The Smoothness of Blood Pressure Control of Ramipril in Essential Hypertensive Thai Patients Evaluation by 24-Hour Ambulatory Blood Pressure Monitoring

Verawan Uchaipichat PhD*,
Banhan Koanantakul MD**, Chuthamanee Suthisisang PhD***

** Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen*
*** Division of Medicine, Bhumibol Adulyadej Hospital, Bangkok*
**** Department of Pharmacology, Faculty of Pharmacy, Mahidol University, Bangkok*

Objective: *Evaluate the efficacy of ramipril 2.5 and 5 mg once daily on the degree and homogeneity of 24-hour blood pressure reduction in essential hypertensive Thai patients.*
Material and Method: *Nineteen male subjects, aged 30 to 60 years, with newly diagnosed essential hypertension were evaluated using the 24-hour ambulatory blood pressure (24-h ABP) measurement.*
Results: *Twelve subjects responded and/or normalized with ramipril once daily, where the office and 24-h ABP were decreased significantly from baseline ($p < 0.01$). The percentage and magnitude of 24-h SBP/DBP loads after treatment were significantly decreased from 92 $\pm$ 9.7/91 $\pm$ 15.9 to 67 $\pm$ 23.8/65 $\pm$ 27.6 ($p < 0.01$) and from 23 $\pm$ 10.6/16 $\pm$ 5.3 mmHg to 17 $\pm$ 10.3/10 $\pm$ 4.8 mmHg ($p < 0.05$). Trough to peak ratio for SBP/DBP was 0.59/0.52 (overall estimated) and 0.68 $\pm$ 0.23/0.52 $\pm$ 0.22 (individual estimated), while the smoothness index was 0.89/1.03.*
Conclusion: *Ramipril 2.5 and 5 mg once daily exerted the smooth 24-hour blood pressure reduction in essential hypertensive Thai patients.*

Keywords: *Hypertension, Blood pressure variability, Angiotensin converting enzyme inhibitor*

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Hypertension is one of the risk factors for myocardial infarction, congestive heart failure, stroke, and kidney diseases[1]. The correlation between blood pressure level control and the reductions of these complications is well established[1]. Indeed, there is now increasing evidence demonstrating that smooth blood pressure control throughout the dosing interval is required for optimal antihypertensive treatment and to protect target-organ damage[2]. Given the importance of smooth blood pressure control or blood pressure variability, long-acting antihypertensive formulations that provide 24-hour efficacy are preferred over short-acting agents.

Correspondence to: Uchaipichat V, Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen 40002, Thailand. Phone: 043-202-378, Fax: 043-202-379

Several parameters were proposed as an indicator to assess blood pressure variability but most attention has focused on the 'trough to peak ratios' (T:P ratios) and the smoothness index (SI). In 1988, the United States Food and Drug Administration (FDA) guidelines proposed an arithmetic indicator based on the term "trough to peak ratio" (T:P ratio)[3]. The guidelines indicated that, during steady-state treatment, in addition to maintaining a useful antihypertensive effect at the end of the dosage interval (trough), the trough effect should be at least 50-66% of the peak effect, once appropriate adjustment has been made for placebo effects[4]. However, some limitations, in particular the lack of correlation of T:P ratios and target organ damage, was illustrated[5]. To overcome this limitation, the SI was proposed as the complementary mean to evaluate the homogeneity of blood pressure

reduction[2,6]. This index is calculated as the inverse of the coefficient of variation of hourly blood pressure changes induced by the treatment, where the higher the value of the index the greater the smoothness in response. It has been demonstrated that SI was inversely correlated with 24-hour blood pressure variability[5,7], and correlated positively with treatment-induced regression of left ventricular hypertrophy[5].

Moreover, it has been suggested that the percentage of blood pressure load or abnormal blood pressure during the day provides a useful predictor of target organ damage. The correlation of blood pressure load and left ventricular mass has been illustrated[8] and other studies have focused on other target organs such as albuminuria and retinopathy[9]. Thus, it appears that not only the 24 hour blood pressure level itself, but also the frequency of blood pressure elevated during 24 hours are important determinants of target organ damage.

Ramipril is a long-acting, non-sulfhydryl angiotensin converting enzyme inhibitor (ACEI). This drug is indicated in the treatment of hypertension, congestive heart failure[10], diabetic and non-diabetic nephropathy[11,12], and cardiovascular protection in high-risk individuals[13]. The antihypertensive effect of ramipril has been demonstrated in large-scale non-comparative studies conducted in general practice[14,15] as well as in many controlled trials[16-18]. Based on the 24-hour blood pressure and T:P ratio estimation, it was shown that once-daily administration of ramipril 2.5 to 10 mg/day achieved a sustained hypertensive effect throughout 24 hours[18-21]. Albeit the established evidence of 24-hour blood pressure control, a comprehensive evaluation (viz, 24-hour blood pressure, T:P ratio, SI and, blood pressure load) of the antihypertensive effect of ramipril, especially in Thai patients, is still limited. Employing ambulatory blood pressure monitoring (ABPM), the authors therefore, assessed the antihypertensive effect of ramipril in essential hypertensive Thai patients in terms of 24-hour blood pressure reduction, T:P ratio, SI, and blood pressure load.

