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Effects of Long-Term Treatment With Pimobendan on Neurohumoral Factors in Patients With Non-Ischemic Chronic Moderate Heart Failure

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Abstract

To evaluate the effects of the addition of pimobendan to an optimal basic regimen on plasma levels of neurohumoral factors in patients with non-ischemic, moderate heart failure during 2-year follow-up.

This prospective, observational study involved 16 patients with non-ischemic, moderate heart failure [New York Heart Association (NYHA) functional class IIM–III] receiving an optimal basic regimen of digitalis, diuretics and angiotensin-converting enzyme inhibitor. Eight patients (Group P) were also administered pimobendan at a dose of 2.5 or 5 mg daily, while the other 8 served as controls (Group C). After 3 months of pimobendan administration, the plasma levels of norepinephrine and atrial natriuretic peptide and brain natriuretic peptide decreased and left ventricular ejection fraction improved. After 1 year, the cardiac symptoms, assessed using the Specific Activity Scale as well as the NYHA functional class, improved and the left ventricular end-diastolic diameter decreased. These improvements in Group P were maintained for 2 years. However, in Group C, the cardiac symptoms and the neurohumoral factor levels remained unchanged or deteriorated during this study, and one patient died of heart failure.

Long-term combination therapy with the optimal basic regimen and pimobendan has potentially beneficial effects on neurohumoral factor levels and cardiac symptoms in patients with non-ischemic, chronic moderate heart failure.

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Key Words

■Heart failure ■Heart failure (treatment) ■Inotropic agents
■Natriuretic peptide (atrial) ■Norepinephrine

INTRODUCTION

Pimobendan, a Ca^{2+}-sensitizer that inhibits phosphodiesterase III [1–3], has beneficial hemodynamic effects[4,5], increases exercise tolerance[6–8], and improves quality of life and reduces hospitalization rates[6] in patients with heart failure. However, the effect of pimobendan on survival in patients with chronic heart failure has not been established[9].

Neurohumoral factors, norepinephrine[10,11] and atrial natriuretic peptide and brain natriuretic peptide[12,13], are predictors of long-time survival in patients with chronic heart failure. Some agents with beneficial effects on the survival of patients

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with chronic heart failure reduce plasma levels of neurohumoral factors. Amlodipine, a long-acting Ca^{2+} antagonist, reduces plasma norepinephrine levels in patients with non-ischemic, moderate-to-severe heart failure[14,15], and carvedilol, a vasodilative beta-receptor antagonist, has the same effect in patients with idiopathic dilated cardiomyopathy[16]. However, the short-acting Ca^{2+} antagonists nifedipine[17] and nisoldipine[18] have no beneficial effect on survival in patients with heart failure, by provoking a reflex neurohumoral activation.

This study investigated the effects of long-term administration of pimobendan on plasma levels of neurohumoral factors, as well as cardiac symptoms, left ventricular function and exercise capacity, in patients with non-ischemic, moderate heart failure.

METHODS

Subjects

This prospective, observational study involved 16 out-patients with non-ischemic, chronically-stable moderate heart failure [New York Heart Association (NYHA) functional class IIM–III] with no important changes in background medication for at least 6 months. Patients had a left ventricular ejection fraction (LVEF) ranging from 26% to 34%, a left ventricular end-diastolic dimension (LVDd) from 60 to 67 mm, and peak oxygen consumption ranging from 14.0 to 19.4 ml/min/kg (**Table 1**). None of the patients could tolerate beta blockers (15–20 mg/day of metoprolol) because of aggravation of heart failure, dizziness due to hypotension and/or bradycardia. Background medication consisted of at least one angiotensin-converting enzyme (ACE) inhibitor (enalapril), diuretics and digitalis. In addition, antiarrhythmic agents, nitrates and denopamine, an oral inotropic agent, which the patients had been taking for at least 6 months before this study, were allowed. No other cardiovascular medications were given.

