randomized aldosterone evaluation study (RALES) (2), as has the beneficial effect of candesartan in the candesartan in heart failure assessment of reduction in mortality and morbidity (CHARM) study (3). Enalapril has also shown beneficial effect in the studies of left ventricular dysfunction (SOLVD) (4). It is thus expected that combination therapy with carvedilol, spironolactone, ACE-I or ARB and furosemide as a potent diuretic agent will be effective in CHF patients. Although carvedilol, spironolactone, ACE-I and ARB have all been associated with induction of hyperkalemia, there has been no study of their effects on serum potassium when administered concomitantly.

METHODS

Subjects

Patients who visited Departments of Cardiovascular Internal Medicine and were diagnosed as having CHF, New York Heart Association (NYHA) Class II to III, at the National Hospital Organization Osaka Medical Center were enrolled after giving informed consent. Our institutional ethics committee approved the study protocol. The investigation period was from January 2000 to December 2005. There were 103 patients who were administered carvedilol, spironolactone, furosemide and an ACE-I or ARB concomitantly during the study period. Of these, 78 were given 25 mg/day of spironolactone and the others 50 mg/day spironolactone. All patients whose prescription was not changed for 12 months were selected for analysis. However, patients who also had diabetes mellitus or who were taking drugs other than those being studied and which might affect the serum concentration of potassium were excluded. Twenty-five patients given 50 mg/day spironolactone were excluded from the analysis because of a change in dosage of concomitant drugs during the study interval or because of addition of other drugs or discontinuation of treatment depending on improvement or aggravation of symptoms. For the same reasons, 19 patients given 25 mg/day spironolactone were excluded from the analysis. Consequently, 59 patients who received 25 mg/day spironolactone were selected for the final analysis of the data.

Study design

Serum potassium, blood urea nitrogen (BUN), serum creatinine (Scr) and serum sodium were measured in every patient at the start of treatment and after 3 and 12 months of treatment. The study groups were: group A patients receiving carvedilol (20 mg/day) + spironolactone (25 mg/day) + furosemide (40 mg/day) + enalapril (5 mg/day) and group B patients administered carvedilol (20 mg/day) + spironolactone (25 mg/day) + furosemide (40 mg/day) + candesartan (8 mg/day).

Statistical analysis

Statistical significance of observed differences were tested using one-way repeated measures analyisis of variance (ANOVA). Paired comparisons were made using Fisher's PLSD (pretreatment vs. 3 months and pretreatment vs. 12 months) when significant change was observed by one-way repeated measures ANOVA. The level of statistical significance was set at 5%. The values were expressed as the mean ± standard deviation.

RESULTS

Thirty-one of the 59 study patients received, carvedilol (20 mg/day), spironolactone (25 mg/day) and furosemide (40 mg/day). Enalapril (5 mg/day) and candesartan (8 mg/day) were additionally used in 31 (group A) and 28 (group B) patients, respectively. The characteristics of the study patients are presented in Table 1. BUN, Scr and serum sodium were not significantly elevated at 3 or 12 months of treatment compared with baseline. The BUN, Scr and serum sodium levels of each group of patients at the different time points are presented in Table 2. At 3 and 12 months of treatment, BUN was significantly higher than baseline in group B but not in group A. At 3 and 12 months of treatment, Scr was not significantly higher compared with the baseline value in either group A or B. The treatments of these patients remained unchanged throughout the 12 months with furosemide given at 40 mg/day in each group.

The serum concentration of potassium at 3 and 12 months of treatment was significantly higher than the pretreatment value in both groups A and

Table 1. The patient characteristics of the study groups (n = 59)

Gender	Age	Item	Pretreatment	3 months of treatment	12 months of treatment	P-value[a]	P-value[b] (pretreatment vs. 3 months)	P-value[b] (pretreatment vs. 12 months)	No. of concomitantly used drug En/Can
Male (43)	65·5 ± 12·6	Na (mEq/L)	140·6 ± 2·8	140·7 ± 2·9	140·0 ± 2·9	0·2335	–	–	31/28
Female (16)	(37–87)	BUN (mg/dL)	22·6 ± 12·5	26·0 ± 15·1	25·9 ± 13·5	0·0543	–	–	
		Scr (mg/dL)	1·12 ± 0·63	1·18 ± 0·54	1·22 ± 0·57	0·0683	–	–	

[a]P-values were determined by one-way repeated measures ANOVA.
[b]P-values were determined by Fisher's PLSD when significant change was observed by one-way repeated measures ANOVA.
Scr, serum creatinine; Car, carvedilol 20 mg/day; En, enalapril maleate 5 mg/day; Sp, spironolactone 25 mg/day; Fu; furosemide 40 mg/day; Can, candesartan cilexetil 8 mg/day.
The values given are mean ± SD.

Table 2. Distribution of patients by the ACE-I and ARB concomitantly used and parameters values at each determination point

Group	Gender	Age	Item	Pretreatment	3 months of treatment	12 months of treatment	P-value[a]	P-value[b] (pretreatment vs. 3 months)	P-value[b] (pretreatment vs. 12 months)	Concomitantly used drug
Group A	Male (25)	65·7 ± 12·4	Na (mEq/L)	140·7 ± 2·8	140·8 ± 3·4	140·2 ± 2·9	0·5360	–	–	Car + En + Sp + Fu
(n = 31)	Female (6)	(37–81)	BUN (mg/dL)	23·7 ± 15·1	25·3 ± 16·3	25·9 ± 13·3	0·6179	–	–	
			Scr (mg/dL)	1·26 ± 0·78	1·28 ± 0·62	1·37 ± 0·64	0·3089	–	–	
Group B	Male (18)	65·3 ± 13·1	Na (mEq/L)	140·6 ± 3·0	140·5 ± 2·3	139·8 ± 3·0	0·4266	–	–	Car + Can + Sp + Fu
(n = 28)	Female (10)	(38–87)	BUN (mg/dL)	21·4 ± 9·0	26·8 ± 13·9	26·0 ± 13·9	0·0369	0·0175	0·0408	
			Scr (mg/dL)	0·96 ± 0·34	1·06 ± 0·41	1·06 ± 0·44	0·0595	–	–	

[a]P-values were determined by one-way repeated measures ANOVA.
[b]P-values were determined by Fisher's PLSD when significant change was observed by one-way repeated measures ANOVA.
Scr, serum creatinine; Car, carvedilol 20 mg/day; En, enalapril maleate 5 mg/day; Sp, spironolactone 25 mg/day; Fu; furosemide 40 mg/day; Can, candesartan cilexetil 8 mg/day.
The values given are mean ± SD.

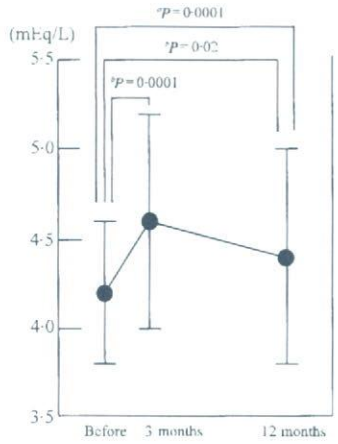

Fig. 1. Changes in serum potassium during the treatment period. Patients administered carvedilol (20 mg/day) plus spironolactone (25 mg/day) plus furosemide (40 mg/day), and enalapril (5 mg/day) or candesartan (8 mg/day) for 12 months ($n = 59$). [a]*P*-values were determined by one-way repeated measures ANOVA. [b]*P*-values were determined by Fisher's PLSD (pretreatment vs. 3 months and pretreatment vs. 12 months) when significant change was observed by one-way repeated measures ANOVA. Mean ± SD; $P < 0.05$; 3 m, at 3 months of treatment; 12 m, at 12 months of treatment.

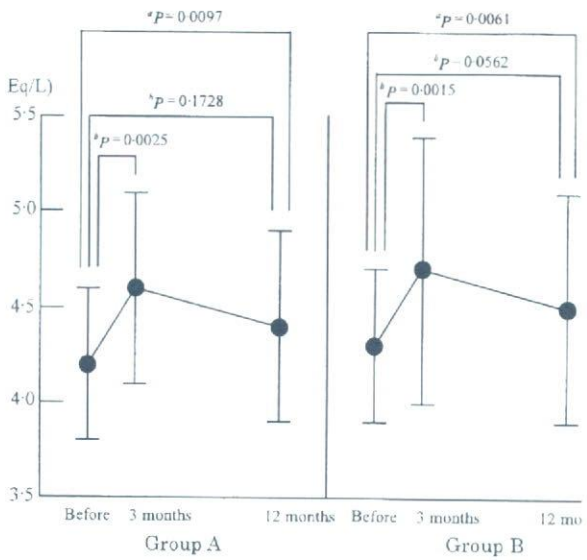

Fig. 2. Changes of serum potassium in group A and group B during the treatment period. Group A: patients administered carvedilol (20 mg/day) + spironolactone (25 mg/day) + enalapril (5 mg/day) + furosemide (40 mg/day) for 12 months ($n = 31$). Group B: patients administered carvedilol (20 mg/day) + spironolactone (25 mg/day) + candesartan (8 mg/day) + furosemide (40 mg/day) for 12 months ($n = 28$). [a]*P*-values were determined by one-way repeated measures ANOVA. [b]*P*-values were determined by Fisher's PLSD (pretreatment vs. 3 months and pretreatment vs. 12 months) when significant change was observed by one-way repeated measures ANOVA. Mean ± SD; $P < 0.05$; 3 m, at 3 months of treatment; 12 m, at 12 months of treatment.

