Amrinone: A New Non-Glycosidic, Non-Adrenergic Cardiotonic Agent Effective in the Treatment of Intractable Myocardial Failure in Man

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SUMMARY Chronic congestive heart failure not controlled by conventional therapy was treated with intravenous amrinone, a new non-glycosidic, non-catecholamine cardiotonic agent. Eight patients with New York Heart Association functional class III-IV symptoms were hemodynamically monitored. At peak effect, cardiac index (CI) increased from $1.84 \pm 0.32$ to $2.74 \pm 0.44/\text{min/m}^2$ (mean $\pm$ SD) ($p < 0.001$) and left ventricular filling pressure (LVFP) decreased from $25.8 \pm 6.2$ to $19.5 \pm 6.8$ mm Hg ($p < 0.05$), while heart rate and mean aortic blood pressure did not change significantly. Mean endocardial circumferential fiber shortening (mean Vcf), determined by echocardiography, increased from $0.61 \pm 0.27$ to $0.89 \pm 0.34$ circ/sec ($p < 0.05$). The duration of action after bolus infusion varied from 60–90 minutes. During continuous infusion of amrinone, sustained increases in CI and reductions in LVFP, similar to those at the time of peak effect after bolus administration, were maintained for 180 minutes. These marked cardiotonic effects of amrinone in patients already taking digitalis for severe heart failure occurred without side effects of arrhythmias or altered arterial pressures. The fact that the drug is orally active makes amrinone a very promising inotropic agent for the treatment of chronic heart failure in man.

HEART FAILURE resulting from depression of myocardial contractility is generally not adequately treated. Despite recent emphasis on the use of vasodilators to improve ventricular performance by reducing the load on the heart, pharmacologic therapy of pump failure continues to rely heavily on augmenting contractility of depressed cardiac muscle with inotropic agents. However, inotropic agents are limited in their usefulness due primarily to their toxic side effects or restricted modes of administration. Digitalis glycosides, which have been available for nearly 200 years, increase the force of cardiac contraction in both normal and failing heart muscle. However, cardiac glycosides are not always beneficial hemodynamically in patients with chronic cardiac failure due to cardiomyopathy or coronary artery disease, and increased doses are commonly limited by toxic side effects. Catecholamines exert a positive inotropic effect by stimulating cardiac $\beta$ receptors, but their usefulness is limited by harmful tachycardias, potentially malignant arrhythmias, undesirable increases or decreases in arterial pressure, and a general requirement for intravenous administration.

Amrinone, a bipyridine derivative* (fig. 1) synthesized by G.Y. Lesher and C.J. Opalka of the Sterling-Winthrop Laboratories, has recently been shown to be cardioactive in both in vitro and in vivo experiments in animals. In in vitro studies, amrinone increased the force of contraction of atrial and ventricular muscle without increasing spontaneous right atrial rate. In in vivo experiments in dogs, it increased cardiac output while reducing ventricular filling pressures. Neither arterial pressure nor heart rate changed significantly. The drug was active both orally and intravenously, and did not produce arrhythmias, even at high doses (Alousi AA, Farah AE, Lesher GY, Opalka CJ Jr: unpublished data). Toxicity in animals consisted solely of modest diastolic hypotension seen at very elevated dose levels. Preliminary studies indicate that the cardiotonic action of amrinone is not attributable to the mechanisms thought to mediate the action of either glycosides or catecholamines. Thus, $\text{Na}^+ - \text{K}^+$ ATPase activity is not inhibited as it is by glycosides. Amrinone actions are not prevented by $\beta$-adrenergic blockade; nor are they diminished when catecholamine stores in the heart are depleted (Alousi AA, Farah AE, Lesher GY, Opalka CJ Jr: unpublished data). Neither adenosine-3',5'-monophosphate levels nor phosphodiesterase activity are altered by the drug.

