The Efficacy and Tolerability of an Angiotensin II Receptor Blocker, Telmisartan, in Thai Patients with Mild to Moderate Essential Hypertension

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Abstract

This open-labeled single-blinded study was performed to evaluate the efficacy and tolerability of telmisartan in the treatment of mild to moderate essential hypertension. Each patient was assigned to take a placebo for 4 weeks followed by once daily-titrated telmisartan (40-80 mg) for 8 weeks. "Office BP" and "24-hour ambulatory BP" measurements (24-h ABPM) were recorded as scheduled. Thirty-one patients (10 males : 21 females) with a mean age of 48.1 years were enrolled. The final SBP/DBP reductions of 14.6 ± 14.2/9.9 ± 6.2 mm Hg were obtained. Full response defined as office DBP reduction of ≥10 mm Hg from baseline and/or DBP <90 mm Hg was achieved in 73.3 per cent of cases. Excluding 5 cases of white coat HT diagnosed by 24-h ABPM, full response rate (DBP reduction of ≥10 mm Hg from baseline and/or <85 mm Hg) was 76 per cent. Trough to peak ratio and smoothness index for SBP/DBP were highly acceptable (0.75/0.76 and 0.97/1.01, respectively). There were 4 cases of adverse events (2 cases of dizziness, 1 case of headache, and 1 case of acute myocardial infarction).

Key word : Hypertension, Treatment, Angiotensin Receptor Blocker

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Hypertension is a common disease in clinical practice. One of the new antihypertensive agents is angiotensin II receptor blocker (ARB), which blocks the final path of renin-angiotensin-system(1). It was reported to have negligible side effects comparable to a placebo(2). ARB had been previously shown to be beneficial in treating those patients with hypertension, left ventricular hypertrophy(3-5), diabetes

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mellitus[6-8], renal failure[9], and congestive heart failure (CHF)[8,10]. Recent long-term clinical trials have shown considerable benefits on many clinical aspects such as; CHF (ELITE-II[10] and Val-HeFT [11]), diabetic nephropathy (IRMA-2[6], IDNT[12], and RENAAL[8]). Telmisartan, a lipophilic insurmountable selective-angiotensin-II-receptor-blocker with a rather long half-life of elimination (25-37 hours) [13], has just recently become available in Thailand. The purpose of this study was to evaluate the efficacy and tolerability of this drug in Thai patients with mild to moderate essential HT. Since the 24-hour ambulatory blood pressure monitoring (24-h ABPM) is a better predictor of clinical outcomes compared to those office BP measurements[5,14], 24-h ABPM was simultaneously performed in those volunteers to confirm clinical efficacy of the drug.

PATIENTS AND METHOD

Study design

An open-labeled single-blinded study was carried out with a placebo for 4 weeks followed by titrated doses of telmisartan for 8 weeks. The study protocol was approved by the Ethics Review Committee, Siriraj Hospital. At each visit, all patients were asked to rest for 5 minutes. A series of office BP's, SBP (Korotkoff I) and DBP (Korotkoff V), were measured in the morning (8:00 a.m. $\pm$ 1 hour) with a well calibrated mercury sphygmomanometer in the same arm throughout the study; three times at 2-minute-interval while supine and two times at immediate rise and 2 minutes later while standing. The office BP's for each visit were averaged from the three supine BP measurements. Cigarette smoking and beverages containing caffeine or alcohol were prohibited for at least 2 hours before BP measurements. During the active treatment period, trough BP measurements were performed approximately 24 $\pm$ 2 hours after the preceding telmisartan doses.