B (Fig. 1). Serum potassium at 3 and 12 months of treatment was significantly higher compared with the baseline value in both groups A and B, but it was still within the normal range in each group. Serum potassium at 3 months of treatment was significantly higher compared with baseline in both groups A and B (Fig. 2).

The frequency of occurrence of hyperkalemia and hypokalemia are presented in Table 3. Seven of 59 (11·9%) patients had hyperkalemia with levels exceeding 5·5 mEq/L and 8·5% (five of 59) had hypokalemia of 3·5 mEq/L or less during 12 months of treatment. In these seven hyperkalemic patients, the administration of spironolactone, ACE-I or ARB was continued with close monitoring.

Table 3. Occurrence of hyperkalemia and hypokalemia

Serum potassium	Group A (%)	Group B (%)	Total (%)
>5·5 mEq/L	3 (9·7)	4 (14·3)	7 (11·9)
≤3·5 mEq/L	2 (6·5)	3 (10·7)	5 (8·5)

DISCUSSION

The present study demonstrated that when carvedilol, spironolactone, furosemide and enalapril or candesartan are used concomitantly, serum potassium increased even with a dose of spironolactone as low as 25 mg/day.

The RALES (2) showed that spironolactone led to a 30% decrease in mortality in CHF patients. The COPERNICUS study demonstrated a 35% decrease in the risk of death with carvedilol (1). With these studies, spironolactone (5–7), an aldosterone antagonist and carvedilol, a non-selective beta-adrenergic blocker with an additional alpha-blocking activity, became widely for treating hypertension after a myocardial infarction. These two drugs have

been administered to CHF patients concomitantly with furosemide, a potent diuretic agent, and ACE-I or ARB.

It is well known that the effect of beta-blockers on potassium levels is very complicated. Potassium is first released from the intracellular to the extracellular space through the alpha-adrenergic action of epinephrine. However, the beta-receptor of epinephrine is subsequently stimulated. As a non-selective beta-adrenergic blocker inhibits the beta-receptor stimulating action of epinephrine, the serum concentration of potassium is expected to increase (8). However there is as yet no clinical evidence to show that carvedilol increases serum potassium.

Shah *et al.* (9) suggested that beta-adrenergic receptor antagonism could suppress the renin-angiotensin-aldosterone system by inhibiting renin secretion from the juxtaglomerular apparatus, predisposing patients to potassium retention. This may explain the high rate of severe hyperkalemia (5·5% at 1 year) in the eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS). This large trial showed that the selective mineralocorticoid receptor antagonist eplerenone was useful in post-myocardial infarction patients with background therapy that included beta-blockers (10).

Spironolactone inhibits sodium reabsorption and potassium excretion in the renal tubule, thereby preventing the development of secondary aldosteronism (5–7). In 1996, Pitt *et al.* (2) and the RALES (11) study reported that at doses of more than 50 mg/day, spironolactone frequently caused serious hyperkalemia. Enalapril (ACE-I), and candesartan (ARB) lower blood pressure through the inhibition of AII (12, 13) and consequently lower aldosterone secretion/production. ACE-I and ARB are all known to be associated with hyperkalemia. Reardon and Macpherson (14), however, observed that patients with normal renal function aged <70 years rarely developed serious hyperkalemia when given ACE-I.

In our previous study, we reported that serum potassium level at 12 months was not significantly higher than baseline with either enalapril (5 mg/day) + furosemide (40 mg/day), losartan (50 mg/day) + furosemide (40 mg/day), or candesartan (8 mg/day) + furosemide (40 mg/day). Furthermore although the 12-month serum concentration of potassium was significantly higher than baseline with enalapril (5 mg/day) + furosemide (40 mg/day) + spironolactone (50 mg/day), losartan (50 mg/day) + furosemide (40 mg/day) + spironolactone (50 mg/day) and candesartan (8 mg/day) + furosemide (40 mg/day) + spironolactone (50 mg/day), and there was no significant elevation when 25 mg/day spironolactone was used. It was clear that the occurrence of hyperkalemia in patients administered spironolactone is influenced by the dose of spironolactone (15). In the present study, however, the serum concentration of potassium at 3 and 12 months was significantly higher compared with the baseline value even with 25 mg/day spironolactone if 20 mg carvedilol was administered concomitantly. It is not clear how carvedilol affects the renin-angiotensin-aldosterone system. Pitt *et al.* (2) reported that single administration of spironolactone at 50 mg/day or more may frequently induce serious hyperkalemia. In our previous study, 8·2% (four of 49) of patients treated concomitantly with spironolactone (50 mg/day), furosemide (40 mg/day) and ACE-I (5 mg/day enalapril) or ARB (50 mg/day losartan or 8 mg/day candesartan) showed hyperkalemia (more than 5·5 mEq/L) at 12 months. When 25 mg/day spironolactone was used concomitantly with either enalapril, losartan, or candesartan, 9·3% (eight of 86) of patients showed hyperkalemia, and 8·1% (seven of 86) of patients hypokalemia. Although the mean serum potassium level at 12 months was not significantly different from baseline, hyperkalemia exceeding 5·5 mEq/L was as frequent as observed with 50 mg/day spironolactone (15).

In the present study, 11·9% (seven of 59) of patients showed hyperkalemia and 8·5% (five of 59) hypokalemia. Although the rates of hyperkalemia and hypokalemia observed in the two studies cannot be compared directly, they appear to be almost the same regardless of whether carvedilol was administered concomitantly.

Although serum potassium at 3 months was higher than at 12 months, the cause is not clear. This study suggests that serum potassium at 3 and 12 months of treatment was significantly increased compared with baseline when 20 mg/day carvedilol, 25 mg/day spironolactone and 40 mg/day furosemide were used concomitantly with either 5 mg/day enalapril or 8 mg/day

candesartan. Group A and B patients showed similar changes.

CONCLUSION

Serum potassium in patients administered spironolactone depends on the dose of spironolactone, but when it is used concomitantly with carvedilol, enalapril or candesartan, the serum concentration of potassium is likely to increase even with a dose of spironolactone as low as 25 mg/day. Severe hyperkalemia may lead to ventricular fibrillation progressing toward cardiac arrest. Serum potassium concentration should therefore be closely monitored when carvedilol and spironolactone are used concomitantly.

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Original Article

Comparison of the Effects of Telmisartan and Olmesartan on Home Blood Pressure, Glucose, and Lipid Profiles in Patients with Hypertension, Chronic Heart Failure, and Metabolic Syndrome

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We compared the effects of telmisartan and olmesartan in 20 patients with chronic heart failure and metabolic syndrome. The subjects underwent once-daily 40 mg telmisartan for at least 3 months before switching to once-daily 20 mg olmesartan for the next 3 months (post 1). They were then treated with 3 months of once-daily 40 mg telmisartan (post 2). Systolic and diastolic blood pressure in the early morning, plasma B-type natriuretic peptide, serum total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were increased at post 1 ($p<0.005$, $p<0.05$, $p<0.05$, $p<0.05$, $p<0.05$, and $p<0.005$ *vs.* baseline, respectively) before returning to their baseline values at post 2. The changes in plasma B-type natriuretic peptide levels correlated significantly with the shifts in systolic and diastolic blood pressure in the early morning at posts 1 and 2. Meanwhile, there were no fluctuations in either blood pressure in the late evening or in the outpatient room; nor were there fluctuations in heart rate. Simultaneously, neither serum high-density lipoprotein cholesterol nor fasting blood sugar levels differed significantly between posts. Moreover, telmisartan had more beneficial effects on glucose and lipid profiles in patients with relatively high HbA1c, serum total and low-density lipoprotein cholesterol, and triglyceride levels. Therefore, we concluded that telmisartan was more beneficial than olmesartan for controlling blood pressure in the early morning, as well as for improving glucose and lipid profiles in patients with hypertension, chronic heart failure, and metabolic syndrome. (*Hypertens Res* 2008; 31: 921–929)

***Key Words*: telmisartan, metabolic syndrome, home blood pressure**

Introduction

To judge and control blood pressure, it is important to monitor blood pressure not only in the outpatient room but also at home (*1–3*). The proper and continued management of blood pressure is important to achieve the final purpose of antihypertensive therapy: protection of the internal organs. To protect the internal organs against damage, the use of long-acting antihypertensive medication is important for controlling "masked" and "early morning" hypertension, which cannot be observed by measuring blood pressure in only the outpatient room (*1*, *3*, *4*). Telmisartan is a long-acting angiotensin II receptor blocker (ARB), with a half-life ($T_{1/2}$) that is two- to six-fold longer than those of other ARBs (*5*). Telmisartan is more useful for controlling morning hypertension than valsartan when given once daily in the morning (*6*, *7*). Therefore, telmisartan is thought to be more advantageous

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than other ARBs in protecting the internal organs of patients with morning hypertension.

