Haemodynamic effects of ICI 118,587 in cardiomyopathy

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SUMMARY The haemodynamic effects of a new β_1 -adrenoceptor partial agonist, ICI 118,587, were studied in 10 patients with dilated cardiomyopathy and moderate to severe cardiac failure. Simultaneous right and left heart catheterisations were performed. Resting central haemodynamic indices were measured before and 15 min after an intravenous dose of 0.05 mg/kg and then 15 min after an additional intravenous dose of 0.15 mg/kg of ICI 118,587. Left ventricular performance was improved—as shown by significant increases in systolic left ventricular pressure, maximum rate of rise in left ventricular pressure (dP/dt max), and cardiac output and a decrease in left ventricular end diastolic pressure—without an undesirable increase in heart rate. The top of the dose response curve was reached after the lower dose. An important unwanted effect was seen in the most severely diseased patient, whose left ventricular systolic pressure, dP/dt max, and cardiac output decreased. This was probably due to the drug's antagonistic property supervening in this patient, who probably had high concentrations of circulating catecholamines. It is concluded that ICI 118,587 has a positive inotropic action and improves cardiac performance in patients with dilated cardiomyopathy and moderate cardiac failure, although care should be exercised when the drug is given intravenously in severe failure.

The standard treatment for cardiac failure has been digitalis, which has a positive inotropic action on the failing myocardium and which is often given with a diuretic. Apart from a narrow therapeutic index,¹ the long term efficacy of digitalis treatment in patients with sinus rhythm has been questioned.² Drugs which have a positive inotropic action by stimulating beta adrenoceptors represent an alternative approach.

The treatment of cardiac failure in dilated cardiomyopathy is particularly difficult and controversial. Drugs with a positive inotropic action such as digitalis and those with negative inotropic properties such as beta blocking agents³ have been used with success. A new drug, ICI 118,587 (Corwin), has recently been introduced for clinical trials. Preliminary studies in the dog have characterised it as a cardioselective beta adrenoceptor partial agonist.⁴ Since it combines stimulating and blocking properties it was

reasonable to expect that it could have beneficial effects on cardiac failure in cardiomyopathy. The present trial was, therefore, performed to evaluate its haemodynamic profile in this condition.

Patients and methods

Ten patients (mean age 41 years) with dilated cardiomyopathy gave their informed consent to participate in the study. Four of them had symptoms in New York Heart Association class II, five in class III, and one in class IV. They were all in sinus rhythm and haemodynamically and angiographically had no valvular or coronary heart disease. None were taking beta blocking agents and five, who were taking digitoxin, had the drug withdrawn six days before the study.

CARDIAC CATHETERISATION

The investigation was performed in the supine position in the catheterisation laboratory after an overnight fast. No premedication was given. Simultaneous right and left heart catheterisations were performed. A Swan-Ganz thermodilution catheter was used on the right side and a Millar tip transducer catheter on the left. Cardiac output was measured by thermodilu-

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tion. Pressures were measured by the tip transducer on the left side and by a liquid filled catheter system on the right with a Siemens-Elema (S-E) transducer 746. All tracings were made on a Minograph 800 (S-E) ink jet recorder. Ten consecutive beats were analysed and the mean pressures calculated.

After the catheters were introduced the patients had a 10 min rest period before central haemodynamic indices were measured. The same indices were again measured 15 min after a 0.05 mg/kg intravenous dose of ICI 118,587 and then 15 min after an additional 0.15 mg/kg intravenous dose, giving a total dose of 0.2 mg/kg. Each injection was given over a 5 min period.

STATISTICAL METHODS

The three different time points in the study were compared in pairs by Student's *t* test for paired observations. Values are expressed as means $\pm$ SEM, and $p < 0.05$ is considered to be significant.

Results

Nine patients completed the study. One patient received only the first dose because his blood pressure decreased and he appeared clinically to be in a state of preshock shortly after receiving the drug. Although he recovered completely within half an hour after raising the legs and receiving an intravenous saline infusion the trial was discontinued in this patient. The statistical evaluation refers to the nine patients (cases 1–9) who completed the study, whereas the results of the latter patient (case 10) are shown separately. The Table summarises the haemodynamic effects after the two drug doses. Since ICI 118,587 is a new drug and is previously untried in patients with dilated cardiomyopathy the haemodynamic indices for each patient are shown in the Figure.

