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Pimobendane (UD-CG 115 BS) in the treatment of severe congestive heart failure. An acute haemodynamic cross-over and double-blind study with two different doses

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1 We compared the effects of two doses (5 and 10 mg) of oral pimobendane (UD-CG 115) on haemodynamics in eight patients suffering from chronic congestive heart failure. The two doses were given according to a randomized cross-over double-blind protocol; haemodynamics and plasma levels of pimobendane and its main metabolite UD-CG 212, were determined 1, 2, 3, 5, 7, 9, 11 and 12 h after each dose.

2 Both doses significantly improved the left and right ventricular functions of these patients, with a peak action 3 h after drug intake and long duration (more than 12 h). A significant dose-effect relationship was observed only for pulmonary wedge pressure and right atrial pressure. Significant correlations were found between UD-CG 212 plasma levels and cardiac index ($r = 0.54$, $P < 0.05$), and pulmonary wedge pressure ($r = 0.74$, $P < 0.001$); no correlation was found between these haemodynamic variables and pimobendane plasma levels.

3 One patient developed a transient drop in blood platelets together with a cutaneous rash, while three others had a transient and mild decrease of thrombocytes.

4 In conclusion, pimobendane improved right and left ventricular functions in severe heart failure. Both doses (5 and 10 mg) were effective. The higher dose induced marked improvement of the haemodynamic variables but the difference between doses was only significant for right atrial and pulmonary wedge pressures.

Keywords pimobendane UD-CG 212 haemodynamics heart failure

Introduction

Pimobendane (UD-CG 115 BS), a benzimidazole-pyridazinone derivative, is one of the new inotropic and vasodilating agents with phosphodiesterase-inhibiting properties (Diederen *et al.*, 1982).

Phosphodiesterase inhibitors show beneficial effects on the failing myocardium by increasing cAMP level in myocardial cells and, as was shown for sulmazole and pimobendane, increasing the sensitivity of myofibrils to calcium ions (Rüegg, 1986).

However, the main observed final effect of pimobendane in animal experiments is vasodilatation of the pulmonary and systemic vascular system (Verdouw *et al.*, 1986). This effect, through a fall in left ventricular filling pressure, is responsible for a decrease in cardiac output and stroke volume in animals without heart failure (Verdouw *et al.*, 1986), in spite of the increase in max LVdP/dt.

The purpose of the present study was to assess the acute haemodynamic effects after oral

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administration of pimobendane in patients with severe congestive heart failure and to compare the effectiveness of the two different doses in a randomized cross-over double-blind protocol.

Methods

Eight patients with a mean age of 64 years (from 59 to 73) were studied. All had severe chronic heart failure (class III or IV of the N.Y.H.A.) due to ischaemic cardiomyopathy, in spite of digoxin (0.25 mg day^{-1}) and frusemide (40 mg day^{-1}) treatment. At the time of their admission to the hospital, two were in class III and six in class IV of the N.Y.H.A. functional classification, and all had pulmonary wedge pressures (PWP) greater or equal to 18 mm Hg.

A Swan-Ganz flow-directed catheter was introduced into the pulmonary circulation for the measurement of pulmonary and right atrial pressures whilst the thermodilution technique was used for cardiac output determination. Systemic blood pressure was measured by sphygmomanometer. The following variables were calculated according to the usual formulae: cardiac index, stroke volume index, mean pulmonary and systemic arterial pressures, systemic vascular resistance and pulmonary vascular resistance.

In order to assess the stability of haemodynamic conditions before the study, the patients were at rest in bed more than 3 days before the Swan-Ganz catheter was introduced. The first haemodynamic measurements were taken 3 h after the catheterization and the study only undertaken if the measurements remained stable for 24 h.

Drug protocol

Oral informed consent was obtained from each patient. At least 24 h prior to the study, all vasodilators were discontinued. Baseline haemodynamic values were established by repeated measurements before drug administration on the first day (D1). A first dose of the drug was administered orally (5 or 10 mg at random and double-blind) and haemodynamic measurements were taken after 1, 2, 3, 5, 7, 9, 11 and 12 h. On the following day (D2), considered as the 'wash-out time', haemodynamic measurements were repeated 24, 27 and 30 h after the first dose to assess the duration of the haemodynamic changes after a single dose of pimobendane. On the third day (D3) and after completion of baseline measurements, the second (alternative) dose of pimobendane was given, the haemodynamic measurements, being repeated with the same timing as before.

