been shown to increase cardiac output with short-term use in patients with heart failure. Shown to be a positive inotropic agent, the clinical significance of this action is now controversial, and peripheral vasodilatation may play an important role in its effect on the intact circulation. Amrinone's biochemical effects have not been clearly defined, although an alteration of calcium ion influx may occur. Despite amrinone's beneficial short-term effects, the usefulness of maintenance therapy has yet to be convincingly demonstrated. Furthermore, disturbing reports of adverse effects with maintenance amrinone therapy have been published. Accordingly, this study was undertaken to examine the potential beneficial and adverse effects of orally given amrinone.

MATERIALS AND METHODS

Patients

Eleven male patients, with a mean age of 54 ± 14 years (range, 29 to 68 years) were entered into the study. Four additional patients who were unable to exercise long enough to satisfy study entry criteria were given amrinone on a compassionate basis and followed up clinically. The 11 patients who underwent exercise testing had been assigned New York Heart Association functional classifications 2 to 3 for dyspnea or fatigue. Heart failure was due to coronary artery disease in nine patients, to aortic insufficiency in one patient, and to dilated cardiomyopathy in one patient. Of the four patients not undergoing exercise, three had heart failure due to coronary artery disease and one had a dilated cardiomyopathy. Profiles for the 11 study participants undergoing exercise are summarized in Table I. The patient with a resting left ventricular ejection fraction of 66 percent had severe mitral regurgitation and three-vessel coronary artery disease demonstrated by cardiac catheterization. Resting biventricular dysfunction, which worsened after exercise, was clinically evident. In all patients, heart failure was present more than six months before study entry. Patients were required to have dyspnea or fatigue as an exercise endpoint on treadmill exercise and to be able to exercise at least eight minutes and not more than 16 minutes. Two consecutive platelet counts ≥150,000/μm were obtained. Patients were excluded from the study if angina limited their exercise ability or if heart failure was due to an obstructive or a restrictive cardiomyopathy. Grossly obese patients and those with severe pulmonary, renal, or liver impairment were excluded. Patients with severe ventricular arrhythmias, marked hypertension, or those taking disopyramide were not included. The study was approved by our University's Standing Committee on Human Research, and informed patient consent was obtained from all study participants.

Study Design

Baseline investigations consisting of a complete history and physical examination, hematologic and biochemical profiles, two treadmill exercise tests differing in exercise duration by no more than two minutes, an M-mode echocardiogram, and supine rest and symptom-limited exercise radionuclide ventriculography were obtained. Measurement of rest and maximal exercise oxygen consumption was obtained during treadmill exercise testing. Amrinone was dose-titrated, commencing at 100 mg three times a day. If adverse effects intervened, this dosage was decreased to 75 mg three times a day. If the platelet count decreased to 50,000 to 100,000/μm, amrinone was transiently reduced to 75 mg three times a day until
Table 1—Patient Profiles and Responses to Treadmill Exercise*

<table>
<thead>
<tr>
<th>Pt</th>
<th>Diagnosis</th>
<th>Medications</th>
<th>Amrinone, mg/day</th>
<th>Rest EF, %</th>
<th>Exercise Duration, sec</th>
<th>Maximal $\dot{V}$O$_2$, ml/min/kg</th>
<th>Anaerobic Threshold, ml/min/kg</th>
</tr>
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<tbody>
<tr>
<td>2</td>
<td>CAD</td>
<td>D, IDN</td>
<td>300</td>
<td>10</td>
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<td>Control: 23.6, Amrinone: 25.3</td>
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<tr>
<td>3</td>
<td>CCM</td>
<td>D, F, Sp</td>
<td>300</td>
<td>18</td>
<td></td>
<td>Control: 18.9, Amrinone: 18.1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CAD,MR</td>
<td>D, F, Sp, Pr</td>
<td>300</td>
<td>66</td>
<td></td>
<td>Control: 10.6, Amrinone: 14.3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>CAD</td>
<td>D, IDN, Sp, F</td>
<td>225</td>
<td>17</td>
<td></td>
<td>Control: 17.9, Amrinone: 14.8</td>
<td></td>
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<tr>
<td>6</td>
<td>CAD</td>
<td>D, IDN, Ox</td>
<td>300</td>
<td>35</td>
<td></td>
<td>Control: 19.8, Amrinone: 18.1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>CAD</td>
<td>F, IDN</td>
<td>225</td>
<td>31</td>
<td></td>
<td>Control: 15.4, Amrinone: 22.2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>AI</td>
<td>D, F, Sp</td>
<td>300</td>
<td>25</td>
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<td>Control: 20.3, Amrinone: 18.6</td>
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</tr>
<tr>
<td>9</td>
<td>CAD</td>
<td>D, F, Sp</td>
<td>225</td>
<td>11</td>
<td></td>
<td>Control: 16.6, Amrinone: 16.2</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td>25</td>
<td>Control: 541, Amrinone: 556</td>
<td>Control: 17.7, Amrinone: 18.3</td>
<td></td>
</tr>
<tr>
<td>± SD</td>
<td></td>
<td></td>
<td></td>
<td>18</td>
<td>Control: 140, Amrinone: 118</td>
<td>Control: 3.7, Amrinone: 3.5</td>
<td></td>
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</tbody>
</table>