Study protocol

Eight patients (Group P) were randomly assigned using the envelope method to receive additional administration of pimobendan 2.5 or 5.0 mg daily for 2 years, which was decreased to 2.5 mg daily if the cardiac symptoms were adequately controlled, while the other 8 served as controls (Group C), assessed using the Specific Activity Scale (SAS)[19] as well as the NYHA functional class. Informed consent was obtained from all patients before participation in the study. LVEF, LVDd, NYHA functional class, SAS score, and levels of neurohumoral factors in both groups were measured at 3 months, 1 year and 2 years from the beginning of the study. The exercise capacity was determined as detailed below, and 24-hour electrocardiography was performed before the study and again after 2 years. Diuretic doses were reduced or increased if necessary. Other medications, except for diuretics, were withheld until admission due to aggravation of heart failure.

Measurements

The exercise capacity was assessed by peak oxygen consumption determined with symptom-limited exercises on a bicycle ergometer and expiratory gas analysis[20]. The LVEF and LVDd were obtained by echocardiography[21]. Blood samples were drawn by venipuncture after at least 30 min rest in the supine position, immediately placed on ice and centrifuged at 3,000 rpm for 10 min. The plasma norepinephrine level was measured by high performance liquid chromatography using electrochemical detection and plasma levels of atrial natriuretic peptide and brain natriuretic peptide were measured by radioimmunoassays[22].

Statistical analysis

All results are expressed as mean values ± standard deviation (SD). Values obtained at baseline and during the study were compared using Student's paired *t*-test. Intergroup differences were tested using Student's unpaired *t*-test. Changes in cardiac symptoms (NYHA functional class and SAS score) during the present study with regard to values at baseline in each group and differences between the 2 groups during the study were analyzed using the Mann-Whitney's *U*-test. A probability value of less than 0.05 was regarded as statistically significant.

RESULTS

Clinical baseline characteristics of Group P and Group C

There were no significant differences between Group P and Group C in etiology, age, heart rate, systolic blood pressure, LVEF, LVDd, cardiac symptom assessed by the SAS score and NYHA functional class, the peak oxygen consumption as determined by the bicycle ergometer and plasma levels of norepinephrine, atrial natriuretic peptide

Table 1 Clinical baseline characteristics of patients in pimobendan group (Group P) and control group (Group C)

	Patients								Group P (n=8)	Group C (n=8)
	1	2	3	4	5	6	7	8		
Age (yr)	57	62	42	63	67	58	59	60	58.5±7.4	57.8±6.9
Sex	M	M	M	M	M	F	F	M	M/F=6/2	M/F=5/3
Etiology of heart failure	DCM	HHD	DCM	DCM	DCM	HHD	DCM	DCM	DCM: 6 HHD: 2	DCM: 5 HHD: 3
ACE inhibitors										
Name	E	E	E	E	E	E	E	E	E	E
Doses (mg/day)	5	7.5	10	7.5	5	10	7.5	5	7.2±0.7	7.5±0.7
Heart rate (beat/min)	68	53	74	68	72	86	70	78	71.1±9.5	73.1±10.3
SBP (mmHg)	100	102	118	102	97	126	108	112	108.1±10.0	109.3±13.2
NYHA class	IIM	III	IIM	III	III	IIM	III	IIM	III: 4 IIM: 4	III: 4 IIM: 4
SAS (MET)	5-6	4-5	5-6	4	4	5-6	4-5	4-5	4: 2 4-5: 3 5-6: 3	4: 3 4-5: 3 5-6: 2
LVDd (mm)	64	65	62	60	67	60	64	65	63.3±2.3	62.8±2.6
LVEF (%)	28	26	30	32	28	34	30	28	29.5±2.6	31.3±3.2
Peak $\dot{V}$ (ml/min/kg)	16.8	14.9	17.6	14.0	14.0	19.0	15.2	16.2	16.0±1.8	15.9±2.8
ANP (pg/ml)	122	215	148	185	342	139	225	205	197.6±69.4	200.7±76.4
BNP (pg/ml)	230	320	196	288	288	182	301	189	249.3±56.1	244.2±82.6
NE (pg/ml)	500	652	453	652	657	391	530	603	554.8±101.8	558.6±109.2
Lown class	1A	1B	2	2	4A	1B	1A	1B	1A: 3 1B: 2 2: 2 4: 1	1A: 4 1B: 3 2: 1

