Milrinone in heart failure

Acute effects on left ventricular systolic function and myocardial metabolism

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SUMMARY Milrinone, a new bipyridine compound related to amrinone, is a potent non-adrenergic inotrope in experimental preparations and also shows vasodilator activity. In the present study the haemodynamic and metabolic effects of milrinone were evaluated in 12 patients with congestive heart failure. Milrinone 5 mg given orally produced a sharp reduction in left ventricular end diastolic pressure without significantly affecting stroke volume. The improvement in left ventricular function was due to a combination of vasodilatation and positive inotropism. Thus small reductions in blood pressure and systemic vascular resistance were associated with increments in the isovolumic indices of left ventricular function. The relation between left ventricular end systolic pressure and dimension was displaced leftwards and downwards. Only reductions in left ventricular cavity dimension were statistically significant, however. Though myocardial oxygen consumption did not change significantly, it tended to increase whereas lactate consumption tended to decrease.

This trend towards oxygen imbalance suggests the need for caution in the use of milrinone in patients with severe coronary artery disease.

Milrinone is a recently introduced derivative of amrinone. Both compounds share a bipyridine ring structure and increase the contractility of isolated heart muscle.¹ The inotropic potency of milrinone, however, is 10-30 times greater than that of its parent compound.² The mechanism of this inotropic effect remains unclear. Milrinone is a potent inhibitor of cyclic adenosine monophosphate adenylic acid (AMP) phosphodiesterase,¹ but peak increments in muscle tension precede maximal increase in intracellular cyclic AMP.² Phosphodiesterase inhibition is unlikely, therefore, to account fully for the inotropic properties of the drug. In addition to its direct cardiac effects, milrinone also relaxes vascular smooth muscle in experimental preparations, though at considerably higher doses than are required to produce a positive inotropic response.²

Recent work has confirmed beneficial haemo-

dynamic responses to milrinone in patients with congestive heart failure.³⁻⁵ The contributions that positive inotropism and vasodilatation make towards the clinical efficacy of the drug are, however, unknown. This question is important because the balance of these separate cardiovascular influences largely determines the effects of treatment on myocardial oxygen demand—a consideration of particular relevance in patients with coronary artery disease.⁶

In the present study, therefore, we measured haemodynamic and metabolic responses to milrinone in patients with congestive heart failure. In particular, we evaluated the effects of this agent on left ventricular systolic function—as determined by contractile performance and loading conditions—and myocardial oxygen consumption.

Patients and methods

PATIENT SELECTION

Twelve patients (10 men, two women; age range 31-64 (mean) 52.7 years) were studied (Table 1). All

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Table 1 Patient characteristics

Case No	Sex/age (yr)	Diagnosis	NYHA class	EF (%)	LVEDP (mm Hg)	Daily frusemide dosage (mg)
1	M/39	CAD	III	10	31	120
2	M/55	CAD	III	27	16	250
3	M/45	CAD	II	44	24	80
4	M/54	CAD	III	13	23	80
5	M/64	CAD	III	NA	17	80
6	M/58	CCM	III	19	28	240
7	F/50	CCM	II	39	8	40
8	M/31	CCM	III	22	14	40
9	M/60	CAD	III	21	24	80
10	F/59	CCM	III	NA	25	160
11	M/53	CCM	III	23	8	120
12	M/64	CAD	III	10	15	120

CAD, coronary artery disease; CCM, congestive cardiomyopathy; EF, angiographic ejection fraction (not available (NA) in two cases); LVEDP, left ventricular end diastolic pressure (measured in the supine position).

were selected on the basis of moderate to severe congestive heart failure (New York Heart Association functional classes II and III) that had responded inadequately to conventional treatment. Ten patients had undergone diagnostic cardiac catheterisation within 12 months of the study. This had confirmed severely impaired left ventricular function with a mean (SEM) angiographic ejection fraction of only 23 (4)%. Seven of the 10 patients had coronary artery disease by angiographic or clinical criteria and the remainder congestive cardiomyopathy of uncertain cause. The patients were all in stable sinus rhythm. Written informed consent was obtained from each patient before inclusion in the study, which had been approved by the hospital ethical committee.