The non-glycosidic, non-catecholamine nature of amrinone, its oral effectiveness, and lack of significant experimental toxicity make it potentially important for clinical use as a cardiotonic agent in the therapy of human myocardial failure. Initial studies in normal, healthy men in which the drug was given intravenously have indicated positive inotropic activity on the basis of ejection time indices. We report the first beneficial use of amrinone for the treatment of heart failure in man.

**Methods**

Subjects

Amrinone therapy was offered to patients in whom
Congestive heart failure was not controlled by conventional treatment with digitalis and diuretics. The nature, potential benefits, and possible risks of the study were fully explained to the patients, who then gave informed consent. The protocol was approved by the Committee on Clinical Investigations of the Albert Einstein College of Medicine. Eight patients, four female and four male, comprised the study group. All patients suffered from symptoms of fatigue and dyspnea sufficient to place them in class III-IV of the New York Heart Association classification. Complete cardiac catheterization with coronary and left ventricular angiography confirmed ventricular enlargement, elevated end-diastolic ventricular pressure, and reduced ejection fraction in each subject. The clinical and diagnostic information are summarized in table 1. No patient had primary valve disease, hypertension, recent myocardial infarction or active ischemia at the time of the study. The cardiac rhythm was sinus in six patients and atrial fibrillation in one; in the eighth patient, a demand ventricular pacemaker had been implanted for sinus node dysfunction during an earlier admission. All subjects were fully digitalized (table 1) and continued to take their usual doses of digoxin and diuretics throughout the study. Several patients had taken vasodilators previously, with minimal benefit; these drugs were discontinued at least 1 week before administration of amrinone.

Hemodynamic Measurements

After a 3-day period of clinical stability, a #7F balloon-tipped triple-lumen thermodilution catheter (Edwards Laboratories, Santa Ana, California) was inserted via cutdown on an antecubital vein and advanced to the pulmonary artery. Right atrial (RA), pulmonary arterial (PA), and pulmonary capillary wedge (PCW) pressures were determined using Gould Statham P23Id transducers and recorded on an Electronics for Medicine VR6 recorder. The PCW has been considered as the left ventricular filling pressure (LVFP), and the latter term was used. Cardiac outputs (CO) were performed in triplicate (less than 10% variation) by thermodilution techniques using iced 5% dextrose in water. CO was computed by a bedside computer (Model 9520, Edwards Laboratories, Santa Ana, California). Systemic arterial pressure was measured in triplicate by two observers using standard cuff technique. Mean arterial pressure (MAP) was derived from the average of these pressures by the formula: diastolic pressure plus one-third pulse pressure. Derived hemodynamic variables were calculated as follows:

- Cardiac index (CI) = \( \frac{CO}{\text{body surface area (BSA)}} \) \( \frac{1}{\text{min/m}^2} \)
- Stroke volume index (SVI) = \( \frac{1000 \text{ CI}}{\text{heart rate (HR)}} \) \( \text{ml/m}^2 \)
- Systemic vascular resistance (SVR) = \( \frac{80 (\text{MAP}-\text{RA})}{\text{CO}} \) \( \text{dyn-sec-cm}^{-5} \)
- Pulmonary vascular resistance (PVR) = \( \frac{80 (\text{Mean PA-PCW})}{\text{CO}} \) \( \text{dyn-sec-cm}^{-5} \)

CI was below 2.5 l/min/m² and PCW exceeded 15 mm Hg in all patients. HR was recorded continuously from a bedside electrocardiographic monitoring device.

