Original Article

Effect of Telmisartan on Ambulatory Blood Pressure Monitoring, Plasma Brain Natriuretic Peptide, and Oxidative Status of Serum Albumin in Hemodialysis Patients

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The effect of telmisartan on ambulatory blood pressure, plasma neurohormonal parameters, and oxidation of serum albumin has not been investigated in hemodialysis (HD) patients. Thirteen hypertensive HD patients were treated with 40 mg telmisartan once daily, and 24-h ambulatory blood pressure monitoring was performed after 0, 4, and 8 weeks of treatment. Plasma renin activity, plasma aldosterone concentration (PAC), brain natriuretic peptide (BNP) level, and serum oxidized albumin level were determined at the same time points. Serum telmisartan concentration was also measured at 4 and 8 weeks. Telmisartan significantly reduced systolic blood pressure and diastolic blood pressure (both awake and sleeping) after 4 weeks, and these pressures showed a further significant decrease after 8 weeks. Plasma levels of aldosterone, BNP, and serum oxidized albumin were markedly decreased after 4 weeks and these lower levels were maintained at 8 weeks. The trough serum telmisartan concentration was not significantly different at 8 weeks compared with 4 weeks. Throughout the treatment period, there were no significant adverse effects. Telmisartan effectively lowers blood pressure and reduces PAC, BNP, and oxidative stress and is safe and well-tolerated by HD patients. A long-term study in a large population is required to determine the influence of telmisartan therapy on cardiovascular mortality and morbidity in HD patients. (*Hypertens Res* 2005; 28: 987–994)

***Key Words*: telmisartan, blood pressure, brain natriuretic peptide, oxidative stress, hemodialysis**

Introduction

Hypertension is one of the most characteristic findings in patients with chronic renal diseases. Because patients with end-stage renal disease chiefly die of cardiovascular disease (CVD) (*1*) and because hypertension has been clearly linked to increased CVD morbidity and mortality in the general pop-

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ulation (*2*), hypertension is regarded as a major CVD risk factor to be targeted for treatment in the dialysis population.

The mechanisms of hypertension in hemodialysis (HD) patients are complex, but the renin–angiotensin–aldosterone system (RAAS) is believed to be an important contributor. Angiotensin II, *via* its type-1 receptor (AT1 receptor), stimulates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and enhances the production of reactive oxygen species (*3*), which in turn contribute to endothelial dysfunction and vascular inflammation (*4*, *5*). Thus the combination of hypertension and oxidative stress induced by stimulation of the RAAS results in accelerated progression of atherosclerosis in HD patients (*6*). Blockade of AT1 receptor in hypertensive patients has been shown to reduce oxidative stress, inflammation, and endothelial dysfunction (*7*). Several studies have shown that treatment with AT1 receptor blockers (ARBs) lowers blood pressure (BP), causes regression of left ventricular (LV) hypertrophy, and improves insulin resistance in HD patients (*8*–*10*).

Telmisartan is an orally active nonpeptide ARB that lowers BP with once-daily administration. Due to its long duration of action, BP control is maintained throughout the 24-h period between doses. The antihypertensive efficacy and excellent tolerability of telmisartan have been demonstrated in short-term and long-term controlled trials (*11*–*17*). However, the antihypertensive, neurohormonal, and antioxidant effects of telmisartan have not been investigated in HD patients.

The present study was designed to evaluate the effect of telmisartan administered once-daily at a dose of 40 mg on ambulatory BP, plasma brain natriuretic peptide (BNP) level, plasma renin activity (PRA), and plasma aldosterone concentration (PAC), as well as its effect on serum oxidized albumin, a marker of protein oxidation (*18*), in HD patients.