*Abbreviations: AI = aortic insufficiency; CAD = coronary artery disease; CCM = congestive cardiomyopathy; EF = ejection fraction; MR = mitral regurgitation; D = digoxin; E = ethacrynic acid; F = furosemide; IDN = isosorbide dinitrate; Ox = oxprenolol; Pr = prazosin; Q = quinidine; Sp = spironolactone.

the count rose to >100,000/cu mm. If the platelet count dropped to <50,000/cu mm, amrinone therapy was discontinued and reinstituted when the platelet count rose to >100,000/cu mm. The dosage was increased to 150 mg three times a day after two weeks if exercise duration did not increase by at least two minutes and if adverse effects did not occur at the initial dosage, but not increased above 450 mg/day. Weekly hematologic and biochemical profiles were obtained during dose-titration and for the first four weeks of a stable dose of amrinone. Other medications were not altered during the time of the amrinone therapy. All investigations were repeated at the end of the four weeks of maintenance amrinone therapy. In addition, radionuclide ventriculography was repeated after three months of amrinone withdrawal in two patients and after two weeks of amrinone withdrawal in five patients.

Exercise Testing and Measurement of Oxygen Consumption

Patients underwent symptom-limited graded treadmill exercise testing using a modified Naughton protocol. Exercise testing was performed one to two hours after the last dose of medication. Upright cuff blood pressure and heart rate were determined at rest, at the end of each stage of exercise, and immediately after exercise. Heart rate was monitored by a single ECG lead. The reason for terminating exercise was recorded. Oxygen consumption was measured at rest and at 15-second intervals throughout exercise using a Morgan Dragon graphic computerized exercise testing system. The oxygen and carbon dioxide analyzers were calibrated daily. Maximal oxygen consumption was considered achieved when oxygen consumption increased by <1 ml/min/kg over that consumed during the preceding workload. Anaerobic threshold was determined visually from the graphic display of the ventilatory gas exchange ratio ($\dot{V}$CO$_2$/ $\dot{V}$O$_2$). If necessary, displays of the minute ventilation ($V_e$) and $\dot{V}$CO$_2$ were used. The severity of heart failure was classified from A to D, depending on maximal oxygen consumption.

Radionuclide Ventriculography

Supine equilibrium radionuclide ventriculography was performed at rest and during symptom-limited exercise. Exercise began at a workload of 10 W and was increased successively by 10 W every three minutes until the termination of exercise. After in vivo labeling of red blood cells with 20 μCi of technetium 99m pertechnetate, cardiac scintigraphy was performed in the left anterior oblique position that best isolated the left ventricle. All images were collected for two minutes using a conventional Anger scintillation camera equipped with a high-sensitivity, parallel-hole collimator interfaced to a dedicated medical computer system (Ohio Nuclear model 460). Data were collected in a continuous ECG mode, with 16 frames spanning the cardiac cycle. Data analysis was done using a mobile medical computer (Ohio Nuclear model 550). Left ventricular ejection fraction was derived by triplicate manual identification of background and left ventricular regions of interest. With this method, radionuclide left ventricular ejection fraction correlated closely with biplane contrast angiography ($r = 0.92$). Interobserver and intraobserver variance, determined by analysis of variance, was 4 percent and 4 percent, respectively. Left ventricular volumes were calculated using a count-based, nongeometric method without individual attenuation correction.