Participants were men and women 18 to 80 years of age with mild to moderate essential HT, recruited from the Outpatient Department, Siriraj Hospital. Mild to moderate HT defined as mean supine diastolic BP (DBP) of $\geq$95 and <110 mm Hg plus the mean of three systolic BP (SBP) of $\geq$140 and <180 mm Hg were considered eligible for the study. Informed consents were required from all patients before enrollment. Women of childbearing age had to be non-pregnant, non-lactating, and using adequate contraception. Major exclusions were a known or suspected secondary HT, significant cardiovascular, cerebrovascular, renal/hepatic impairments, or significant retinal exudates/hemorrhages. Type 1 and poorly controlled type 2 diabetes mellitus, chronic user of anticoagulant, digoxin, imipramine group antidepressants, lithium, neuroleptics, short acting nitrate, high doses of NSAID/aspirin, salt substitutes containing potassium chloride, alcoholic or drug dependent were excluded. In addition, patients receiving any investigational therapy within one month prior to signing the informed consent and patients suffering from significant hyponatremia (serum Na <130 mmol/L), significant hypokalemia (serum K <3.0 mmol/L) or hyperkalemia (serum K >5.5 mmol/L), and shift workers were also not enrolled.

Patients were instructed to take their medication at the same time every morning, maintaining an interval as close as possible to 24-hours between doses. They were asked not to take the medication on the day of visit. Compliance was examined at each visit by interviewing and drug count. Non-compliance was defined as taking <80 per cent or >120 per cent of the prescribed medication. BP measurements were accepted for analyses only if patients were able to take their medication during the last 3-days prior to visit.

On visit 1 (week-4), eligible participants meeting the above criterias entered a 4-week of a single blinded placebo period. If the morning mean supine DBP ranging from $\geq$95 to <110 mm Hg, SBP ranging from $\geq$140 to <180 mm Hg (visit 2, week 0) with a difference in means supine DBP of $\leq$7 mm Hg between visit 1 and visit 2 were obtained, patients were given an initial 4-week once daily telmisartan (40 mg). On visit 3 (week 4), the same dose was continued for another 4 weeks in those with adequate BP response (DBP <90 mm Hg). If adequate BP control was not achieved, the dosage of telmisartan was increased to 80 mg once daily for another 4 weeks. Visit 4 (week 8) was the end of the study.

BP response to treatment was subsequently stratified into 3 groups. Group 1 (full response); defined as a reduction of supine DBP at a trough of $\geq$10 mm Hg from baseline and/or a trough supine DBP of <90 mm Hg. Group 2 (partial response); defined as a reduction of supine DBP at a trough of 5 to <10 mm Hg with a trough supine DBP of $\geq$90 mm Hg. And, group 3 (minimal response); defined as

a reduction of supine DBP at a trough of <5 mm Hg with supine DBP of ≥90 mm Hg, or any increase in supine DBP at trough.

24-h ABPM

In this study, 24-h ABPM was also carried out at visit 2 (week 0) and visit 4 (week 8) in all patients using a 24-h ABPM device ("Quiet Trak" Model 5100-01, Welch Allyn Tycos Inc., NC, USA) of which the performance has been described and validated previously[15]. Patients would have a 24-h ABPM device attached in the morning (8.00 a.m. ± 1 hour) and received monitoring throughout the 24-hour-period. When the device was in operation, subjects were instructed to remain motionless and keep their arms still[16]. They were also asked to follow their ordinary daily activities. BP's were measured every 30 minutes during the daytime-period (6 a.m. to 11 p.m.) and every 1 hour during the nighttime-period (11 p.m. to 6 a.m.). Only data from patients with ≥80 per cent of successful BP readings were acceptable for analyses.

Variables such as daytime BP levels, nighttime BP levels and differences between the daytime and nighttime BP levels were calculated. Patients with average SBP <135 mm Hg and average DBP <85 mm Hg by 24-h ABPM while casual SBP and/or DBP were ≥140 mm Hg and/or ≥90 mm Hg, respectively, were defined as having white coat hypertension (WCH)[17,18]. Subjects with >10 per cent decline in the mean SBP and/or the mean DBP levels compared between the daytime and nighttime periods obtained from the 24-h ABPM machine were classified as "dipper"[17]. Morning surge (MS) was defined as a rise in SBP of >50 mm Hg during 3-hour after awakening compared to that of 3-hour before awakening[17]. Smoothness index (SI) was calculated according to the following procedures. Firstly, calculating the average BP values for each hour of the 24-hour monitoring period, both before and after active treatment, all hourly changes in BP induced by treatment were obtained. The absolute changes of these hourly BP's (△BP) were computed together with their standard deviations [SD (△BP)], which represent the dispersion of the antihypertensive effect over the 24-hour values. Finally, the value obtained by △BP divided by [SD (△BP)] indicating the degree of smoothness, the SI[19]. Trough-to-peak ratio (T : P ratio) was calculated for both SBP and DBP in patients whose adequate BP control had been achieved by post-dose titration. The T : P ratio was calculated by dividing trough (T) values by peak (P) values[20,21]. The T : P ratio defined as the ratio between the effect of an antihypertensive agent at the end of interval between doses (trough) and at the time of its maximum effect (peak)[22,23]. T values defined as mean of the differences in values taken 22-24 hours after the drug administration (excluding the time of administration) and P-values defined as mean of the differences in values taken 2 to 8 hours after the drug administration between the placebo period and the active treatment period. The BP loads defined as the percentage of BP readings recorded by 24-h ABPM that are abnormal during 24-hour (SBP >140 and DBP >90 mm Hg)[24].