Strategies to prevent cardiovascular disease should include measures for the treatment and prevention of metabolic syndrome, as the morbidity rates of cardiovascular disease are higher in subjects with metabolic syndrome than in those without (*8–10*). The main causes of the syndrome are type-2 diabetes and high blood pressure, which are common background factors in insulin resistance. Therefore, drug therapy should be considered for hypertensive patients with metabolic syndrome to improve insulin resistance, while also regulating lipid and glucose metabolism (*11, 12*). Telmisartan has recently been reported to have unique activity as a partial agonist of peroxisome proliferator–activated receptor γ (PPAR-γ) (*13–15*), which plays an important role in regulating lipid and glucose metabolism (*16, 17*).

Therefore, the current study was performed to compare the effects of telmisartan *vs.* olmesartan in controlling home blood pressure and improving lipid and glucose metabolism regulation in patients with chronic heart failure (CHF) and metabolic syndrome.

Methods

This 6-month, open-label study involved 20 outpatients (12 men and 8 women, 66.1±4.7 years old) with chronic, stable, moderate CHF (New York Heart Association [NYHA] class II or III) and metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III classification (*18*) (Table 1). All patients had been taking once-daily 40 mg oral telmisartan for more than 3 months and had home blood pressure of <135/85 mmHg in the early morning (EM) and late evening (LE). The causes of heart failure were old myocardial infarction without current angina pectoris in 8 cases, hypertensive heart disease with left ventricular systolic dysfunction in 10 cases, and aortic valve insufficiency in 2 cases. Patients with complications such as secondary hypertension, hyponatremia (serum Na <135 mEq/L), hypokalemia (serum potassium <3.5 mEq/L), or renal insufficiency (serum creatinine >3.0 mg/dL) were excluded from the study. In addition to the telmisartan or olmesartan, 18 patients (90%) were also given antihypertensive medications, calcium channel blockers, β-receptor blockers, or diuretics; 14 patients (70%) were prescribed antidiabetic medication other than thiazolidinediones; and 18 (90%) received statins (Table 1). Other cardiovascular medications are shown in Table 1. The background cardiovascular medications were given for at least 1 year for β-receptor blockers and at least 3 months for the others, and they were maintained throughout the study period. Patients were instructed to take their antihypertensive medications, including telmisartan and olmesartan, after breakfast. The Institutional Ethics Committee of our hospital approved the protocol, and all patients provided written informed consent prior to participation in the study.

Table 1. Patient Profiles

20 outpatients: 12 males, 8 females	
Age (years old)	66.1±4.7 (59–74)
Height (m)	1.63±0.09 (1.50–1.77)
Body weight (kg)	72.8±8.7 (60.0–89.0)
BMI (kg/m^2)	27.4±2.4 (25.9–30.9)
NYHA class II/III	19/1
Treatment for hypertension (n=18 [90%])	
CCB	8 patients
BB	8 patients
Diuretics	10 patients
ACE I	12 patients
Treatment for diabetes (n=14 [70%])	
Sulfonylureas	10 patients
α-Glucosidase inhibitors	5 patients
Biguanides	1 patients
Treatment for dyslipidemia (n=18 [90%])	
Atorvastatin	13 patients
Simvastatin	3 patients
Pravastatin	2 patients
Other cardiovascular medications	
Diuretics	19 patients
Digitalis	6 patients
Pimobendan	2 patients

BMI, body mass index; NYHA, New York Heart Association; CCB, calcium channel blockers; BB, β-blockers, ACE I, angiotensin-converting enzyme inhibitors.

Study Protocol

Patients were enrolled in a 6-month, open-label study and given 20 mg of oral olmesartan once daily in place of 40 mg telmisartan, with comparable antihypertensive efficacy. After 3 months of olmesartan, the medication was switched back to telmisartan at the baseline (40 mg) dose. Outcome parameters evaluated at baseline (pre), after 3 months of olmesartan administration (post 1), and after 3 months of telmisartan re-administration (post 2) included: 1) systolic (SBP) and diastolic blood pressure (DBP) and heart rate at home and in the clinic; 2) plasma B-type natriuretic peptide (BNP) level; 3) lipid profile (serum total cholesterol [TC], low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglyceride [TG] levels); and 4) glucose profile (fasting blood glucose [FBS] and glycosylated hemoglobin [HbA1c]).

Measurements

Blood pressure was measured at home using validated oscillometric Omron HEM-705CP devices (Omron Healthcare, Kyoto, Japan). After 5 min of rest in the sitting position, patients performed 3 successive self-measurements of SBP and DBP twice daily; in the EM between 6 and 9 AM (within

Table 2. Changes in the Parameters

	Pre (T)	Post 1 (O)	Post 2 (T)
Home blood pressure			
SBP in EM (mmHg)	129.0±4.1	130.9±5.3***	129.0±4.7##
DBP in EM (mmHg)	75.9±4.5	77.5±4.5*	76.2±3.9#
SBP in LE (mmHg)	127.5±4.1	127.2±5.2	127.2±5.2
DBP in LE (mmHg)	71.1±6.2	70.0±6.1	70.6±5.4
Clinic blood pressure			
SBP (mmHg)	129.9±5.9	129.3±5.0	129.5±5.2
DBP (mmHg)	73.2±6.2	72.1±5.9	72.7±5.3
Heart rate			
EM (/min)	71.0±7.1	70.8±6.0	71.3±6.4
LE (/min)	67.9±4.9	67.0±4.9	68.1±4.9
Outpatients room (/min)	70.7±5.2	69.9±5.0	70.6±5.7
Body weight (kg)	72.8±8.7	72.9±8.2	72.6±8.2
BNP (pg/mL)	191.0±67.9	197.3±75.9*	188.6±68.0###
Glucose metabolism			
FBS (mg/dL)	111.0±13.2	111.4±14.3	110.7±13.8
HbA1c (%)	6.0±0.7	6.1±0.8*	6.0±0.7#
Lipid metabolism			
TC (mg/dL)	217.7±17.9	220.1±19.3*	218.4±17.9#
LDL cholesterol (mg/dL)	127.8±19.2	130.4±18.3*	127.7±19.0#
HDL cholesterol (mg/dL)	39.9±5.8	39.6±5.4	39.6±4.9
Triglyceride (mg/dL)	218.0±74.3	226.8±82.5***	218.6±75.4###

T, once-daily telmisartan 40 mg; O, once-daily olmesartan 20 mg; SBP, systolic blood pressure; DBP, diastolic blood pressure; EM, the early morning; LE, the late evening; BNP, B-type natriuretic peptide; FBS, fasting blood sugar; TC, total cholesterol, LDL, low-density lipoprotein; HDL, high-density lipoprotein. *$p<0.05$, ***$p<0.005$ *vs.* pre; #$p<0.05$, ##$p<0.01$, ###$p<0.005$ *vs.* post 1.

1 h after rising, post-urination, but before breakfast and medication intake) and in the LE between 9 and 11 PM (just prior to sleep). The mean of 3 successive measurements obtained at 1-min intervals was taken as the home blood pressure value. Home blood pressures at baseline, post 1, and post 2 were determined as the average values of each of 3 consecutive days. A physician measured the blood pressure of seated patients at clinic between 9 AM and 2 PM with a conventional mercury sphygomomanometer. The first and fifth Korotkoff sounds were taken to identify SBP and DBP, respectively.

Blood samples were drawn by venipuncture after a 12-h overnight fast and after at least 30 min of rest with the patient in the supine position. Serum FBS, HbA1c, TC, HDL cholesterol, LDL cholesterol, and TG levels were measured immediately using an autoanalyzer (AU 5200; Olympus, Tokyo, Japan). Plasma BNP levels were measured by a subcontract by radioimmunoassay using commercial kits (Shionoria BNP Kit; Shionogi, Osaka, Japan) (FALCO Biosystems, Osaka, Japan). The intra-assay coefficient of variation (2.13% to 7.84%) and inter-assay coefficient of variation (6.81% to 12.15%) increased from high (650.8 pg/mL) to low (18.7 pg/mL) BNP.

Statistical Analysis

All results are expressed as means±SD. Comparisons of baseline and post-study data were performed using the paired *t*-test or Wilcoxon's single-rank test as appropriate. Linear regression analysis was used to test the correlations between continuous variables. Probability values less than 0.05 were regarded as statistically significant.