CARDIAC CATHETERISATION

The patients were studied in the supine position after fasting. Premedication with diazepam 5–10 mg orally was given. Heparin 1000 IU/hour was administered by continuous intravenous infusion for 12 hours before and during each study. All catheterisation procedures were performed under fluoroscopic control using up to 20 mg of lignocaine local anaesthetic. A balloon tipped triple lumen thermodilution catheter (Edwards Laboratories Inc) was placed in the pulmonary artery. This permitted technically adequate right sided pressure measurements in all the patients except one, in whom baseline error made data interpretation impossible. In a second patient a satisfactory pulmonary capillary wedge pressure recording could not be obtained. The mean of at least four thermodilution cardiac output recordings was taken for each measure of cardiac output. Arterial pressure was monitored, and blood samples obtained, through the sidearm of a short sheath positioned in the femoral artery. A micromanometer tipped catheter (Millar Instruments Inc) was introduced through the femoral arterial sheath and positioned in the left ventricle for high fidelity pressure recordings. All pressures were measured

with reference to the mid-chest and were recorded with an electrocardiogram on a Mingograph 82 recorder (Siemens Ltd). Coronary sinus cannulation with a dual thermistor catheter (Wilton Webster Ltd) was performed in 10 patients using the techniques described by Ganz *et al.*⁷ This permitted determination of coronary sinus flow by continuous thermodilution. Adequate coronary sinus blood sampling for metabolic measurements was possible in eight of these patients.

ECHOCARDIOGRAPHY

In seven patients M mode echocardiograms (Hewlett Packard phased array sector scanner) of the left ventricular cavity were obtained at a level just below the free margins of the mitral valve leaflets where the septum and posterior wall were clearly visible. These images were recorded simultaneously with the left ventricular pressure signal at a paper speed of 100 mm/s. During these recordings the atrium was paced at a fixed preselected rate (15–20 beats/minute in excess of the control heart rate). The isovolumic indices of left ventricular function were also measured during fixed rate atrial pacing.

DRUG ASSAY

Serum samples for estimating milrinone concentrations were obtained in seven patients. A high pressure liquid chromatographic assay was used and was performed at the Sterling-Winthrop Research Centre.

STUDY PROTOCOL

Vasodilator drugs were withdrawn four days before the study. All other regular medications were withheld on the morning of the study. After placement of the catheters the patients were permitted to rest for 15 minutes, and two sets of control haemodynamic measurements were then obtained 20 minutes apart. At the same time blood samples were withdrawn from the coronary sinus and the femoral artery for later

Table 2 Haemodynamic responses to milrinone in 12 patients with congestive heart failure. Values are mean (SEM)

	Before milrinone 5 mg (min)		After milrinone 5 mg (min)			p value†
	20	0	30	60	90	
Heart rate (beats/min)	84 (5)	84 (5)	87 (5)	90 (5)*	89 (5)	<0.01
Cardiac index (l/min per m ²)	2.4 (0.2)	2.4 (0.1)	2.5 (0.1)	2.7 (0.1)**	2.7 (0.2)*	<0.001
Stroke volume index (ml/beat per m ²)	29 (2)	29 (2)	30 (1)	31 (2)	31 (2)	NS
Systolic blood pressure (mm Hg)	139 (7)	141 (7)	136 (7)	134 (7)	130 (7)**	<0.01
Diastolic blood pressure (mm Hg)	82 (2)	81 (3)	79 (3)	77 (3)	78 (3)	<0.05
Mean blood pressure (mm Hg)	101 (4)	102 (4)	97 (4)	94 (4)*	95 (5)*	<0.01
Systemic vascular resistance (units)	23 (1)	23 (1)	20 (1)	18 (1)***	19 (2)**	<0.001
Mean right atrial pressure (mm Hg) (n=11)	10 (2)	10 (2)	8 (2)*	7 (2)***	8 (2)*	<0.001
Mean pulmonary artery pressure (mm Hg) (n=11)	30 (3)	29 (3)	23 (3)**	22 (3)***	23 (3)***	<0.001
Pulmonary capillary wedge pressure (mm Hg) (n=10)	21 (2)	21 (2)	13 (2)***	10 (2)***	10 (2)***	<0.001
Left ventricular end diastolic pressure (mm Hg)	19 (2)	20 (2)	13 (2)**	9 (2)***	8 (2)***	<0.001
Left ventricular max dP/dt (mm Hg/s)	1160 (124)	1167 (119)	1278 (150)	1283 (150)*	1228 (124)	<0.01
Left ventricular max dP/dt/P (s ⁻¹)	22 (2)	22 (2)	31 (3)***	37 (3)***	35 (3)***	<0.001
Left ventricular min dP/dt (mm Hg/s)	-1096 (54)	-1091 (50)	-1237 (97)*	-1238 (91)*	-1250 (88)**	<0.01
Coronary sinus flow (ml/min) (n=10)	108 (12)	106 (12)	113 (14)	125 (21)	136 (25)	NS
Coronary resistance (units) (n=10)	0.96 (0.11)	0.98 (0.11)	0.92 (13)	0.86 (0.13)	0.83 (0.13)	NS