HAEMODYNAMIC RESPONSE

The individual response of the heart rate to the drug was variable with increases and decreases at both dosages. The overall effect was a small increase, which

was not significant at either dosage. The basal heart rate for the patient in case 10 was 100 beats/min and showed a slight reduction to 95 beats/min after the lower dose.

The response of the systolic blood pressure was measured as the left ventricular peak systolic pressure (Figure a). ICI 118,587 produced a dose related significant increase in systolic blood pressure. The mean increase was 8% ($p < 0.01$) after the first and 10% ($p < 0.001$) after the second dose. The systolic pressure in the patient in case 10 decreased by 30 mm Hg. The drug decreased left ventricular end diastolic pressure in all patients at both dosages although not always in relation to the dosage (Figure b). Mean baseline left ventricular end diastolic pressure decreased by 26% ($p < 0.01$) after 0.05 mg/kg ICI 118,587, and increasing the dose to 0.2 mg/kg gave no further decrease in mean pressure.

The mean change in contractile function, as indicated by maximum rate of rise in left ventricular pressure (dP/dt max) was significantly increased by 47% ($p < 0.001$) by the lower dose with no significant additional change after the higher dose (Figure c). The patient in case 10 responded with a reduction in left ventricular dP/dt max. There was an 11% ($p < 0.05$) increase in cardiac output after the first dose (Figure d). Five of the nine patients completing the trial responded with a dose related increase in cardiac output, but overall there was no significant additional effect with the second dose. Right atrial and pulmonary systolic pressures were virtually unchanged throughout the study. The haemodynamic values indicate, as does the clinical classification, that most of the patients had a minor degree of heart failure at the time of the study.

Discussion

Wide clinical experience with dobutamine and dopamine, both of which are pure agonists, has established that they produce positive inotropic effects in patients with cardiac failure, even in severe grades.⁵ Experiments in the dog have shown that ICI 118,587

Table Haemodynamic effects of ICI 118,587 given intravenously in dilated cardiomyopathy. Values are means $\pm$ SEM ($n=9$). (The results in parentheses are for one patient, who received only one dose because of undesirable side effects.)

	Control values	After 0.05 mg/kg	After 0.2 mg/kg
Left ventricular peak systolic pressure (mm Hg)	133.0 $\pm$ 8.7 (130)	143.4 $\pm$ 9.8** (100)	146.2 $\pm$ 9.3***
Left ventricular end diastolic pressure (mm Hg)	19.3 $\pm$ 2.8 (46)	13.6 $\pm$ 2.4** (38)	13.6 $\pm$ 2.3**
Left ventricular dP/dt max (mm Hg/s $\times 10^{-3}$)	2114 $\pm$ 144 (1702)	3112 $\pm$ 231*** (1288)	3083 $\pm$ 249***
Cardiac index (l/min/m ²)	3.4 $\pm$ 0.2 (1.2)	3.8 $\pm$ 0.2* (1.0)	4.0 $\pm$ 0.2*
Heart rate (beats/min)	72.3 $\pm$ 3.8 (100)	77.2 $\pm$ 3.8 (95)	76.4 $\pm$ 5.1
Right atrial pressure (mm Hg)	8.4 $\pm$ 1.4 (11)	9.1 $\pm$ 1.8 (21)	7.9 $\pm$ 1.9
Pulmonary artery systolic pressure (mm Hg)	25.8 $\pm$ 2.2 (75)	24.3 $\pm$ 2.1 (70)	28.0 $\pm$ 2.2

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Figure Effect of two different doses of ICI 118,587 on (a) left ventricular (LV) peak systolic pressure, (b) left ventricular end diastolic pressure, (c) left ventricular dP/dt max, and (d) cardiac index.

is a β_1 adrenoceptor partial agonist, producing positive inotropic effects, but being a partial agonist it will also act as an antagonist to a pure agonist such as noradrenaline.⁴ Both positive and negative inotropic drugs have been used in the treatment of patients with dilated cardiomyopathy.³ It was therefore of particular interest to study the effect of ICI 118,587 in patients with this condition, which results in depressed left ventricular function and evidence of cardiac failure.