Results

Serial Changes in Home and Clinic Blood Pressure, BNP, and Parameters of Lipid and Glucose Profiles

Table 2 shows the changes in the parameters examined in this study. SBP and DBP in the EM, plasma BNP levels, serum TC, LDL cholesterol, TG, and HbA1c were increased significantly at post 1 but returned to baseline values at post 2. Meanwhile, SBP and DBP in the LE and at the clinic, as well as heart rate, did not differ significantly. In addition, no changes were observed in serum HDL cholesterol or FBS or in body weight during this study. These results suggested that telmisartan was more beneficial than olmesartan for the management of blood pressure in the EM, heart failure, and both

Table 3. Changes in the Parameters in the Subgroups Divided According to the Baseline BMI

		Pre (T)	Post 1 (O)	Post 2 (T)
Home blood pressure				
SBP in EM (mmHg)	H	129.7±5.4	132.4±5.8*	129.4±5.8#
	L	128.2±5.1	129.3±5.7	128.6±5.9
DBP in EM (mmHg)	H	75.7±4.9	77.4±5.2*	76.0±4.9#
	L	76.5±4.9	77.9±3.0	76.9±2.4
Body weight (kg)	H	76.2±8.3	76.1±8.3	76.0±8.3
	L	69.4±7.7	69.6±7.5	69.4±7.9
BNP (pg/mL)	H	195.8±63.3	207.2±71.4*	194.6±64.5##
	L	186.2±58.9	187.4±56.3	182.5±57.9
Glucose metabolism				
FBS (mg/dL)	H	119.2±8.4	120.1±8.3	118.7±9.4
	L	102.8±5.5	102.6±6.2	102.6±5.3
HbA1c (%)	H	6.6±0.5§	6.8±0.5**,§	6.6±0.5##,§
	L	5.5±0.2	5.4±0.2	5.4±0.2
Lipid metabolism				
TC (mg/dL)	H	220.4±23.3	221.7±25.1	219.7±23.6
	L	215.0±14.6	218.6±17.3	217.1±15.4
LDL cholesterol (mg/dL)	H	125.5±21.4	127.1±21.9	125.5±20.6
	L	130.1±15.0	133.7±16.4	129.8±15.8
HDL cholesterol (mg/dL)	H	41.9±5.7	41.2±5.8	41.3±5.2
	L	37.8±6.0	37.9±6.7	37.8±5.5
Triglyceride (mg/dL)	H	232.5±73.4	242.1±82.3*	233.6±75.0#
	L	204.1±58.6	211.5±66.2*	203.6±58.4#

BMI, body mass index; H, patients with high BMI (≥27.0 kg/m^2) at the baseline (n=10); L, patients with low BMI (<27.0 kg/m^2) at the baseline (n=10). Other abbreviasions as in Table 2. *p<0.05, **p<0.01 *vs.* pre; #p<0.05, ##p<0.01 *vs.* post 1; §p<0.005 *vs.* L.

lipid and glucose metabolism in patients with CHF and metabolic syndrome.

Moreover, these favorable effects of telmisartan, except that on lipid metabolism, were more overt in patients with relatively high body mass index (BMI) (≥27.0 kg/m^2) than in patients with relatively low BMI (<27.0 kg/m^2) (Table 3).

Correlation between Changes in Blood Pressure, BNP, and Parameters of Lipid and Glucose Profiles

Increases in plasma BNP level correlated with the rises in SBP and DBP in the EM at post 1 (Fig. 1A and C), and the decreases in plasma BNP level correlated with the reductions in SBP and DBP in the EM at post 2 (Fig. 1B and D). There were no similar correlations between BNP and SBP or DBP in the LE. Body weight did not change significantly throughout this study and was independent from all parameters, including plasma BNP levels, SBP, and DBP. These observations suggested that it is important to control home blood pressure in the EM for the management of heart failure in patients with CHF and metabolic syndrome.

On the other hand, the trend in lipid and glucose profiles did not seem to correlate with those in SBP or DBP in the EM, LE, or at the clinic. Therefore, the beneficial effects of telmisartan on lipid and glucose profiles were separate from its antihypertensive effect.

Effects of Telmisartan on Parameters of Lipid and Glucose Metabolism

To investigate the effects of telmisartan on lipid and glucose metabolism parameters, we compared serial changes in these parameters between the 2 groups, stratified according to the mean serum TC, LDL cholesterol, TG, and HbA1c levels at post 2. Figure 2A shows the serial changes in TC in patients with relatively high TC (≥220.1 mg/dL at post 2; mean value, 232.3 mg/dL) and low TC (<220.1 mg/dL at post 2; mean value, 197.4 mg/dL). In comparison with olmesartan, telmisartan decreased TC concentrations in patients with relatively high TC, whereas patients with relatively low TC showed no difference between the groups. Similarly, telmisartan had more beneficial effects than olmesartan on serum LDL cholesterol in patients with relatively high serum LDL cholesterol (≥130.4 mg/dL at post 2; mean, 146.5 mg/dL) (Fig. 2B) and on TG levels (≥226.8 mg/dL at post 2; mean, 297.4 mg/dL) (Fig. 3A) and HbA1c (≥6.1% at post 2; mean, 6.9%) (Fig. 3B) at post 2. However, no differences were observed between the medications for patients with relatively low LDL cholesterol (<130.4 mg/dL; mean, 114.3 mg/dL) (Fig. 2B),

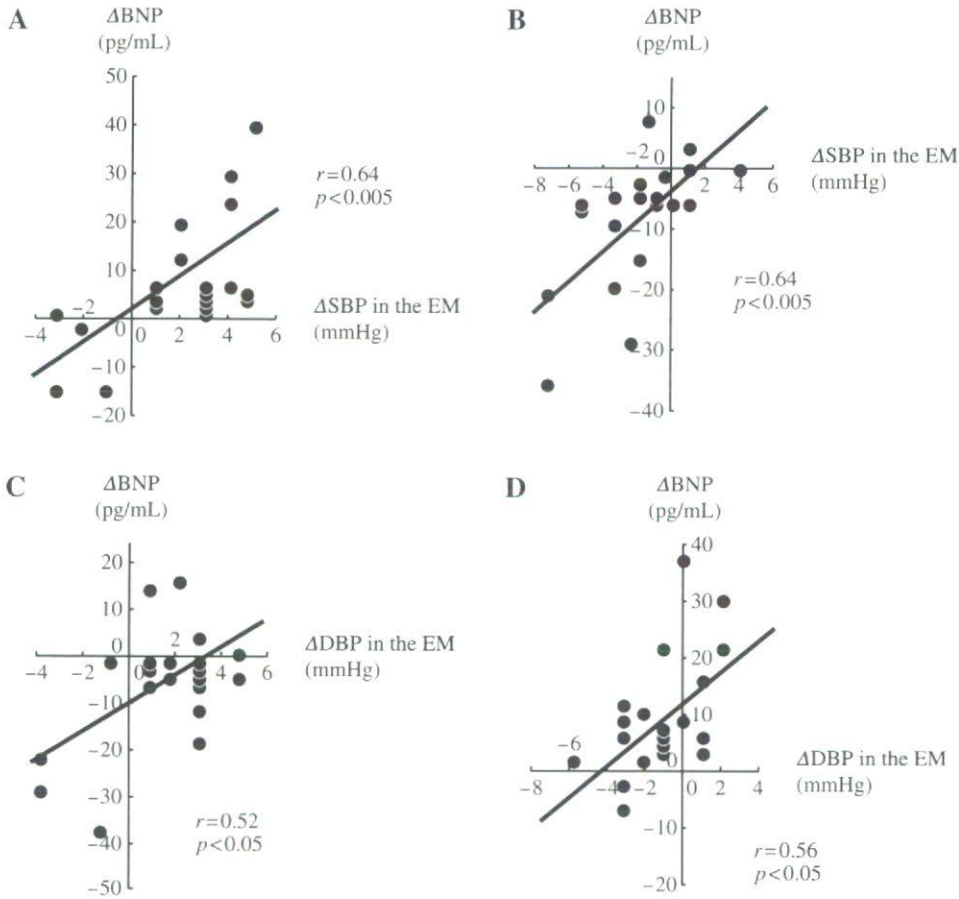

Fig. 1. *Correlation between ΔBNP and ΔSBP in the EM. BNP, B-type natriuretic peptide; SBP, systolic blood pressure; DBP, systolic blood pressure; EM, early morning. A: Correlation between ΔBNP and ΔSBP in the EM from pre to post 1. B: Correlation between ΔBNP and ΔSBP in the EM from post 1 to post 2. C: Correlation between ΔBNP and ΔDBP in the EM from pre to post 1. D: Correlation between ΔBNP and ΔDBP in the EM from post 1 to post 2.*

TG (<226.8 mg/dL; mean, 169.0 mg/dL) (Fig. 3A) or HbA1c (<6.1%; mean, 5.6%) at post 2 (Fig. 3B). Consequently, telmisartan showed marked effects on lipid and glucose profiles only in patients with serious dysfunction in lipid or glucose metabolism.