Laboratory tests

Laboratory tests were performed at visit 1, visit 3 and visit 4 including complete blood count, serum electrolytes, creatinine, blood urea nitrogen, glucose, uric acid, cholesterol, triglycerides, HDL cholesterol, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, albumin, globulin, bilirubin, urine analysis, and standard 12-lead electrocardiogram. At each visit, adverse drug reactions were recorded.

Statistical analyses

Results were demonstrated as mean ± SD or per cent (%) where appropriate. Statistical analyses were performed using Statistical Packages for Social Sciences (SPSS) version 9.0. Student's *t*-test and Chi-square test were used to compare the continuous and categorical data between each pair of the placebo and telmisartan treatment period, respectively. Repeated measures ANOVA (Bonferroni for multiple comparisons) were used to compare different measurements of the same attribute (BP measurements). A p-value of <0.05 was considered statistically significant.

RESULTS

Of the 39 participants screened, 31 mild to moderate essential HT patients were enrolled. There were 10 males (32.3%) and 21 females (67.7%). The mean age was 48.1 ± 10.9 years (24-64 years). Body mass index was 27.1 ± 4.9 kg/m^2 (17.9-36.4 kg/m^2) (Table 1). All patients, except one, were known HT patients, 8 cases were diagnosed between 1-5 years. The mean office SBP on entry was 155.3 ± 11.0 mm Hg (average individual SBP's ranged from 132.0 to 174.7 mm Hg) and DBP was 98.6 ± 3.0 mm Hg

Table 1. Demographic data of patients on entry.

Variable	All (31 cases)
Age (years old)	48.1 ± 10.9 (24-64)
Female cases (%)	67.7
Duration of treatment (years)	9.7 ± 8.0 (<1-30)
Body Mass Index (kg/m^2)	27.1 ± 4.9 (17.9-36.4)

(average individual DBP's ranged from 95.3 to 108 mm Hg). The mean heart rate (HR) on entry was 80.3 ± 8.3/min (60-96/min). There were statistically significant differences between the mean supine SBP/DBP after a 4-week telmisartan treatment (11.6 ± 10.7/6.2 ± 4.9 mm Hg, p<0.001), and after an 8-week telmisartan treatment (14.6 ± 14.2/9.9 ± 6.2 mm Hg, p<0.001) (Table 2 and Fig. 1). There were no significant differences in mean BMI, and HR during visits (Table 2). There were also no significant changes in the laboratory results and electrocardiographic findings between visit 1, visit 3 and visit 4, except slight elevation of serum potassium was observed (4.0 ± 0.42, 4.3 ± 0.39, 4.2 ± 0.35, p=0.03) (Table 3).

Eleven adverse events were reported in 9 out of 31 patients. At visit 2, 4 cases had dizziness and 2 of them the symptom persisted at visit 3, 2 cases had upper respiratory tract infection, 1 case had herpes zoster infection and another case had cough and dyspepsia. At visit 3, one of the patients who had respiratory tract infection at visit 2 had headache. Only one patient was withdrawn during active treatment after visit 3 due to acute inferior wall myocardial infarction. She recovered uneventfully upon after an extended follow-up period without complication.