†Overall significance of changes by analysis of variance; NS, not significant; significance of individual changes with respect to second set of control readings (at 0 min): *p<0.05, **p<0.01, ***p<0.001.

Fig. 1 Effects of milrinone on (a) cardiac index, (b) left ventricular end diastolic pressure, (c) systemic vascular resistance, and (d) left ventricular maximum dP/dt/P in 12 patients. Mean (SEM) values are shown at baseline and 90 minutes after milrinone.

biochemical analysis. Milrinone 5 mg was given orally, and haemodynamic measurements and blood sampling were repeated 30, 60, and 90 minutes later. The simultaneous left ventricular echocardiogram and pressure recordings were obtained at the same time intervals but always after the other haemodynamic variables had been measured and the blood samples had been taken.

DATA ANALYSIS

Measurements of stroke volume and vascular resistance (expressed in arbitrary units) were derived by standard formulae. Cardiac output and stroke volume were normalised for body surface area. Isovolumic indices of left ventricular function—the rate of rise of pressure (dP/dt) and the quotient of dP/dt and instantaneous pressure (P)—were derived by simultaneous analogue processing of the left ventricular pressure signal. The simultaneous records of left ventricular pressure and septal and posterior wall endocardial echoes were digitised between two consecutive R waves on the electrocardiogram using a high resolution (0.1 mm) digitising tablet (Summagraphics Ltd) interfaced with a microcomputer system (Commodore).

Arterial and coronary sinus blood samples were assayed for whole blood lactate.⁸ Whole blood oxygen and haemoglobin concentrations were measured using a Radiometer OSM2 Hemoximeter; oxygen content was derived by the standard formula. Arterio-coronary sinus concentration differences in whole blood were calculated and the myocardial extraction ratios derived by dividing the arterio-coronary sinus differences by the arterial concentrations expressed as a

Table 3 Serum milrinone concentrations. Values are mean (SEM) (n=7)

	Before milrinone 5 mg (min)		After milrinone 5 mg (min)		
	20	0	30	60	90
Serum milrinone concentration (ng/ml)	ND	ND	89.3 (37.3)	123.9 (25.8)	102.5 (13.2)

ND, not detectable.

percentage. Myocardial uptake was calculated as the product of arteriocardiac sinus concentration difference in whole blood and coronary sinus flow.

STATISTICAL ANALYSIS

Two way analysis of variance was used to test the significance of the overall changes in individual haemodynamic and metabolic variables across time. Those variables which changed significantly ($p<0.05$) were then subjected to a modified *t* test—using the Bonferroni method—to identify the source of the differences.⁹

Results

No drug related side effects occurred during the study.

HAEMODYNAMIC RESPONSES

Table 2 summarises the haemodynamic responses to milrinone and Fig. 1 shows the individual patient data. Table 3 gives the serum milrinone concentrations.