Blood samples for determination of the plasma levels of UD-CG 115 and its metabolite, UD-CG 212, were collected at the time of each haemodynamic measurement. To evaluate possible side effects of the drug, the following laboratory tests were performed before (DO) and after (D4) drug administration: haematology, glucose + insulin, uric acid, creatinine, bilirubin, proteinogram, blood coagulation tests and plasma enzyme activity (CK, AspAT, A1AT, LDH, alkaline and acid phosphatase, γ GT). ECGs were evaluated each day during the 4 day study.

Statistics

All data are expressed as mean ± s.e. mean. We used the two-way analysis of variance for repeated measurements to assess the evolution of haemodynamic parameters in relation to time, followed by Dunnett's method for multiple comparisons with the baseline (Dunnett, 1964). The area under the curve for the comparison of the two doses was assessed by latin squares analysis of variance and randomized block(s) analysis of variance, where applicable. Baseline values for D1 and D3 were compared by the use of the *t*-test for paired variables to highlight possible 'hang-over' effects on D3.

Results

UD-CG 115 and UD-CG 212 plasma levels

Mean values of UD-CG 115 and 212 after both doses are presented in Figure 1. As predicted by analysis of variance for interaction the two curves (after 5 and 10 mg) are not parallel ($P < 0.01$). Peak mean plasma UD-CG 115 level (19.5 ± 3.1 ng ml^{-1}) was reached 3 h after the 5 mg dose and 2 h after the 10 mg dose (39.3 ± 6.2 ng ml^{-1}). The peak mean plasma level of UD-CG 212 was reached within 3 h after both doses of pimobendane and was approximately twice as high after 10 mg (44.0 ± 8.8 ng ml^{-1}) than after 5 mg (20.8 ± 2.1 ng ml^{-1}). Twelve hours after the drug's administration, UD-CG 115 was still present in the plasma of one 5 mg patient and three 10 mg patients.

Haemodynamic results

Mean values of heart rate, cardiac index, stroke volume index, systemic and pulmonary pressures, pulmonary wedge pressure, right mean atrial pressure, pulmonary and systemic vascular resistances after both doses are presented (Figures 2, 3 and 4).

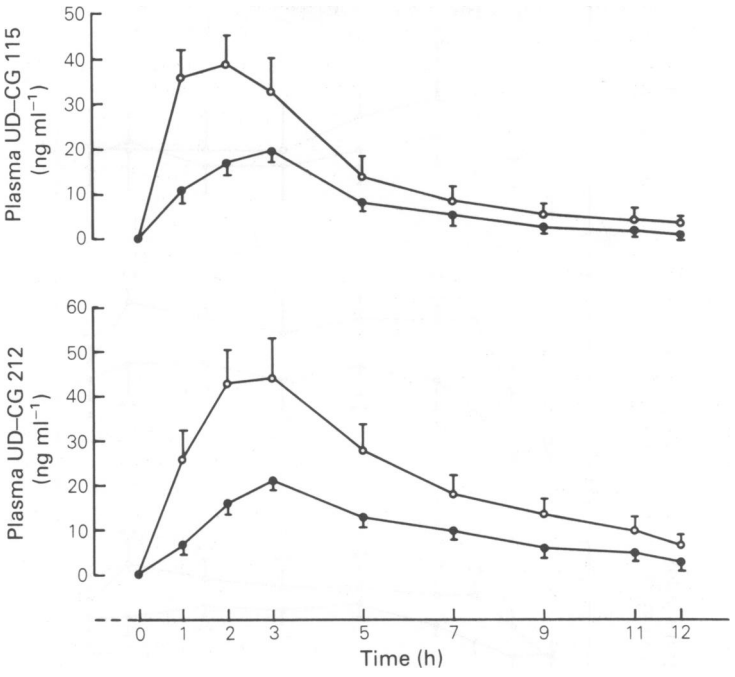

Figure 1 Mean ± s.e. mean (n = 8) values of pimobendane (UG-CG 115) and UD-CG 212 plasma levels determined after oral administration of 5 (•) and 10 mg (○) of pimobendane.