When the efficacy of telmisartan was evaluated by the conventional office BP in 30 patients who were able to complete the trial, 6 patients (20%) remained on a 40-mg/day dose while 24 patients (80%) required an 80-mg/day dose. After giving a 4-week course of 40 mg once daily of telmisartan treatment, the mean office SBP/DBP were significantly reduced from baseline by 11.6 ± 10.7/6.2 ± 4.9 mm Hg (158.4 ± 10.9/99.0 ± 3.1 *vs* 146.8 ± 16.1/92.8 ± 4.8 mm Hg, p=0.0016 for systolic and p<0.0001 for diastolic) (Fig. 1). After giving an 8-week course of telmisartan treatment, significant further reductions in SBP/DBP were observed. With significant average reductions of 14.6 ± 14.2 mm Hg systolic and 9.9 ± 6.2 mm Hg diastolic from baseline (158.4 ± 10.9/99.0 ± 3.1 *vs* 143.2 ± 18.8/89.1 ± 5.1 mm Hg, p=0.0003 for systolic and p<0.0001 for diastolic) were noted. When compared mean BP at visit 3 and visit 4, average further reductions of 3.3 ± 10.5 mm Hg systolic and 3.8 ± 4.6 mm Hg diastolic were achieved (146.8 ± 16.1/92.8 ± 4.8 *vs* 143.2 ± 18.8/89.1 ± 5.1 mm Hg, p=0.43 for systolic, and p=0.004 for diastolic) (Fig. 1).

At visit 3 while 40 mg of telmisartan was given to all 31 patients, the overall numbers of BP normalization (DBP <90 mm Hg) were 6 out of 31 patients (19.4%), while 18 out of 30 patients (60%) was observed at visit 4 (Table 4). "Full response" was achieved in 29.0 per cent (9/31) on visit 3 compared to 73.3 per cent (22/30) at visit 4. Orthostatic hypotension was not observed in this study. If both SBP and DBP were used for criteria of BP normalization (<140/90 mm Hg), 9.7 per cent (3/31) of patients had achieved that levels at visit 3 and 43.3 per cent (13/30) at visit 4. There were 6.7 per cent (2/

Table 2. BMI and office BP measurements: A comparative study between after 4 weeks of placebo (visit 2), after 4 weeks of telmisartan (visit 3) and 8 weeks of telmisartan (visit 4) treatment.

	Visit 1	Visit 2	Visit 3	Visit 4
BMI (kg/m^2)	27.1 ± 4.9	27.0 ± 4.8	27.1 ± 4.9	27.2 ± 4.8
Supine SBP (mm Hg)	155.3 ± 11.0	158.4 ± 10.9	146.8 ± 16.1*	143.2 ± 18.8*
Supine DBP (mm Hg)	98.6 ± 3.0	99.0 ± 3.1	92.8 ± 4.8*	89.1 ± 5.1*,**
Supine HR (per minute)	80.3 ± 8.3	80.1 ± 13.4	78.7 ± 9.6	78.0 ± 10.9
Standing SBP (mm Hg)	148.2 ± 12.9	149.9 ± 14.2	141.6 ± 17.4***	136.1 ± 17.3*
Standing DBP (mm Hg)	96.2 ± 4.0	96.7 ± 4.7	91.6 ± 5.7 *	86.8 ± 5.0*,**
Standing HR (per minute)	85.6 ± 8.0	87.5 ± 12.9	87.6 ± 9.4	85.8 ± 10.2

* p-value was significant at <0.001 between visit 2 *vs* visit 3, and visit 2 *vs* visit 4

