Comparison of the Efficacy of Morning Versus Evening Administration of Telmisartan in Essential Hypertension

Ramón C. Hermida, Diana E. Ayala, José R. Fernández, Carlos Calvo

Abstract—Valsartan administration at bedtime as opposed to on wakening improves the sleep time–relative blood pressure decline toward a more dipper pattern without loss in 24-hour efficacy. Yet to be determined is whether this administration time-dependent efficacy is a class-related feature, characteristic of all angiotensin receptor blockers or specific only to valsartan. Terminal half-life is a major difference between angiotensin receptor blockers, being largest (≈24 hours) for telmisartan. This trial investigated the administration time-dependent antihypertensive efficacy of telmisartan. We studied 215 patients with hypertension (114 men and 101 women), 46.4±12.0 years of age, randomly assigned to receive telmisartan (80 mg/d) as a monotherapy either on awakening or at bedtime. Blood pressure was measured for 48 hours before and after 12 weeks of treatment. The significant blood pressure reduction after treatment was similar for both groups. Bedtime administration of telmisartan, however, was more efficient than morning dosing in reducing the nocturnal blood pressure mean. The sleep time–relative blood pressure decline was slightly reduced after telmisartan on awakening but significantly increased with bedtime dosing, thus reducing the prevalence of nondipping from baseline by 76%. Telmisartan administered at bedtime, as opposed to morning dosing, improved the sleep time–relative blood pressure decline toward a more dipper pattern without loss in 24-hour efficacy. Nocturnal BP regulation is significantly better achieved with bedtime dosing of telmisartan. Results from this prospective trial suggest that these beneficial features of bedtime dosing may be class related for angiotensin receptor blockers. These results should be taken into account when prescribing this class of antihypertensive medication for treatment of essential hypertension. **(*Hypertension.* 2007;50:715-722.)**

Key Words: telmisartan ■ essential hypertension ■ ambulatory blood pressure monitoring ■ circadian rhythm ■ chronotherapy ■ dipper ■ nondipper ■ angiotensin receptor blockers

Angiotensin II receptor blockers (ARBs) are antihypertensive medications that selectively and specifically antagonize the action of angiotensin II, a potent vasoconstrictor that exerts a wide variety of physiological effects on blood pressure (BP) and its regulation. ARBs are becoming more popular for the treatment of hypertension because they are effective and very well tolerated.[1,2] Telmisartan is an ARB highly selective for the AT_1 receptor.[3] Previous studies using ambulatory BP monitoring (ABPM) established that, at the recommended once-daily dose of 40 to 80 mg, telmisartan remains effective for an entire 24 hours without alteration of the day-night BP pattern.[4]

Previously, we compared the antihypertensive efficacy of the ARB valsartan when ingested by subjects with hypertension for 3 months as a monotherapy, either in the morning after awakening from nighttime sleep or at bedtime before the commencement of the nocturnal sleep span. Significant BP reduction was achieved throughout the entire 24 hours, independent of the treatment time.[5] However, valsartan administration at bedtime as opposed to on wakening resulted in an improved sleep time–relative BP decline (or diurnal/nocturnal BP ratio), a greater efficacy in decreasing nocturnal BP, and a significant increase in the percentage of patients with controlled BP after treatment.[5–7] These results may be particularly relevant, because independent prospective studies have concluded that nighttime BP is a better predictor of cardiovascular outcome than the diurnal or the 24-hour means of BP.[8–10]

Yet to be determined is whether this administration time–dependent efficacy is a class-related feature, characteristic of all ARBs, or specific only to valsartan, a drug with a peak effect 4 to 6 hours after morning dosing. Terminal half-life is a major difference between ARBs,[11] being largest (≈24 hours) for telmisartan. Accordingly, this prospective trial was designed to compare, using BP data collected by 48-hour ABPM, the antihypertensive efficacy of the ARB telmisartan ingested as a monotherapy when ingested either in the morning after awakening from

Received May 16, 2007; first decision June 3, 2007; revision accepted June 19, 2007.