Methods

Patients

The study protocol was approved by the Institutional Review Board of Kumamoto University. Patients who met the following inclusion criteria were included in the study: 1) predialysis BP $>140/90$ mmHg for 6 consecutive dialysis sessions; 2) no current treatment with RAAS inhibitors; 3) stable dry weight for at least 3 months before enrollment; 4) a weight gain between dialysis sessions of less than 5% of dry weight. Written informed consent was obtained from 13 stable HD patients (5 men, 8 women) aged 53–79 (mean, 65.7 ± 7.6) years with a dialysis duration of 1 to 21 (mean 8.8 ± 5.9) years. Four patients were already being treated with calcium channel blockers (CCB) but had poorly controlled BP ($>140/90$ mmHg). The causes of end-stage renal disease were glomerulonephritis ($n=7$), diabetic nephropathy ($n=5$), and systemic lupus erythematosus ($n=1$). At enrollment, all patients were on regular bicarbonate HD for 4–5 h 3 times weekly using high-flux polysulfone hollow-fiber dialyzers. They were not treated with antioxidants such as vitamin E and C or with intravenous iron supplements during the 3 months before inclusion in the study. Since telmisartan is excreted in feces *via* bile, patients with reduced hepatic function were excluded.

Study Design

The study consisted of a 4-week placebo baseline period followed by an 8-week, open-label active treatment period during which patients received telmisartan once daily in the morning at a dose of 40 mg. In patients already on CCB therapy, telmisartan was added to the previous drug. After 0, 4, and 8 weeks of telmisartan therapy, blood samples were obtained from each patient before the first HD session of the week for measurement of PRA, PAC, plasma BNP, serum oxidized albumin, and serum telmisartan concentration. To measure the trough serum level of telmisartan, patients were told not to take the medication in the morning on blood sampling days. In addition, 24-h ambulatory BP monitoring (ABPM) was performed in each patient after 0, 4, and 8 weeks. To avoid any bias with respect to body fluid condition and dialysis efficiency for BP, ABPM was performed on the first non-dialysis day after the first HD session of the week. The drugs, dialysis conditions, and dry weight of each patient were not changed during either the 4-week placebo period or the 8-week treatment period.

Twenty-Four-Hour ABPM

Noninvasive ABPM was performed on a non-dialysis day after the initial dialysis session of the week with a device (ES-H531; Terumo Corp., Tokyo, Japan) that automatically recorded BP and pulse rate every 30 min for 24 h. The ambulatory data used in the present study were obtained by the oscillometric method. The definitions of several parameters used for the analysis of ABPM data were previously described by Kario *et al*. (*19*). Sleeping BP was defined as the average BP from the time when the patient went to bed until the time of rising, and waking BP was defined as the average BP recorded during the non-sleeping period. Morning BP was defined as the average BP during the 2-h period after rising (4 BP readings). The lowest BP was defined as the average of 3 readings centered on the lowest nighttime value (*i.e.*, the lowest BP plus the readings immediately before and after). Morning BP surge (MBPS) was calculated as the morning systolic BP (SBP) minus the lowest SBP.

Measurement of PRA, PAC, and Plasma BNP

Plasma samples obtained from each patient were immediately frozen and stored at -80°C. Plasma BNP levels were measured by radioimmunoassay (RIA) at a contract laboratory (SRL, Inc., Tokyo, Japan). PRA and PAC were also measured by RIA at a contract laboratory (Japan Clinical Laboratories,

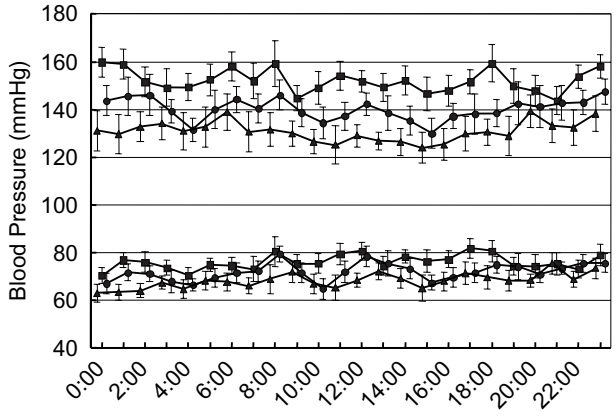

Fig. 1. *Mean 24-h ambulatory blood pressure monitoring profile of hourly mean systolic blood pressure and diastolic blood pressure at baseline (■), 4 weeks (●), and 8 weeks (▲) of telmisartan 40 mg/day.*

