Acute Hemodynamics of Pimobendan in Chronic Heart Failure

A Comparative Crossover Study of Captopril and Pimobendan

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SUMMARY

Acute hemodynamics of pimobendan were compared to captopril in a crossover trial in patients with chronic heart failure (NYHA II—III). Heart failure had been stabilized by conventional therapy with diuretics and digitalis for more than 2 weeks. Patients receiving vasodilators were excluded. The hemodynamics were analyzed using a Swan-Ganz catheter at the bedside during drug administration.

Following an intravenous injection of 2.5 mg of pimobendan, there was a significant increase in heart rate and decrease in mean pulmonary artery pressure, total pulmonary resistance, mean arterial pressure, systemic vascular resistance and mean right atrial pressure 2 hours after the injection. Captopril (12.5 mg, orally) significantly decreased mean arterial pressure, systemic vascular resistance and double product 2 hours after administration. In this study, the inotropic effect was evaluated through the relation between the stroke volume index and diastolic pulmonary artery pressure, and also between the stroke volume index and mean arterial pressure. Although decreases of diastolic pulmonary artery pressure and mean arterial pressure were seen with both drugs, the differences in stroke volume index were not significant.

In comparison with captopril, the acute hemodynamics of pimobendan are characterized as follows: 1) the systemic arteriovasodilating effects of the two drugs were equal, 2) the pulmonary arteriovasodilating effect of pimobendan was marked, 3) a venodilating effect, documented through a decrease of mean right atrial pressure, was seen only with pimobendan.

This study concluded that pimobendan is a stronger arterio-venodilator than captopril.

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CURRENTLY, in the treatment of congestive heart failure, digitalis and diuretics have played primary roles in practical clinical therapy, in addition to basic nonpharmacological treatment such as rest, weight reduction and low-salt diet. In addition, vasodilators have been employed as adjunctive therapy. One class of these vasodilator agents, angiotensin-converting enzyme (ACE) inhibitors, have become a focus of attention because of their ability to correct neurohumoral conditions produced by the hemodynamics of chronic heart failure and also their capability to improve myocardial metabolism.^{1),2)} At the same time, several inotropes, for example phosphodiesterase inhibitors and dopamine-like agents, emerged as candidates for adjunctive therapy and are being evaluated in the treatment of chronic heart failure. Among these new agents, inodilators occupy a unique position because they are expected to produce inotropic and vasodilating actions simultaneously.³⁾

Pimobendan is a representative inodilator.⁴⁾ This drug is an inhibitor of phosphodiesterase, but it has been shown that an increase of cyclic AMP contributes less to inotropism of the heart than other agents like amrinone or milrinone.⁵⁾ The positive inotropic effect of pimobendan is also produced through an increase in the sensitivity of calcium ions to cardiac myofibrils.⁶⁾ Thus, the effect of pimobendan differs from other compounds in that its positive inotropism does not start immediately, but is delayed for a few hours after intravenous administration.⁶⁾

Thus, this study was designed to characterize the acute hemodynamics of pimobendan in chronic heart failure in comparison with the representative ACE inhibitor, captopril.

MATERIALS AND METHODS

Patient profile: This study was performed in 10 patients with chronic heart failure (NYHA class II—III), who had experienced several times previously either pulmonary or peripheral congestion. They were composed of 9 men and 1 woman; the mean age was 62 ± 5 years old. Their clinical profiles are shown in Table I. Five patients were diagnosed as having dilated cardiomyopathy and the other 5 patients regurgitant valvular heart disease. The heart failure had been stabilized by conventional therapy with diuretics and digitalis for more than 2 weeks. Chronic heart failure was defined by three criteria: cardiomegaly on chest X-ray (cardiothoracic ratio

Table I. Clinical Profiles of Patients

Case (No.)	Age (yr) & Sex	Diagnosis	NYHA (class)	CTR (%)	EDVI (ml/m ²)	ESVI (ml/m ²)	EF (%)
1	68 M	AR	III	65	156	122	22
2	70 M	DCM	II	51	115	74	36
3	55 F	DCM	III	52	124	62	50
4	65 M	OMI+MR	II	62	189	130	31
5	64 M	MR	III	64	113	67	40
6	57 M	DCM	II	39	98	63	35
7	58 M	AR	II	58	141	58	59
8	68 M	MR+TR	III	59	134	58	56
9	56 M	DCM	III	61	152	125	18
10	58 M	DCM	II	59	173	94	46

DCM=dilated cardiomyopathy; AR=aortic regurgitation; MR=mitral regurgitation; TR=tricuspid regurgitation; OMI=old myocardial infarction; CTR=cardiothoracic ratio; EDVI=end-diastolic volume index; ESVI=end-systolic volume index; EF=ejection fraction.

