Beneficial Effects of Amrinone-Hydralazine Combination on Resting Hemodynamics and Exercise Capacity in Patients with Severe Congestive Heart Failure

LEWIS A. SIEGEL, M.D., EDMUND KEUNG, M.D., STEVEN J. SISKIND, M.D., ROBERT FORMAN, M.D., HALBERT FEINBERG, M.D., JOEL STROM, M.D., DORIS EFSTATIHKIS, R.N., EDMUND H. SONENBLICK, M.D., AND THIERRY H. LEJEMTEL, M.D.

SUMMARY The effects of combined administration of low-dose amrinone (100 mg) and hydralazine (75–100 mg) on resting hemodynamics and exercise capacity were studied in nine patients with severe congestive heart failure. Five patients were in New York Heart Association (NYHA) functional class IV and four were in class III. Cardiac index increased from 1.92 ± 0.36 l/min/m² (mean ± SD) to 3.23 ± 0.63 l/min/m² (p < 0.001); pulmonary wedge pressure decreased from 23.6 ± 4.1 to 15.1 ± 4.7 mm Hg (p < 0.001) and systemic vascular resistance from 1666 ± 210 to 1063 ± 189 dyn-sec-cm⁻¹ (p < 0.001). Mean arterial pressure and heart rate were not significantly changed. The onset of action ranged from 30–150 minutes and the duration of action from 4–6 hours after oral administration. When compared with amrinone alone (100 mg) or hydralazine alone (75–100 mg), the increase in stroke volume index and the decrease in pulmonary wedge pressure induced by the combined therapy were significantly greater (p < 0.01). The hemodynamic benefits at rest were associated with an improvement in NYHA functional class in all but one patient during chronic therapy. Exercise capacity (Naughton protocol) increased during the first week of therapy from 6.1 ± 4.3 to 10.6 ± 5.3 minutes (p < 0.01). This increase in exercise capacity was sustained or further improved at 3 weeks. Thus, the hemodynamic effects of low-dose amrinone can be amplified by simultaneous administration of a vasodilator such as hydralazine in patients with severe congestive heart failure. This combined therapy results in a substantial and sustained improvement in functional class and exercise capacity.

AMRINONE, a recently synthesized, nonglycosidic, nonadrenergic inotropic agent, has been shown to increase contractile force in a cat papillary muscle preparation and the instrumented dog heart. In man, the positive inotropic action of i.v. amrinone has been reflected by an increase in rate of left ventricular pressure development of the failing heart, accompanied by a decrease in left ventricular filling pressure and an increase in cardiac output. Sustained beneficial effects on cardiac and renal function have been reported in patients with refractory heart failure given oral amrinone at doses of 300–900 mg/day. However, chronic therapy has been complicated by the occurrence of thrombocytopenia, which has required withdrawal of amrinone in a few patients despite their marked clinical improvement. The thrombocytopenia appears to be dose-related, generally modest in degree, unaccompanied by depression of megakaryocytes, and readily reversible with reduction of drug dosage. Moreover, it has not occurred in patients treated with a daily dose of 300 mg or less of amrinone.

In patients with chronic congestive heart failure, the hemodynamic benefits of amrinone seem to result from a positive inotropic action with low doses and a direct arterial vasodilatory effect with higher doses. Because thrombocytopenia may limit the use of higher doses of amrinone, it was theorized that a combined therapy using low doses of amrinone and a vasodilator such as hydralazine could be beneficial in patients with chronic congestive heart failure refractory to conventional therapy. The present study was therefore undertaken to assess the hemodynamic effects of low doses of amrinone administered alone and in combination with hydralazine. The effect of this combination of drugs was evaluated to assess whether beneficial hemodynamic effects resulted and whether they were accompanied by an improvement in exercise performance.

Methods

Subjects

Five men and four women with chronic congestive heart failure and an average age of 54 years (range 20–74 years) were studied. Six patients had ischemic heart disease with resultant congestive failure as documented by past myocardial infarctions or coronary arteriograms. No patient had angina. Two patients had cardiomyopathy of unknown etiology and one had a postpartum cardiomyopathy. No patient had hypertension or a recent myocardial infarction at the time of the study. The duration of heart failure varied from 6 months to 6 years. All patients were moderately or severely restricted in activity despite treatment with digitalis and diuretics, and were
clinically stable (New York Heart Association) [NYHA] functional class III or IV). All patients were in sinus rhythm.