Discussion

This is the first direct comparison of the effects of telmisartan and olmesartan on home blood pressure and both lipid and glucose profiles in hypertensive patients with CHF and metabolic syndrome. Our findings indicated that once-daily telmisartan at a dose of 40 mg reduced morning blood pressure and improved lipid and glucose metabolism as compared with once-daily 20 mg olmesartan, suggesting that telmisartan may be more beneficial than olmesartan in the management of hypertension, CHF, and metabolic syndrome.

Internal Organ Protection by Long-Acting Antihypertensive Medication

Telmisartan's antihypertensive action consistently shows a longer half-life than those of other ARBs and amlodipine (*6, 7, 19, 20*). In the present study, after the switch from telmisartan (once daily, 40 mg) to olmesartan (once daily, 20 mg), EM blood pressure was elevated at approximately 24 h post-administration, while there was little variation in LE at approximately 12 h or approximately 3–5 h after administration at our clinic (Table 2). These results indicated that telmisartan's antihypertensive action lasts longer than olmesartan's.

For CHF patients with hypertension, it is important to control blood pressure continuously throughout the day (*1, 21, 22*). Therefore, it is recommended to monitor their home blood pressure both at home and in the outpatient room (*1–3*). Insufficient EM hypertension management is responsible for difficulty in preventing and recovering from hypertensive

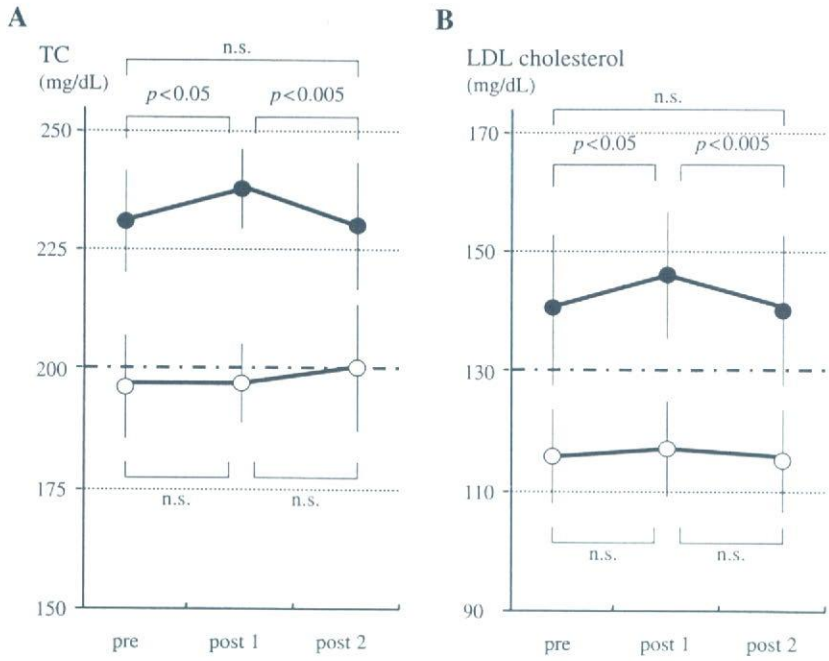

Fig. 2. *Serial changes in TC and LDL cholesterol. A: TC, total cholesterol. ●, patients with TC ≥220.1 mg/dL at post 2 (mean: 232.3 mg/dL; n = 13); ○, patients with TC < 220.1 mg/dL at post 2 (mean: 197.4 mg/dL; n = 7). B: LDL cholesterol, low-density lipoprotein cholesterol. ●, patients with LDL cholesterol ≥130.4 mg/dL at post 2 (mean: 146.5 mg/dL; n = 10); ○, patients with LDL cholesterol < 130.4 mg/dL at post 2 (mean: 114.3 mg/dL; n = 10). Note that telmisartan had significant effects on serum TC or LDL cholesterol levels in patients with TC ≥220.1 mg/dL (A) or LDL cholesterol ≥130.4 mg/dL (B) at post 2.*

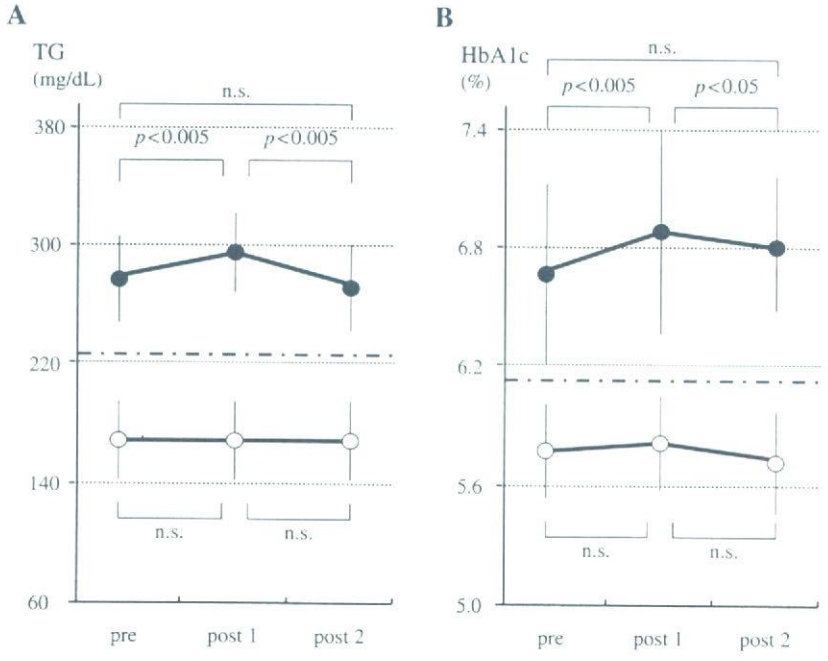

Fig. 3. *Serial changes in TG and HbA1c. A: TG, triglyceride. ●, patients with TG ≥226.8 mg/dL at post 2 (mean: 297.4 mg/dL; n = 9); ○, patients with TG < 226.8 mg/dL at post 2 (mean: 169.0 mg/dL; n = 11). B: HbA1c, glycosylated hemoglobin. ●, patients with HbA1c ≥6.1% at post 2 (mean: 6.9%; n = 8); ○, patients with HbA1c < 6.1% at post 2 (mean: 5.6%; n = 12). Note that telmisartan had significant effects on serum TG or HbA1c levels in patients with TG ≥226.8 mg/dL (A) or HbA1c ≥6.1% (B) at post 2.*

organ damage and can lead to deterioration of cardiac function in CHF patients with hypertension (*1*, *3*, *4*). Cardiologists usually evaluate the management state of CHF patients by monitoring their plasma BNP levels (*23*, *24*). Plasma BNP level is a useful indicator for screening the heart failure state. ARBs have been reported to decrease plasma BNP levels *via* the effects of the reduction of afterload and preload and, more importantly, *via* myocardial protection through their suppressive action on the renin-angiotensin-aldosterone system (*25–29*). In the present study, the transition of plasma BNP levels correlated with the transition of SBP and DBP in the EM (Fig. 1). On the other hand, it is believed that the changes in both SBP and DBP in the LE (less than 0.3 mmHg and 1.1 mmHg, respectively) were not significant and did not influence plasma BNP level. These observations suggested that control of morning blood pressure is important and that telmisartan is more effective than olmesartan in managing CHF patients with hypertension, partially due to its longer antihypertensive action.

Effects of ARBs on Glucose Metabolism

Although ARBs improve insulin resistance as a class through their inhibitory effects on AT1 receptors (*30*), telmisartan also has a PPAR-γ–activating effect that acts synergistically to further improve insulin resistance (*13*, *16*, *31*). It has been reported that this action of telmisartan is about 1/2 titer per mol/L of the thiazolidinedione, pioglitazone (*15*). Indeed, telmisartan's effect on improving glucose metabolism has been reported to be superior to those of other ARBs, losartan (*32*), candesartan, and valsartan (*33*, *34*), due to its effects that improve insulin resistance (*13*, *27*, *35*, *36*). In the current study, HbA1c rose when the treatment regimen was switched from telmisartan to olmesartan but decreased after the return to telmisartan (Fig. 3B). Meanwhile, there were no changes in FBS throughout the study. These observations did not directly demonstrate that telmisartan improved insulin resistance in the present study, since the transition of the insulin value and resistance were not measured directly. The discrepancy in the effects of telmisartan on FBS and HbA1c in our study may have been caused by the prescription of oral anti-diabetic medicine, sulfonylureas, and others for most patients, and their FBSs were controlled under relatively low values. Further studies are needed to investigate the effects of telmisartan *vs.* olmesartan on FBS and HbA1c in diabetic patients who are not being treated by such medicine.