Radiculone and contrast angiography correlated well over a broad range of values for left ventricular end-diastolic volume ($r = 0.95$) and end-systolic volume ($r = 0.97$).

Echocardiography

M-mode echocardiography was obtained with an E for M echocardiograph using standard techniques. Left ventricular end-diastolic and end-systolic dimensions were measured in a blinded fashion by one experienced observer. Paradoxic septal motions were not measured.

Statistical Analysis

Two-way analysis of variance was used to determine the significance of changes induced by amrinone on variables derived during radionuclide ventriculography. If significance was detected, Tukey's multiple comparison test was used to compare means. The Student's $t$ test for paired samples was used to examine the significance of changes occurring from rest to exercise in all variables measured. Probability of 5 percent or lower was considered significant.

Results

Of the initial 11 study patients, two did not undergo treadmill exercise testing and four did not undergo radionuclide ventriculography during maintenance amrinone therapy (Tables 1 and 2). Treadmill exercise testing was not obtained due to sudden death in one patient and the development of exertional angina in another patient. Of the remaining nine patients, one died suddenly and one had a syncopal episode before radionuclide ventriculography could be obtained. The mean amrinone dosage received was 292 ± 70 mg/day. After the initial dose, amrinone was increased to

CHEST / 86 / 3 / SEPTEMBER, 1984

395
450 mg/day in four patients due to an unsatisfactory therapeutic response. This increase was maintained in two patients, while in two patients adverse effects necessitated a reduction to 300 mg/day, with subsequent discontinuation in one. No dosage increase was attempted in six patients due to adverse effects at the initial dose, with subsequent discontinuation of amrinone in two. The initial dose was maintained in three patients due to a satisfactory therapeutic response.

**Heart Rate, Blood Pressure, and Ambulatory ECG Monitoring**

During upright treadmill evaluation (mean ± SD), the control heart rate increased from 79 ± 13 beats/min at rest to 120 ± 20 beats/min during exercise. No significant change occurred with amrinone therapy (rest 86 ± 14 beats/min, exercise 128 ± 25 beats/min). Control systolic blood pressure increased from 114 ± 17 mm Hg at rest to 141 ± 24 mm Hg during exercise, and no change occurred with amrinone therapy (rest 112 ± 15 mm Hg, exercise 142 ± 27 mm Hg). Control rate-pressure product increased from 90 ± 18 mm Hg/min × 10⁶ at rest to 175 ± 60 mm Hg/min × 10⁶, which remained similar during amrinone therapy (rest, 97 ± 16 and exercise, 185 ± 65 mm Hg/min × 10⁶). During supine evaluation, resting heart rate increased significantly (p < 0.05) from 84 ± 16 beats/min at control to 92 ± 16 beats/min with amrinone therapy. No other differences were observed in the supine position among control, amrinone therapy, and amrinone therapy withdrawal values. Four patients underwent 24-hour ambulatory Holter monitoring before and after receiving amrinone. During the control period, all patients had premature ventricular depolarizations, and three patients had episodes of ventricular tachycardia. No differences were noted after the institution of amrinone therapy.

**Exercise Performance and Oxygen Consumption**

Exercise duration did not change significantly with amrinone therapy (Table 1). Compared to the control values, two patients had a decrease and two patients had an increase of 10 percent or more in exercise duration. Exercise was terminated due to dyspnea in seven patients and to fatigue in two patients. No change occurred with amrinone therapy. Subjectively, three patients stated that they felt their quality of life had improved. Resting oxygen consumption was 4.9 ± 1.2 ml/min/kg during the control period and 4.9 ± 1.5 ml/min/kg with amrinone therapy. Maximal oxygen consumption did not change significantly with amrinone therapy. During the control period, three patients achieved true maximal oxygen consumption (defined as an increase of <1 ml/min/kg from the previous workload); seven patients achieved this level of oxygen consumption with amrinone therapy. Anaerobic threshold was reached in all patients but remained unchanged by amrinone therapy. Functional class was determined from maximal oxygen consumption. During the control period, two patients were functional class A, five patients were functional class B, and two patients were functional class C. No change in this functional class occurred during therapy with amrinone.