The patients were admitted to the hospital 4 days before hemodynamic evaluation and continued to take their usual doses of digoxin and diuretics throughout the study. Serum digoxin levels were within therapeutic range in all patients (average 1.4 ng/ml, range 0.9–1.8 ng/ml). A dietary regimen containing 2 g of sodium per day was prescribed. Ejection fraction was determined at rest by use of gated nuclear scanning and averaged 19% (range 12–25%).

Hemodynamic Measurements

After 36 hours of bed rest, right-heart catheterization was performed using a flow-directed, balloon-tipped thermodilution catheter (Gould Laboratories). Mean pulmonary arterial, pulmonary capillary wedge and right arterial pressures were recorded on a photographic recorder (Electronics for Medicine). Cardiac output was determined in triplicate by thermodilution techniques using iced 5% dextrose in water, with less than 10% variation. Cardiac output was computed with a bedside computer (Gould Laboratories Model SP 1425) and was confirmed periodically by appropriate integration of recorded curves. Systemic arterial pressure was measured by two observers using standard cuff techniques. Mean arterial pressure (MAP) was taken as diastolic plus one-third of the pulse pressure. Derived hemodynamic variables were calculated as follows:

\[ CI = \frac{CO}{BSA} \]
\[ SVI = 1000 \times \frac{CI}{HR} \]
\[ SVR = 80 \left( \frac{MAP - MRAF}{CO} \right) \]

where CI = cardiac index (l/min/m²), CO = cardiac output, BSA = body surface area, SVI = stroke volume index (ml/m²), HR = heart rate, SVR = systemic vascular resistance (dyn-sec-cm⁻⁵), and MRAF = mean right atrial pressure. The control cardiac index was less than 2.5 l/min/m², while the pulmonary wedge pressure exceeded 15 mm Hg in all patients. The ECG was monitored continuously from a single lead throughout the study.

Assessment of Exercise Capacity

Exercise capacity was determined on a treadmill according to the protocol of Naughton et al. Exercise was performed in an air-conditioned laboratory with the temperature maintained at 23–25°C. The heart rate and ECG were monitored from a standard V₁ lead. Exercise was stopped when the patient experienced shortness of breath, severe leg pain or extreme fatigue. The exercise tests were performed 24 hours apart to determine reproducibility and were repeated during the first and third week of chronic therapy.

Drug Administration

Amrinone alone, hydralazine, and the combination of amrinone and hydralazine were administered on separate days in variable order. Three patients received the sequence as amrinone, hydralazine and then both. For the next three, the sequence was hydralazine, amrinone and then both, while the last three patients received hydralazine, the combination and then amrinone. Patients were evaluated in the postprandial state. The drug was administered after two similar sets of control measurements were obtained 30 minutes apart. Hemodynamic values were measured at 30-minute intervals for 2 hours and then hourly until they returned to control values. Each patient received 100 mg of oral amrinone, which resulted in an average dose of 1.65 mg/kg (range 0.9–2.4 mg/kg). Oral hydralazine was administered to patients at a dose of 75 mg. Patients who did not increase their cardiac index by more than 30% were given 100 mg 6 hours later. On the day of combined therapy, each patient received 100 mg of amrinone and 75 or 100 mg of hydralazine. After the acute hemodynamic study was completed, chronic therapy was initiated and amrinone and hydralazine were given every 8 hours. Patients were evaluated clinically every week and exercise capacity was determined during the first and third week of chronic therapy.

Consent Form

The nature, potential benefits and possible risks of the drug were explained to all patients, who then gave informed written consent. The treatment protocol was approved in advance by the Committee on Clinical Investigation of the Albert Einstein College of Medicine.

Statistical Analysis

Maximal hemodynamic changes were tested for significance using the paired t test. Comparisons of all cardiac indexes were performed using analysis of covariance. Each patient was observed under three treatment conditions: amrinone, hydralazine, and amrinone plus hydralazine. The criterion score for each treatment was the cardiac index determined after administration of the drug. Using the analysis of covariance model, criterion scores were statistically adjusted before analysis, using a single covariate under each treatment, which was the patient’s baseline index immediately before the treatment. This covariance adjustment was made to reduce random sampling errors in the criterion scores that could be attributed to random differences between baseline conditions.