A previous study indicated HbA1c reduction after telmisartan treatment (*32*), although others noted no such effect (*35*, *37*, *38*). These reports were difficult to compare because the baseline characteristics of the subjects and the telmisartan dose differed from study to study. When differences in physical characteristics due to race are taken into consideration, the BMIs were relatively high in both the former study (*32*) and the present study, while they were relatively low in the latter reports, except in Nagel *et al.* (*38*). Therefore, telmisartan may reduce HbA1c only in obese patients, in whom insulin resistance will be remarkable. In the present study, telmisartan had more additive beneficial effects on HbA1c in patients with relatively high HbA1c (≥6.1%) or BMI (≥27.0 kg/m^2), but patients with relatively low HbA1c (<6.1%) or BMI (<27.0 kg/m^2) showed no such effects between telmisartan and olmesartan (Fig. 3 and Table 3). These observations suggested that the reduction in HbA1c induced by telmisartan was striking only in cases with marked glucose metabolism dysfunction. This may explain why there were no HbA1c fluctuations after telmisartan treatment in the report by Nagel *et al.* (*38*), in which baseline HbA1c was as low as 5.5%.

Effects of ARBs on Lipid Metabolism

PPAR-γ, activated by telmisartan, affects fat cell differentiation (*39*). Telmisartan shows excellent effects in controlling body weight and fat accumulation in the internal organs and reduces adipose cell size better than valsartan (*34*). Moreover, telmisartan has also been reported to increase low serum adiponectin levels (*40–42*) in patients with metabolic syndrome. In the present study, serum TC, LDL cholesterol, and TG levels increased after the switch from telmisartan to olmesartan, and dropped once more after the return to telmisartan (Figs. 2A, B, and 3A). Previous studies indicated reduced TC, LDL cholesterol, and TG levels after treatment with telmisartan (*37*, *43*, *44*), while other studies noted no such findings (*35*, *42*, *45*). Although these reports were difficult to compare because the baseline lipid profiles of the subjects and telmisartan doses differed among the studies, the baseline TC, LDL cholesterol, and TG were higher in the former than in the latter reports. In the present study, telmisartan had more beneficial effects on lipid profiles in patients with relatively high TC (≥220.1 mg/dL), LDL cholesterol (≥130.4 mg/dL), and TG (≥226.8 mg/dL) levels and showed no additive effects on lipid profiles in patients with relatively low TC (<220.1 mg/dL), LDL cholesterol (<130.4 mg/dL), and TG (<226.8 mg/dL) levels. These results suggest that the molecular mechanism underlying the favorable effects of telmisartan on lipid disorder may differ from those of statins, and that the lipid metabolism improvement is a unique effect of telmisartan not shared by other ARBs. These results were mostly in agreement with a recent report, which stated that severely altered baseline lipid parameters are necessary to see an improvement in lipid metabolism with telmisartan treatment (*44*). This mechanism of action of telmisartan remains unclear, but could perhaps be explained by the high lipophilicity of this agent as compared with other ARBs, including olmesartan (*46*), by PPAR-α–activating effects but not PPAR-γ–activating effects (*13*), or by unknown molecular effects to fat cells.

In conclusion, the results of our study demonstrated that the antihypertensive effect of once-daily telmisartan continued to the next morning and before the next administration, resulting in more favorable management of CHF than occurs with olm-

esartan treatment. In addition, telmisartan showed more beneficial effects on lipid and glucose metabolism than olmesartan, especially in patients with relatively severe disorders in lipid and glucose profiles. Further studies with larger numbers of patients should compare the effects of telmisartan and olmesartan in controlling home blood pressure and improving the regulation of lipid and glucose metabolism. Moreover, further studies are needed also to investigate the effects of telmisartan *vs.* olmesartan on FBS and HbA1c in diabetic patients who are not being treated with oral anti-diabetic medicine. Furthermore, additional investigations of the molecular mechanisms of the favorable effects of telmisartan on lipid disorder are required.

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Additional Effects of Bosentan in Patients With Idiopathic Pulmonary Arterial Hypertension Already Treated With High-Dose Epoprostenol

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Background Combination therapy has been proposed in treatment algorithms for idiopathic pulmonary arterial hypertension (IPAH), so the additional effects of bosentan in IPAH patients already treated with high-dose epoprostenol (EPO) was evaluated in the present study.

Methods and Results Bosentan (62.5 mg twice daily) was administered to 8 IPAH patients already being treated with high-dose EPO (average dose 99.6±43.4 ng·kg^{-1}·min^{-1}). Hemodynamics were assessed at baseline and at 2 days and then 1 year after the initiation of bosentan. Because a remarkable elevation of mixed venous oxygen saturation was observed at the initiation of bosentan, the dosage of EPO was reduced in 7 patients (from 99.6±43.4 to 82.8±31.3 ng·kg^{-1}·min^{-1}, $p<0.05$). There was a significant decrease from the baseline value for systolic pulmonary artery pressure (80.1±19.3 to 66.8±16.5 mmHg, $p<0.05$). These effects were maintained for 1 year without progression of PAH in 6 patients whose condition had been stabilized at baseline.

Conclusions The additional use of bosentan for IPAH patients whose condition has been stabilized by high-dose EPO is safe and effective. (*Circ J* 2008; **72:** 1142–1146)

Key Words: Bosentan; Combination therapy; Epoprostenol; Idiopathic pulmonary arterial hypertension

Dramatic advances have been made over the past decade in the treatment of pulmonary arterial hypertension (PAH). Current treatment algorithms recommend prostanoid analogs (iloprost, treprostinil), bosentan, sildenafil, and epoprostenol (EPO), depending on disease severity[1,2] Although each of these drugs has been reported to improve hemodynamics and exercise capacity in PAH patients,[3–15] improvement of long-term survival in patients with idiopathic PAH (IPAH) has been achieved only with EPO,[4–6] treprostinil[13] and bosentan.[10]

PAH is a complex disease with multifactorial pathophysiology.[16] More than 1 signaling pathway appears to be affected,[1] including the endothelin, nitric oxide and prostaglandin signaling pathways. Treatment that targets more than 1 pathogenic mechanism at the same time by using a combination of agents with different modes of action might maximize the clinical benefit, so combination regimens have been studied.[17–22] The combination of EPO and bosentan was studied in the BREATHE-2 trial, which showed a trend, but with no statistical significance, for improvement in hemodynamics or clinical improvement in PAH patients,[19] and the addition of bosentan to treatment of children with IPAH already treated with EPO enabled the EPO dosage to be reduced, which decreased its associated side-effects without deterioration of clinical and hemodynamic conditions.[20]

The main therapy for PAH in Japan has been continuous intravenous infusion of EPO, because drugs that can improve hemodynamics and exercise capacity, such as iloprost, treprostinil, bosentan and sildenafil, were not approved for use in Japan until recently. Because of the lack of lung transplantation donors, the dosage of EPO had to be continuously increased until the patient's condition stabilized, so most of our patients have been treated with high-dose EPO, and their survival is similar to that previously reported.[4–6]

Recently, bosentan became available in Japan as a therapeutic agent for IPAH. Its pharmacological mechanism differs from that of EPO and we therefore expected that the additional use of bosentan would generate a synergistic effect in IPAH patients already treated with high-dose EPO. The aim of the present study was to evaluate the effects of additional bosentan therapy in patients with IPAH already treated with high-dose EPO.

Methods

Patient Selection

Sixteen patients were being treated with EPO in the Division of Cardiology, National Hospital Organization, Okayama Medical Center and were followed up under a diagnosis of IPAH based on the World Health Organization (WHO) criteria.[23,24] Patients selected for this study were clinically stable, had not required an increase in the dosage of EPO for at least 6 months, were in WHO functional class II, and had no clinical evidence of heart failure. Patients

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who did not clearly meet these criteria were excluded from the study and a total of 8 patients were enrolled. Diuretics and supplemental oxygen were being used by all patients, and digitalis was used by 2 patients. All the enrolled patients were stabilized with current medication, which had not been changed for more than 6 months before the initiation of bosentan. Patients were aware that bosentan is a novel drug with unexplored long-term safety and efficacy, and that studies on combination treatment are lacking. The local institutional review boards approved the study protocol and all patients gave written informed consent for participation in the study.

Study Design

Baseline information, including demographic data, current medical therapy and clinical characteristics prior to the initiation of bosentan, was available for all patients. Chest radiography, electrocardiography, blood examination and 6-min walking test were performed within 1 week prior to the initiation of bosentan. Patients remained on concomitant medications after the initiation of bosentan.

Bosentan therapy was initiated at a dose of 62.5 mg twice daily under hemodynamic monitoring with a Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA, USA). Cardiopulmonary hemodynamic parameters (systolic pulmonary artery pressure [sPAP], right atrial pressure [RAP], mixed venous oxygen saturation [SvO_2], pulmonary vascular resistance [PVR], noninvasive blood pressure [NIBP], and heart rate [HR]) were determined before and 2 h after bosentan administration at 2 days after the initiation of treatment. If the SvO_2 value increased, the dosage of EPO was decreased for 2 days under Swan-Ganz monitoring while maintaining the SvO_2 at never less than the initial value. When the EPO dosage could be decreased, we reduced it in 2–7 $ng \cdot kg^{-1} \cdot min^{-1}$ steps in individual cases. Bosentan therapy was continued for all patients after removal of the Swan-Ganz catheter. Chest radiography, electrocardiography, blood examination and 6-min walking test were performed at 1 week after initiation of bosentan.