Material and Method

Patients

Twenty male subjects, aged 30 to 60 years, with newly diagnosed essential hypertension defined as supine SBP $\geq$ 140 mmHg and supine DBP $\geq$ 90 mmHg were considered eligible for the present study. Patients were excluded if one of the following conditions were present: severe hypertension (SBP $\geq$ 180 mmHg or DBP $\geq$ 110 mmHg), suspected secondary hypertension, renal impairment (determined by out of the normal range value of BUN and SCr) or hepatic impairment (AST and ALT are elevated higher than 3 times of normal value), and other chronic diseases such as gastrointestinal or cardiovascular disease (measured by using standard 12-lead electrocardiogram). All subjects gave their informed consent and the trial was approved by the Bhumibol Adulyadej Hospital Ethics Committee.

Study design

A placebo run-in, open study design was performed in the present study. After a week of placebo run-in period, office blood pressure measurement was performed as baseline data, and blood samples for routine laboratory assessment and standard ECG record were taken. The eligible patients were measured for 24-hour blood pressure by using ABPM and started 2.5 mg ramipril once-daily. Patients were advised to take medication at approximately the same time in the morning and were asked not to take medication on the day of visit. After taking 2.5 mg ramipril for two weeks, patients were classified as normalized BP (office DBP $\leq$ 90 mmHg), responder (office DBP lower from baseline $\geq$ 10 mmHg), and non-responder (office DBP lower from baseline < 10 mmHg). The patients with normalized BP and the responders were monitored for the 24-hour blood pressure, while the non-responders were started on 5 mg ramipril for 2 weeks. Then, the 24-hour ABPM was performed for the patients with normalized BP and/or the responders. At the end of the present study, only the responders and normalized BP patients were included in the evaluation of antihypertensive effect of ramipril.

BP measurements

Office BP was measured with a mercury sphygmomanometer (Korotkoff I for SBP and Korotkoff IV for DBP) in the left arm, after the patients had been resting for 10 minutes. The two consecutive measurements (with at least 1-minute interval) were averaged. Blood pressure was measured in the morning, at the same time during each visit, just prior to the daily dose of ramipril. Twenty-four hour ABPM were determined from the left arm of each subject by portable, non-invasive recorder (A&D Company Limited; Japan). Readings were obtained automatically at 30-minute interval from 9:00 AM to 12:00 AM on the following day. The blood pressure was detected by the oscillometric method with assistance of Korotkoff's method. Average 24-hour blood pressure was calculated from

9:00 AM to 9:00 AM on the successive day. Average day- and night- time were obtained from the period in which the subjects were awake or asleep.

Trough to peak ratio and the smoothness index determination

The T:P ratio have been defined as the ratio between the effects of an antihypertensive agent at the end of dosing interval (trough effect) and those at the time of maximal effect (peak effect). Trough SBP and DBP values were calculated as the average of BP reduction during 23-24 hour after the dose, while the peak values were averaged with two adjacent BP reading of the maximal BP fall between 2 and 8 hours after the dose. The T:P ratios were presented as the mean of the individual T:P ratios (individual estimated) and that resulted from using mean trough and peak values (overall estimated).

To estimate SI, the hourly changes in blood pressure from baseline induced by treatment are firstly calculated. The average of these hourly blood pressure changes were then calculated, together with its standard deviation (SD). The SI is the ratio between the average of hourly blood pressure changes and its SD[5].

Blood pressure load determination

With the observation of blood pressure measured throughout the day, the SBP/DBP values that were higher than 140/90 mmHg during the daytime and 120/80 mmHg during the night-time were judged as abnormal BP values or 'BP loads'[8]. BP loads were expressed as the percentage or frequency and the absolute value of elevated blood pressure.

Statistical analysis

Results were presented as mean $\pm$ SD. The office BP, 24-hour BP, and BP load data before and after treatment were compared by using paired t-test ($p < 0.05$).

Results

Hypertensive subjects characteristics

Of twenty subjects entered in the present study, one subject withdrew from the study during the placebo run-in period. The characteristics of nineteen hypertensive subjects enrolled in the present study are reported in Table 1. All subjects were newly diagnosed essential hypertension. The average age and BMI values were 45 $\pm$ 7.8 years and 25.6 $\pm$ 5.5 kg/m^2, respectively. Four of the subjects were currently smoking cigarettes, whereas eleven had a history of social alcoholic drinking. The routine laboratory data are shown in Table 1. The liver and kidney function tests of all subjects were in the normal range. However, the majority of these subjects had high levels of plasma cholesterol and triglyceride.

Baseline office and 24-hour blood pressure of hypertensive subjects

Office BP at the screening visit and after placebo run-in-period is shown in Table 1. The blood pressure after taking placebo was used as the baseline level for comparing the drug effects. Office BP and 24-hour ambulatory BP at baseline is presented in Table 2. Office BP at baseline was 159 $\pm$ 12.4/107 $\pm$ 8.1 mmHg, whereas the average 24-hour BP was 156 $\pm$ 10.6/ 101 $\pm$ 6.4 mmHg. Of the 24-hour BP, the average daytime BP and the average night-time BP were 161 $\pm$ 10.7/ 104 $\pm$ 6.0 mmHg and 143 $\pm$ 12.3/93 $\pm$ 8.1 mmHg, respectively.