The time course of the indexes examined was tested first using a within-subjects analysis of variance, with each subject being observed at all points along the time course. The first period of the time course was a control or baseline level. Subsequently, the mean values at each time period were compared with the baseline mean using Dunnet’s t statistic, a procedure for comparing a series of means with a control.
Table 1. Maximal Hemodynamic Effects of 100 mg of Oral Amrinone

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Mean 65.5 ± 21.6 79.4 ± 7.5 79.4 ± 7.5 24.4 ± 2.87 24.4 ± 19.1 1653 ± 1201

*p* NS NS < 0.001 < 0.001 < 0.001

Abbreviations: NR = heart rate; MAP = mean arterial pressure; CI = cardiac index; PCW = pulmonary capillary wedge pressure; SVR = systemic vascular resistance; C = control; A = amrinone.

Results

Acute Hemodynamic Effects

The maximal response of the nine patients to 100 mg of oral amrinone is given in table 1. Cardiac index increased from 1.95 ± 0.34 to 2.87 ± 0.48 l/min/m² (p < 0.001), mean pulmonary wedge pressure decreased from 24.4 ± 3.0 to 19.1 ± 3.1 mm Hg (p < 0.001) and systemic vascular resistance decreased from 1653 ± 223 to 1201 ± 226 dyn/sec/cm⁻⁴ (p < 0.001). Heart rate and mean arterial pressure were not changed significantly.

The maximal hemodynamic effects of hydralazine are given in table 2. The dose of hydralazine was 100 mg for six patients and 75 mg for three patients. Cardiac index increased from 1.92 ± 0.32 to 2.67 ± 0.54 l/min/m² (p < 0.001), pulmonary wedge pressure decreased from 23.6 ± 4.4 to 21.1 ± 5.2 mm Hg (p < 0.001) and systemic vascular resistance decreased from 1670 ± 235 to 1257 ± 231 dyn/sec/cm⁻⁴ (p < 0.001). Mean arterial pressure decreased from 80.5 ± 4.9 to 78.6 ± 5.3 mm Hg, but this change was not significant.

The maximal hemodynamic response induced by the combination of amrinone and hydralazine is given in table 3 for the nine patients. At the time of peak effect, which occurred at 90 minutes (range 30–150 minutes), cardiac index increased from 1.92 ± 0.36 to 3.23 ± 0.63 l/min/m² (p < 0.001), pulmonary wedge pressure decreased from 23.6 ± 4.1 to 15.1 ± 4.7 mm

Table 2. Maximal Hemodynamic Effects of Oral Hydralazine

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Mean 91.0 ± 21.2 80.5 ± 78.6 1.91 ± 2.67 23.6 ± 21.1 1670 ± 1257

*p* NS NS < 0.001 < 0.001 < 0.001

Abbreviations: HR = heart rate; MAP = mean arterial pressure; CI = cardiac index; PCW = pulmonary capillary wedge pressure; SVR = systemic vascular resistance; C = control; H = hydralazine.
were similar. Hg (p < 0.001) and the systemic vascular resistance decreased from 1666 ± 210 to 1063 ± 189 dyn/sec/cm² (p < 0.001). No significant change in heart rate or mean arterial pressure was observed.

The time course of the mean hemodynamic changes in cardiac index and pulmonary capillary wedge pressure after combined administration of amrinone and hydralazine is shown in figure 1. Cardiac index was significantly increased for 4 hours and pulmonary capillary wedge pressure was significantly decreased for 5 hours after combined therapy.

Control hemodynamic values for the nine patients were similar on each of the three successive days of the hemodynamic study. The combined administration of amrinone and hydralazine induced changes that were significantly greater than either therapy alone (fig. 2). The increase in stroke volume index on combined therapy is 72.7 ± 28.0%, which is significantly higher than the values obtained with amrinone alone, 49.5 ± 24.3% (p < 0.01), or the increase produced by hydralazine alone, 36.9 ± 20.5% (p < 0.01). Similarly, the reduction in wedge pressure in combined therapy was greater than with amrinone alone (37.4 ± 15.0% vs 22.0 ± 4.9%, p < 0.01) or with hydralazine (37.4 ± 15.0% vs 11.8 ± 7.6%, p < 0.01). On the basis of a higher stroke volume and a lower wedge pressure, the improvement in myocardial performance with combined therapy was greater than with either therapy alone (fig. 3).