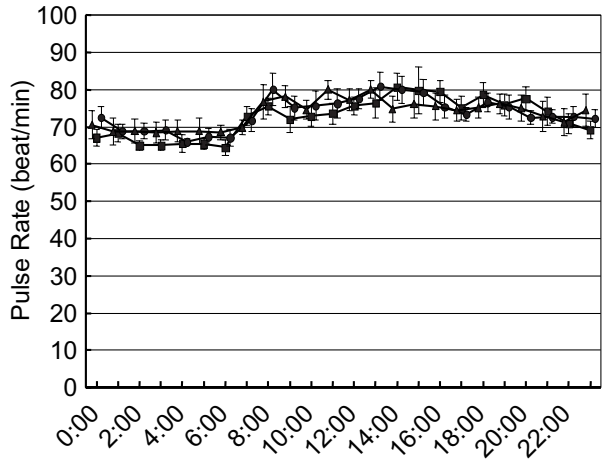

Fig. 2. *Mean 24-h ambulatory blood pressure monitoring profile of hourly mean pulse rate at baseline (■), 4 weeks (●), and 8 weeks (▲) of telmisartan 40 mg/day.*

Table 1. Analysis of 24-h Ambulatory Blood Pressure Monitoring Data at 0, 4, and 8 Weeks of Telmisartan

	0 weeks	4 weeks	8 weeks
Waking SBP (mmHg)	151.2±5.1	139.4±4.6*	129.9±5.0*,†
Waking DBP (mmHg)	76.8±3.6	72.7±3.2*	67.9±3.1*,†
Sleeping SBP (mmHg)	154.2±5.1	142.0±5.5*	132.8±7.0*,†
Sleeping DBP (mmHg)	74.5±2.8	70.0±2.7*	66.3±3.1*,†
Morning SBP (mmHg)	156.4±7.3	143.5±4.8*	133.7±6.7*,†
Morning DBP (mmHg)	76.1±4.7	74.4±3.4	67.6±3.8*,†
Lowest SBP (mmHg)	143.6±6.3	137.0±5.0	128.6±7.2*,†
Lowest DBP (mmHg)	70.4±2.7	67.9±1.9	62.5±2.9*,†
MBPS SBP (mmHg)	12.8±4.8	6.5±6.0	5.1±5.1
MBPS DBP (mmHg)	5.7±3.0	6.4±1.9	5.1±2.4

SBP, systolic blood pressure; DBP, diastolic blood pressure; MBPS, morning blood pressure surge. *$p<0.05$ *vs*. at 0 weeks; †$p<0.05$ *vs*. at 4 weeks.

Inc., Osaka, Japan).

Measurement of Serum Telmisartan Concentration

Serum levels of telmisartan were determined at Japan Clinical Laboratories, Inc. using the validated reverse-phase high-performance liquid chromatography method as previously reported by Tatami *et al*. (*20*).

Chromatography of Serum Albumin

High-performance liquid chromatography (HPLC) was performed to analyze serum albumin as described previously (*18*). Serum samples obtained from each patient were immediately frozen and stored at −80°C until analysis. Then 5 μl aliquots of serum were analyzed by using a Shodex Asahipak ES-502N column (Showa Denko Co., Ltd., Tokyo, Japan). From the HPLC profile, the content of each albumin fraction (human mercaptalbumin, f(HMA); human nonmercaptalbumin-1, f(HNA-1); human nonmercaptalbumin-2, f(HNA-2)) was estimated as the area of each fraction divided by the total area of the serum albumin peak.

Statistics

Statistical significance was evaluated by 2-tailed paired Student's *t*-test for comparison between 2 mean values and by ANOVA followed by Newman-Keuls test for comparison among >2 mean values. For all analyses, values of $p<0.05$ were regarded as statistically significant. Results are reported as the mean±SEM.