Heart rate increased significantly 3 h after the administration of 10 mg (from 89 ± 5 to 98 ± 7 beats min^{-1}, $P < 0.05$).

Cardiac index increased from 1.9 ± 0.2 to 2.4 ± 0.2 l min^{-1} m^{-2} ($P < 0.01$) after administration of 5 mg of pimobendane, and from 1.8 ± 0.2 to 2.7 ± 0.2 l min^{-1} m^{-2} ($P < 0.01$) after 10 mg. Although a gradual increase in cardiac and stroke volume indices was observed within 5 h after 5 mg doses, after 10 mg, an obvious increase in cardiac and stroke indices was already present within 2 h; a plateau was observed after both doses, the effect being significantly maintained until the 12th hour.

Pulmonary wedge pressure decreased from 29 ± 3 to 19 ± 4 mm Hg ($P < 0.01$) after 5 mg and from 27 ± 4 to 14 ± 3 mm Hg ($P < 0.01$) after 10 mg; the right atrial pressure decreased from 9 ± 3 to 2 ± 1 mm Hg ($P < 0.01$) after 5 mg and from 9 ± 2 to 1 ± 1 mm Hg ($P < 0.01$) after 10 mg of pimobendane. The peak effect on pulmonary wedge pressure was observed after 3 h for the 5 mg dose and after 2 h for the 10 mg dose.

A slight decrease in systolic and diastolic systemic arterial pressures was observed after both doses with maxima between 5 and 7 h after pimobendane administration, but this fall was only significant after 10 mg. There was also a significant ($P < 0.01$) decrease in pulmonary and systemic vascular resistances which were maximal 5 h after both doses.

Comparison of the area under the curve for the haemodynamic effects of each dose and statistical analysis shows a significant difference between the doses for pulmonary wedge pressures ($P < 0.05$), diastolic and mean pulmonary pressures ($P < 0.01$) and right atrial pressure ($P < 0.05$). No significant difference was found between the doses for heart rate, systemic (systolic and diastolic) arterial pressures, systolic pulmonary pressure, systemic and pulmonary vascular resistances, cardiac index and stroke volume index. It is interesting to emphasize that after 10 mg the decrease of the systemic vascular resistance and the increase of cardiac and stroke indices occur earlier (2 h) than after 5 mg (5 h).

Baseline haemodynamic values on D1 were analysed looking for a 'hang-over' effect of the first dose. For such haemodynamic parameters as cardiac index, stroke volume index, pulmonary wedge pressure and systemic as well as pulmonary vascular resistance, 90–110% confidence limits were established on D1 for baseline values. The calculated mean times of return of these variables to confidence limits of baseline values after the first dose were as follows: for cardiac and stroke

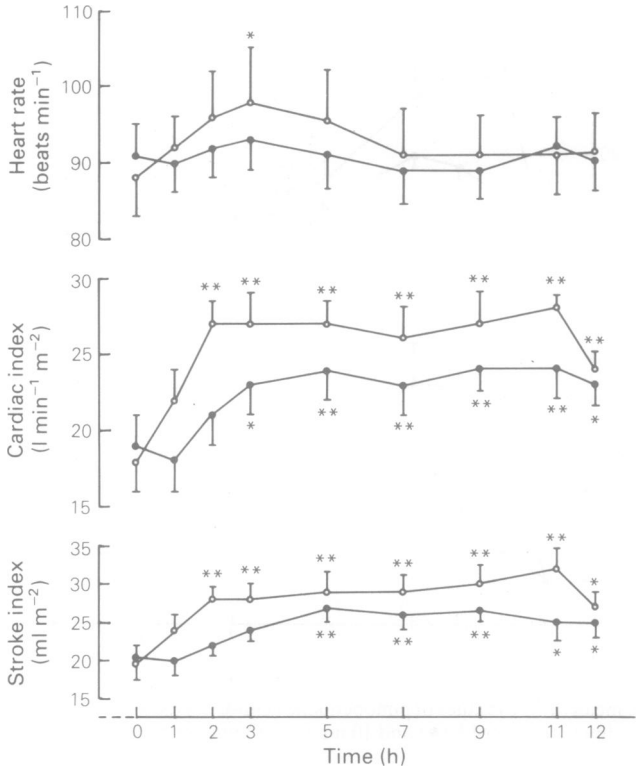

Figure 2 Evolution of heart rate, cardiac index, and stroke index after the oral administration of 5 (●) and 10 mg (○) of pimobendane. Values are mean ± s.e. mean, $n = 8$ $^{*}P < 0.05$, $^{**}P < 0.01$.