Maintenance Therapy

Eight of the nine patients studied acutely were maintained on chronic therapy with amrinone and
Hydralazine. However, patient 2 experienced very severe and persistent headaches within 48 hours of the onset of therapy. When hydralazine was discontinued, headaches stopped.

All eight patients were followed for at least 3 weeks. All have experienced a significant subjective amelioration of exertional fatigue and dyspnea. The mean reduction in body weight of 2.4 kg (range 1.5–3 kg) that occurred during hospitalization has been maintained outside the hospital on similar (five patients) or on smaller doses of diuretics (three patients). Functional status improved in all but one patient. The functional improvement tended to be more consistent in patients who were initially in NYHA class III, while patients initially in NYHA class IV had a more variable or blunted response (fig. 4). No overt adverse effect was observed clinically; in particular, no patient had thrombocytopenia. The mean platelet count for the eight patients was 234,000 ± 63,000 per mm$^3$ before therapy and 235,000 ± 77,000 per mm$^3$ after 3 weeks. Although most of the patients experienced an increase in appetite during treatment with amrinone and hydralazine, two patients, despite marked improvement, experienced mild anorexia.

Exercise capacity was determined during the first and third week of therapy in all patients except patient 3, in whom a brain tumor was diagnosed during the second week of therapy. The improvement in exercise performance is illustrated in figure 4. Control exercise capacity was established in duplicate just before the patients began taking the drug on a chronic basis. During the first week of therapy, the mean exercise tolerance increased from 6.1 ± 4.3 to 10.6 ± 5.8 minutes ($p < 0.01$). Further improvement in exercise...
duration was noted in five patients during the third week. The increase in exercise capacity tended to be more consistent and greater in patients in NYHA class functional III than in patients who were initially in class IV. Among these latter four patients, only one had an increase in exercise tolerance comparable to that in the former patients.

Discussion

Amrinone is a new inotropic drug that increases contractility in the isolated myocardium of the cat and the intact heart of the dog.1, 2 In man, these inotropic effects are characterized by an increase in the rate of left ventricular pressure development and cardiac output, accompanied by a decrease in ventricular filling pressures.3, 4 Vasodilatation also occurs as peripheral vascular resistance falls, which may reflect a direct action of the drug as well as secondary a withdrawal of peripheral sympathetic tone which is augmented in heart failure. The drug is of special interest because it does not affect the myocardial Na+ - K+-stimulated ATPase, which is the putative site of digitalis glycoside action, nor does it affect the adenylcyclase system, which is the biochemical pathway for the action of catecholamines.1, 2 Further, adrenergic blockade does not inhibit its effects. Amrinone is effective both orally and parenterally.7

In a previous report,8 the effectiveness of orally administered amrinone was demonstrated in 10 patients with very severe congestive heart failure. Despite prior therapy, including the use of digitalis glycosides, diuretics and vasodilators, the patients remained severely disabled. The average dose of amrinone was 4.3 mg/kg (range 0.9–4.3 mg/kg). Hemodynamic improvement at rest was characterized by increases in cardiac output and ejection fraction and decreases in ventricular filling pressures. Subsequent study showed that these initial salutary hemodynamic benefits were accompanied by an improvement in exercise tolerance (unpublished data).