Echocardiographic Measurements of Left Ventricular Function

M-mode echocardiograms were recorded in three patients who had been shown by ventriculograms to have symmetrical contraction patterns. Echocardiographic examinations were performed with a Hoffrel ultrasonoscope Model 101C using a 2.25 mHz, 13 mm diameter transducer focused at 7.5 cm at a pulse repetition rate of 1000 Hz. Strip chart tracings were made on a Honeywell Visicorder Model 1856A at a paper speed of 100 mm/sec. Left ventricular ejection time (LVET) was derived from carotid pulse tracing recorded simultaneously with the echocardiogram. Left ventricular dimensions were determined just inferior to the posterior mitral leaflet and measured from the endocardial echoes of the left septal and posterior ventricular walls. End-diastolic dimensions (Dd) were taken at the peak of the electrocardiographic R-wave and end-systolic dimensions (Ds) at the onset of the second heart sound. Mean circumferential fiber shortening velocity of the left ventricular endocardium (mean Vcf) was determined as reported by Quinones et al.\(^2\): mean Vcf (circ/sec) = \( \frac{Dd - Ds}{Dd - Ds} \times \text{LVET} \). All reported values represent the mean of five successive cycles.

Amrinone Administration

Patients were evaluated in the postabsorptive state 4–6 hours after receiving their daily oral dose of diuretics. The protocol was identical in all patients. After two similar sets of baseline hemodynamic measurements were recorded, a bolus of amrinone lactate (compound 40680, Sterling-Winthrop Research

\[ \text{H} \]

\[ \text{N} \]

\[ \text{K} \]

\[ \text{NH}_2 \]

\text{FIGURE 1. Structural formula of amrinone.}
Table 1. Hemodynamic Effects of Amrinone

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<th>Patient</th>
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<th>Digoxin level (ng/ml)</th>
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<th>LVEDP (mm Hg)</th>
<th>LVDVI (ml/m²)</th>
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*p = SD 0.2

MAP (mm Hg)

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**Abbreviations:** HF = heart failure; LVEDP = left ventricular end-diastolic pressure; LVDVI = left ventricular diastolic volume index; HR = heart rate; MAP = mean arterial pressure; CI = cardiac index; PCW = pulmonary capillary wedge pressure; MPAP = mean pulmonary artery pressure; RAP = right atrial pressure; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; C = control; A = amrinone; CAD = coronary artery disease.

Institute, Rensselaer, New York), diluted in normal saline, was administered intravenously at a rate of 1 mg/sec. Hemodynamic determinations were obtained at 5-, 10-, 20-, 60-, and 90-minute intervals after the injection or until a return to control. The procedure was then repeated on successive days at progressively higher doses. In the first two patients, the initial bolus dosage was 0.25 mg/kg body weight, with increments...

**Figure 2. Maximum effects (A) of amrinone bolus on heart rate, mean arterial pressure, cardiac index and left ventricular filling pressure in the eight patients compared with control (C).**
of 0.25 mg/kg/day to a maximum bolus dosage of 0.75 and 1.5 mg/kg, respectively. After the experience with these two patients revealed no significant change in HR or arterial pressure, the starting dosage was increased to 0.75 mg/kg and the daily dosage increment was raised to 0.5 or 0.75 mg/kg, depending on the control LVFP and the response to the initial 0.75 mg/kg bolus. When the total dose per injection exceeded 1.5 mg/kg body weight, the rate of administration was slowed to 0.5 mg/sec. In the last six subjects, the maximum amount of amrinone administered in a single bolus was 2.5 mg/kg, except for one patient who received 3 mg/kg. However, at any dosage level, a fall in the LVFP to or below 10 mm Hg was considered a contraindication to raising the dose.

To determine whether sustained hemodynamic benefit would result, a continuous infusion of amrinone was initiated concomitantly with the bolus injection in three patients. The rate of infusion varied from 6–10 μg/kg/min, with a duration of 10 hours.

**Statistical Methods**

Statistical analysis of the data used the t test for paired data and analysis of variance.