volume indices 27–31 h, for pulmonary wedge pressure 12–24 h, for systemic vascular resistance 24–27 h and for pulmonary vascular resistance 24–31 h. This suggests that, after a single dose of pimobendane, cardiac and stroke volume indices as well as pulmonary vascular resistance, are altered for a longer time than pulmonary wedge pressure. The 24 h wash-out period was sufficient since the baseline values before the first and second doses (administered 48 h after the first one) of pimobendane were not significantly different.

The UD-CG 115 and 212 plasma levels (regardless of dose given) were compared with the cardiac index and pulmonary wedge pressure to find a possible dose-response relationship. No significant correlation was found between UD-CG 115 plasma levels and cardiac index or pulmonary wedge pressure values. However, UD-CG 212 levels were related to cardiac index ($r = 0.54$, $P < 0.05$) and even more to pulmonary wedge pressure ($r = 0.74$, $P < 0.001$).

Side effects

Pimobendane given together with heparin induced a cutaneous rash and a fall in blood platelets (from 150.000 to 46.000/mm^3) in one patient but this reaction was relieved 4 days after the drug was stopped. Three other patients developed thrombocyte counts below the normal limit of 150.000/mm^3 (from 131.000 to 110.000/mm^3) but these patients were also receiving heparin which can induce a fall in blood platelets (Bell, 1976).

Discussion

Trials with non-glycoside, non-catecholamine drugs which have both potent inotropic and vasodilating effects are among the most promising recent developments in the field of heart failure. Among them, amrinone, milrinone and MDL 17043 have already been tested clinically in short and long-term studies, but these drugs are not free of side-effects and their usefulness requires further clinical information (Colucci *et al.*, 1986; Likoff *et al.*, 1984).

Pimobendane is a new phospho-diesterase inhibitor which has shown some promising results in animal studies (Diederen *et al.*, 1982; Verdouw *et al.*, 1986).

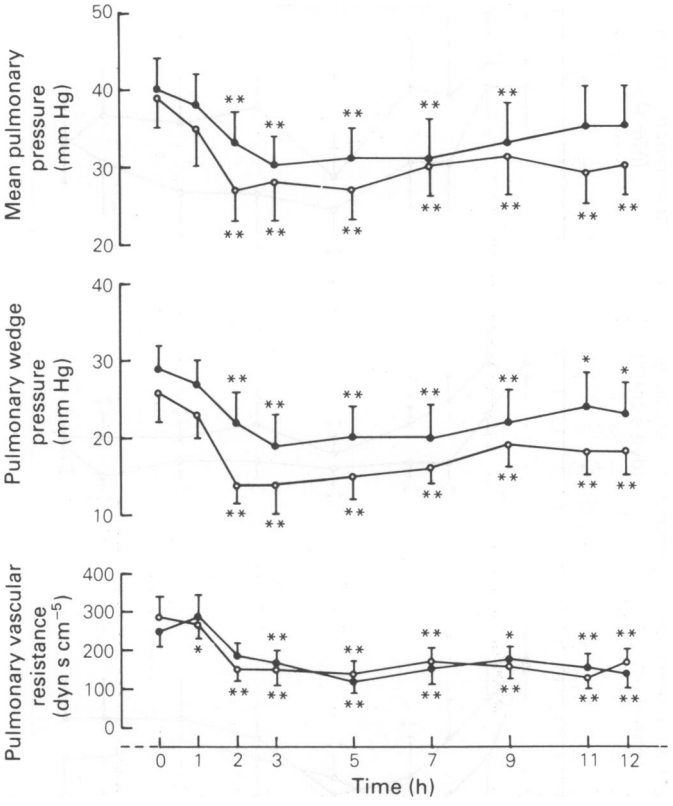

Figure 3 Evolution of mean pulmonary pressure, pulmonary wedge pressure and pulmonary vascular resistance after the oral administration of 5 (●) and 10 mg (○) of pimobendane. Values are mean ± s.e. mean, $n = 8$ *$P < 0.05$, **$P < 0.01$.