We followed all patients after discharge from our center. At each visit, we collected data for current medications, WHO functional class, potential side-effects of therapy, vital signs, chest radiography, electrocardiography, blood examination and 6-min walking distance. Right heart catheterization was recommended within 1 year after the initiation of bosentan.

Serum transaminases and bilirubin were monitored during hospitalization for combination therapy and at each subsequent visit (FDA requirement for bosentan administration: FDA, 2003). Standard recommendations for dose reduction or discontinuation were followed. In asymptomatic patients, if the aspartate aminotransferase and alanine aminotransferase levels were more than 3-fold over the upper limit of normal or their baseline values, liver function tests were immediately repeated. If liver function test abnormalities were confirmed, the drug was stopped, and the values were rechecked. In the event of any symptoms of liver dysfunction (eg, anorexia, nausea), administration of the drug was stopped.

The doses of EPO and bosentan were kept constant during the observation period unless patients experienced intolerable side-effects from EPO.

Statistical Analysis

Results are presented as means ± SD. Results obtained at the start of EPO therapy, baseline, and after 2 days, 7 days and approximately 1 year of bosentan therapy were compared using 1-way repeated ANOVA, followed by the post-hoc Dunnett's test. A p-value <0.05 was considered significant.

Results

Demographic Characteristics at Initiation of Bosentan

The characteristics and hemodynamic parameters before and after the addition of bosentan administration to EPO therapy are shown in Table 1. The patients were predominantly female (7 of the 8 patients). All patients were treated with high-dose EPO (average dosage 99.6±43.4 $ng \cdot kg^{-1} \cdot min^{-1}$ [41.0–189.1]) for a long duration (average 1,239.1± 527.4 days [713–2,217]) at baseline. None of the patients had elevated liver enzymes at baseline and all were in a stable clinical condition.

Cardiopulmonary Hemodynamics, Dosage of EPO and Value of SvO_2

Changes in various hemodynamic measurements are shown in Fig 1. A significant decrease in sPAP (from 110.7± 20.7 mmHg to 80.1±19.3 mmHg, $p<0.05$) and a significant increase in SvO_2 (from 64.6±9.4% to 75.3±4.9%, $p<0.05$) occurred after the start of EPO therapy.

At the initiation of bosentan, 7 patients showed remarkable elevation of SvO_2 and had complaints such as flushing and headache because of the high cardiac output. The dose of EPO was safely decreased from 99.6±43.4 to 82.8± 31.3 $ng \cdot kg^{-1} \cdot min^{-1}$ ($p<0.05$), with a maximal decrease of 50 $ng \cdot kg^{-1} \cdot min^{-1}$ in patient no. 6 (from 189.1 to 140.0 $ng \cdot kg^{-1} \cdot min^{-1}$) (Fig 1A). Despite efforts to maintain the initial value of SvO_2, a slight but significant increase from baseline values occurred (from 75.3±4.9% to 79.7±3.2%, $p<0.05$) (Fig 1B).

Significant decreases from baseline values occurred for sPAP (from 80.1±19.3 to 66.8±16.5 mmHg, $p<0.05$) (Fig 1C) and PVR (from 9.7±3.1 to 8.1±3.2 Wood units, $p<0.05$); however, there were no significant changes in RAP (from 6.4±1.7 to 5.0±1.4 mmHg, $p=0.17$), HR or systolic NIBP.

WHO Functional Class and 6-min Walking Test

The WHO functional class at study entry improved in comparison with the value at the start of EPO therapy. At study entry, all patients were in WHO functional class II. At 1 week after the initiation of bosentan, the WHO functional class had not changed in any of the patients. The distance attained in the 6-min walking test tended to increase at 1 week after the initiation of bosentan.

Side-Effects and Safety

Side-effects of EPO were monitored after the initiation of bosentan. All patients experienced flushing and 1 had nausea and headache; however, these side-effects were relieved by reducing the EPO dosage. None of the patients showed elevation of liver enzyme levels at 1 week after the initiation of bosentan (aspartate aminotransferase, from 13.9±4.0 to 13.5±3.5 IU/L, $p=0.48$; alanine aminotransferase, from 14.5±11.0 to 13.3±10.5 IU/L, $p=0.03$). None of the patients experienced any adverse effects leading to discontinuation of bosentan and there were no deaths during the observation period.

Table 1 Patients' Characteristics and Hemodynamic Effects Before and After the Addition of Bosentan to EPO Therapy

Patient no.	Age (years)	Sex	WHO functional class				6MWD				BNP				NISBP				HR			
			S	B	1 week	FU	S	B	1 week	FU	S	B	1 week	FU	S	B	2-day	FU	S	B	2-day	FU
1	34	F	IV	II	II	II	0	420	395	410	85.1	14.3	16.0	10.5	120	97	94	100	88	86	77	76
2	30	F	IV	II	II	II	0	425	435	425	452	20.5	37.0	29.6	90	95	90	90	100	80	75	80
3	28	F	III	II	II	III	260	435	435	345	196	72.3	136	138	95	102	92	113	53	61	64	89
4	26	F	III	II	II	II	370	325	470	440	37.9	9.1	6.0	6.2	101	100	100	81	71	84	75	68
5	21	M	IV	II	II	II	0	375	415	395	474	28.4	30.4	18.8	90	111	107	128	110	86	79	65
6	32	F	IV	II	II	II	0	420	415	425	320	4.8	13.6	5.5	94	94	97	90	75	76	84	82
7	33	F	III	II	II	†	210	415	400	†	113	52.1	25.5	†	85	94	86	†	72	77	76	†
8	50	F	IV	II	II	II	0	325	330	325	589	28.7	16.7	26.0	136	115	121	108	95	110	104	100
Mean	32						105	392*	411	395	283	28.8*	35.2	33.5	101	101	98.4	101.4	83	82.5	79.3	75.7
SD	8.5						151	45.2	40.7	43.7	205	22.9	41.9	47.0	17.5	8	11.2	16.1	18.6	13.7	11.5	13.5

*Late failure; *p<0.05 vs start of EPO therapy.

EPO, epoprostenol; WHO, World Health Organization; 6MWD, 6-min walking distance; BNP, B-type natriuretic peptide; NISBP, non-invasive systolic blood pressure; HR, heart rate; S, start of EPO therapy; B, baseline; 1 week, 1 week after initiation of bosentan; FU, follow-up; 2-day, 2 days after initiation of bosentan.

Fig 1. Changes in hemodynamic measurements and dose of epoprostenol (EPO) from the start of EPO therapy to the end of the follow-up period. Data for individual patients are shown. Means±SD represented by vertical lines. (A) Dosage of epoprostenol; (B) mixed venous oxygen saturation; (C) systolic pulmonary artery pressure.

Follow-up After Initiation of Bosentan

The combination of EPO and bosentan was continued in 6 patients for an average of 381±120 days. It had to be discontinued in 1 patient because of adverse events (patient no. 7) who had an asymptomatic elevation of liver enzyme levels at 2 months after the initiation of bosentan, which was subsequently discontinued, and EPO was returned to

the original dosage. Right-heart failure occurred in 1 patient (patient no. 3), who required hospitalization for an episode of hemoptysis at 9 months after the initiation of bosentan. Right-heart catheterization was performed, and sPAP was found to be elevated (from 97 to 116 mmHg). The patient required diuretic medication and increased dosage of EPO after the catheterization. The other 6 patients did not experience liver dysfunction or right heart failure leading to hospitalization.

Right-heart catheterization was performed in 7 patients, including the patient with right-heart failure. Various assessments of these patients are shown in Fig 1 and Table 1. The dose of EPO (from 86.8±31.6 to 83.7±32.3 $ng \cdot kg^{-1} \cdot min^{-1}$, p=0.79), SvO_2 (from 79.6±3.4% to 77.7±3.2%, p=0.21), sPAP (from 65.9±17.6 to 69.7±22.0 mmHg, p=0.51) and PVR (from 10.2±4.1 to 7.9±1.5 Wood units, p=0.41) were not significantly different from the values immediately after the initiation of bosentan.

The distance attained in the 6-min walking test tended to be decreased at 1 year after the initiation of bosentan. The serum BNP level was not significantly different from that immediately after the initiation of bosentan.

Discussion

The results of the present study suggest that the addition of bosentan to high-dose EPO could have synergistic effects in patients with IPAH. SvO_2 significantly increased in all patients on initiation of bosentan, resulting in a high cardiac output state in 7 patients, and the dose of EPO had to be decreased despite a significantly decrease in sPAP. Furthermore, these effects were maintained for at least 1 year without progression of PAH in 6 patients.

