Acute haemodynamic comparison of amrinone and pirbuterol in chronic heart failure

Additional effects of isosorbide dinitrate

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SUMMARY A randomised, within patient comparison was made in patients with severe chronic heart failure, to study the acute haemodynamic effects of oral agents which have inotropic and vasodilator properties. A non-glycosidic non-adrenergic positive inotropic agent with vasodilator properties (amrinone) was compared with a beta-agonist which has vasodilator and positive inotropic effects (pirbuterol). To assess whether combined treatment with a venodilator might be advantageous, the effect of adding isosorbide dinitrate was studied.

Oral amrinone or pirbuterol were given in random order to each of 13 patients, on successive days, and oral isosorbide dinitrate was added after two-and-a-half hours. Control values before amrinone or pirbuterol were similar, and both drugs increased cardiac index while reducing left ventricular filling pressure, right atrial pressure, and systemic vascular resistance. Heart rate and blood pressure were unchanged. The magnitude of the changes caused by amrinone and pirbuterol were not significantly different. The addition of isosorbide dinitrate caused further falls in left ventricular filling pressure and right atrial pressures, and a fall in heart rate with each drug. Other measurements remained unchanged.

Although amrinone and pirbuterol have different pharmacological properties, their acute haemodynamic effects in patients with chronic heart failure are indistinguishable.

In chronic heart failure, conventional treatment with diuretics and digoxin often fails to relieve the symptoms of breathlessness and fatigue. This has led to the development of a range of new vasodilator and inotropic drugs, such as amrinone and pirbuterol. Amrinone, a bipyridine derivative, is a positive inotropic agent in experimental preparations, and initial evaluation in man has shown its beneficial effects in heart failure after acute and chronic oral administration, both at rest and on exercise. Its mode of action is unknown but it is unrelated to the inotropic effects of glycoside or catecholamine stimulation, or to changes in phosphodiesterase activity or cyclic AMP concentrations. Recent work with amrinone has suggested that, in man, a direct vasodilator effect may predominate over the positive inotropic action. A serious adverse effect of amrinone is thrombocytopenia, which is reversible with reduction of drug dosage.

Pirbuterol is an orally active beta adrenergic agonist. Animal experiments have shown that it can exert a positive inotropic effect, and also cause systemic vasodilatation. In patients with heart failure, the predominant effect is probably vasodilatation, producing symptomatic and haemodynamic benefit after acute and chronic oral administration.

Few studies have compared the effects of positive inotropic and vasodilator drugs within the same patients with heart failure. We report a randomised, within patient, open, comparison of the acute haemodynamic responses to oral amrinone and pirbuterol, to compare the effects of pharmacologically different agents with positive inotropic and vasodilator actions. In order to determine whether combined treatment with oral nitrates might be advantageous, we added...
oral isosorbide dinitrate after the acute administration of each drug.

Patients and methods

Thirteen patients who had been in clinical heart failure for three or more months were studied. They were 11 men and two women, with an average age of 62 years, range 44 to 77 years. The aetiology of heart failure was ischaemic heart disease in eight patients and dilated cardiomyopathy in five patients. All patients were severely symptomatic: four had dyspnoea at rest while nine had dyspnoea on mild exertion. There was radiological cardiomegaly (cardiothoracic ratio greater than 0.5) and pulmonary venous congestion in all patients despite diuretics (frusemide 80 to 250 mg daily, combined with spironolactone 100 mg or amiloride 10 to 20 mg daily). Only the four patients who were in atrial fibrillation received digoxin, for control of ventricular rate. No patient was receiving vasodilators at the time of their study. Patients were studied during a stable phase of their illness, with a constant weight and no peripheral oedema. Informed consent was obtained in all cases.

The patients were studied while supine, at rest, and without premedication, at least three hours after their usual morning medication. Right atrial, pulmonary arterial, and wedge pressures were recorded, using a triple-lumen, balloon-tipped, thermodilution catheter (CV1 model No. 600-017) positioned in the pulmonary artery, using the mid-chest as a zero reference point. Wedge pressure or pulmonary artery end-diastolic pressure was used as an indirect measure of left ventricular filling pressure. Cardiac output was measured by the thermodilution technique (CV1 computer Model No. 600): the mean of three readings with less than 10% variation was used. Blood pressure was measured with a sphygmomanometer; mean blood pressure was calculated as diastolic pressure plus a third of the pulse pressure. Heart rate was measured from a simultaneously recorded electrocardiogram. Systemic vascular resistance and cardiac index were calculated using standard formulae.