Results

Twenty-Four-Hour BP Profile

Figure 1 shows the mean 24-h ABPM profiles (SBP and diastolic BP [DBP]) after 0, 4, and 8 weeks of treatment with telmisartan. The baseline ABPM profile showed an "inverted dipper" pattern in this patient population. Telmisartan therapy caused an impressive reduction of both SBP and DBP throughout the 24-h period, but did not change the circadian rhythm of BP. The results of analysis of the 24-h ABPM data are summarized in Table 1. Telmisartan therapy significantly reduced waking and sleeping SBP and DBP at 4 weeks *vs*. baseline ($p<0.05$). These values showed a further significant decrease at 8 weeks ($p<0.05$ *vs*. at 4 weeks). Morning SBP was reduced at 4 weeks ($p<0.05$ *vs*. at 0 weeks) but DBP was not changed. After 8 weeks, morning SBP and DBP were markedly decreased ($p<0.05$ *vs*. at 0 weeks and 4 weeks).

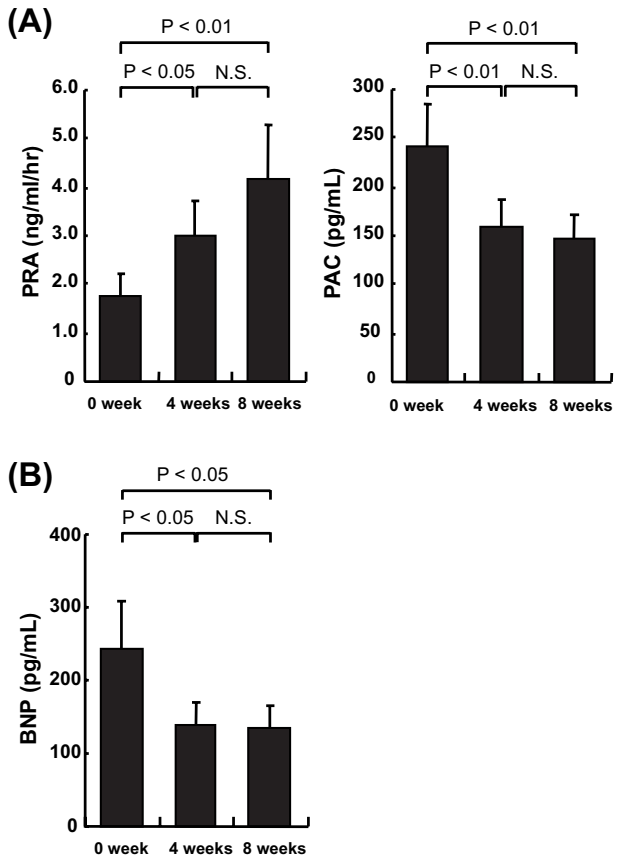

Fig. 3. *Effect of telmisartan on neurohormonal parameters. A: Effect of telmisartan on plasma renin activity (PRA; left panel) and plasma aldosterone concentration (PAC; right panel). B: Effect of telmisartan on plasma brain natriuretic peptide (BNP) level. Plasma samples were obtained before the first dialysis session at 0, 4, and 8 weeks of telmisartan therapy. PRA, PAC, and BNP were measured by radioimmunoassay. Values are expressed as the mean±SEM.*

Significant reductions of lowest SBP and DBP were observed at 8 weeks ($p<0.05$ *vs*. at 0 weeks and 4 weeks). Although systolic MBPS was reduced by telmisartan after both 4 and 8 weeks, there were no significant changes in systolic and diastolic MBPS. These findings strongly suggest that telmisartan has a significant long-acting BP-lowering effect in HD patients at a daily dose of 40 mg and that ≥8 weeks are required to reach the maximum antihypertensive effect. A longer observation period would be required to determine the treatment period that achieves maximal BP reduction. As shown in Fig. 2, pulse rate was not significantly altered by telmisartan therapy at 0, 4, or 8 weeks, indicating that telmisartan does not induce reflex tachycardia, as often occurs with CCB therapy.