Based on the known pathobiological mechanisms of PAH, combination therapy with agents targeting different pathways has been proposed in treatment algorithms, although the criteria for instituting combination therapy have not been defined. Combination therapy is used in 3 scenarios. First, drugs with different actions are additionally administered to PAH patients with an insufficient response to monotherapy. Hoeper et al reported that the addition of bosentan led to marked improvements in refractory patients already receiving iloprost or beraprost,[17] and Channick et al found that the addition of inhaled treprostinil for PAH patients who were symptomatic despite bosentan therapy led to improvement.[18] Second, drugs with different actions are administered to patients who are in transition from infusion therapy, such as EPO or treprostinil, to less complicated oral therapy.[19–22] Third, drugs with different actions are administered to patients whose condition has been stabilized by monotherapy to enable further clinical improvement or to suppress side-effects resulting from high doses. In the present study, we administered additional bosentan to patients whose condition had been stabilized with EPO therapy in order to achieve further clinical and hemodynamic improvements. Hemodynamic parameters improved in 7 patients at the initiation of bosentan and these improvements were maintained in 6 patients. The dose of EPO was decreased because the addition of bosentan led to high cardiac output. Although patients experienced flushing, nausea and headache because of this, these symptoms quickly improved after reducing the dosage of EPO. There have been a few studies in which the possibility of reducing the EPO dose was examined.[20–22] In a study of children, Ivy et al[20] demonstrated that bosentan facilitated a reduction in the EPO dose, and the associated side-effect severity, without deterioration of clinical and hemodynamic parameters. Patients with a successful reduction were treated with high-dose (average dose 86±37 $ng \cdot kg^{-1} \cdot min^{-1}$) and long-term EPO (average duration 7.6±2.3 years) and showed normal or near normal PAP (mean PAP of 49±27 mmHg). Our results also suggest that the addition of bosentan enabled a reduction of the EPO dose in patients whose condition had already been stabilized by high-dose and long-term EPO therapy. In our study, patients with a successful reduction in the EPO dose had been treated by high-dose (average dose 104.5±48.6 $ng \cdot kg^{-1} \cdot min^{-1}$) and long-term (average duration 3.69±1.6 years) therapy.

The BREATHE-2 study showed that the combination of bosentan and EPO was effective for improving hemodynamics, exercise capacity and WHO functional class, but had no significant benefit compared with EPO monotherapy.[19] Those results differ from ours, because the patients enrolled in the BREATHE-2 study were untreated and in a serious condition without stabilization, whereas almost all of the present patients were already stabilized. We had to discontinue combination therapy in 1 patient because of progression of right-heart failure. The sPAP and BNP levels in that patient were higher than those in other patients at baseline, so PAH might not have been completely stabilized by EPO at enrollment, and the dosage of EPO would therefore have been insufficient. Thus, combination therapy might not be successful in IPAH patients who have not been stabilized.

To generate synergistic effects by the addition of bosentan, baseline stabilization of PAH with high-dose EPO appears to be necessary. We speculate that high-dose EPO therapy would alter the vasoreactivity of the pulmonary artery to different drugs, so selection of patients stabilized on EPO therapy is necessary for successful combination therapy. Most of the significant hemodynamic improvements occurred at the initiation of bosentan and would be the result of vasodilatation caused by bosentan. The additional effects at the initiation of bosentan could be maintained for at least 1 year, a chronic effect that might be related to inhibition of disease activity, such as pulmonary artery remodeling. However, further synergistic effects were not achieved, so bosentan can not reverse established pulmonary artery remodeling.

The dosage of bosentan was maintained at 62.5 mg twice daily and was not titrated to 125 mg twice daily, which might have given further chronic clinical and hemodynamic improvements. The dosage of bosentan was based on the data presented by Humbert et al in the BREATHE-2 study: dose of bosentan per body weight was 3.11 mg/kg (2.00–5.45 mg/kg).[19] Therefore, the dose of bosentan used in the present study (2.62 mg/kg [1.68–3.37 mg/kg]) was seemed sufficient and it was thought that up-titration of bosentan would not provide further improvements.

Study Limitations

The patient population was small and the study design was non-randomized, non-blinded, and open label. We could not increase the number of patients in our sample because almost all of the recent patients had already been treated with bosentan at the time of their first visit to us. Significant results could not be achieved because of the small sample size, so we decided we could not conduct a double-blind and controlled study. Although the addition of bosentan was successful in 6 patients treated with high-dose

EPO, the median follow-up for hemodynamic data was only 1 year, which does not necessarily constitute "long-term" follow-up. Thus, no conclusions regarding long-term safety and efficacy can be reached. However, significant hemodynamic improvements during the introduction period and the maintenance of these effects for 1 year indicate a benefit of the addition of bosentan to high-dose EPO therapy. Large-scale and long-term investigations are required to prove the effectiveness of the combination of bosentan and high-dose EPO therapy.

Conclusion

The addition of bosentan to the treatment of IPAH patients whose condition has been stabilized by high-dose EPO can generate synergistic effects.

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Complete Atrioventricular Block Secondary to Lithium Therapy

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Sinus node dysfunction has been reported most frequently among the adverse cardiovascular effects of lithium. In the present case, complete atrioventricular (AV) block with syncopal attacks developed secondary to lithium therapy, necessitating permanent pacemaker implantation. Serum lithium levels remained under or within the therapeutic range during the syncopal attacks. Lithium should be used with extreme caution, especially in patients with mild disturbance of AV conduction. (*Circ J* 2008; **72:** 847–849)

Key Words: Complete atrioventricular block; Lithium carbonate

Lithium carbonate is widely used for the treatment of manic–depressive disorders, but it has various cardiovascular side-effects, the majority of which involve sinus node dysfunction (SND) and sino-atrial blockage, according to previous reports![1–6] We report an exceptional case of a patient with manic–depressive psychosis who had complete atrioventricular block (CAVB) during lithium treatment, necessitating permanent pacemaker implantation.

Case Report

A 57-year-old male without history of syncope was admitted to hospital for the treatment of manic–depressive disorder in February 2005. His history showed no evidence of organic heart disease. Physical examination and non-invasive cardiovascular tests, including electrocardiography, prior to therapy had indicated first-degree atrioventricular (AV) block (Fig 1). Lithium carbonate and carbamazepine had been administered 6 days before admission, at a daily dose of 300 mg and 300 mg, respectively. On admission, zotepine, promethazine, nitrazepam, chlorpromazine, and phenobarbiturate were additionally administered. The serum lithium level was below the therapeutic range, at 0.3 mmol/L (normal range, 0.60–1.20 mmol/L). A chest radiograph revealed no abnormality. Laboratory test results were normal for blood electrolytes, renal function, cardiac enzymes, and thyroid function.

Five days after admission the patient felt discomfort and experienced sudden bradycardia with low systolic pressure and the attached cardiac monitor revealed paroxysmal CAVB without ventricular escape for a maximum of approximately 5 s causing an Adams-Stokes attack (Fig 2). During transportation to the emergency room, he had a cardiopulmonary arrest caused by ventricular fibrillation. After successful resuscitation by defibrillation, with epinephrine and atropine sulfate administration, a temporary pacemaker was inserted. Transient liver and renal function disorders because of the cardiogenic shock and hypoxia occurred after resuscitation.

Treatment with carbamazepine was discontinued because it can cause AV block, as indicated by the prescription information.

Because of the low serum lithium concentration and deteriorated psychotic status, lithium was resumed at a daily dose of 300 mg, and then increased to 500 mg. As the adverse cardiovascular effect of tachyarrhythmia is described in the prescription information for 3 of the other medications [zotepine, promethazine and chlorpromazine], these were also withdrawn.

No further ventricular tachycardia or CAVB occurred for 7 days under backup pacing after the syncopal attack, and temporary pacing was removed. Residual first-degree AV block with changing PP interval (240–280 ms) was observed. Without lithium administration, there was no worsening of AV block related to the heart rate increase.

Valproate sodium and levomepromazine were added for depressive mood 7 days later. Additional haloperidol and piperidine chloride were administered. Because general fatigue, retarded sinus bradycardia, and depressive mood occurred (serum lithium concentration 1.4 mmol/L), lithium carbonate was reduced and then stopped 37 days after the first syncopal attack. However, lithium and valproate were resumed without any other medications for re-occurrence of manic state in May.

The Adams-Stokes syndrome recurred in June and the patient was found to be in paroxysmal CAVB without ventricular escaped beat for approximately 6 s and a temporary pacemaker was inserted (Fig 3). The serum lithium level was in the therapeutic range, at 0.85 mmol/L, and laboratory data were normal for renal function and electrolytes. However, because there have been no reports of cardiovascular side-effects of valproate, lithium was regarded as a possible cause for the syndrome and was discontinued.

Because lithium carbonate was needed for the unstable mental state of the patient, a permanent pacemaker was

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