The enthusiasm for these promising initial results has been hampered by the development of thrombocytopenia in 10–15% of patients receiving amrinone on a chronic basis (unpublished observations). The thrombocytopenia has been characterized by a moderate decline in platelets occurring generally 2–4 weeks after drug administration. There has been no evidence of bone marrow depression or an immunologic mechanism.8

With these results in mind, the present study was initially planned to explore the usefulness of lower doses of amrinone in the therapy of congestive heart failure. In an attempt to amplify the beneficial hemodynamic effects of the drug, hydralazine was also used for its vasodilating action. Hydralazine offered the additional benefits of renal arteriolar vasodilatation.9–11

In the present study, the beneficial effects of lower doses of amrinone combined with hydralazine on cardiac and exercise performance were evaluated in nine patients with severe congestive heart failure. The addition of hydralazine to amrinone resulted in a more consistent and greater improvement in cardiac output and a decrease in pulmonary wedge pressure. The only patient (no. 2) who failed to demonstrate a clear advantage of the combination of amrinone and hydralazine experienced a drop in left ventricular filling to 4 mm Hg, which probably prevented an increase in cardiac output. Such excessive reduction in left ventricular filling pressure has been observed occasionally when amrinone was used alone.4

Although the patients in the present report were initially symptomatic despite optimal doses of digitalis and diuretics, they were not entirely comparable to those described in our previous report,9 as their exercise tolerance was not as severely limited and they showed beneficial responses to afterload-reducing therapy. This may explain why six of the nine patients showed a satisfactory response to amrinone alone at doses below 2 mg/kg, whereas these doses were not generally effective in the previously reported group of patients.5

At rest, the hemodynamic effectiveness of the combination of amrinone and hydralazine was greater than that of either drug alone (fig. 3). The significant improvement in exercise tolerance is even more important. Average exercise duration significantly increased from 6.1–10.6 minutes. In patients initially in NYHA class III, the increase was from 11 to 18 minutes, and their clinical status improved to either class I or II (fig. 4). These improvements in exercise tolerance and clinical status that occurred with the combination of amrinone and hydralazine are greater than those reported with the use of vasodilators alone in patients with similar functional disability.12–17 However, as the patients were not compared with a control group, we are unable to evaluate the possible contribution of a placebo effect on the results. The initial improvement in exercise tolerance in the first week of therapy was followed by further improvement. This may reflect a training effect that occurred during therapy, which can then be sustained on a more chronic basis.

In conclusion, amrinone and hydralazine have been combined effectively for the treatment of severe congestive heart failure. A lower dose of amrinone has been shown to be effective in increasing cardiac output and lowering ventricular filling pressures and these salutary effects have been amplified by hydralazine. In addition, hemodynamic improvement at rest is accompanied by substantial improvement in exercise tolerance. However, a larger study for a longer period of time is required for evaluating the long-term results and possible side effects of low-dose amrinone combined with hydralazine therapy.

References

Treatment of Variant Angina with Drugs:
A Survey of 11 Cardiology Institutes in Japan

EIICHI KIMURA, M.D., AND HIROSHI KISHIDA, M.D.

SUMMARY  Data from 11 cardiology institutes in Japan were examined to determine the effectiveness of drug therapy, especially with calcium antagonists, on variant angina. The subjects were 243 males and 43 females, most of whom were 40–59 years old. Coronary artery lesions were found in 92 of 162 patients (56.7%) in whom cinecoronary arteriograms were done. The efficacy rates of nifedipine, diltiazem and verapamil were 94.0%, 90.8% and 85.7%, respectively. Regardless of the presence or absence of organic coronary artery lesions, the drugs were effective in 92.3% of the patients with normal or nearly normal coronary arteries and in 82.6% of those with stenosis of more than 50% of the luminal diameter. These findings suggest that the drugs are effective through their antispasmodic actions.

VARIANT ANGINA pectoris, as described by Prinzmetal et al. was considered to be a rather rare syndrome. However, with the introduction of devices such as the long-term continuous recording electrocardiograph and the pocket electrocardiograph, it has become easier to record ECGs during anginal attacks and the prevalence of this disease has been found to be higher than was once thought.

As to the pathogenesis of the disease, coronary arteriography has revealed that, in addition to cases where there are definite organic obstructive lesions in coronary arteries, there are also cases with normal or nearly normal coronary arteries. According to current views, attacks of variant angina are caused by coronary spasm.

The effectiveness of nitroglycerin and other nitrates in relieving anginal pain has been confirmed empirically, but it is also important to prevent anginal episodes that might be accompanied by life-threatening arrhythmias.

Kimura et al. and Muller and Gunther reported that calcium antagonists, such as nifedipine, diltiazem and verapamil, are effective in suppressing anginal attacks and the results of a systematic study have been
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