**Results**

**Hemodynamics**

All eight patients responded to amrinone with an improvement in hemodynamics. The maximum alterations in HR, MAP, CI and LVFP at the time of peak drug effect, compared with control values, are detailed in table 1 and illustrated in figure 2. While HR and MAP did not vary significantly, mean CI increased from 1.84 ± 0.32 to 2.74 ± 0.44 l/min/m² (49%, p < 0.01) and mean LVFP decreased from 25.8 ± 0.62 to 19.5 ± 6.8 mm Hg (p < 0.05). Mean PA and RA pressures fell from 37.7 ± 6.2 to 31.2 ± 6.9 mm Hg and 8.8 ± 4.8 to 6.5 ± 4.6 mm Hg, respectively (p < 0.05 for both parameters). Mean SVR decreased from 2035 ± 291 to 1448 ± 278 dyn-sec-cm⁻⁵ (p < 0.001) and mean PVR fell from 345 ± 133 to 211 ± 80 dyn-sec-cm⁻⁵ (p < 0.05). As expected, mean SVI increased from 25.8 ± 3.1 to 36.9 ± 5.1 ml/m²/pulse (p < 0.01). Individual changes in SVI are plotted as a function of LVFP in figure 3. Reduction of LVFP was uniformly associated with an augmentation of the SVI. This shift upward and to the left is consistent with an improvement of left ventricular function in all patients.

In every instance, the peak increase occurred 2–10 minutes after administration of the drug, as shown in figure 4. Cardiac index was significantly increased at 10 and 30 minutes after the bolus of intravenous amrinone, while PCW pressure was significantly reduced as long as 90 minutes after the drug administration.
Maximum responses were obtained at differing dose levels in different patients. After the initial experience in two patients revealed no change in HR or MAP at dosages up to 1.5 mg/kg, we attempted to increase the bolus dosage in the subsequent patients to at least 2.5 mg/kg. This was achieved in three patients: one received 3 mg/kg of amrinone, with an augmentation of CI of 73%; the two others responded at 2.5 mg/kg, with an increase in CI of 42% and 53%, respectively. In the three remaining patients, the maximum dosage was not administered due to decreases in LVFP to 10 mm Hg or below. One patient developed a drop in LVFP from 20 to 7 mm Hg after the initial 0.75 mg/kg bolus, with a concomitant increase in CI of 21%. Reduction of the dose to 0.5 mg/kg the next day in the same patient resulted in a greater augmentation of CI (to 33%), while LVFP fell only moderately, from 21 to 16 mm Hg. Similar changes in LVFP and CI were demonstrated at dosage levels of 1.5 and 1.0 mg/kg in a second patient. In the final patient, LVFP fell to 10 mm Hg after 2 mg/kg with a marked rise in CI (78%). Therapy was then terminated in this patient without a trial at 2.5 mg/kg.

Figure 5 depicts the maximum increase in CI at each dose of amrinone administered to the eight patients. In general, the greatest increase in CI above control values was obtained at the highest doses. Since the LVFP did not fall below 12 mm Hg in the patients taking 2.5 mg/kg and 3 mg/kg, it is possible that higher doses of the drug would have further increased CI.

The last three subjects received prolonged infusions of amrinone, immediately preceded by a bolus injection. The hemodynamic effects in one patient are illustrated in figure 6. After the bolus of 2 mg/kg, the CI rose and LVFP fell abruptly, and returned to baseline within 60 minutes. Over the next 6 hours, the drug was infused at a constant rate of 8 μg/kg/min and a gradual increase in CI and a reduction in LVFP were noted. Seven hours after the onset of the infusion, CI and LVFP equalled the peak values recorded after the bolus injection. These responses were maintained at a steady level for the last 3 hours of the constant infusion. Tachyaphylaxis was not observed during study. After termination of the infusion, both parameters returned to within 10% of the control value by 3 hours. The two other patients receiving continuous drug infusion showed similar sustained effects.

Echocardiography

Echocardiographic determinations of left ventricular function were made in three patients who had no regional abnormality of ventricular contraction. Despite the fact that measurements were obtained 15 minutes after bolus administration (slightly after peak effect), mean Vcf increased significantly in all three patients, from 0.61 ± 0.27 to 0.89 ± 0.34 cm/sec (p < 0.05). When echocardiography was performed, significant changes in HR or in systolic or diastolic arterial pressures did not occur.