**Left Ventricular Function and Volumes**

For the seven patients who underwent both rest and exercise radionuclide ventriculography (Fig 1 to 3), resting left ventricular ejection fraction during the control period ranged from 10 to 66 percent (mean 27 ± 20 percent); no significant change occurred with amrinone therapy (mean 28 ± 19 percent, range 10 to 64 percent). Maximal supine exercise ejection fraction ranged from 8 to 66 percent (mean 30 ± 21 percent); no significant change occurred with amrinone therapy (mean 29 ± 20 percent, range 13 to 66 percent). Two patients had an exercise-induced increase of 5 percent (absolute value) or more, and five patients had no significant change. Following amrinone withdrawal, rest (mean 27 ± 17 percent, range 9 to 64 percent) and exercise (mean 28 ± 19 percent, range 14 to 64 percent) ejection fraction values were unchanged compared to values obtained before and during amrinone therapy. Rest and exercise end-diastolic and end-systolic volume indexes (Fig 1) did not change significantly with amrinone therapy when compared to control and postwithdrawal indexes. The slight changes noted from rest to exercise in these parameters were not significant. Rest and exercise stroke volume index and cardiac index (Fig 2) did not change significantly with

<table>
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<th>Highest Dose Reached, mg/day</th>
<th>Final dose, mg/day</th>
<th>Adverse Effects</th>
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<tbody>
<tr>
<td>Pt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>450</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>300</td>
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</tr>
<tr>
<td>3</td>
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<td>300</td>
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<td>6</td>
<td>300</td>
<td>Palpitations</td>
</tr>
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<td>7</td>
<td>300</td>
<td>Thrombocytopnea</td>
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<td>8</td>
<td>300</td>
<td>Sudden death</td>
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<td>9</td>
<td>450</td>
<td>Syncpe, depression</td>
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<tr>
<td>10</td>
<td>Discontinued</td>
<td>Sudden death</td>
</tr>
<tr>
<td>11</td>
<td>300</td>
<td>Thrombocytopnea, amrinone discontinued due to exertional angina</td>
</tr>
<tr>
<td>12</td>
<td>Discontinued</td>
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<tr>
<td>13</td>
<td>Discontinued</td>
<td>Severe nausea, vomiting</td>
</tr>
<tr>
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<td>None</td>
</tr>
<tr>
<td>15</td>
<td>300</td>
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</table>
Figure 1. Effect of amrinone therapy and withdrawal on end-systolic volume index (ESVI) and end-diastolic volume index (EDVI) at rest (R) and during exercise (E). No significant differences occurred either with amrinone or after amrinone withdrawal. No significant changes occurred in any parameters from rest to exercise. Values are mean ± SEM.

Figure 2. Effect of amrinone therapy and withdrawal on stroke volume index (SVI) and cardiac index (CI) at rest (R) and during exercise (E). No significant differences occurred either with amrinone or after amrinone withdrawal. Cardiac index increased significantly (p<0.01) from rest to exercise at control and with amrinone due to an increase in heart rate. Values are mean ± SEM.

Figure 3. Effect of amrinone on resting M-mode echocardiographic dimensions. Although a trend to reduce dimension was noted, the change was not significant. Values are mean ± SEM.

Amrinone therapy compared to values of the control and after withdrawal of amrinone. Changes from rest to exercise in stroke volume were not significant. Cardiac index increased (p<0.01) from rest to exercise during control and with amrinone therapy. M-mode echocardiograms were obtained in six of the seven patients who underwent radionuclide ventriculography. Although end-diastolic and end-systolic dimensions (Fig 3) decreased slightly in five patients with amrinone therapy, these changes were not significant.