Two control measurements were made at an interval of 30 minutes to establish that the haemodynamic state was stable. Amrinone (100 mg) or pirbuterol (20 mg) were given orally in random order to each patient on successive days. Measurements were made after one, two, and two-and-a-half hours, at which time isosorbide dinitrate (20 mg) was given orally to 10 of the 13 patients, and further measurements made at half an hour and one hour. Earlier work has shown that the maximal effects of oral amrinone and pirbuterol occur within two hours.10 20

Results after amrinone or pirbuterol have been compared with control, but after isosorbide dinitrate results have been compared both with control and with values at two-and-a-half hours, just before administration of isosorbide dinitrate.

In seven of the patients, blood samples for plasma amrinone assay were taken at the time of peak cardiac index. Plasma free amrinone was measured in duplicate by high performance liquid chromatography, and the average of two results from each sample was taken.

A low oral dose of amrinone was used in this study in an attempt to avoid the problem of thrombocytopenia which, it has been suggested, may be a dose-related phenomenon.12

Results are expressed as means ± SEM. Statistical analysis was performed using one-way analysis of variance, and when indicated, Students’ t test for paired data.

Results

There were no significant changes in any variable during the control measurements, and control values were not significantly different before amrinone or pirbuterol were given.

After one hour, both drugs produced significant (p<0.01) increases in cardiac index and falls in left ventricular filling pressure and systemic vascular resistance (Fig. 1 and 2). Heart rate was unchanged by either drug, so the increased cardiac index represents an increase in stroke volume (p<0.001). Blood pressure was not significantly altered by either drug. Right atrial pressure fell slightly after each drug.

The values at two-and-a-half hours were not significantly different from those at one hour, indicating that maximal changes had been achieved at the time that isosorbide dinitrate was added. After isosorbide dinitrate there were further falls in left ventricular filling pressure (p<0.01) and right atrial pressure (p<0.05) while blood pressure, systemic vascular resistance, and cardiac index did not change significantly, though there was individual variation in the effect on cardiac index.

The data have also been analysed to compare peak drug effect: for amrinone and pirbuterol this was defined as occurring in each patient at the time of greatest cardiac index, but for isosorbide dinitrate it was defined as occurring at the time of lowest left ventricular filling pressure (Fig. 3 to 5 and Table).

After amrinone, the overall peak effect occurred at a mean of two hours, when cardiac index increased by 65%, left ventricular filling pressure fell by 27%, systemic vascular resistance fell by 33% (all p<0.001), and right atrial pressure fell by 16% (p<0.05).

After pirbuterol, peak effect occurred at a mean of one-and-a-half hours, when cardiac index increased
Table Haemodynamic variables in 13 patients at control and peak effect of amrinone (A) and pirbuterol (P), and isosorbide dinitrate in 10 of the patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Peak amrinone and pirbuterol</th>
<th>2½ hour</th>
<th>Peak additional isosorbide dinitrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>A 93±3</td>
<td>94±5</td>
<td>95±4</td>
<td>92±4</td>
</tr>
<tr>
<td></td>
<td>P 90±4</td>
<td>91±3</td>
<td>95±3</td>
<td>9±1  **</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>A 83±3</td>
<td>84±3</td>
<td>8±1</td>
<td>8±1  5±1**</td>
</tr>
<tr>
<td></td>
<td>P 86±3</td>
<td>8±1**</td>
<td>8±1</td>
<td>5±1**</td>
</tr>
<tr>
<td>Right atrial pressure (mmHg)</td>
<td>A 10±1</td>
<td>8±1**</td>
<td>8±1</td>
<td>5±1**</td>
</tr>
<tr>
<td></td>
<td>P 10±1</td>
<td>8±1**</td>
<td>8±1</td>
<td>5±1**</td>
</tr>
<tr>
<td>Left ventricular filling pressure (mmHg)</td>
<td>A 28±2</td>
<td>21±2***</td>
<td>24±2</td>
<td>17±2**</td>
</tr>
<tr>
<td></td>
<td>P 27±2</td>
<td>22±2***</td>
<td>23±2</td>
<td>17±2**</td>
</tr>
<tr>
<td>Cardiac index (l/min per m²)</td>
<td>A 1.7±0.1</td>
<td>2.7±0.2***</td>
<td>2.3±0.2</td>
<td>2.3±0.3</td>
</tr>
<tr>
<td></td>
<td>P 1.9±0.1</td>
<td>2.8±0.3***</td>
<td>2.5±0.3</td>
<td>2.5±0.3</td>
</tr>
<tr>
<td>Stroke work index (g m per m²)</td>
<td>A 14±2</td>
<td>26±3***</td>
<td>21±3</td>
<td>21±2</td>
</tr>
<tr>
<td></td>
<td>P 17±2</td>
<td>26±2***</td>
<td>22±3</td>
<td>25±2</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne s⁻¹ cm⁻²)</td>
<td>A 2125±215</td>
<td>1351±116***</td>
<td>1645±142</td>
<td>1636±160</td>
</tr>
<tr>
<td></td>
<td>P 2047±175</td>
<td>1355±146***</td>
<td>1562±204</td>
<td>1443±182</td>
</tr>
</tbody>
</table>