Values of age, the doses of ACE inhibitors, heart rate, SBP, LVDd, LVEF, peak $\dot{V}$, ANP, BNP, and NE are mean±SD.
M=male; F=female; DCM=idiopathic dilated cardiomyopathy; HHD=hypertensive heart disease; ACE=angiotensin-converting enzyme; E=enalapril; SBP=systolic blood pressure; NYHA=New York Heart Association; SAS=specific activity scale; LVDd=left ventricular end-diastolic dimension; LVEF=left ventricular ejection fraction; peak $\dot{V}$=peak oxygen consumption; ANP=atrial natriuretic peptide; BNP=brain natriuretic peptide; NE=norepinephrine.

and brain natriuretic peptide in peripheral blood (**Table 1**).

Clinical events and outcome

One patient (Patient 5) in Group P was admitted to the National Cardiovascular Center because of hypovolemia due to appetite loss caused by respiratory infection after 8 months of pimobendan administration. This patient and 4 other patients (Patients 2, 4, 6 and 8) in Group P showed an improvement of urinary excretion, so that we could reduce the dose of the oral diuretics within 3 to 11 months of the study start. We initially prescribed 5 mg/day of pimobendan to Patients 1, 2 and 5, and 2.5 mg/day to Patients 3, 4, 7 and 8, and then reduced the dose to 2.5 mg/day at 3 months for Patients 2 and 5 because their cardiac symptoms had significantly improved.

One patient in Group C died due to aggravation of heart failure despite admission and intravenous administration of diuretics and catecholamines 1.6 years from the beginning of the study. Five of the 7 remaining patients in Group C were given extra oral diuretics (5 patients) or denopamine (one patient) during the present study due to deterioration of heart failure.

Cardiac symptoms and left ventricular function

In Group P, 4 patients (Patients 2, 4, 5 and 7) were classified in NYHA functional class III and 4 patients (Patients 1, 3, 6 and 8) in NYHA IIM at

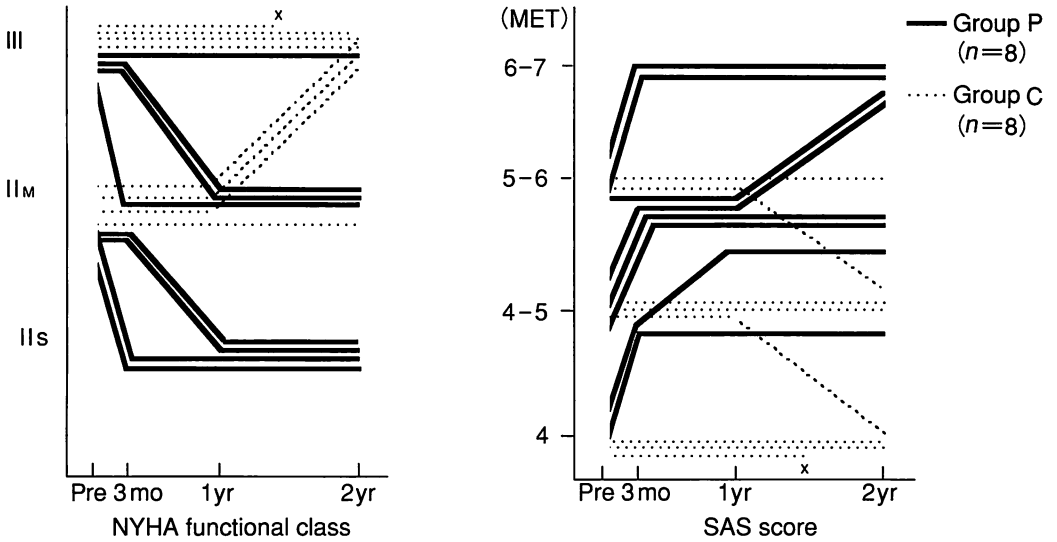

Fig. 1 Changes in NYHA functional class and SAS score
Serial changes in NYHA functional class (*left*) and SAS score (*right*) in Group P and Group C.
× indicates death due to aggravation of heart failure in Group C.
Pre=at the baseline; 3mo, 1yr, 2yr=at 3 months, 1 year, 2 years after the beginning of the study, respectively. Other abbreviations as in Table 1.

baseline. After 1 year of pimobendan administration, the NYHA functional class ($p < 0.005$ vs at baseline, $p < 0.005$ vs Group C) and SAS score ($p < 0.005$ vs at baseline, $p < 0.005$ vs Group C) improved (**Fig. 1**). This improvement was maintained for the rest of the study period. In contrast, the NYHA functional class and/or the SAS score of 3 patients in Group C worsened within 1 to 2 years from the beginning of the study, and those of the 4 remaining patients in Group C remained unchanged compared with baseline values.