The frequency and absolute values of BP loads at baseline are illustrated in Table 2. Overall, the

Table 1. Characteristics of hypertensive subjects

Characteristics	No.of subject = 19
Subject characteristics	
Age (years)[a]	45.0 $\pm$ 7.8
Weight (kg)[a]	70.8 $\pm$ 15.9
Body Mass Index (BMI) (kg/m^2)[a]	25.6 $\pm$ 5.5
Cigarettes smoking (no.)	4
Alcoholic (no.)	11
Laboratory data[a]	
Glucose (70-110 mg/dl)	89.8 $\pm$ 11.24
BUN (5-20 mg/dl)	12.3 $\pm$ 3.04
Cr (0.5-1.4 mg/dl)	1.2 $\pm$ 0.19
Cholesterol (130-200 mg/dl)	230.9 $\pm$ 58.93
Triglyceride (50-155 mg/dl)	146.3 $\pm$ 55.91
HDL (32-68 mg/dl)	48.0 $\pm$ 15.82
AST (0-35 u/l)	25.7 $\pm$ 9.75
ALT (0-43 u/l)	27.0 $\pm$ 17.72
Office BP at the screening visit[a]	
SBP (mmHg)	160.0 $\pm$ 14.1
DBP (mmHg)	106.0 $\pm$ 8.1
MAP (mmHg)	124.0 $\pm$ 9.2
HR (bpm)	76.0 $\pm$ 7.3
Office BP after placebo (baseline BP)[a]	
SBP (mmHg)	159.0 $\pm$ 12.4
DBP (mmHg)	107.0 $\pm$ 8.1
MAP (mmHg)	125.0 $\pm$ 8.4
HR (bpm)	77.0 $\pm$ 8.3

[a] Data presented as mean $\pm$ SD

Table 2. Office blood pressure and 24-hour ambulatory blood pressure in hypertensive subjects after placebo run-in period[a]

	Office BP (mmHg)	24-hour ABP								
		Average BP (mmHg)			BP load[b]					
		24-hour BP	Day-timeBP	Night-timeBP	24-hourBP		Day-timeBP		Night-timeBP	
					Frequency[c] (%)	Absolute[d] (mmHg)	Frequency[c] (%)	Absolute[d] (mmHg)	Frequency[c] (%)	Absolute[d] (mmHg)
SBP	159 ± 12.44	156 ± 10.55	161 ± 10.71	143 ± 12.26	92 ± 8.14	24 ± 9.69	91 ± 8.70	24 ± 10.53	97 ± 7.88	24 ± 11.00
DBP	107 ± 8.13	101 ± 6.39	104 ± 6.01	93 ± 8.10	90 ± 13.32	16 ± 4.86	91 ± 11.71	16 ± 4.52	90 ± 21.51	15 ± 6.71
MAP	125 ± 8.36	119 ± 7.19	123 ± 6.68	110 ± 8.97						
HR	77 ± 8.25	77 ± 8.28	81 ± 9.72	65 ± 8.91						

[a] Data presented as mean ± SD
[b] BP loads were BP values that higher than 140 or 120 mmHg for SBP and 90 or 80 mmHg for DBP during day-time and night-time, respectively
[c] Frequency of BP loads in percentage
[d] Absolute value of pressure of BP loads in mmHg

frequency of BP loads for SBP and DBP during day-time and night-time was approximately higher than 90%. The absolute values of elevated SBP/DBP were 24 ± 9.7/16 ± 4.9 mmHg, 24 ± 10.5/16 ± 4.5 mmHg, and 24 ± 11.0/15 ± 6.7 mmHg for 24-hour, day-time, and night-time blood pressure, respectively.

As shown in Fig. 1, the 24-hour BP profile showed the diurnal rhythm profile where BP was maintained at a high level during awakening and was declined to a lower level during sleep time. Blood pressure started to decrease when subjects went to bed, which is approximately at 8:00 PM, and continued declining to the nadir point at approximately 01:00 AM. The nadir SBP/DBP was 143 ± 15.0/94 ± 10.4 mmHg, which corresponded to the MAP value of 110 ± 11.2 mmHg. After nadir point, BP tended to increase throughout the early morning hours although they were sleeping, and BP increased further when they woke up (approximately 06:00 AM) to a high level of day-time BP. The 24-hour heart rate also exhibited diurnal rhythm as observed from the BP profile.

Antihypertensive effect evaluation

Office and 24-hr blood pressure evaluation

After taking ramipril 2.5 mg/day for 2 weeks, four subjects achieved the target BP with two normalized subjects (office DBP ≤ 90 mmHg) and two responders (office DBP reduction ≥ 10 mmHg). Fifteen subjects required the higher dose of 5 mg ramipril/day. Of these subjects, three achieved normal level of BP, whereas five subjects had DBP reduction more than 10 mmHg (responders). Seven subjects did not accomplish the target BP and were defined as non-responders. The 24-hour ABP monitoring was performed in all subjects

Fig. 1 The 24-hr BP profile pf 19 hypertensive subject at baseline

including non-responders, however, data obtained from only normalized BP subjects (5 subjects) and responders (7 subjects) were included in the analysis of the antihypertensive efficacy of ramipril.