Adverse Effects

Two patients died during the course of this study. Of the remainder, only four patients did not experience an adverse reaction. In four patients, amrinone therapy had to be discontinued, and in four the dosage was reduced to control an adverse effect. Although a fall in platelet count of 50,000/cu mm or more occurred in ten of the patients, thrombocytopenia (defined as a platelet count of <100,000/cu mm) occurred in five patients. With one exception, the platelet count returned to normal with reduction in the amrinone dose alone. One patient with a control platelet count of 300,000/cu mm had a fall to 30,000/cu mm after 14 days of therapy. Amrinone therapy was discontinued, and the platelet count dropped further to 18,000/cu mm before rebounding to >100,000/cu mm. Nasal and rectal bleeding occurred. Subsequent investigation revealed the presence of a folic acid deficiency. The only indication of megaloblastic anemia before institution of amrinone was an increase in the mean corpuscular volume to 113 fl. Gastrointestinal (GI) symptoms occurred in four
patients. In three of the patients, this was a mild influenza-like illness; it was not possible to determine whether amrinone was directly related. In one patient, however, amrinone therapy had to be stopped because of severe G1 upset.

Of the two patients who died suddenly, one died 18 hours after institution of amrinone and the second died one day after amrinone was increased to 450 mg/day. Another patient experienced a syncopal episode which resulted in a motor vehicle accident one week after the amrinone dosage was increased to 450 mg/day. Frequent premature ventricular depolarizations were observed upon admission to hospital, and procainamide therapy was begun while continuing amrinone therapy. Due to increased mental depression, administration of both agents was discontinued, with improvement in the patient's condition. One patient had exertional angina two weeks after commencing therapy with amrinone; he was withdrawn from the study when a reduction in the amrinone dose failed to change the pattern of angina.

**DISCUSSION**

*Effects of Amrinone on Functional Capacity*

Contrary to earlier investigations, the present study failed to demonstrate significant symptomatic improvement or an increase in exercise capacity. This lack of beneficial effect occurred despite the use of an open trial design in which placebo effect could not be assessed. Also, patients in this study demonstrated mainly mild-to-moderate cardiac failure, providing a study population with less irreversibly damaged myocardium and presumably more contractile reserve. A positive inotrope would be expected to exert a more powerful action in such patients. Recently, DiBianco et al. reported preliminary results from a multicenter, double-blind, placebo-controlled study in which amrinone was found to be unhelpful in heart failure of varying severity. In that study, exercise duration was not altered, and symptoms of heart failure remained unchanged during the randomized portion of the trial. Moreover, withdrawal of amrinone therapy was unassociated with any deterioration in symptoms. Why earlier investigations demonstrated beneficial effects on functional capacity is not clear. Possibly, patient motivation improved with the use of the open study designs used. In addition, a training effect may have led to improved exercise capacity in these patients. Such factors may have played a role in the prerandomization findings of DiBianco et al., who noted that amrinone prolonged exercise duration before but not after the randomization. Patients entering the present study demonstrated only a mild-to-moderate functional disability and were fully ambulatory prior to study entry. Study participation was less likely to result in an increase in motivation or physical activity.

Besides the lack of change in functional capacity, we were unable to demonstrate an improvement in maximal oxygen consumption with the amrinone therapy. Again, these results contrast with reports from other investigators. Although the measurement of oxygen consumption provides a quantitative description of peripheral oxygen utilization, it does not permit separation of drug effect from physical conditioning, and both may result in an increase in oxygen extraction. The limitation of measuring oxygen consumption during symptom-limited exercise is apparent with this study; only three patients were able to reach their maximal level of oxygen consumption prior to receiving amrinone therapy. Consequently, a pharmacologic effect on oxygen uptake may not be differentiated from other factors which may potentially alter oxygen consumption. The failure of amrinone therapy to alter this parameter is evidence of its lack of effect on left ventricular function. Measurement of anaerobic threshold which was reached by all our patients provided a more satisfactory parameter by which drug effect was measured. Again, this was unchanged by amrinone therapy.

An important consideration when using cardiotonic or vasodilatory agents is the distribution of additional blood volume which may result from improved cardiac output. For example, greater blood flow may not necessarily occur to the skeletal muscle groups during exercise. This could account for the lack of improvement in oxygen consumption and exercise duration in some studies using short-term amrinone administration. Even if the appropriate distribution of blood volume did occur, a time lapse may be required to permit physical conditioning and/or improved oxygen extraction to occur.

*Effects of Amrinone on Left Ventricular Function*

Most short-term studies have shown amrinone to be associated with improved left ventricular performance. Ventricular filling pressure decreases and cardiac index increases. Despite these findings, it has not yet been clearly demonstrated that amrinone's short-term beneficial hemodynamic effect persists with maintenance therapy. In this regard, it has been recently shown that short-term response to antifailure medications may not correctly predict these agents' long-term actions. In agreement with another study the results of the present investigation would suggest that maintenance amrinone therapy does not exert a clinically beneficial action on left ventricular function either at rest or during exercise.