*p<0.05  **p<0.01  ***p<0.001.

by 55% (p<0.01), left ventricular filling pressure fell by 19%, systemic vascular resistance fell by 32% (both p<0.001), and right atrial pressure fell by 21% (p<0.01). The magnitude of the changes caused by amrinone and pirbuterol were not significantly different.

When isosorbide dinitrate was added to amrinone, the peak effect occurred after a mean of three-quarters of an hour, when left ventricular filling pressure fell by a further 30% (p<0.01) and right atrial pressure fell by 37% (p<0.05).

When isosorbide dinitrate was added to pirbuterol, the peak effect occurred after a mean of half an hour, when left ventricular filling pressure fell by a further 29% and right atrial pressure fell by 32% (both p<0.01). Heart rate fell slightly, from 95±4 to 92±3 beats/min, when isosorbide dinitrate was added to each drug. Blood pressure, systemic vascular resis-
Amrinone and pirbuterol in chronic heart failure

Fig. 2 Changes with time in left ventricular filling pressure, right atrial pressure, and systemic vascular resistance in 13 patients given oral amrinone and pirbuterol and in 10 after the addition of oral isosorbide dinitrate.

Fig. 3 Percent changes in cardiac index and left ventricular filling pressure in 13 patients after oral amrinone and pirbuterol, and further changes in 10 patients after the addition of oral isosorbide dinitrate. Significance of change from control values (*) and from 2½ hour value (○) are shown. NS, not significant.

Fig. 4 Percent changes in right atrial pressure and systemic vascular resistance in 13 patients after oral amrinone or pirbuterol, and further changes in 10 patients after the addition of oral isosorbide dinitrate.
Cardiac index and amrinone (isosorbide dinitrate)
tance, and cardiac index did not change significantly at peak effect of isosorbide dinitrate, with either drug.

There was wide individual variation in initial cardiac index, left ventricular filling pressure, and systemic vascular resistance. There was less variation in response to amrinone and pirbuterol. There was less variability in the effect of isosorbide dinitrate on filling pressures and vascular resistance (Fig. 6 to 8).

Unfortunately, pretreatment haemodynamic values could not predict any individual response to these drugs.

**PLASMA AMRINONE LEVELS**

Plasma amrinone concentrations, measured at the time of peak effect in seven of the patients, ranged from 0.56 to 1.33 μg/ml (mean 0.93±0.12 μg/ml). Though little is known of amrinone's pharmacokinetics in man, these concentrations are lower than those achieved by intravenous infusion or with larger oral doses of the drug, because we used a lower dose to avoid side effects.

**PLASMA PIRBUTEROL LEVELS**

Plasma pirbuterol concentrations were not measured in this study, because earlier work has shown that an oral dose of 20 mg eight hourly produces almost maximal blood levels, sufficient to obtain maximal haemodynamic effect.

**FOLLOW-UP AND ADVERSE EFFECTS**

Eleven of the 13 patients reported subjective improvement during the studies. No adverse effects were noted during acute administration of any of the drugs, other than mild headache after isosorbide dinitrate. There was no angina and arrhythmias.

After the acute challenge, 10 of the patients began chronic treatment: seven receiving pirbuterol, 20 mg t.i.d., and three amrinone, 100 mg t.i.d. Of the patients continued on pirbuterol, two died within three months of refractory heart failure. No adverse effect was reported with pirbuterol, but one patient failed to improve clinically despite an initial response, and was therefore started on amrinone, with pronounced clinical improvement. Of the four patients who thus received amrinone chronically, one died of bronchopneumonia, and two had to be withdrawn because of adverse effects: intolerable gastrointestinal disturbance in one and a thrombocytopenic reac-
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Fig. 7 Individual variation in left ventricular filling pressure after amrinone, pirbuterol, and additional isosorbide dinitrate.