Ramipril at an individualized dose of 2.5 and 5 mg/day significantly reduced office SBP and DBP from 160 ± 13.7/109 ± 8.4 to 141 ± 15.3/95 ± 8.8 mmHg ($p < 0.01$). MAP was also significantly lowered from 127 ± 8.9 to 111 ± 10.4 mmHg ($p < 0.01$), however HR was not affected by the treatment (Table 3). The statistically important changes from baseline of 24-hour, day-time and night-time BP were evident during treatment with 2.5 and 5 mg (Table 3). After treatment, the average 24-hour of SBP and DBP were significantly decreased from 155 ± 12.3/101 ± 7.4 to 146 ± 13.7/92 ± 9.0 mmHg ($p < 0.01$) with the mean decreases of 9.3 ± 7.1/10 ± 5.1 mmHg. Mean day-time SBP and DBP were significantly lowered from 160 ± 11.4/104 ± 6.8 to 152 ± 12.8/95 ± 7.9 mmHg ($p < 0.01$). For the night-time period, mean SBP and DBP were also decreased from 142 ± 14.5/ 94 ± 9.3 to 132 ± 18.2/85 ± 11.6 mmHg ($p < 0.01$). The mean decreases in SBP/DBP during day-time and night-time were 8 ± 8.3/10 ± 5.9 and 10 ± 8.3/9 ± 5.0 mmHg, respectively. However, the mean 24-hour, day-time and night-time HR were not affected by the treatment. The 24-hour BP profile demonstrating the BP reductions for both SBP and DBP throughout 24 hours is shown in Fig. 2. The circadian BP rhythm with the night-time BP reduction or dip in BP during was also maintained after treatment. The nocturnal BP was approximately 20 and 10 mmHg reduced from day-time SBP and DBP or with the average reduction of 13 and 11%, respectively. The 24-hour HR profile did not appear to be affected by ramipril treatment (Fig. 3).

In the non-responder group, the office BP did not shown significant reduction (Table 3). In addition, with the 24-hour BP results obtained after taking 5 mg ramipril, the reductions of 24-hour, day-time and

Table 3. Office blood pressure and 24-hour ambulatory blood pressure at baseline and after treatment[a]

Parameters	Normalized BP[b] and responders[c] (n = 12)		Non-responders[d] (n = 7)	
	Baseline	Treatment	Baseline	Treatment
Office BP (mmHg)				
SBP	160 ± 13.72	141 ± 15.29**	157 ± 10.45	154 ± 13.93 (ns)
DBP	109 ± 8.42	95 ± 8.83**	103 ± 6.53	105 ± 5.99 (ns)
MAP	127 ± 8.85	111 ± 10.37**	121 ± 6.27	121 ± 8.37 (ns)
HR (bpm)	76 ± 8.39	76 ± 9.86 (ns)	80 ± 8.12	77 ± 11.69 (ns)
24-hour ABP (mmHg)				
Average 24-hour				
SBP	155 ± 12.29	146 ± 13.74**	159 ± 6.83	156 ± 13.36 (ns)
DBP	101 ± 7.35	92 ± 8.96**	100 ± 4.69	98 ± 4.79 (ns)
MAP	119 ± 8.63	109 ± 10.10**	119 ± 4.32	117 ± 7.68 (ns)
HR (bpm)	76 ± 9.83	74 ± 7.67(ns)	78 ± 5.26	79 ± 9.69 (ns)
Average day-time (awake)				
SBP	160 ± 11.39	152 ± 12.80**	164 ± 9.60	161 ± 12.82 (ns)
DBP	104 ± 6.84	95 ± 7.90**	103 ± 4.62	100 ± 6.45 (ns)
MAP	123 ± 7.85	113 ± 8.75**	123 ± 4.56	120 ± 8.45 (ns)
HR (bpm)	82 ± 10.60	79 ± 7.99 (ns)	78 ± 8.32	78 ± 14.15 (ns)
Average night-time (sleep)				
SBP	142 ± 14.48	132 ± 18.15**	145 ± 7.59	142 ± 14.82 (ns)
DBP	94 ± 9.32	85 ± 11.61**	93 ± 6.11	89 ± 7.61 (ns)
MAP	109 ± 10.51	100 ± 13.36**	110 ± 6.19	106 ± 9.48 (ns)
HR (bpm)	63.17 ± 8.79	63 ± 6.89 (ns)	69 ± 8.47	70 ± 9.12 (ns)

[a] Data are presented as mean ± SD

[b] Office DBP ≤ 90 mmHg (5 subjects)

[c] Office DBP lower from baseline ≥ 10 mmHg (7 subjects)

[d] Subjects who had office DBP > 90 mmHg and DBP reduction < 10 mmHg after treatment with 5 mg ramipril