The data in Tables 1 and 2 confirm the severe

baseline left ventricular impairment that characterised this group of patients. Angiographic ejection fraction was depressed, and despite treatment with frusemide both the left ventricular end diastolic pressure and the echocardiographic cavity dimensions were considerably increased (Fig. 2). Cardiac index and stroke volume index, on the other hand, showed variable reductions below the normal range.

Although milrinone produced a prompt reduction in the increased left ventricular filling pressures (as reflected by the changes in left ventricular end diastolic pressure and pulmonary capillary wedge pressure) and a small reduction in right atrial pressure, cardiac index was increased. Stroke volume index, however, did not change significantly because of a small increase in heart rate. Reductions in blood pressure and systemic vascular resistance, though significant, were not pronounced. The isovolumic indices of left ventricular systolic function (max dP/dt and max dP/dt/P) both increased, the rise in max dP/dt/P being particularly prominent. A tendency for coronary sinus flow to increase and for coronary resistance to decline was not significant.

Milrinone produced a leftward shift in the relation

Fig. 2 (a) and (b). Effects of milrinone on the relation between left ventricular (LV) pressure and dimension in two separate patients. Values before treatment (C1 and C2) and 30, 60, and 90 minutes after milrinone (M30, M60, M90) are shown. Open circles indicate the pressure-dimension relation at end systole.

Table 4 Changes in left ventricular end systolic pressure and dimension. Values are mean (SEM) (n=7)

Left ventricular end systolic values	Before milrinone 5 mg (min)		After milrinone 5 mg (min)			p value†
	20	0	30	60	90	
Pressure (mm Hg)	109 (5)	108 (5)	105 (6)	102 (5)	105 (6)	NS
Dimension (cm)	6.3 (0.3)	6.3 (0.3)	6.0 (0.3)*	5.9 (0.3)**	5.8 (0.3)**	<0.001

†Overall significance of changes by analysis of variance: NS, not significant; significance of individual changes with respect to second set of control readings (at 0 min): *p<0.05, **p<0.01.

between end systolic pressure and dimension (Fig. 2). The reduction in dimension was significant and was slightly more pronounced than the reduction in pressure (Table 4). In one patient reduction in the left ventricular end systolic cavity dimension occurred during a progressive increase in pressure (Fig. 2a). More commonly, however, small reductions in end systolic pressure were observed (Fig. 2b).

METABOLIC RESPONSES

Table 5 summarises the effects of milrinone on oxygen and lactate metabolism. Arterial oxygen saturation and myocardial oxygen extraction remained remarkably constant during the study. Myocardial oxygen uptake, however, tended to increase though the trend was not statistically significant. The arterial concentration of lactate was also unaffected by milrinone, but the myocardial utilisation of this substrate declined; the fall in lactate extraction was significant. No patients showed lactate production during this study.

Discussion

This study has shown that the acute administration of milrinone to patients with heart failure is well tolerated and leads to a useful improvement in resting left ventricular function. The data indicate that positive inotropism and vasodilatation combine to produce this beneficial effect.

The patients included in this study all had moderate to severe degrees of heart failure caused by coro-

nary artery disease or congestive cardiomyopathy. Milrinone produced only a small improvement in cardiac output, but the left ventricular filling pressures fell and in most patients were within the normal range 60–90 minutes after drug administration. This reduction in filling pressures during maintenance of cardiac output must reflect an improvement in left ventricular function.

In studies of this type analysis of the mechanisms responsible for changes in left ventricular function is difficult. The effects of milrinone on the isovolumic indices of left ventricular performance and the relation between end systolic pressure and dimension, however, strongly suggest a positive inotropic response to the drug. The isovolumic indices of ventricular performance provide a measure of contractile function but are also influenced by heart rate and loading conditions.^{10,11} In the present study the changes in loading that occurred in response to milrinone would have tended to reduce left ventricular max dP/dt.¹⁰ Because atrial pacing controlled for changes in heart rate, the increase in left ventricular max dP/dt during the study is best explained by an increase in contractility. Left ventricular max dP/dt/P is less susceptible to the influence of loading conditions,¹¹ and the drug induced improvement in this measure of contractile function strengthens the conclusion that positive inotropism contributed towards the beneficial effects of milrinone.