From the Bioengineering and Chronobiology Laboratories (R.C.H., D.E.A., J.R.F.), University of Vigo, Campus Universitario, Vigo, Spain; and the Hypertension and Vascular Risk Unit (C.C.), Hospital Clínico Universitario, Santiago de Compostela, Spain.

Correspondence to Ramón C. Hermida, Bioengineering and Chronobiology Labs, E.T.S.I. Telecomunicación, Campus Universitario, Vigo (Pontevedra) 36200, Spain. E-mail rhermida@uvigo.es

Hypertension **is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.107.094235**

nighttime sleep or at bedtime for a 3-month span in patients with essential hypertension.

Methods

Subjects

This prospective trial was conducted at the Hospital Clínico Universitario, Santiago de Compostela, Spain, between January 2005 and October 2006. Shift workers, heavy drinkers (alcohol intake >80 g/d), heavy smokers (>20 cigarettes per day), and heavy exercisers were excluded, as were individuals with either severe arterial hypertension (grade 3, eg, BP ≥180/110 mm Hg), type 1 diabetes, or secondary arterial hypertension and cardiovascular disorders, including concomitant unstable angina pectoris, heart failure, stroke, life-threatening arrhythmia, nephropathy, and retinopathy or previous (within the last year) myocardial infarction or coronary revascularization as revealed by thorough clinical evaluation according to the standardized protocol at the hypertension unit of the hospital. Inclusion criteria required age ≥18 years and a diagnosis of grade 1 or 2 essential hypertension using the criteria of the European Society of Hypertension-European Society of Cardiology guidelines,[2] based on repeated conventional BP measurements (systolic BP [SBP] between 140 and 179 mm Hg and/or diastolic BP [DBP] between 90 and 109 mm Hg), and corroboration by ABPM at the time of recruitment. A positive diagnosis of hypertension based on ABPM required that either the diurnal (awake) mean be >135/85 mm Hg for SBP/DBP or the nocturnal (sleep time) mean be >120/70 mm Hg.[12,13]

The sample size for this trial was calculated as follows: assuming a standard deviation of 9 mm Hg for ABPM, with 105 subjects per arm, the study could have 90% power to show as significant at the 95% level differences in efficacy of 4 mm Hg in daytime or nighttime BP mean between treatment groups. During the inclusion period, we screened 262 diurnally active patients and identified 231 who met the inclusion/exclusion criteria. Among these, 215 (114 men and 101 women), 46.4±12.0 years of age, completed the study and provided all of the required information for this trial.

After providing informed consent to participate in this prospective, randomized, open-label, blinded end point, parallel-group chronotherapy trial, patients were randomly assigned to 1 of 2 groups according to the time of day, either in the morning on awakening from nighttime sleep or at bedtime at night, of ingestion of the single daily tablet of telmisartan (80 mg/d, the highest recommended dose in Spain) for 12 weeks. The demographic characteristics of the 2 groups of participants (at baseline and after the 12 weeks of treatment) are described in Table 1. One member of the research team, according to the order of recruitment, following an allocation table constructed by a computerized random-number generator, assigned the subjects to treatment groups. The assignment of subjects to the respective treatment groups was blinded from the research team members performing the statistical analysis of the data. Compliance was evaluated on the basis of tablet count and a personal interview with each volunteer at the final visit. The State Ethics Committee of Clinical Research approved this trial, part of the prospective Monitorización Ambulatoria de Presión arterial y Eventos Cardiovasculares Study (www.clinicaltrials.gov, code NCT00295542) designed to investigate whether normalizing the circadian BP profile toward a more dipper pattern by time-specified treatment reduces cardiovascular risk.

Blood samples were obtained in the clinic from the antecubital vein after nocturnal fasting between 8:00 AM and 9:00 AM on the same days when 48-hour ABPM was initiated, both immediately before and after 12 weeks of treatment. Clinic BP measurements (6 per study visit after being seated for ≥5 minutes, on the same day just before starting ABPM) were always obtained by the same investigator with a validated automatic oscillometric device (HEM-737, Omron Health Care Inc).[14]