** $p < 0.01$, * $p < 0.05$ versus baseline, ns = not significant

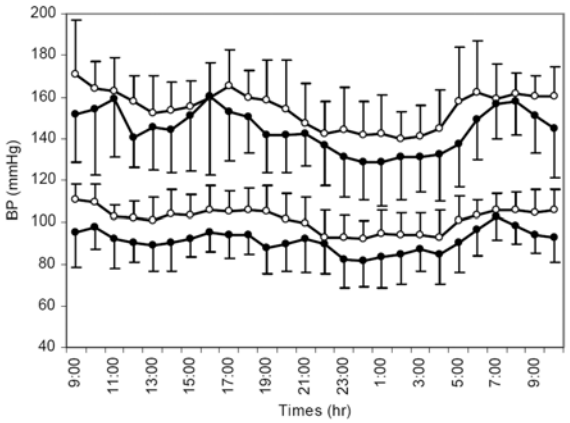

Fig. 2 The 24-hour BP profile of 12 responders after treatment with 2.5 and 5 mg rampril: baseline (open circles), the end of treatment (full circles)

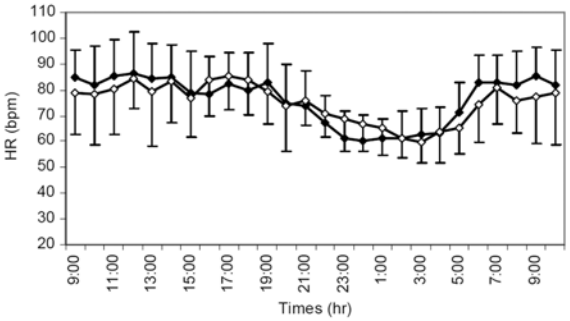

Fig. 3 The 24-hr HR profile of 12 responders after treatment with 2.5 and 5 mg ramipril: baseline (open circles), the end of treatment (full circles)

night-time BP were not significantly changed from the baseline (Table 3).

Trough to peak ratio and smoothness index evaluation

According to the 24-hour BP profile, overall and individual estimated T:P ratio of 12 subjects whose blood pressure were normalized or responded to treatment were calculated (Table 4). The average magnitude BP fall at peak of SBP and DBP were 18 $\pm$ 19.8 and 18 $\pm$ 12.0 mmHg without producing the adverse hypotensive effect. The average SBP and DBP fall at trough induced by antihypertensive treatment were 11 $\pm$ 6.2 and 10 $\pm$ 6.0 mmHg. By dividing the average trough BP change with the average peak BP change, the T:P ratio of 59% for SBP and 52% for DBP were obtained (Table 4). The individual T:P ratios of each subject were also estimated. It was found that seven and eight patients had T:P ratio > 50% for SBP and DBP, respectively. The average individual estimated T:P ratio for SBP and DBP were 68 $\pm$ 23.3% (ranging from 42-100%) and 52 $\pm$ 22.6% (ranging from 15-75%), respectively. The SI obtained from the present study were 0.89 $\pm$ 0.53 (0.01-1.84) and 1.03 $\pm$ 0.36 (0.51-1.55) for SBP and DBP, respectively.

Blood pressure load evaluation

In comparison to baseline, ramipril significantly reduced BP loads, either the frequency or the absolute value, throughout 24 hours (Table 5). The percentage of 24-hour BP loads were significantly decreased from 92 $\pm$ 9.7% to 67 $\pm$ 23.8% ($p < 0.01$) and 91 $\pm$ 15.9% to 65 $\pm$ 27.6% ($p < 0.01$) for SBP and DBP, respectively. The absolute values of the 24-hour BP loads for SBP and DBP were significantly lowered from 23 $\pm$ 10.6 mmHg to 17 $\pm$ 10.3 mmHg ($p < 0.05$) and 16 $\pm$ 5.3 mmHg to 10 $\pm$ 4.8 mmHg ($p < 0.01$). Considering the data in separate between day-time and night-time BP, the reductions of the percentage and the magnitude of BP loads during awake and sleep were comparable to those throughout 24-hrs, although the absolute values of SBP loads during awake and sleep were not significantly reduced from baseline (Table 5). In the non-responder group, the frequency and abnormal BP values of 24-hour, day-time and night-time after treatment did not show significant reduction from baseline (Table 5).

Discussion

The present study demonstrates the blood pressure-lowering effect and the smoothness of blood pressure control of ramipril with a once-daily dosage regimen. Using before and after design with the placebo run-in period for one week and office blood pressure measurement during dose titration period, ramipril 2.5 and 5 mg once daily significantly reduced office SBP and DBP from the baseline ($p < 0.01$) without changing in heart rate. The magnitude of office blood pressure reduction were 19 and 14 mmHg for SBP and DBP, respectively, which are consistent with the result reported previously[22]. Ramipril in the dose of 2.5 and 5 mg once daily produced 26% of normalized rate (office DBP $\leq$ 90 mmHg) and 37% of responder rate (office DBP reduction $\geq$ 10 mmHg). Thirty-seven percent of subjects did not respond to 2.5 and 5 mg ramipril. The sum of normalized and response rates obtained from the present study were 63%. These rates are slightly lower than that reported previously, which

Table 4. The trough and peak BP changes and the trough to peak ratios of normalized blood pressure[a] and responders[b]

	Overall estimated[c] (n = 12)			Individual estimated (n = 12)	
	Trough	Peak	T:P ratio (%)	T:P ratio[c] (%) (range)	No. of patients with T:P ratio > 50%
SBP	-11 ± 6.24	-18 ± 19.80	59	68 ± 23.29 (42-100)	7 from 12 patients
DBP	-10 ± 6.03	-18 ± 11.95	52	52 ± 22.55 (15-75)	8 from 12 patients