The LVEF significantly increased in Group P after 3 months of pimobendan administration, and remained at the same level until the end of the study (**Fig. 2−left**). The LVDd significantly decreased in Group P after 1 year of pimobendan administration, and did not increase again during the rest of the study (**Fig. 2−right**). In Group C, the LVEF significantly worsened and the LVDd significantly increased by the end of the study compared with baseline values. Consequently, the LVEF was significantly higher ($p < 0.05$), and the LVDd was significantly lower ($p < 0.05$) in Group P than in Group C at the end of the study (**Fig. 2**).

Neurohumoral factors

Fig. 3 shows the effects of long-term administration of pimobendan on neurohumoral factors. In Group C, the plasma levels of norepinephrine, atrial natriuretic peptide and brain natriuretic peptide did not change from those at baseline, but significantly decreased in Group P after 3 months (from 554.8±101.8 to 456.0±121.0 pg/m*l*, $p < 0.01$; from 197.6±69.4 to 150.3±67.4 pg/m*l*, $p < 0.01$; from 249.3±56.1 to 186.1±81.7 pg/m*l*, $p < 0.01$, respectively), and remained at low levels for the rest of the study period. Plasma brain natriuretic peptide levels in Group P were significantly lower than those in Group C after 1 year of treatment with pimobendan (178.2±69.3 vs 260.5±75.2 pg/m*l*, $p < 0.05$), and plasma norepinephrine and atrial natriuretic peptide levels were significantly lower in Group P than those in Group C at the end of the study.

Exercise capacity and ventricular arrhythmia

Neither the mean heart rate nor the mean blood pressure changed in Group P. Exercise capacity expressed as peak oxygen consumption improved at the end of the study in Group P (from 16.0±1.8 to 18.4±3.2 m*l*/min/kg, $p < 0.05$), but did not change in Group C [from 15.9±2.5 to 14.2±2.4 m*l*/min/kg ($n=7$), NS], and consequently there was a significant difference in exercise capacity between the 2 groups at the end of the study ($p < 0.05$). The severity of ventricular arrhythmia, classified using

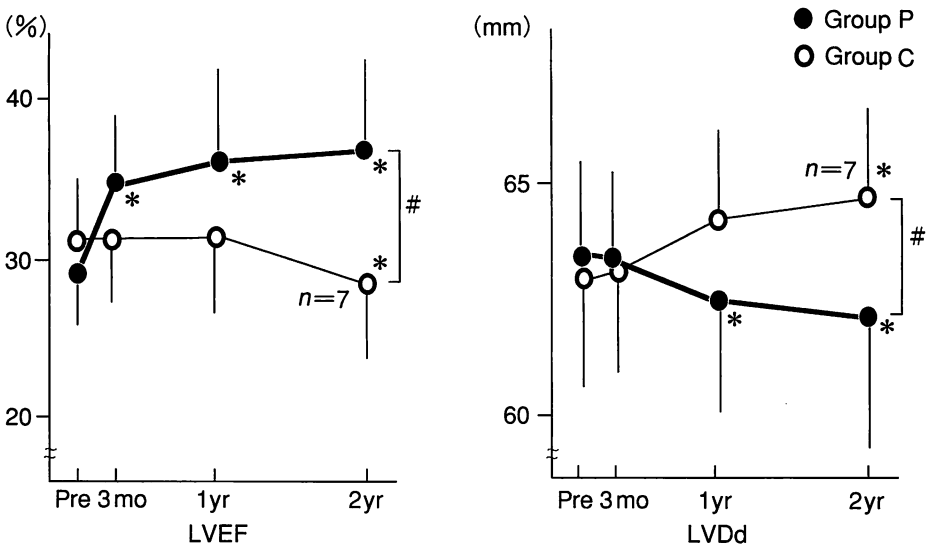

Fig. 2 Changes in left ventricular functions
Serial changes in LVEF (*left*) and LVDd (*right*) as determined by echocardiography in Group P and Group C. Each point and bar represents the mean value ± SD.
$^{\#}p < 0.05$ vs Group C, $^{*}p < 0.05$ vs at the baseline.
Abbreviations as in Table 1, Fig. 1.