** p-value was significant at <0.004 between visit 3 and 4

*** p-value was significant at 0.04 between visit 2 and 3

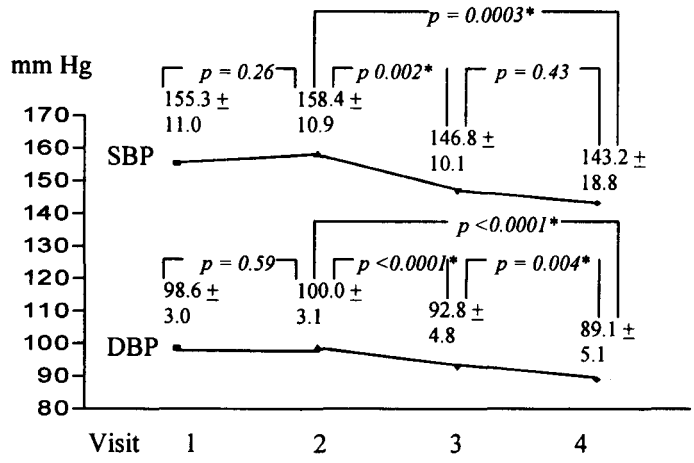

Fig. 1. Changes from baseline in trough supine systolic and diastolic blood pressure.

Table 3. Laboratory characteristics of the study subjects

	Visit 1	Visit 3	Visit 4	P-value
Hemoglobin (g/dl)	14.2 ± 1.6	14.0 ± 1.4	14.0 ± 1.7	0.88
Hematocrit (%)	43.1 ± 4.1	42.7 ± 4.0	42.5 ± 4.9	0.86
Red cell count (10^{12}/L)	4.9 ± 0.5	4.9 ± 0.6	4.9 ± 0.6	0.93
White cell count (10^9/L)	6.9 ± 1.7	7.1 ± 1.8	7.1 ± 1.8	0.89
Platelet count (10^9/L)	295.2 ± 62.9	289.6 ± 81.7	299.7 ± 72.7	0.87
Blood glucose (mg/dl)	101.1 ± 14.9	99.9 ± 13.8	101.2 ± 14.4	0.92
Creatinine (mg/dl)	1.1 ± 0.4	1.1 ± 0.2	1.1 ± 0.2	0.80
BUN (mg/dl)	14.2 ± 3.6	14.3 ± 3.3	13.6 ± 3.6	0.71
SGOT (U/L)	23.0 ± 6.0	21.4 ± 5.8	22.3 ± 6.3	0.59
SGPT (U/L)	24.7 ± 10.4	24.8 ± 11.5	28.0 ± 15.9	0.52
Na (mmol/L)	145.5 ± 2.5	145.9 ± 2.3	145.3 ± 2.9	0.64
K (mmol/L)	4.0 ± 0.4	4.3 ± 0.4	4.2 ± 0.4	0.03*
Cholesterol (mg/dl)	225.3 ± 49.7	222.4 ± 44.8	223.6 ± 38.7	0.97
Uric acid (mg/dl)	6.7 ± 1.8	6.4 ± 1.9	6.5 ± 1.9	0.71

* p-value considered significant at <0.05

30) of patients who received an 8-week course of telmisartan treatment and achieved "partial response" (Table 4).

All patients were subjected to 24-h ABPM to evaluate treatment response and eliminate individuals who had WCH. Since, 30 mild to moderate HT patients were, finally, able to complete an 8-week course of active treatment, hence there were 24-h ABPM data from 31 patients prior to active treatment and only from 30 patients at the end of the study. Five cases identified as WCH were found. Supplementary analyses to evaluate treatment response were then performed on 25 patients who had sustained HT (SHT).

When excluding those with WCH, office BP's achieved normalization in 6 out of 26 patients (23.1%) at visit 3 and 16 out of 25 patients (64.0%) at visit 4 (Table 4). Full response could be achieved in 34.6 per cent (9/26) and 76.0 per cent (19/25) at visit 3 and visit 4, respectively (Table 4). If both SBP and DBP had to be normalized (<140/90 mm Hg), 11.5 per cent (3/26) at visit 3 and 44.0 per cent (11/

Table 4. Treatment response in telmisartan treated HT patients.

	4 weeks	%	8 weeks	%
All cases				
Normalization	19.4	6/31	60.0	18/30
Full response	29.0	9/31	73.3	22/30
Partial response	41.9	13/31	6.7	2/30
Minimal response	29.0	9/31	20.0	6/30
Excluded WCH cases				
Normalization	23.1	6/26	64.0	16/25
Full response	34.6	9/26	76.0	19/25
Partial response	38.5	10/26	4.0	1/25
Minimal response	26.9	7/26	20.0	5/25

25) at visit 4 achieved the target BP. There was only 1 patient (4%) classified as "partial response". This left 20 per cent (5/25) of patients classified as "minimal response" (Table 4).