[a] Office DBP ≤ 90 mmHg (5 subjects)
[b] Office DBP lower from baseline ≥ 10 mmHg (7 subjects)
[c] Data are presented as mean ± SD

Table 5. BP loads at baseline and after treatment[a]

Parameters	Normalised BP[b] and responders[c] (n = 12)		Non-responders[d] (n = 7)	
	Baseline	Treatment	Baseline	Treatment
Frequency of BP loads (%)				
24-hour SBP	92 ± 9.70	67 ± 23.83**	94 ± 4.83	84 ± 24.20 (ns)
24-hour DBP	91 ± 15.91	65 ± 27.64**	90 ± 8.24	83 ± 10.05 (ns)
Day-time SBP	90 ± 10.09	66 ± 23.70**	92 ± 6.27	82 ± 21.81 (ns)
Day-time DBP	92 ± 13.03	64 ± 26.12**	89 ± 9.67	82 ± 13.46 (ns)
Night-time SBP	96 ± 9.73	70 ± 35.17*	100 ± 0	89 ± 30.24 (ns)
Night-time DBP	88 ± 25.90	67 ± 36.69*	93 ± 11.75	82 ± 21.30 (ns)
Absolute value of BP loads (mmHg)				
24-hour SBP	23 ± 10.62	17 ± 10.29*	27 ± 7.93	27 ± 8.56 (ns)
24-hour DBP	16 ± 5.28	10 ± 4.83**	15 ± 4.39	14 ± 4.20 (ns)
Day-time SBP	22 ± 10.21	17 ± 11.07 (ns)	27 ± 11.17	26 ± 7.93 (ns)
Day-time DBP	16 ± 4.85	10 ± 4.63**	15 ± 4.18	13 ± 4.60 (ns)
Night-time SBP	24± 13.08	19 ± 15.64 (ns)	26 ± 6.77	27 ± 13.77 (ns)
Night-time DBP	16 ± 7.41	10 ± 5.82**	15 ± 5.83	14 ± 5.96 (ns)

[a] Data are presented as mean ± SD
[b] Office DBP ≤ 90 mmHg (5 subjects)
[c] Office DBP lower from baseline ≥ 10 mmHg (7 subjects)
[d] Subjects who had office DBP > 90 mmHg and DBP reduction < 10 mmHg after treatment with 5 mg ramipril
** $p < 0.01$, * $p < 0.05$ versus baseline, ns = not significant

were approximately 85% after 4-8 weeks treatment with ramipril 2.5 or 5 mg/day[15,22].

Since ABPM provides superior outcomes to the measurement of office blood pressure in terms of their reproducibility and prediction of target-organ involvement[23], the antihypertensive of ramipril 2.5 and 5 mg once-daily were additionally evaluated by using this machine. The result of the present study shows that after taking 2.5 or 5 mg ramipril once daily for 2 weeks, the mean 24-hour, day-time and night-time BP were significantly decreased from baseline without interference with the normal BP circadian profiles. However, the 24-hour, day-time and night-time heart rate were not significantly changed from baseline. This suggested the absence of reflex tachycardia from the drug. The absolute reduction of mean 24-hour SBP/DBP observed in the present study were 9.3 ± 7.1/10 ± 5.1 mmHg which is comparable to those reported by Spieker et al of 7/10 mmHg[20] but lower than those reported previously by Perticone et al of 27/20 mmHg[21]. The difference of the response rate and the magnitude of 24-hour blood pressure reduction compared to the previous studies may be explained from the different design and other aspects of previous trials such as blood pressure level at baseline, the longer duration of drug intake, and the higher number of subjects.

The blood pressure load or abnormal blood pressure value, defined as the percentage or absolute value of blood pressure readings that were higher than 140 or 120 mmHg for SBP and higher than 90 or 80 mmHg during day-time and night-time, respectively, was evaluated in the present study by using ABPM. Apart from the significant reduction of 24-hour, day-time and night-time blood pressure, ramipril significantly reduced the frequency and absolute value of blood pressure load throughout the day. The reduction in BP loads reflects the clinical important of ramipril because several data support the view that the frequency of this parameter had been demonstrated to have the relationship to indices of the hypertensive disease processes (e.g. left ventricular hypertrophy and vascular compliance)[8,9].

T/P ratios and the SI were employed in the present study to evaluate whether the 24-hour blood pressure control of ramipril are in a smooth and consistent profile. In terms of T:P ratio evaluation, the US-FDA guidelines indicate that the antihypertensive effect at the end of the dose interval (trough) should be no less than 50% to 66% of the peak effect[4]. The T:P ratios from the present study were calculated based on the data from responder and normalized BP patients because the data from non-responder patients may cause the extremely erratic T:P ratios[24]. The presented data show that 2.5 and 5 mg ramipril once daily, when administered to essential hypertensive patients, were effective in reducing 24-hour blood pressure with a favorable T:P ratio. The mean T:P ratio, either overall or individual estimated, were higher than 50% for SBP and DBP, which correlates to the results reported previously[19]. This indicated that the 24-hour duration of action of ramipril could provide the BP control over the night and especially in the early morning hours. However, consistent with the previous study[6], a wide range of the individual estimated T:P ratio values were also observed in the present study (i.e., 15% to 75% for DBP). According to the individual estimation, the authors found that seven and eight patients from 12 patients had T:P ratio > 50% for SBP and DBP, respectively. This suggested ramipril given once-daily may provide the consistency of BP reduction or good BP control throughout 24 hours only in some subjects. It should be noted that most of the patients who have T:P ratio less than 50% can control trough blood pressure but they showed extreme blood pressure reduction at peak such as 40 or 50 mmHg. Although the adverse hypotensive effect were not observed, the twice daily doses of ramipril may provide the better 24-hour BP profile to these patients.