Table II. Intrapulmonary Shunt After Pimobendan Trial

Time	PaO ₂ (mmHg)	PaCO ₂ (mmHg)	SAT _v (%)	CI (l/min/m ²)	Oxygen Delivery (ml/min/m ²)
baseline	74.3	37.6	65.4	3.30	840
4 hours after injection	54.2	37.6	64.8	4.70	1154

CI=cardiac index; SAT_v=mixed venous oxygen saturation.

>55%), increased left ventricular end-diastolic volume index (>100 ml/m²) and reduced left ventricular ejection fraction (<50%) on left ventriculography. Patients receiving vasodilators were excluded.

Methods: A Swan-Ganz catheter was inserted through the internal jugular vein at the bedside. Mean pulmonary artery pressure (PAP), diastolic pulmonary artery pressure (PADP), mean right atrial pressure (RAP) and cardiac output were monitored serially. In case of tricuspid regurgitation, the cardiac output was measured by the Fick method. Systemic arterial pressure was measured directly and shown as mean arterial pressure (MAP). Blood to determine mixed venous oxygen saturation (SAT_v), arterial oxygen saturation (SAT_a) and arterial oxygen pressure (PaO₂) was sampled at each interval, namely with pimobendan, before administration and 30 min, 1, 2, 4 and 6 hours later; and with captopril, before administration and 1, 2 and 4 hours later. Hemodynamic indices of cardiac index (CI), stroke volume index (SVI), total pulmonary resistance (TPR), systemic vascular resistance (SVR), arterio-venous oxygen difference (AV-O₂) and double product (DP) were calculated according to the conventional formulas.

Heart rate (HR) was obtained from the ECG record.

Drug protocol: After catheter insertion, the patient was ordered to keep at absolute rest for more than 30 min. Baseline hemodynamic state was determined through three repeated measures before drug administration. On the first day, captopril was given orally (12.5 mg). Hemodynamics were checked after 1, 2 and 4 hours, respectively. On the next day, when more than 12 hours had passed from captopril washout, baseline values were confirmed again for the next administration. Pimobendan (2.5 mg) was dissolved in 5 ml of solvent and was diluted in 20 ml of 5% glucose. After a bolus of 2.5 mg pimobendan was injected intravenously, hemodynamics were checked at intervals of 30 min, 1, 2, 4 and 6 hours. The plasma levels of pimobendan (UD-CG 115) and its metabolite (UD-CG 212) were analyzed at each interval using a high-pressure liquid chromatographic assay.

Statistics: The data are expressed as the mean $\pm$ standard error. Two-way analysis of variance was used to assess hemodynamic change after administration, and Dunnett's method was employed for multiple comparisons with the baseline. Probability values less than 0.05 were denoted as significant differences.

RESULTS

Hemodynamic changes: Mean values of HR, CI, SVI, PAP, PADP, TPR, MAP, SVR, RAP, AV-O₂, PaO₂ and DP after administration of both drugs are presented (Figs. 2, 3, 4 and 5).

After captopril, MAP significantly decreased from 88 ± 11 to 75 ± 9 mmHg ($p < 0.001$), SVR from 2675 ± 1188 to 2200 ± 724 dyne $\cdot$ sec $\cdot$ cm⁻⁵ ($p < 0.01$), and DP from 10063 ± 1398 to 8136 ± 1347 mmHg $\cdot$ beats/min ($p < 0.001$). The effects of captopril on these variables were noted within be-

Fig. 1. Study protocol. Arrows show times of hemodynamic measurements.

Fig. 2. Changes in heart rate (upper panel), cardiac index (middle) and stroke volume index (bottom) after administration of 12.5 mg captopril (oral) and 2.5 mg pimobendan (intravenous bolus) in the same patients with chronic heart failure. Mean values are represented at each point and bars indicate standard error. *, **, ***: $p < 0.05$, $p < 0.01$, $p < 0.001$, respectively.

Fig. 3. Changes in mean pulmonary artery pressure (upper), diastolic pulmonary artery pressure (middle) and total pulmonary vascular resistance (bottom).

Fig. 4. Changes in mean arterial pressure (upper), systemic vascular resistance (middle) and mean right atrial pressure (bottom).