Side Effects

No subjective or objective clinical manifestations of toxicity were observed with either bolus injection or
continuous infusion of amrinone. HR and arterial pressures did not change significantly. As previously noted, two patients experienced a marked reduction in LVFP which was, nevertheless, associated with an increase in CI.

Discussion

The present study shows that amrinone, a newly synthesized bipyridine derivative, is a very effective cardiotonic drug for the treatment of heart failure in man. This agent, which is neither a glycoside nor a catecholamine, increased CO substantially while decreasing LVFP. No significant changes occurred in MAP or HR, and arrhythmias did not develop. These effects were observed even though the drug was administered to patients on maintenance digitalis and diuretics.

The hemodynamic mechanisms of action of amrinone to produce the beneficial effects are complex. The effects to decrease LVFP while augmenting CO and Vcf can result from either an increase in myocardial contractility or a decrease in impedance to ventricular ejection or both. The former effect is supported in dog experiments in which direct measurements of contractile force and left ventricular rate of pressure development (dp/dt) were shown to rise. Preliminary studies in two patients in our laboratory demonstrated a similar increase in left ventricular dp/dt despite a decrease in left ventricular end-diastolic pressure. The latter effect of decreasing arterial impedance also occurred, with a decrease in SVR, i.e., CO rose while MAP was unchanged. This could also have contributed to an increase in ejection fraction and reduced diastolic ventricular pressures, but would not have augmented left ventricular dp/dt. Thus, we would conclude that the effects of amrinone were the result of both an increase in cardiac contractility and a decrease in peripheral arterial resistance.

The vasodilatory effects of amrinone may be mediated directly by action on the systemic arteriolar bed and indirectly by withdrawal of heightened sympathetic tone in the presence of severe heart failure. The direct vasodilatory effects of amrinone are suggested from studies in normal dogs in which very high doses of amrinone induced hypotension. No such reductions in arterial pressure were noted with the doses of the drug used in the present investigation. Indirect withdrawal of sympathetic tone to reduce SVR resulting from improved cardiac contractility probably occurred in our patients with severe failure in a manner similar to that observed after administration of digitalis glycoside under similar conditions.

All of our patients experienced a significant fall in LVFP. Although these reductions could be mediated by improvement in contractility with enhanced systolic emptying of the left ventricle, the marked decreases in LVFP in three patients strongly suggest that amrinone may also produce direct venodilatation. As suggested by the results in two of these patients, an excessive reduction in LVFP may limit the ability of the drug to further increase CI.

The activity of amrinone was dose-dependent, although the threshold for activity was somewhat variable. After a single intravenous dose, the onset of action was noted within 2 minutes, reached a maximum by 10 minutes, and lasted 60–90 minutes. The salutary hemodynamic effects were readily maintained by continuous infusion of the drug, with no evidence of tachyphylaxis. Toxic side effects were notably absent with doses as high as 3 mg/kg in this acute study. However, no long-term studies in man are available.

The mode of action of amrinone has not been determined. It does not alter the biochemical systems thought to mediate the action of either cardiac
glycosides or catecholamines. Whether amrinone affects excitation-contraction coupling directly or modifies interactions of contractile protein is unknown. All inotropic agents are thought to affect contraction by making more calcium available to the myofilaments. Whether this is true for amrinone and how it is mediated remains to be defined. The fact that amrinone augments myocardial contractility in patients who are already fully digitalized supports the view that residual contractile reserve can be mobilized in the severely failing heart.

Our data indicate that amrinone may be very beneficial in the treatment of heart failure in man. Further studies are in progress to define the specific use of oral amrinone in the long-term therapy of this disease.

References


Addendum

T H LeJemtel, E Keung, E H Sonnenblick, H S Ribner, M Matsumoto, R Davis, W Schwartz, A A Alousi and D Davolos

Circulation. 1979;59:1098-1104
doi: 10.1161/01.CIR.59.6.1098

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