The patients in this study all had idiopathic dilated cardiomyopathy, the diagnosis of cardiac failure being based on symptoms and chest x ray findings. Cardiac catheterisation confirmed the diagnosis in all patients and showed a moderate degree of cardiac failure, except in one patient in whom the various indices of left ventricular function were grossly abnormal indicating severe impairment of cardiac performance.

With the exception of this one patient, ICI 118,587 produced an increased left ventricular performance in all the patients as shown by increases in left ventricular systolic pressure, left ventricular dP/dt max, and cardiac output as well as a decrease in left ventricular end diastolic pressure. The most impressive effect was an approximate 50% increase in left ventricular dP/dt max, which is generally accepted as being a sensitive index of ventricular contractility. This confirms that the agonist action in human volunteers, as shown by a decrease in systolic time intervals,⁶ is also produced in patients with cardiac failure. Even when a positive acute response is found, a relatively rapid tolerance to sympathomimetic agents usually occurs during long term treatment. The possibility that a partial agonist, which produces only a submaximal stimulation, may avoid this problem needs to be investigated.

The indices of left ventricular performance were not increased when the dose of ICI 118,587 was raised from 0.05 to 0.2 mg/kg. This shows that the top of the dose response curve had been reached with the lower dose. Neither arrhythmias nor other adverse effects were noted, and the haemodynamic state was improved without an undesirable tachycardia. This confirms results in the conscious dog, which showed that the positive inotropic action was not accompanied by a rise in heart rate, in contrast to the results in an areflexic dog preparation, suggesting that this was probably due to an increased reflex vagal tone.

ICI 118,587 is a partial agonist and may act as either an agonist or an antagonist depending on the level of sympathetic activity. This has been shown in the dog, where it acted as an agonist when the sympathetic tone was low but reduced the maximum heart rate response to high concentrations of endogenous noradrenaline released by maximal stimulation of the sympathetic nerves.⁴ This effect has also been shown in multistage exercise testing in humans, in whom the heart rate was unaffected by ICI 118,587 at moderate exercise levels but was reduced during more intense exercise indicating the antagonist action.⁷ This may account for the effects in the most seriously ill patient (case 10), who responded to the drug with decreases in systolic pressure, left ventricular dP/dt max, cardiac output, and heart rate indicating a decrease in pumping function, although there was a decrease in the filling pressure. The response could be explained in two ways. The patient may have had a vasovagal attack, the peripheral vasodilatation producing a decreased venous return resulting in a reduced cardiac contractility and output. Alternatively, he may have had a high background sympathetic tone as a compensatory reflex to the severe cardiac failure. It has been shown that patients in severe cardiac failure have a reflex compensatory increase in sympathetic tone reflected by increased concentrations of circulating noradrenaline.⁸ In such patients the positive inotropic agonist effect of the beta adrenoceptor partial agonist may not be manifest in the presence of high circulating concentrations of catecholamines, and it could act as an antagonist producing negative inotropic effects. If these conditions prevailed in this patient ICI 118,587 could have acted as an antagonist, and the time relation between dose and response supports this view, although complete recovery occurred long before the effect of the dose could have been expected to disappear. Care should, therefore, be exercised when ICI 118,587 is given by rapid intravenous injection to patients in severe cardiac failure. Limited clinical experience with prenalterol, another beta adrenoceptor partial agonist, has, however, shown

positive inotropic effects in patients with cardiac failure.^{9,10}

Nevertheless, this small study shows that in most of the patients investigated ICI 118,587 acted as a positive inotropic agent and produced improved cardiac performance in those with cardiomyopathy, as has been reported earlier in patients with coronary artery disease.¹¹ This does not, however, imply better long term prognosis, and further studies are therefore needed comprehensively to define the role of chronic oral treatment with the drug in managing cardiac failure due to various causes, especially in the mild to moderate grades.

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