Fig. 5. Changes in arterio-venous oxygen difference (upper), arterial oxygen pressure (middle) and double product (bottom).

tween 1 and 4 hours.

Following pimobendan injection, HR significantly increased from 75 ± 16 to 92 ± 10 beats/min ($p < 0.001$). PAP significantly decreased from 20 ± 11 to 16 ± 9 mmHg ($p < 0.01$), TPR from 628 ± 422 to 422 ± 214 dyne·sec·cm⁻⁵ ($p < 0.01$), MAP from 79 ± 11 to 72 ± 7 mmHg ($p < 0.001$), SVR

Fig. 6. Influence of captopril (C) and pimobendan (P) on systemic vascular resistance (upper), total pulmonary vascular resistance (middle) and mean right atrial pressure (bottom). B=baseline; n.s.=not significant.

from 2430 ± 789 to 1884 ± 415 $\text{dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$ ($p < 0.01$) and RAP from 5 ± 3 to 2 ± 2 mmHg ($p < 0.001$). The effects of pimobendan on these variables were noted within between 1 and 6 hours.

The effects of pimobendan on the venous, pulmonary and systemic vascular systems of patients with chronic heart failure were compared to those of captopril (Fig. 6). At baseline and 2 hours after drug administration, both drugs significantly decreased SVR, but a significant decrease of TPR and RAP was limited to pimobendan.

The inotropic effect was evaluated using the relationships between SVI and PADP, and between SVI and MAP (Fig. 7). At the baseline and 2 hours after drug administration, decreases of PADP and MAP were seen with both drugs, but changes in SVI were not significant. Therefore, inotropism with pimobendan was not recognizable through the two relations.

UD-CG 115 and UD-CG 212 plasma levels: Peak mean plasma UD-CG 115 level and UD-CG 212 level were reached 30 min after pimo-

Fig. 7. Relation between stroke volume index and diastolic pulmonary artery pressure (left panel), and between stroke volume index and mean arterial pressure (right panel).

Fig. 8. Mean $\pm$ SE of pimobendan (UD-CG 115) and UD-CG 212 plasma levels determined after intravenous administration of 2.5 mg pimobendan.

bendan injection (Fig. 8). At 6 hours after administration, UD-CG 115 almost disappeared but UD-CG 212 was still present in the plasma of patients.

DISCUSSION

Positive inotropic effects of pimobendan have been demonstrated in

isolated heart preparations of various animals,⁵⁾ in vivo experiments in anesthetized or conscious animals^{4),6)} and clinical trials.⁶⁾⁻¹⁰⁾ But, why did stroke volume not significantly increase in these patients? Two factors might be responsible: (1) the patients investigated in the present study had slightly elevated systemic vascular resistance. The increase in stroke volume subsequent to reduction in afterload is known to be more pronounced in patients with increased systemic vascular resistance; (2) the marked decrease in left ventricular preload may counteract the inotropic effect from the point of view of the Frank-Starling mechanism. In the present study, pimobendan showed a tendency to cause preload reduction documented by the decrease of diastolic pulmonary artery pressure (Fig. 3). This suggests that cardiac index did not increase mainly due to preload reduction.

Transient but significant tachycardia was seen after pimobendan injection. The phenomenon was the only undesirable effect.⁷⁾⁻⁹⁾ This may have appeared through a sympathetic reflex. The other possibility may be as a result of an increase in cyclic AMP activity caused by myocardial phosphodiesterase inhibition. After intravenous bolus injection of pimobendan, the pharmacodynamics did not correlate to plasma levels.^{7),8)} The tachycardia started 60 min after the injection and it still remained 6 hours later in spite of the fact that mean arterial pressure recovered to normal. Therefore, the tachycardia may have been due to an increase of cyclic AMP in the myocardium produced by pimobendan.

In this study pimobendan was compared with captopril, since an ACE inhibitor is a standard agent for adjunctive therapy of chronic heart failure. The systemic hemodynamic effect of pimobendan was at least equal to that of captopril and the effect lasted longer. Furthermore, a demonstrable effect on the pulmonary and venous system is exaggerated with pimobendan.¹¹⁾ Because as is well known, a maximal hemodynamic response with ACE inhibitors may occur even after several weeks, a long-term comparative study between the two drugs is required.¹²⁾

When baseline hemodynamic values were compared, only MAP was significantly lower prior to pimobendan than before captopril ($p < 0.01$). It was speculated, that, in part, the blood pressure gap was due to daily variation and in other cases, some arteriovasodilating effect of captopril might remain until the next day. Certainly, the lower value of MAP could cause an underestimation of the arteriovasodilating effect of pimobendan.