ABPM Assessment

The SBP, DBP, and heart rate (HR) of each participant were automatically measured every 20 minutes from 7 AM to 11 PM and every 30 minutes during the night for 48 consecutive hours with a properly calibrated SpaceLabs 90207 device (SpaceLabs Inc). Subjects were studied by ABPM under baseline conditions and again after 12 weeks of the timed therapy. Participants were instructed to go about their usual activities with minimal restrictions but to follow a similar schedule during the 2 days of ABPM and to avoid daytime napping. No one was hospitalized during monitoring. ABPM always began between 10 AM and 12 PM. BP series were not considered valid for analysis if >30% of the measurements were lacking, if they had missing data for >2-hour spans, or if data were collected from subjects while experiencing an irregular rest-activity schedule or a nighttime sleep span <6 hours or >12 hours during monitoring. Protocol-correct data series were collected from 215 subjects and, therefore, are included in this efficacy study. Baseline BP profiles of 16 additional subjects (10 originally assigned to telmisartan on awakening and 6 to telmisartan at bedtime) were eliminated, because the subjects from which they were derived either failed to return for the second ABPM after 12 weeks of intervention (11 subjects) or because they were withdrawn from the trial because of adverse effects (4 on awakening dosing and 1 on bedtime dosing).

Actigraphy

Every participant wore a Mini-Motion-Logger Actigraph (Ambulatory Monitoring Inc) on the dominant wrist to monitor physical activity every minute of the day and night throughout each 48-hour ABPM session. This compact (about half the size of a wristwatch) device functions as an accelerometer. The internal clock of the Actigraph and the ABPM devices were synchronized through their respective interfaces by the same computer. The actigraphy data were used to determine the onset and offset times of diurnal activity and nocturnal sleep so as to accurately determine the diurnal and nocturnal BP means of each subject. The mean activity for the 5 minutes before each BP reading was then calculated for further statistical analysis of the circadian variability of activity level following previously established procedures.[15,16]

Statistical Methods

Each individual's clock hour BP and HR values were first referenced to hours after awakening from nocturnal sleep, based on the data obtained by wrist actigraphy. This transformation avoided the introduction of bias because of slight differences among subjects in their sleep/activity routine.[15] BP and HR time series were then edited according to conventional criteria to remove measurement errors and outliers.[17] Thus, readings with SBP >250 or <70 mm Hg, DBP >150 or <40 mm Hg, and pulse pressure (difference between SBP and DBP) >150 or <20 mm Hg were automatically discarded. For descriptive purposes, the circadian rhythm of BP, HR, and wrist activity before and after treatment was objectively assessed by population multiple-component analysis,[18] a method applicable to nonsinusoidal-shaped hybrid time series data (time series of data collected from a group of subjects) consisting of values distributed at equal or unequal intervals.

The circadian rhythm parameters of midline estimating statistic of rhythm (average value of the rhythmic function fitted to the data) and overall amplitude (one half of the difference between the maximum and the minimum values of the best fitted curve) obtained for each timed therapy group at baseline and after treatment were compared using a paired nonparametric test developed to assess differences in parameters derived from population multiple-component analysis.[19] Hourly BP means obtained before and after treatment were compared by *t* test corrected for multiple testing by means of the Holm procedure.[20] The daily (24-hour), diurnal (active-span), and nocturnal (resting-span) means of BP were further compared among groups by ANOVA. The demographic and clinical characteristics in Table 1 were compared among groups by ANOVA (quantitative variables) or nonparametric χ^2 test. Comparisons within each treatment group for each variable included in Table 1 measured before and after intervention were performed by paired *t* test.