The SI were additionally estimated in the present study as this parameter has been shown to be a better predictor for the regression in left ventricular hypertrophy than the T/P ratios[5]. In addition, Rizzoni et al showed the superiority of the SI over the T/P ratios for predicting changes of carotid wall thickness during antihypertensive therapy[7]. To date, there is no reference value for the SI[5]. However, by its definition, the greater the SI values (i.e. greater than 1) of the drug represents the more homogeneity of antihypertensive effect[2]. The SI obtained from the present study was 0.89 and 1.03 for SBP and DBP, respectively. These values appear to be in an acceptable range as they are comparable to those from other once-daily antihypertensive drugs such as amlodipine (SI 0.8-1.0)[25], delapril (SI 1.4-1.5)[26], losartan (SI 1.1)[27], lisinopril (SI 0.9-1.3)[27,28], and telmisartan (SI 0.9-1.5)[28,29].

In conclusion, ramipril 2.5 and 5 mg once daily exerted the smooth 24-hour blood pressure reduction throughout a day, as demonstrated by (1) significantly lower the office, and the 24-hour, day-time and night-time blood pressure; (2) significantly lower percentage and absolute value of BP loads; and (3) provide the mean overall and individual estimated T:P ratio > 50%, and an acceptable range of the SI values.

References

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289: 2560-72.
2. Parati G. Blood pressure variability: its measurement and significance in hypertension. J Hypertens Suppl 2005; 23: S19-25.
3. Meredith PA, Elliott HL. FDA guidelines on trough: peak ratios in the evaluation of antihypertensive agents. United States Food and Drug Administration. J Cardiovasc Pharmacol 1994; 23 (Suppl 5): S26-30.
4. Elliott HL, Meredith PA. Methodological considerations in calculation of the trough: peak ratio. J Hypertens Suppl 1994; 12: S3-6.
5. Parati G, Omboni S, Rizzoni D, Agabiti-Rosei E, Mancia G. The smoothness index: a new, reproducible and clinically relevant measure of the homogeneity of the blood pressure reduction with treatment for hypertension. J Hypertens 1998; 16: 1685-91.
6. Meredith PA. Trough: peak ratio and smoothness

index for antihypertensive agents. Blood Press Monit 1999; 4: 257-62.
7. Rizzoni D, Muiesan ML, Salvetti M, Castellano M, Bettoni G, Monteduro C, et al. The smoothness index, but not the trough-to-peak ratio predicts changes in carotid artery wall thickness during antihypertensive treatment. J Hypertens 2001; 19: 703-11.
8. White WB, Dey HM, Schulman P. Assessment of the daily blood pressure load as a determinant of cardiac function in patients with mild-to-moderate hypertension. Am Heart J 1989; 118: 782-95.
9. Mule G, Nardi E, Andronico G, Cottone S, Raspanti F, Piazza G, et al. Relationships between 24 h blood pressure load and target organ damage in patients with mild-to-moderate essential hypertension. Blood Press Monit 2001; 6: 115-23.
10. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993; 342: 821-8.
11. Ruggenenti P, Perna A, Gherardi G, Gaspari F, Benini R, Remuzzi G. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Ramipril efficacy in nephropathy. Lancet 1998; 352: 1252-6.
12. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000; 355: 253-9.
13. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000; 342: 145-53.
14. Carre A, Zannad F, Vasmant D. The French multicentre study of ramipril in ambulatory patients with mild-to-moderate hypertension. Clin Physiol Biochem 1992; 9: 105-12.
15. Kaplan NM, Sproul LE, Mulcahy WS. Large prospective study of ramipril in patients with hypertension. CARE Investigators. Clin Ther 1993; 15: 810-8.
16. Zabludowski J, Rosenfeld J, Akbary MA, Rangoonwala B, Schinzel S. A multi-centre comparative study between ramipril and enalapril in patients with mild to moderate essential hypertension. Curr Med Res Opin 1988; 11: 93-106.
17. Ruddy MC, Mroczek WJ. Comparison of ramipril and enalapril in patients with essential hypertension. Pharmacotherapy 1993; 13: 224-8.
18. Yasky J, Verho M, Erasmus TP, Luus HG, Angela M, Grandin L, et al. Efficacy of ramipril versus enalapril in patients with mild to moderate essential hypertension. Br J Clin Pract 1996; 50: 302-10.
19. McCarron D. 24-hour blood pressure profiles in hypertensive patients administered ramipril or placebo once daily: magnitude and duration of antihypertensive effects. Ramipril Multicenter Study Group. Clin Cardiol 1991; 14: 737-42.
20. Spieker C, Zidek W, Vetter H, Rahn KH. Ambulatory 24-h blood pressure monitoring in essential hypertensives treated with the angiotensin-converting enzyme inhibitor ramipril. J Int Med Res 1991; 19: 39-43.
21. Perticone F, Pugliese F, Ceravolo R, Mattioli PL. Amlodipine versus ramipril in the treatment of mild to moderate hypertension: evaluation by 24-hour ambulatory blood pressure monitoring. Cardiology 1994; 85: 36-46.
22. Frampton JE, Peters DH. Ramipril. An updated review of its therapeutic use in essential hypertension and heart failure. Drugs 1995; 49: 440-66.
23. White WB. How well does ambulatory blood pressure predict target-organ disease and clinical outcome in patients with hypertension? Blood Press Monit 1999; 4 (Suppl 2): S17-21.
24. Zanchetti A. Trough:peak ratio of the blood pressure response to dihydropyridine calcium antagonists. Italian Nifedipine GITS Study Group. J Hypertens Suppl 1994; 12: S97-106.
25. Palatini P, Malacco E, Di SS, Carretta R, Dorigatti F, Bertocchi F, et al. Trough:peak ratio and smoothness index in the evaluation of 24-h blood pressure control in hypertension: a comparative study between valsartan/hydrochlorothiazide combination and amlodipine. Eur J Clin Pharmacol 2002; 57: 765-70.
26. Omboni S, Fogari R, Mancia G. A smooth blood pressure control is obtained over 24 h by delapril in mild to moderate essential hypertensives. Blood Press 2001; 10: 170-5.
27. Stergiou GS, Efstathiou SP, Skeva II, Baibas NM, Roussias LG, Mountokalakis TD. Comparison of the smoothness index, the trough: peak ratio and the morning: evening ratio in assessing the features of the antihypertensive drug effect. J