In this study, ventricular arrhythmia was increased at 4 hours after pimobendan injection in 2 patients. But serious ventricular arrhythmias were not seen.^{13),14)}

It has already been reported that pimobendan might induce an intra-

pulmonary shunt flow. Only one patient experienced a decreased PaO_2 and increased oxygenation of mixed venous blood. This might have been due to the presence of an intrapulmonary shunt. Such effects on the blood gas levels have already been reported with some vasodilators,^{1b)} and the decrease in PaO_2 was not critical because oxygen delivery was maintained or improved.⁸⁾

REFERENCES

1. Parmley WW, Cohn JN, Levine TB, Awan NA, Mason DT, Faxon DP, Creager M, Gavras HP, Fouad FM, Tarazi RC, Hollenberg NK, Dzau V, LeJemtel TH, Sonnenblick EH, Turini GA, Brunner HR: A cooperative multicenter study of captopril in congestive heart failure: Hemodynamic effects and long-term response. *Am Heart J* **110**: 439, 1985
2. The CONSENSUS Trial Study Group: Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *New Engl J Med* **316**: 1429, 1987
3. Opie LH: INODILATORS. *Lancet* **1**: 1336, 1986
4. van Meel JCA, Diederens W: Hemodynamic profile of the cardiotonic agent pimobendan. *J Cardiovasc Pharmacol* **14** (suppl 2): S1, 1989
5. Fujino K, Sperelakis N, Solaro RJ: Sensitization of dog and guinea pig heart myofilaments to Ca^{2+} activation and the inotropic effect of pimobendan: Comparison with milrinone. *Circ Res* **63**: 911, 1988
6. Pouleur H, Hanet C, Schröder E, Col J, Mechelen HV, Etienne J, Rousseau MF: Effects of pimobendan (UD-CG 115BS) on left ventricular inotropic state in conscious dogs and in patients with heart failure. *J Cardiovasc Pharmacol* **14** (suppl 2): S18, 1989
7. Walter M, Liebens I, Goethals H, Renard M, Dresse A, Bernard R: Pimobendane (UD-CG 115BS) in the treatment of severe congestive heart failure. An acute haemodynamic cross-over and double-blind study with two different doses. *Br J Clin Pharmacol* **25**: 323, 1988
8. Renard M, Walter M, Liebens I, Dresse A, Bernard R: Pimobendan (UD-CG 115BS) in chronic congestive heart failure. Short-term and one-month effects of a new inotropic vasodilating agent. *Chest* **93**: 1159, 1988
9. Hagemeyer F, Brand HJ, van Mechelen R: Hemodynamic effects of pimobendan given orally in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* **63**: 571, 1989
10. Hasenfuss G, Holubarsch C, Heiss W, Just H: Influence of UDCG-115 on hemodynamics and myocardial energetics in patients with idiopathic dilated cardiomyopathy. *Am Heart J* **118**: 512, 1989
11. Hauf GF, Grom E, Jahnchen E, Roskamm H: Acute and long-term hemodynamic effects of pimobendan (UD-CG 115BS) in comparison with captopril. *J Cardiovasc Pharmacol* **14** (suppl 2): S49, 1989
12. Packer M, Medina N, Yushak M, Meller J: Hemodynamic patterns of response during long-term captopril therapy for severe chronic heart failure. *Circulation* **68**: 803, 1983
13. Lynch JJ, Kitzen JM, Hoff PT, Lucchesi BR: Effects of pimobendan (UD-CG 115BS), a new positive inotropic agent, on ventricular tachycardia and ischemic ventricular fibrillation in a conscious canine model of recent myocardial infarction. *J Cardiovasc Pharmacol* **12**: 547, 1988
14. Lynch JJ, Uprichard ACG, Frye JW, Driscoll EM, Kitzen JM, Lucchesi BR: Effects of the positive inotropic agents milrinone and pimobendan on the development of lethal ischemic arrhythmias in congestive dogs with recent myocardial infarction. *J Cardiovasc Pharmacol* **14**: 1585, 1989

15. Pierpont G, Hale KA, Franciosa JA, Cohn JN: Effects of vasodilators on pulmonary hemodynamics and gas exchange in left ventricular failure. *Am Heart J* **99**: 208, 1980