Table 1. Demographic and Analytical Characteristics of Subjects Investigated

Variable	Telmisartan on Awakening*	Telmisartan at Bedtime	*P* for Group Comparison
Patients, n	107	108	
Sex, % men	54.2	51.9	0.729
Age, y	46.4±11.5	46.5±12.6	0.937
Height, cm	164.2±10.0	164.9±10.7	0.649
Before treatment			
Weight, kg	73.4±15.6	76.4±16.0	0.176
BMI, kg/m^2	27.1±4.2	28.0±4.7	0.098
Waist, cm	89.8±13.3	91.7±13.1	0.282
Hip, cm	102.1±8.5	104.8±8.7	0.195
SBP, mm Hg†	151.8±16.2	153.5±13.8	0.393
DBP, mm Hg†	90.9±11.6	91.6±9.4	0.625
PP, mm Hg†	60.9±8.6	61.9±10.5	0.423
HR, bpm†	74.6±10.1	76.5±11.5	0.185
Glucose, mg/dL	99.6±21.4	98.6±12.6	0.673
Creatinine, mg/dL	0.97±0.24	0.92±0.19	0.137
Uric acid, mg/dL	5.5±1.7	5.5±1.5	0.752
Cholesterol, mg/dL	215.4±37.3	212.5±40.3	0.587
Triglycerides, mg/dL	116.4±77.1	110.8±75.1	0.592
After treatment			
Weight, kg	73.5±15.6 (0.915)	76.7±15.9 (0.311)	0.125
BMI, kg/m^2	27.0±4.1 (0.978)	28.2±4.7 (0.324)	0.056
Waist, cm	90.6±12.6 (0.093)	92.3±12.6 (0.291)	0.330
Hip, cm	102.5±7.8 (0.177)	104.8±9.2 (0.978)	0.241
SBP, mm Hg†	137.5±16.9 (<0.001)	141.3±14.0 (<0.001)	0.067
DBP, mm Hg†	82.5±11.4 (<0.001)	84.7±8.0 (<0.001)	0.092
PP, mm Hg†	55.0±9.5 (<0.001)	56.6±11.1 (<0.001)	0.251
HR, bpm†	73.0±8.8 (0.028)	72.5±9.9 (<0.001)	0.705
Glucose, mg/dL	101.8±24.1 (0.192)	98.5±12.6 (0.948)	0.208
Creatinine, mg/dL	0.97±0.22 (0.630)	0.93±0.18 (0.407)	0.139
Uric acid, mg/dL	5.5±1.8 (0.154)	5.5±1.5 (0.675)	0.887
Cholesterol, mg/dL	219.5±43.4 (0.222)	210.3±34.6 (0.664)	0.093
Triglycerides, mg/dL	113.0±79.0 (0.754)	109.7±90.6 (0.928)	0.787

Data in parenthesis are *P* values from comparison with values before treatment. PP indicates pulse pressure; BMI, body mass index.
*All values shown as mean±SD.
†Values correspond with the average of 6 conventional BP measurements obtained on each subject in the clinic before commencing 48-hour ABPM.

Results

Demographic Characteristics and Analytical Parameters

The baseline physical characteristics of the 2 treatment-time groups of subjects (Table 1) were similar, and they remained unchanged after treatment. Clinic BP measurements (average of the 6 conventional morning measurements obtained just before ABPM), including pulse pressure, were significantly reduced after treatment (14.3/8.4 mm Hg in SBP/DBP after morning dosing; 12.2/6.9 mm Hg after bedtime treatment; $P<0.001$ from baseline; $P>0.067$ between groups). Clinic HR was also slightly but significantly reduced after treatment, mainly in the group receiving telmisartan at bedtime (Table 1). The serum values of glucose, creatinine, cholesterol, triglycerides, and the other laboratory chemistry variables of the 2 treatment groups were comparable at baseline and were not significantly changed after treatment (Table 1).

Telmisartan on Awakening

Figure 1 (left) shows the circadian rhythm of SBP and DBP measured by 48-hour ABPM before and after 12 weeks of telmisartan on awakening in the morning. The dark shading along the lower horizontal axis of the graphs represents the average hours of nocturnal sleep across the patients. Results did not vary between the 2 consecutive days of sampling. Therefore, we decided to pool the BP data over an idealized single 24-hour profile to simplify the graphic display of the results. Three-month morning telmisartan treatment resulted in a statistically significant reduction of the 24-hour mean BP from baseline (decrease of 10.5/7.9 mm Hg of SBP/DBP; $P<0.001$; Table 2). After treat-