Telmisartan was able to decrease office DBP in 5 patients with WCH (153.7 ± 8.9/98.4 ± 2.7 mm Hg at visit 2 *vs* 147.0 ± 8.8/90.7 ± 2.4 mm Hg at visit 4, p=0.26 for systolic and p=0.001 for diastolic) (data not shown). However, there was no significant difference in the mean BP's between visit 2 and visit 4 determined by 24-h ABPM (Table 5).

Concerning 24-h ABPM data, the efficacy of telmisartan on BP lowering was evaluated in 25 SHT patients. Telmisartan produced significant reductions in the mean 24-h, daytime, and nighttime SBP/DBP levels in patients when compared with those obtained from visit 2 and visit 4 (11.7 ± 11.8/10.7 ± 10.4 mm Hg, 12.0 ± 12.1/10.7 ± 10.2 mm Hg, and 11.6 ± 13.7/11.6 ± 11.3 mm Hg, respectively) (Table 5). The observed BP loads were also significantly reduced in the active treatment period (visit 4) compared to those of the placebo period (visit 2) (29.4 ± 22.9 *vs* 54.3 ± 26.6 mm Hg systolic, p<0.001 and 31.1 ± 22.6 *vs* 63.8 ± 21.7 mm Hg diastolic, p<0.001). When both SBP and DBP were considered to be normalized (<135/85 mm Hg), it was found in 8 out of 25 (32%). The number of non-dippers comprised 73.1 per cent (19/26) at baseline was decreased to 68.0 per cent (17/25) at the end of the study period (p=0.86). BP circadian profiles from all patients considered either at baseline or at the end of the study were classified under a non-surge type. There were peak SBP/DBP reductions of 23.4 ± 13.6/18.6 ± 10.4 mm Hg and trough SBP/DBP reductions of 16.3 ± 10.0/12.7 ± 9.7 mm Hg after an 8-week course of telmisartan treatment in full responders. T : P ratio for SBP and DBP were 0.75 ± 0.18 (0.52-0.98) and 0.76 ± 0.14 (0.44-0.94), respectively. SI for SBP and DBP were 0.97 ± 0.72 (0.05-2.83) and 1.01 ± 1.26 (0.02-5.53), respectively.

DISCUSSION

The present study has demonstrated that telmisartan could produce a significant BP lowering effect in treating mild to moderate HT patients. At visit 3, telmisartan could reduce SBP and DBP notably when compared to baseline data. Giving telmisartan for another 4 weeks further reduced DBP to a greater extent (92.8 ± 4.8 *vs* 89.1 ± 5.1 mm Hg, p=0.004) while there was no significant change for SBP (146.8 ± 16.1 *vs* 143.2 ± 18.8, p=0.43) (Fig. 1). Apparently, the absolute reduction of SBP from visit 3 to visit 4 was significantly less than that of visit 2 to visit 3 (11.6 ± 10.7 *vs* 3.3 ± 10.5 mm Hg, p=0.003) conformed with the findings suggested by Smith et al in 1998[25]. The BP lowering effect of telmisartan was similarly observed in the study of Neutel et al in 1999[26]. In his study, an 8-week course of telmisartan treatment was given to 385 mild to moderate HT patients with the mean age of 53.5 years, SBP/DBP reductions of 13.9/11.8 mm Hg was reported. There were no significant changes in HR observed throughout the present study (visit 2 *vs* visit 3: 80.1 ± 13.4 *vs* 78.7 ± 9.6/min, p=0.62; visit 2 *vs* visit 4: 80.1 ± 13.4 *vs* 78.0 ± 10.9/min, p=0.50). Therefore, telmisartan may not cause a sympathetic stimulation.

The percentage of BP normalization and full responders in the telmisartan treated individuals were increased with increasing dosage[2]. The normalization rate (DBP <90 mm Hg) in the present study was highly conformed to another previous report[26] (60% *vs* 67%, p=0.57). Similar results were also obtained when excluding those with WCH (64% *vs* 67%, p=0.93). The high response rate whether WCH patients

Table 5. 24-h ABPM: A Comparative study between after a 4-week course of placebo (visit 2) and after an 8-week course of telmisartan treatments (visit 4).