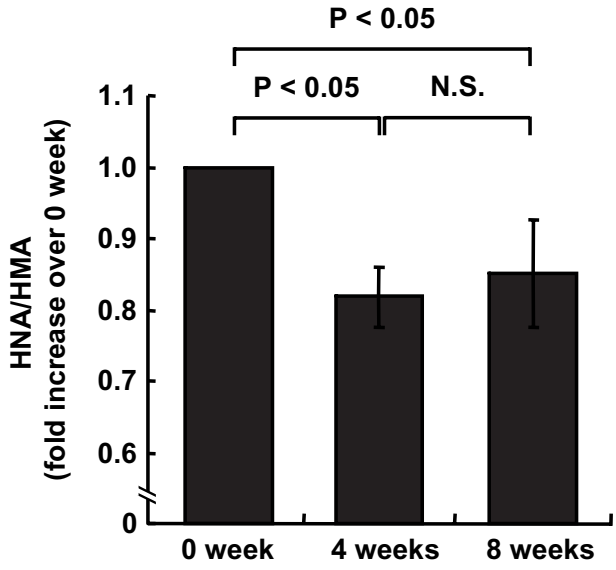

Fig. 4. *Effect of telmisartan on HPLC profiles of serum albumin. Aliquots (5 μl) of serum were obtained at 0, 4, and 8 weeks of telmisartan therapy and subjected to HPLC using a Shodex Asahipak ES-502N column. From the HPLC profile of serum albumin, the size of each albumin fraction (human mercaptalbumin, f(HMA); human nonmercaptalbumin-1, f(HNA-1); human nonmercaptalbumin-2, f(HNA-2)) was estimated as the peak area of each fraction divided by the total area of the serum albumin peak. The ratio of oxidized albumin to reduced albumin was then calculated ((HNA-1 + HNA-2)/HMA). Values are expressed as increases* vs. *the control (0 week) (mean±SEM).*

Neurohormonal Parameters

The effects of telmisartan on PRA, PAC, and plasma BNP over time are shown in Fig. 3. A significant increase of PRA and decrease of PAC were observed at 4 weeks of telmisartan therapy (PRA: from 1.75±0.48 ng/ml/h at 0 weeks to 3.03±0.69 at 4 weeks; $p<0.005$; PAC: from 240.7±44.9 pg/ml at 0 weeks to 158.7±26.8 at 4 weeks; $p<0.01$). After 8 weeks of telmisartan therapy, there was a slight but not significant further increase of PRA and decrease of PAC (PRA: 4.19±1.09 ng/ml/h; PAC: 146.8±25.0 pg/ml). The plasma BNP level was markedly decreased at 4 weeks (from 244.8±65.9 pg/ml at 0 weeks to 138.8±27.5 at 4 weeks; $p<0.05$) and the lower BNP level was maintained after 8 weeks (134.1±29.6 pg/ml). Since several studies have shown that BNP levels are influenced by volume overload in HD patients, we compared the predialysis body weight of each patient after 0, 4, and 8 weeks, but no significant differences were detected (data not shown).

Table 2. Trough Serum Telmisartan Concentration, Hematocrit, and Serum Potassium Levels

	0 weeks	4 weeks	8 weeks
Trough serum telmisartan concentration (ng/ml)	<0.50	51.4±15.5	64.7±24.5
Hematocrit (%)	29.8±1.2	29.7±1.1	30.2±1.0
Serum potassium (mEq/l)	5.3±0.3	5.5±0.4	5.4±0.3

Oxidative Stress

As shown in Fig. 4, treatment with telmisartan caused a significant decrease (18.2±4.2%) of HNA/HMA ratio at 4 weeks ($p<0.05$ *vs*. at 0 weeks), although no further reduction was observed at 8 weeks.

Serum Telmisartan Concentration and Adverse Effects

As shown in Table 2, the trough telmisartan level was 51.4±15.5 ng/ml at 4 weeks and 64.7±24.5 ng/ml at 8 weeks, and there was no significant difference between the 2 values, suggesting that telmisartan did not accumulate in HD patients when administered at a dose of 40 mg daily for 8 weeks. Because the effect of ARBs on renal anemia and on the response to erythropoietin therapy is still controversial, we also measured hematocrit before and after telmisartan treatment, and found no significant changes of hematocrit during the treatment period (Table 2). Furthermore, telmisartan did not alter serum potassium levels at 4 or 8 weeks (Table 2). No adverse effects were observed during the treatment period.