The leftward displacement of the relation between left ventricular end systolic pressure and dimension that occurred in response to milrinone was due to a

Table 5 Metabolic responses to milrinone in eight patients with congestive heart failure. Values are mean (SEM)

	Before milrinone 5 mg (min)		After milrinone 5 mg (min)			p value†
	20	0	30	60	90	
Oxygen:						
Arterial saturation (%)	96.4 (0.5)	96.5 (0.9)	97.0 (0.8)	96.4 (0.8)	95.0 (0.9)	NS
Myocardial extraction (%)	64.7 (2.0)	63.3 (2.5)	63.8 (2.5)	63.3 (2.4)	63.3 (2.2)	NS
Myocardial uptake (ml/min)	13.9 (2.0)	13.3 (1.7)	14.5 (2.4)	16.0 (3.2)	18.2 (4.1)	NS
Lactate:						
Arterial concentration (mmol/l)	1.1 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	NS
Myocardial extraction (%)	29.5 (5.2)	29.7 (5.4)	23.5 (6.9)	21.9 (6.5)	16.4 (5.3)***	<0.001
Myocardial uptake (μmol/min)	35.0 (7.0)	33.9 (6.8)	30.8 (10.4)	34.1 (12.5)	25.9 (9.1)	NS

†Overall significance of changes by analysis of variance: NS, not significant; significance of individual changes with respect to second set of control readings (at 0 min): ***p<0.001.

significant reduction in cavity dimension. The reduction in end systolic pressure was not significant (unlike the change in peak systolic pressure measured in larger numbers of patients). Indeed in one case left ventricular pressure increased during simultaneous reductions in cavity dimension. Though we have previously emphasised the caution that is necessary in interpreting data of this type¹² (extrapolation from pressure-volume relations in the normal heart to pressure-dimension relations in the failing heart has not, as yet, been validated experimentally¹³) the reduction in end systolic dimension without pronounced alteration in end systolic pressure suggests a positive inotropic response to the drug.¹⁴ The response to milrinone should be contrasted with the response to felodipine—a potent vasodilator—which produces a pronounced downward displacement in the relation between the end systolic pressure and dimension in patients with heart failure.¹²

The useful reduction in left ventricular filling pressures that occurred during this study is explained in part by the effects of milrinone on diastolic ventricular function. Preliminary work has shown that this drug improves indices of left ventricular diastolic relaxation and chamber distensibility in patients with heart failure.¹⁵ Our finding of a significant increase in left ventricular min dP/dt supports this observation. Associated systemic venous pooling, however, is likely to have contributed to the reduction in ventricular filling pressures, and the small reductions in blood pressure and systemic vascular resistance point to associated arteriolar dilatation. Vasodilatation, therefore, appears to make an important contribution to the beneficial haemodynamic effects of milrinone as indicated by the data of Cody *et al.*¹⁶

The metabolic consequence of antifailure treatment is an important consideration in the assessment of new agents. Milrinone produced a small increase in heart rate in addition to enhancing contractility. Increments in myocardial oxygen demand, however, were to some extent offset by associated reductions in wall tension caused by diminished left ventricular cavity dimensions and vasodilatation.¹⁷ Thus myocardial oxygen consumption and lactate production did not change significantly. Both variables, however, tended to increase and the associated rise in myocardial lactate extraction was statistically significant. Though the determinants of lactate extraction are complex,¹⁸ our data do not exclude an adverse effect on myocardial ischaemia: further work is necessary to evaluate this issue.

The beneficial haemodynamic effects of milrinone in congestive heart failure are confirmed in the present study. The drug, which is well tolerated, improves left ventricular systolic function as a result of simultaneous positive inotropism and vasodilata-

tion. The combination of these separate cardiovascular influences to some extent protects against myocardial ischaemia. The changes that occurred in oxygen and lactate metabolism, however, although not statistically significant, suggest the need for caution in the use of milrinone in patients with severe coronary artery disease.

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