	24-h BP (mm Hg)			Daytime BP (mm Hg)			Nighttime BP (mm Hg)		
	Visit 2	Visit 4	P-value*	Visit 2	Visit 4	P-value*	Visit 2	Visit 4	P-value*
SHT (non-WCH) cases									
SBP	140.8 ± 9.3	129.0 ± 13.4	<0.001*	142.6 ± 8.4	130.6 ± 13.9	<0.001*	134.0 ± 14.0	122.4 ± 14.5	0.006*
DBP	94.5 ± 6.2	83.8 ± 9.4	<0.001*	95.4 ± 6.3	84.7 ± 9.6	<0.001*	91.7 ± 7.7	80.1 ± 9.0	<0.001*
WCH cases									
SBP	121.8 ± 4.1	123.4 ± 7.8	0.69	124.8 ± 5.0	123.6 ± 8.5	0.79	112.2 ± 6.1	123.2 ± 10.8	0.08
DBP	79.2 ± 2.8	77.0 ± 4.4	0.37	81.2 ± 3.0	77.4 ± 4.5	0.15	72.4 ± 5.0	74.6 ± 10.4	0.68

*p-value between visit 2 and 4 and considered significant at <0.05

were excluded or not (73.3% *vs* 76.0%, p=0.94) confirmed the drug efficacy. A 62-year-old female was reported to have acute myocardial infarction after visit 3. This documented episode has not been reported as a significantly increasing event in patients treated with ARB compared to that of the placebo[6,8,12]. It was unlikely to be due to excessive BP lowering caused by the investigational drug since the studies of 24-h ABPM in those patients with WCH demonstrated that telmisartan does not have any significant influence on their 24-h, daytime, and nighttime BPs. Furthermore, this is not a case of WCH. There were 2 cases of dizziness and another case of headache which had disappeared when they came for follow-up at visit 4. They were the 2 most common drug adverse effects reported previously[2]. A slight increase in the serum potassium levels found in the presented patients treated with telmisartan was similar to another study using ARB[11]. Since, ARB can cause hyperkalemia, precaution is needed in prescribing the drug to patients with problems in potassium handling e.g. renal insufficiency and congestive heart failure etc[12].

The most intriguing results came from 24-h ABPM data. Although 24-h ABPM is not commonly required for regulatory antihypertensive drug monitoring, this technique has been shown to be superior to the traditional office BP measurements. The use of 24-h ABPM devices will enable physicians to enroll SHT patients in the trial and eliminate individuals with WCH[17]. Therefore, the data obtained from 24-h ABPM are more reliable and accurate than those obtained from office BP measurements since inclusion of normotensive patients to the trial and unnecessary antihypertensive treatment can be avoided[27-29]. A progressive lowering of office BPs after giving an 8-week course of telmisartan treatment, as mentioned previously, was subsequently confirmed by 24-h ABPM. There were significant reductions in the mean 24-h, daytime, nighttime BPs and BP loads without interference with the normal BP circadian profiles. There were no significant differences between the number of cases with normalization of office BP criteria (<140/90 mm Hg) compared to that of the 24-h ABPM criteria at the end of the trial (<135/85 mm Hg) (43.3% *vs* 50%, p=0.79). This implied that accurate office BP measurements could be as good as those obtained from 24-h ABPM. Since several data supported the view that BP loads are better predictors of cardiac and vascular complications than either office BPs or the mean 24-h ambulatory BP

values, the reductions in the BP loads found in this study ensured its clinical importance[24].