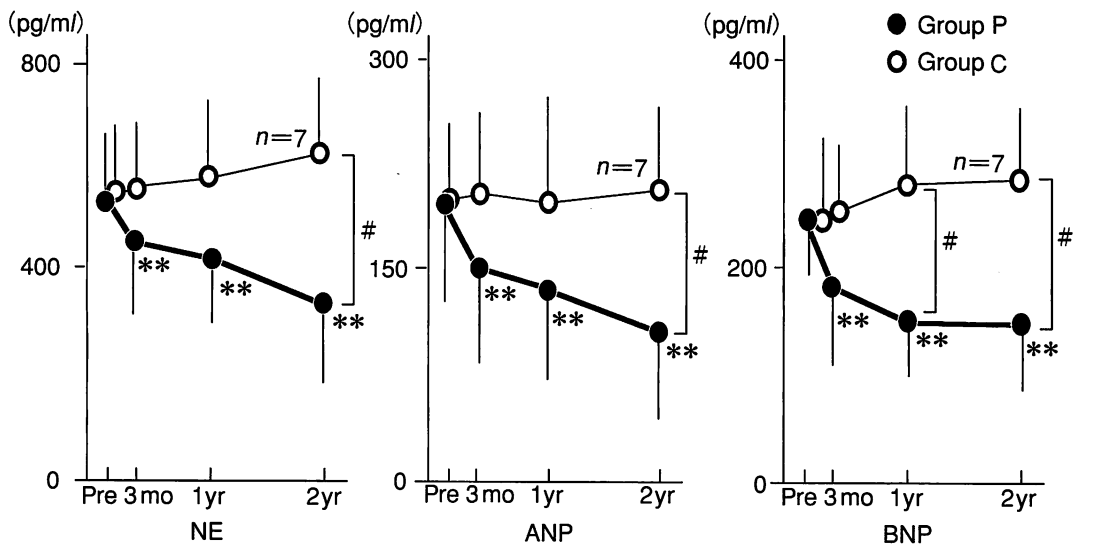

Fig. 3 Changes in neurohumoral factors
Serial changes in plasma levels of NE (*left*), ANP (*middle*) and BNP (*right*) in Group P and Group C. Each point and bar represents the mean value ± SD.
$^{\#}p < 0.05$ vs Group C, $^{**}p < 0.01$ vs at the baseline.
Abbreviations as in Table 1, Fig. 1.

the Lown classification with 24-hour electrocardiography, was not increased in either group at the end of the study. The mean heart rate did not change significantly during the study in either group compared with the baseline value.

DISCUSSION

Neurohumoral effects of pimobendan

This study demonstrated that long-term administration of pimobendan as coadjuvant to an optimal basic regimen had beneficial effects on the levels of

neurohumoral factors in patients with non-ischemic, moderate heart failure. Pimobendan reduced plasma levels of norepinephrine, atrial natriuretic peptide and brain natriuretic peptide after 3 months of treatment, and these effects were maintained for 2 years.