Discussion

In the present study we demonstrated that telmisartan 40 mg daily for 8 weeks had a significant and long-acting BP-lowering effect in HD patients as determined by 24-h ABPM. Furthermore, telmisartan substantially decreased PAC, plasma BNP, and oxidative stress as estimated by HPLC of serum albumin and did not produce accumulation of the drug, hyperkalemia, or impaired response to erythropoietin therapy.

The antihypertensive efficacy of telmisartan has already been demonstrated in clinical studies using 24-h ABPM (*21–24*). Confirmation of the efficacy and duration of the action of telmisartan has been provided by comparison with other antihypertensive agents with proven long duration of action. In the study reported by Lacourcière *et al*., telmisartan 40–120 mg daily was compared with amlodipine 5–10 mg daily in a double-blind, placebo-controlled, randomized trial in patients with mild-to-moderate hypertension who received active treatment for 12 weeks (*25*). Telmisartan and amlodipine produced similar reductions of SBP and DBP throughout the 24-h period compared with the pretreatment values. Another double-blind, placebo-controlled, randomized study compared the BP-lowering effect of telmisartan 40 or 80 mg daily with losartan 50 mg daily by ABPM (*17*). Telmisartan caused significantly greater reductions of 24-h mean, nighttime, and morning SBP and DBP than losartan. Telmisartan 40 mg/hydrochlorothiazide 12.5 mg has also been shown to significantly reduce BP in patients with mild-to-moderate hypertension, compared to losartan 50 mg/hydrochlorothiazide 12.5 mg (*26*). In the present study, telmisartan produced significant reductions of waking, sleeping, and morning SBP and DBP in HD patients. These findings provide good evidence that telmisartan is an effective drug with a very long duration of action in HD patients as well as in patients with essential hypertension who do not have renal dysfunction. In our study, HD patients showed an "inverted dipper" ABPM profile pattern. Further, telmisartan did not change the circadian rhythm of BP despite a significant reduction in BP. Diuretics are able to shift the circadian rhythm of BP from a non-dipper to a dipper pattern in essential hypertension (*27*). However, since the inverted dipper pattern is often associated with end-stage organ damage, and non-dipping of BP is believed to be the consequence of the loss of renal function (*28*), we speculate that antihypertensive treatment may not be effective for changing the circadian rhythm in patients with irreversible severe organ damage, such as HD patients.

In nonuremic cardiac disease, plasma BNP levels increase in proportion to severity (*29–32*), and the ARB valsartan has been shown to cause sustained reduction of the plasma BNP level in patients with chronic heart failure (*33*, *34*). Zoccali *et al*. (*35*) reported that levels of cardiac natriuretic peptides are independently linked to LV mass and LV function in dialysis patients and can be used to predict overall and cardiovascular mortality (*35*). There have also been several reports regarding the relationship between plasma BNP and LV function, but the influence of ARB therapy on plasma BNP levels has not been investigated in HD patients. Since the plasma BNP level of HD patients is affected by volume overload, care should be taken when attempting to use plasma BNP as a noninvasive parameter for monitoring cardiac conditions. In the present study, we measured plasma BNP levels before the first dialysis session of the week, and the predialysis body weight of each patient did not differ significantly among the time points. Therefore the reduction of plasma BNP levels by telmisartan was not related to changes in the fluid volume status. Although we did not investigate cardiac function in our patients, telmisartan may have improved LV function and LV mass index in proportion to the decrease of BNP levels.

Oxidative stress has long been incriminated in the development of dialysis complications such as β_2-microglobulin amyloid arthropathy and acceleration of atherosclerosis (*36*).