In keeping with another report, discontinuation of amrinone therapy did not result in deterioration of either resting or exercise left ventricular function. This finding was in keeping with the lack of change in left ventricular function observed during therapy with
amrinone in the present study. We can offer no obvious explanation for the difference between our results and those of a previous study of patients with severe heart failure in which a deterioration in left ventricular function was noted upon withdrawal of amrinone therapy. Possibly in the presence of severe left ventricular dysfunction, the vasodilatory effect of amrinone is more important than its inotropic action for improved function. 

The lack of change in mean resting M-mode echocardiographic dimensions in this study corresponded to results of DiBianco et al. It is of interest that five of the six patients measured had a slight reduction in end-systolic and end-diastolic dimensions following amrinone therapy. This suggestion of improved left ventricular function was surprising when compared to the radionuclide findings, which showed no improvement in function. Due to regional asynery in patients with coronary artery disease, echocardiography is regarded as a less reliable method of detecting ventricular size changes. It is possible that a regional left ventricular response due to amrinone was not detected by measuring global ejection fraction.

The rise in resting heart rate with amrinone during supine radionuclide ventriculography remains unexplained; this may be an incidental finding. Unless amrinone exerts a direct positive chronotropic effect, this response would be unexpected from an agent capable of improving left ventricular hemodynamics.

Adverse Effects and Amrinone Therapy

The high incidence of both mild and severe adverse reactions encountered in this study and others does not speak favorably for the routine use of long-term amrinone therapy. Although the two sudden deaths and one syncopal episode could not be definitely related to the use of amrinone in this population of high-risk patients, the events occurred shortly after commencing therapy or increasing the amrinone dosage. Thrombocytopenia was a regular finding. In all but one patient, who was later found to have a folic acid deficiency, the platelet count rebounded with either continued treatment or a dosage reduction. The patient with folic acid deficiency demonstrated a marked decline in platelet count and may have been susceptible to amrinone due to a shortened platelet survival.

One patient with frequent premature ventricular depolarizations during control underwent several 24-hour ambulatory recordings before and during amrinone therapy with no change in the arrhythmia pattern detected.

Limitations of This Study

This study represents a preliminary assessment of maintenance oral amrinone in ambulatory patients presenting with mild-to-moderate functional disability due to heart failure. The study was an open investigation and may have been affected by patient and investigator bias. Every attempt was made to ensure that patients were fully ambulatory and familiar with the exercise tests before study participation in order to prevent an inappropriate change in exercise capacity due to either learning or physical conditioning. The use of radionuclide-derived left ventricular ejection fraction function in the presence of heart failure has recently been questioned. In a study by Firth et al., the only significant correlation between invasively determined hemodynamic parameters and radionuclide ventriculography was between pulmonary capillary wedge pressure and end-diastolic volume. Although radionuclide changes were generally less marked, the mean values for invasive and radionuclide measurements changed significantly and in a similar direction. These findings suggest that radionuclide measurements are less sensitive than invasive measurements for the detection of pharmacologic effects in patients with left ventricular dysfunction. However, radionuclide ventriculography has been a noninvasive standard for left ventricular function for some years and continues to be used as a measure of drug effect.

Clinical Implications

Amrinone’s favorable short-term hemodynamic effects have been clearly documented by previous investigators. This study examined the effects of amrinone during maintenance therapy and found no improvement in exercise or in oxygen utilization. No improvement was noted in rest or exercise left ventricular function. Even if amrinone afforded some beneficial effect not detected by this study, it would be largely obviated by the high incidence of adverse effects. Indeed, this low therapeutic index has led to the recent withdrawal of oral amrinone from further clinical investigation. A derivative of amrinone, Milrinone, presently being investigated for clinical use, appears to have fewer adverse effects. The results of the present study would suggest the need for a careful examination of potential beneficial and adverse effects of this new agent before its release for use in the treatment of heart failure. Evaluation using a double-blind, placebo-controlled study involving patients with varying degrees of severity of left ventricular function will be required.

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