Kubo *et al.*[6] reported that 3 months administration of pimobendan did not affect the plasma levels of norepinephrine in patients with heart failure, and Erlemeier *et al.*[23] reported no change after 6 months, either at rest or after exercise. The discrepancies between their results and ours were probably due to these factors: Firstly, there was a difference in the etiology of heart failure between the studies. Ischemic heart disease was dominant (47%) in the pimobendan group in the former[6] and 11 patients out of 12 in the latter had ischemic heart disease[23], whereas no patient had ischemic heart disease and 6 of 8 patients in Group P had idiopathic dilated cardiomyopathy in our study. Pimobendan exerts inotropic effects on impaired ventricular myocardia via Ca^{2+}-sensitizing and phosphodiesterase Ⅲ inhibitory effects. Consequently, irreversible damage to the myocardium due to ischemia is not supposed to respond well to the inotropic effect of pimobendan. Actually, LVEF did not improve after administration of pimobendan in the study of Kubo *et al.*[6], but improved significantly after 3 months of treatment in our study. Secondly, there was a difference in baseline characteristics between the patient populations. Heart failure was more severe in the former study[6] than in ours, as patients were in NYHA functional class Ⅲ－Ⅳ (ⅡM－Ⅲ in ours), had a lower LVEF ranging from 20.8% to 23.5% (from 26% to 34% in ours) and higher plasma levels of norepinephrine ranging from 685 to 820 pg/ml (554.8±101.8 pg/ml in Group P). Advanced damage to myocardium in more severe heart failure is also not supposed to respond well to pimobendan. Thirdly, all patients in our study were given digitalis, diuretics and an ACE inhibitor, whereas none of the patients in the pimobendan group in the study by Erlemeier *et al.*[23] were given ACE inhibitors. Therefore, the differences in background medications may have influenced the effects of pimobendan on neurohumoral factors. Consequently, the neurohumoral effects of pimobendan are discernible in patients with ischemic heart disease, advanced heart failure, or in patients not receiving an optimal basic regimen including digitalis, diuretics and ACE inhibitors.

The present study is the first to demonstrate that long-term administration of pimobendan reduces plasma levels of atrial natriuretic peptide and brain natriuretic peptide and improves cardiac symptoms (**Figs. 1, 3**). Plasma atrial natriuretic peptide and brain natriuretic peptide levels reflect hemodynamic parameters[12,22], cardiac symptoms[24] and the prognosis[12,13,25] in patients with heart failure. Brain natriuretic peptide and atrial natriuretic peptide are secreted from the left ventricular myocardium in patients with heart failure according to the elevation in left ventricular end-diastolic pressure (LVEDP)[22], which is one of the indicators of left ventricular diastolic dysfunction[26]. The increase in heart rate during exercise results in elevation of LVEDP, which easily causes dyspnea, in patients with left ventricular diastolic dysfunction. Pimobendan did not increase the mean heart rate in our study, so pimobendan probably improved left ventricular diastolic function via its inhibitory effects on phosphodiesterase Ⅲ, reducing LVEDP, and consequent reduction of plasma atrial natriuretic peptide and brain natriuretic peptide levels and the improvement of the cardiac symptoms.

Clinical course and prognosis after administration of pimobendan

Our study provides further evidence of the beneficial effects of pimobendan, since left ventricular function and exercise capacity improved whereas ventricular arrhythmia did not worsen during treatment with pimobendan, as previously reported[6-8,19]. These effects were maintained during the 2-year administration period. The LVDd was significantly decreased by the end of the 2-year administration period, a new finding because previous studies were limited to as short as 6 months.

Kubo *et al.*[6] reported that 5 mg of pimobendan significantly improved exercise capacity compared with patients given placebo, whereas 10 mg caused a slightly smaller increase in exercise capacity. A PICO study[8] showed that the effects of pimobendan on exercise duration in patients with moderate heart failure did not differ between those given 2.5 mg and patients given 5 mg. Based on racial differences in physique, the adequate dose of pimobendan to improve the exercise tolerance in Japanese patients with heart failure is probably 2.5 mg. In fact, administration of 2.5 mg of pimobendan daily had beneficial effects on clinical parameters and neurohumoral factors in our study.

Although the PICO study[8] showed that pimobendan failed to exert a beneficial effect on the prognosis of patients with heart failure, in our study, one of 8 patients in Group C died due to aggravation of heart failure, whereas none of the 8 patients in Group P died. In addition, 5 of the 7 remaining patients in Group C required extra cardiovascular medication during the study due to aggravation of heart failure, whereas none of those in Group P needed extra medication. The discrepancy between the previous results and ours may be due to differences in the etiology of heart failure and baseline medications as mentioned earlier. Because a coronary event easily induces fatal arrhythmia causing sudden death[27], improvement of cardiac function with pimobendan does not necessarily reduce mortality due to ischemic heart disease. Actually, in the PICO study[8], sudden death accounted for 7 of 10 cardiac deaths (70%) in the placebo group and 22 of 33 (67%) in the pimobendan group. Consequently, pimobendan may little improve prognosis in a population affected mainly by ischemic heart disease, as in the PICO study or in other previous studies. On the other hand, Sasayama *et al.*[19,28] reported that pimobendan had a beneficial effect on the prognosis of patients with heart failure in a small scale study, in which 9 of the 11 patients in the pimobendan group and 7 of the 10 in the placebo group did not have ischemic heart disease. Therefore, pimobendan can probably improve the prognosis of patients with non-ischemic left ventricular dysfunction, as reported in animal models[29].