Until recently, direct evidence of *in vivo* oxidative stress in HD patients was almost entirely limited to measurement of lipid peroxidation by-products such as malondialdehyde and thiobarbituric acid-reactive substances (*37*). Despite the observation that proteins are highly susceptible to oxidative stress, there have been few reports about oxidatively modified proteins. Measurement of markers of protein oxidation such as advanced protein oxidation products and of carbonyl content has recently been performed to assess oxidative stress under pathological conditions (*36–41*). In 2001, Himmelfarb and McMonagle (*42*) reported that oxidation of albumin accounts for almost all of the excess plasma protein oxidation in uremic patients, as demonstrated by SDS-PAGE and immunoassay using anti-2,4-dinitrophenylhydrazine (anti-DNP) antibody. HPLC achieves clear separation of serum albumin into HMA and HNA (*43*) and is used for determination of redox state under various pathophysiological conditions (*44–47*). We recently demonstrated that serum albumin shows high levels of oxidation in HD patients by HPLC and immunoassay using anti-DNP antibody compared with age- and gender-matched healthy subjects (*18*). We have also shown that HPLC of serum albumin can be useful for quantitative and qualitative evaluation of oxidative stress in HD patients (*18*). Angiotensin II has been demonstrated to modulate NADPH oxidase activity in a number of studies, and aldosterone has also been implicated in the generation of reactive oxygen species (*17*, *48*). In this context, RAAS blockade by ARBs is theoretically effective for reduction of oxidative stress. Indeed, our study clearly demonstrated that telmisartan decreased the levels of oxidized albumin in HD patients after 4 weeks of treatment and that the antioxidant effect was maintained at 8 weeks. These results suggest that telmisartan might be useful to prevent progression of atherosclerosis in HD patients by reducing oxidative stress. Recently, Takai *et al*. (*49*) demonstrated the protective role of telmisartan against vascular remodeling through the reduction of NADPH oxidase activity. Their observation also supports the antioxidant effect of telmisartan.

Most ARBs are eliminated as unchanged parent drug in feces and urine, whereas >98% of telmisartan and its metabolites are eliminated in feces (*14*). Therefore, for patients with impaired renal function, such as HD patients, telmisartan is useful unless a patient also has hepatic dysfunction. In the present study, the mean trough level of serum telmisartan after 4 and 8 weeks of therapy was 51.4±15.5 and 64.7±24.5 ng/ml, respectively. Ogihara *et al*. (*50*) reported that trough levels of telmisartan in patients with mild (serum creatinine [SCr]: 1.5–2.9 mg/dl) and moderate (SCr: 3.0–4.0 mg/dl) renal failure were 37.29±38.30 and 37.47±55.39 ng/ml, respectively, after 7 days of treatment. Our values were slightly higher than their data, but the range of serum telmisartan concentrations in their patient population was large, so it is difficult to conclude that trough telmisartan levels were increased in HD patients. At least, the trough level was not significantly increased at 8 weeks compared with 4 weeks. It is well known that angiotensin-converting enzyme (ACE) inhibitors can worsen renal anemia and reduce the efficacy of recombinant human erythropoietin therapy in HD patients. However, the effect of ARBs on renal anemia in HD patients remains unclear. There are reports that the ARB losartan has no effect on renal anemia in HD patients (*51*, *52*), but the opposite result has also been reported (*53*, *54*). In the present study, we found that 8 weeks of treatment with telmisartan had little effect on renal anemia or on the response to erythropoietin. In addition, we found that telmisartan had no effect on serum potassium levels in HD patients, although our study population was small and had relatively high potassium levels at baseline. In patients with renal failure, urinary potassium excretion is decreased, but intestinal potassium excretion shows a significant increase (*55*). A recent study has suggested that enhanced colonic secretion of potassium in renal failure is mediated by upregulation of angiotensin II receptors rather than *via* a direct effect of aldosterone (*56*). Knoll *et al*. (*57*) demonstrated that treatment with ACE inhibitors and ARB is independently associated with increased risk of hyperkalemia in chronic HD patients. Although our data indicate that there was no effect of telmisartan on serum potassium levels in HD patients after 8 weeks of treatment, careful monitoring should be performed.

In summary, telmisartan is effective for lowering BP as well as for reducing PAC, BNP, and oxidative stress and is safe and well tolerated in HD patients. However, a long-term study in a large population is required to elucidate the influence of telmisartan therapy on CVD mortality and morbidity in HD patients.

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