Fig. 8 Individual variation in systemic vascular resistance after amrinone, pirbuterol, and additional isosorbide dinitrate.

tion in the other. This latter patient did not have a high plasma amrinone concentration (2.08 μg/ml) just before his maintenance dose at the time of this reaction, and was found to have a pronounced increase in antiplatelet IgG antibodies. The fourth patient on long term amrinone has improved clinically, without any fall in platelet count.

In five patients, left ventricular filling pressure was not reduced to less than 20 mmHg by amrinone or pirbuterol alone, but did fall to less than 20 mmHg after additional isosorbide dinitrate. These five patients received additional long term oral isosorbide dinitrate (80 mg daily), with improvement in their breathlessness.

Of the three patients who were not continued on chronic therapy with either drug, one died of intractable heart failure, and two are on other vasodilator therapy, with little clinical improvement.

Discussion

This study shows that the acute haemodynamic effects of amrinone and pirbuterol are indistinguishable in patients with chronic heart failure. Both drugs produce equal increases in cardiac output, accompanied by reductions in left ventricular filling pressure and systemic vascular resistance, while the blood pressure remains unchanged. Though left and right ventricular filling pressures are reduced by both drugs, this effect is not maximal and can be enhanced by the addition of a nitrate.

Three previous studies have compared the effects of
positive inotropic and vasodilator drugs in chronic heart failure in the same patient. When the beta-1 agonist, dobutamine, was compared with the "balanced" vasodilator, nitroprusside,22 blood pressure was higher with dobutamine and filling pressure lower with nitroprusside, but other hemodynamic variables were altered equally. When dobutamine was compared with pirbuterol,23 the reduction in systemic vascular resistance and filling pressure was greater with pirbuterol, which also reduced blood pressure. In a comparison of amrinone with hydralazine,12 amrinone caused a greater fall in filling pressure, neither drug altered blood pressure, and systemic vascular resistance was reduced equally.

Although animal experiments suggest that amrinone is a positive inotropic agent,5 there is, in fact, only limited evidence of a positive inotropic action in man. Initial reports showed improvement of systolic time intervals in normal volunteers,26 and increased left ventricular dp/dt in five patients with heart failure.7 Otherwise, a positive inotropic effect has only been implied by the acute haemodynamic effect of increased cardiac output and reduced ventricular filling pressure. Such effects, however, give an unreliable indication of positive inotropic action27 28 and may be produced by pure vasodilators.29 The apparent vasodilator effects of amrinone could be a result of a direct vasodilator action, but might also be the result of a withdrawal of vasoconstrictive influences after the improved cardiac output produced by a positive inotropic effect.

The exact mechanism of action of these drugs is difficult to establish in man. If both amrinone and pirbuterol act as vasodilators with additional positive inotropic effect, such a combined action would have certain advantages in chronic heart failure. A pure positive inotropic effect might be expected to increase myocardial oxygen consumption30 31 which would be detrimental in heart failure caused by ischaemic heart disease. A pure vasodilator on the other hand, while reducing myocardial oxygen consumption, might not increase cardiac output and regional perfusion, and may be harmful, if the myocardium cannot respond appropriately to the reduction in preload or afterload.32 When vasodilatation occurs in the presence of a positive inotropic effect, the overall reduction in ventricular wall tension with decreased end-diastolic and end-systolic volumes, allows contractility to increase without increasing myocardial oxygen consumption. Neither amrinone33 nor pirbuterol20 increases myocardial oxygen consumption in man at rest, despite improving ventricular function by increasing cardiac output at lower filling pressures.

A reduction in ventricular filling pressure is often attributed to venodilatation, though such an effect may also occur after arterial vasodilatation simply from the reduction in ventricular volumes. Though both amrinone and pirbuterol reduced ventricular filling pressures in our study, further reduction in ventricular filling pressure could be achieved with the predominant venodilator isosorbide dinitrate. This appears to be beneficial since the increased cardiac output was maintained with lower filling pressures. The addition of a nitrate should therefore be considered if breathlessness or pulmonary oedema are not corrected by amrinone or pirbuterol alone.

It is difficult to predict any possible long-term benefit with drugs in heart failure from their acute haemodynamic effects. Many complex considerations determine long-term benefit, including the natural progression of the disease, attenuation of drug action, and unwanted effects of the drugs. Whereas pirbuterol is well tolerated and has no serious adverse effects during chronic treatment, amrinone can cause thrombocytopenia even if a low dose is used.

There is no clear evidence as yet that treatment with any inotropic or vasodilator drug improves survival in chronic heart failure, but the patient's quality of life is often improved by such treatment. The careful use of these agents should be considered when conventional treatment fails to produce clinical improvement.

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References

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