As for baseline medications, digitalis was given to only 59 % of the subjects who participated in the PICO study[8], although all were given an ACE inhibitor and diuretics. On the other hand, Kubo *et al.*[6] reported that mortality did not differ between the placebo group (6%) and the pimobendan group (5%) over the 24-week study in which ACE inhibitors, digitalis and diuretics were given to 80%, 88% and 98% of the subjects in each group, respectively. Hagemeijer *et al.*[30] reported that therapy with pimobendan added to digoxin, diuretics and ACE inhibitor produced a sustained improvement in many patients with severe heart failure. These results, together with ours showing that plasma levels of norepinephrine, atrial natriuretic peptide and brain natriuretic peptide decreased after the addition of pimobendan to an optimal basic regimen, suggest that pimobendan has potentially beneficial effects, and does not affect the prognosis of patients with non-ischemic heart failure who are given an optimal basic regimen including digitalis, diuretics and ACE inhibitors.

Study limitations

In this small scale study, the addition of pimobendan to the optimal basic regimen had a beneficial effect on neurohumoral factors in patients with non-ischemic, moderate heart failure. However, because this study was not a randomized, double-blind study involving a large sample size and was not designed as a mortality trial, it cannot be concluded that pimobendan has beneficial effects on neurohumoral activation or on the prognosis of patients with heart failure. Therefore, further prospective, randomized, double-blind studies involving a large number of patients with non-ischemic, moderate heart failure receiving treatment with optimal doses of digitalis, diuretics and ACE inhibitors are needed.

Part of this paper was presented at the 46th Scientific Session of the Japanese College of Cardiology in September, 1998.

要　約

非虚血性の中等度慢性左室不全患者に対するピモベンダン長期投与が体液性因子に及ぼす効果

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非虚血性の中等度慢性左室不全患者に対するピモベンダン長期投与の臨床効果を検討するために，New York Heart Association(NYHA)分類IIM－IIIの慢性左室不全患者16例(拡張型心筋症11例，高血圧心5例)を対象とし，無作為にピモベンダン(2.5－5.0mg/day)を追加投与した8例(投与群)と投与しない8例(非投与群)に2分した．NYHA分類，身体活動能力，心エコー図法による左室拡張末期径と左室駆出率，自転車エルゴメーター試験による最大酸素摂取量(ml/min/kg)，末梢静脈血中の心房性Na利尿ペプチド，脳性Na利尿ペプチド，ノルエピネフリン濃度を2年間，経時的に観察した．

投与群ではNYHA分類，身体活動能力は3ヵ月後に7例で改善，残る1例も1年後に改善した．左室拡張末期径は全例縮小し，左室駆出率，最大酸素摂取量も全例改善したが，左室駆出率は3ヵ月で，左室拡張末期径は1年で改善が明らかであった．血中心房性Na利尿ペプチド，脳性Na利尿ペプチド，ノルエピネフリン濃度はいずれも3ヵ月後に全例低下し，2年後までさらに低下傾向にあった．また5例で経口利尿薬を減量しえた．期間中の心室期外収縮は不変であった．非投与群ではNYHA分類，身体活動能力，左室拡張末期径，左室駆出率，最大酸素摂取率および心房性Na利尿ペプチド，脳性Na利尿ペプチド，ノルエピネフリン濃度は不変ないし悪化し，1例は期間中に心不全増悪により死亡した．

ピモベンダン長期投与は非虚血性の中等度慢性左室不全患者の自覚症状，左室機能，運動耐容能のみならず体液性因子動態を著明に改善した．

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