Hypertens 2003; 21: 913-20.
28. Stergiou GS, Efstathiou SP, Roussias LG, Mountokalakis TD. Blood pressure- and pulse pressure-lowering effects, trough:peak ratio and smoothness index of telmisartan compared with lisinopril. J Cardiovasc Pharmacol 2003; 42: 491-6.
29. Buranakitjaroen P, Phoojaroenchanachai M, Saravich S, Sangprasert P. The efficacy and tolerability of an angiotensin II receptor blocker, telmisartan, in Thai patients with mild to moderate essential hypertension. J Med Assoc Thai 2002; 85: 968-77.

การประเมินความราบเรียบของการควบคุมความดันโลหิตของยารามิพริลในการรักษาโรคความดันโลหิตสูงชนิดปฐมภูมิในผู้ป่วยไทยโดยใช้เครื่องวัดความดันโลหิตชนิดพกพาตลอด 24 ชั่วโมง

วีรวรรณ อุชายภิชาติ, บรรหาร กออนันตกูล, จุฑามณี สุทธิสีสังข์

การศึกษานี้มีจุดมุ่งหมายเพื่อประเมินประสิทธิภาพของยา ramipril ในขนาด 2.5 และ 5 มิลลิกรัม รับประทานวันละครั้งต่อระดับความดันโลหิต และความต่อเนื่องของการลดความดันโลหิต 24 ชั่วโมง ในผู้ป่วยโรคความดันโลหิตสูงชนิดปฐมภูมิ โดยใช้เครื่องวัดความดันโลหิตอัตโนมัติ 24 ชั่วโมงชนิดพกพา การศึกษาจากผู้ป่วยชาย 19 รายที่มีคุณสมบัติเข้าเกณฑ์การศึกษา พบผู้ป่วย 12 ราย ที่ตอบสนองและ/หรือ มีความดันโลหิตลดลงเป็นปกติจากการได้รับยา ramipril โดยมีระดับความดันโลหิตที่ได้รับการตรวจบันทึกด้วยหูฟัง และเครื่องวัดความดันโลหิตอัตโนมัติ 24 ชั่วโมงลดลงอย่างมีนัยสำคัญทางสถิติ ($p < 0.01$) ค่าร้อยละและระดับของ 24-h SBP/DBP load ลดลงอย่างมีนัยสำคัญทางสถิติจาก $92 \pm 9.7/91 \pm 15.9$ เป็น $67 \pm 23.8/65 \pm 27.6$ ($p < 0.01$) และจาก $23 \pm 10.6/16 \pm 5.3$ mmHg เป็น $17 \pm 10.3/10 \pm 4.8$ mmHg ($p < 0.05$) ตามลำดับ trough to peak ratio สำหรับ SBP/DBP มีค่า 0.59/0.52 (คำนวณจากค่าความดันโลหิตที่ลดลงโดยรวม) และ $0.68 \pm 0.23/0.52 \pm 0.22$ (คำนวณจากค่าความดันโลหิตที่ลดลงในผู้ป่วยแต่ละราย) ในขณะที่ smoothness index มีค่าเท่ากับ 0.89/1.03

โดยสรุป ramipril ในขนาด 2.5 และ 5 มิลลิกรัม รับประทานวันละครั้ง มีประสิทธิภาพในการลดระดับความดันโลหิตได้อย่างต่อเนื่องตลอด 24 ชั่วโมงในผู้ป่วยความดันโลหิตสูงชนิดปฐมภูมิ