T : P ratio and SI were important indicators to show whether the drug was appropriate for once daily use. Based on the assumption that patients with hypertension are likely to receive the most benefit from therapy if antihypertensive effects do not vary greatly during the day. The US-FDA guidelines indicate that the effect of any antihypertensive drugs at the end of the dose interval (trough) should be no less than half to two-thirds of the peak effect[30]. Therefore, a T : P ratio of 50-66 per cent is generally required to assure that they can be given once daily [23]. In this study, the T : P ratios of the investigational drug for both SBP and DBP were higher than 50 per cent. This confirmed that the antihypertensive effect of telmisartan was still present in the last hours of dosing interval, resulting from a long duration of action of this drug. As in the previous reports, the high T : P ratios indicated a favorable effect of telmisartan, once daily dosage over a 24-h BP control, especially during the last 6 hours of dosing interval [31-33]. One interesting study using 24-h ABPM demonstrated that telmisartan had a comparable antihypertensive effect to amlodipine on the 24-hour BP control[33]. Although this long acting ARB appeared to have similar efficacy to that of the widely used calcium channel blocker, detailed analyses of the 24-hour BP profiles, however, showed two potentially important differences between telmisartan and amlodipine treatments. First, during the final 4 hours of the dosing interval (the early morning hours prior to taking the next dose), there was a small but significantly better advantage in the telmisartan treated group. Second, as an extension of the first observation, during the 6-hour period between 6 am and 12 noon, the time of day at which patients are most vulnerable to serious clinical cardiovascular events, telmisartan also exhibited a somewhat greater efficacy than the other agent.

In conclusion, the availability of the paired 24-h ABPM data prior to and after receiving an 8-week course of telmisartan treatment, was a necessity to ensure physicians on the drug ability to control BP whole day[29].

SUMMARY

In conclusion, telmisartan used as once-daily-monotherapy provides an effective control of 24-hour BP and is generally well tolerated in ambulatory mild to moderate HT patients.

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การศึกษาประสิทธิภาพและความปลอดภัยในการรักษาโรคความดันโลหิตสูงในผู้ป่วยไทยชนิดอ่อนถึงปานกลางด้วยยาต้านแองจิโอเท็นซิน II รีเซ็พเตอร์, เทลมิสาร์แทน

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เป็นการศึกษาแบบเปิด single blinded เพื่อดูประสิทธิภาพและความปลอดภัยของยา telmisartan ในการรักษาความดันโลหิตสูงชนิดปฐมภูมิระดับอ่อนถึงปานกลาง ผู้ป่วยทุกรายจะได้รับยาหลอกเป็นเวลา 4 สัปดาห์ตามด้วยยา telmisartan ปรับขนาด (40–80 มิลลิกรัม) วันละครั้งเป็นเวลา 8 สัปดาห์ ระดับความดันโลหิตจะได้รับการตรวจบันทึกด้วยหูฟังและด้วยเครื่องวัดความดันโลหิตอัตโนมัติ 24 ชั่วโมงชนิดพกพาตามกำหนด มีผู้ป่วย 31 ราย (ชาย 10 ราย, หญิง 21 ราย) อายุเฉลี่ย 48.1 ปีเข้าร่วมโครงการ พบว่าร้อยละ 73.3 ระดับความดันโลหิตลดดีตอบสนองเต็มที่ (DBP ลด > 10 มม.ปรอท และ/หรือ ลด < 90 มม.ปรอท) โดยเมื่อจบการศึกษาระดับ SBP/DBP ลดลงจากเดิม 14.6 ± 14.2/9.9 + 6.2 มม.ปรอท เมื่อตัดผู้ป่วยที่เป็น white coat hypertension 5 รายออกไปโดยใช้เครื่องตรวจวัดอัตโนมัติ พบว่าร้อยละ 76 มีการตอบสนองเต็มที่ (DBP ลด > 10 มม.ปรอท และ/หรือ ลด < 85 มม.ปรอท) Trough to peak ratio และ smoothness index สำหรับ SBP/DBP อยู่ในระดับดีมาก (0.75/0.76 และ 0.97/1.01 ตามลำดับ) ในระหว่างการศึกษาพบผู้ป่วย 4 ราย เกิดผลแทรกซ้อนระหว่างการศึกษา (มึนศีรษะ 2 ราย, ปวดศีรษะ 1 ราย และกล้ามเนื้อหัวใจขาดเลือดอย่างเฉียบพลัน 1 ราย)

คำสำคัญ : ความดันโลหิตสูง, การรักษา, ยาต้านแองจิโอเท็นซิน II รีเซ็พเตอร์

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