In our group of eight patients with chronic, severe congestive heart failure (mean PWP 27–29 mm Hg) we administered two different doses of pimobendane in a double-blind and randomized cross-over design. We observed beneficial effects on cardiac index, stroke volume index, pulmonary wedge pressure, right atrial pressure and systemic as well as pulmonary vascular resistance after both doses. The effects were more obvious after 10 mg for most of these variables (Figures 2, 3 and 4) but a significant difference between doses was found for only pulmonary and right atrial pressures. The maximum changes in cardiac and stroke volume indices were observed 5 h after the 5 mg dose; this occurred 2 h after the peak decrease in pulmonary wedge pressure. After 10 mg an almost maximum effect on cardiac and stroke volume indices was already observed after 2 h, together with their maximum decrease of pulmonary wedge pressure, systemic vascular resistances and the highest observed UD-CG 115 plasma level.

The role of active pimobendane metabolites still remains controversial as regards the evolution of haemodynamic variables. Although plasma levels of UD-CG 115 and 212 increased at a similar rate, we found significant correlation only between UD-CG 212 plasma levels and values of pulmonary wedge pressure and cardiac index. This relationship could be due to chance in a small sample but may possibly be explained by the role of the metabolite, UD-CG 212, on the haemodynamic changes.

After pimobendane administration we observed a transient decrease of blood platelets in four patients which was severe in one of them. This effect was already reported for other phosphodiesterase inhibitors (Colucci *et al.*, 1986) and further evaluation of this side effect is required. However four patients were also treated with heparin which can induce a fall in blood platelets (Bell, 1976). No arrhythmias or hyperglycaemia were observed.

Although further studies are required to fully

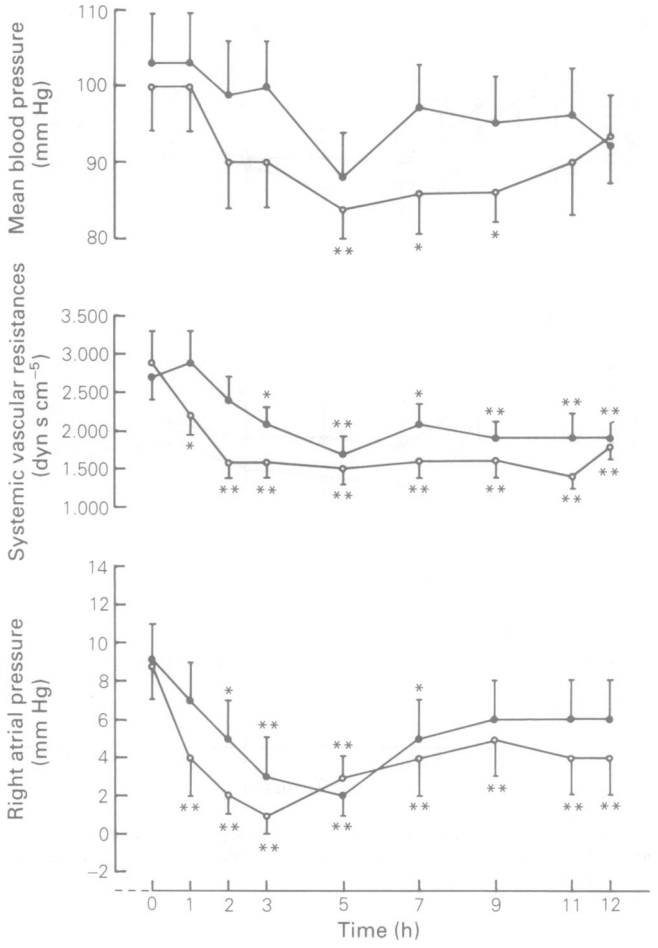

Figure 4 Evolution of mean blood pressure, systemic vascular resistance and right atrial pressure after the oral administration of 5 (●) and 10 mg (○) of pimobendane. Values are mean ± s.e. mean, $n = 8$, $^{*}P < 0.05$, $^{**}P < 0.01$.

assess the clinical usefulness of pimobendane, our results suggest its beneficial influence on ventricular function in severe, congestive heart failure refractory to conventional treatment, at least in short-time therapy.

A significant dose-effect relationship was observed only at pre-load level (pulmonary and right atrial pressures).

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