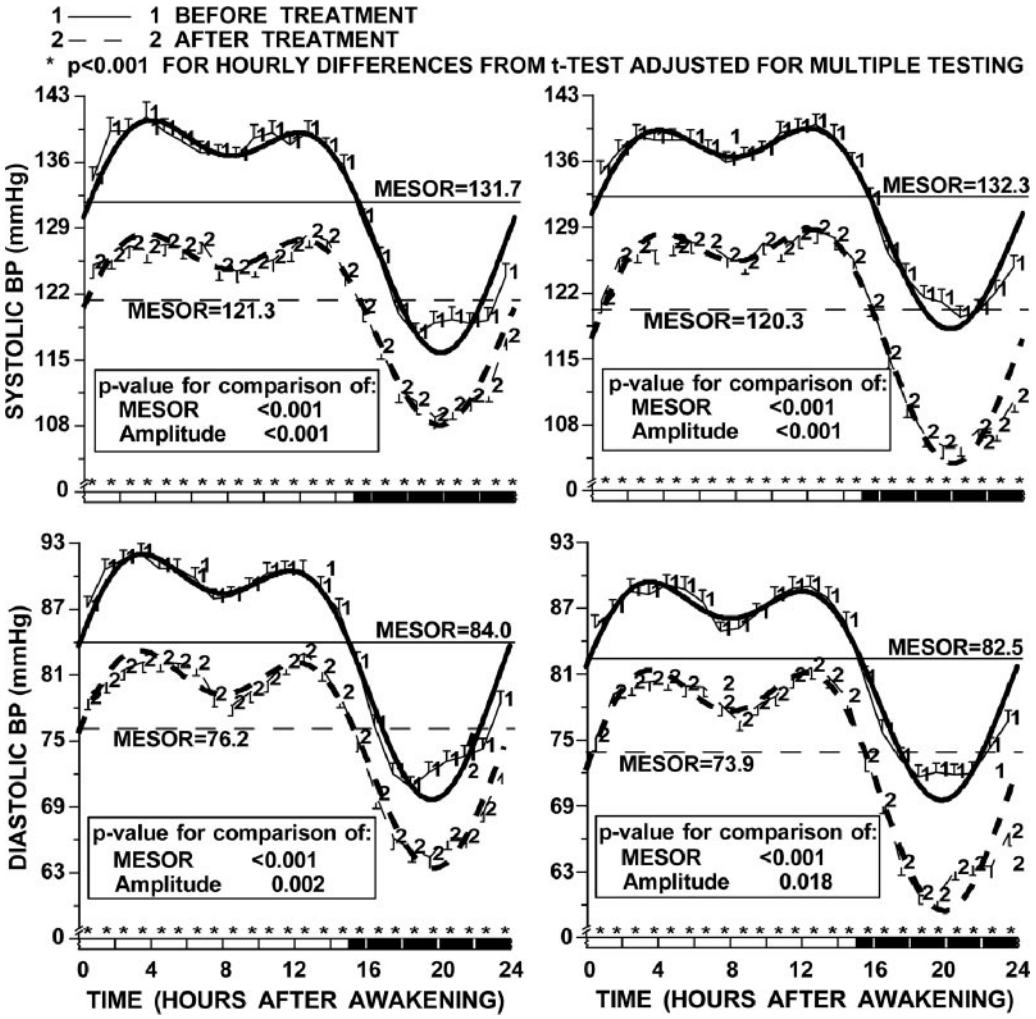

Figure 1. Changes in the circadian pattern of SBP (top) and DBP (bottom) with telmisartan (80 mg/d) ingested on awakening (n=107; left) or at bedtime (n=108; right) in patients with grade 1 or 2 essential hypertension sampled by 48-hour ABPM. Each graph shows the hourly means and SEs of data collected before (continuous line) and after (dashed line) 12 weeks of timed treatment. Dark shading along the lower horizontal axis of the graphs represents the average hours of nocturnal sleep across the patient sample. The nonsinusoidal-shaped curves correspond with the best-fitted waveform model determined by population multiple-component analysis. MESOR (midline estimating statistic of rhythm) is the average value of the rhythmic function fitted to the data. Amplitude is one half of the difference between the maximum and the minimum values of the best-fitted curve.

ment, 49.5% of the subjects in this group showed controlled values of ABPM, ie, values below the diagnostic thresholds mentioned above.[12,13] The circadian amplitude of BP was slightly but significantly reduced after treatment (Figure 1, left). Thus, the effects of treatment were greater on the diurnal than on the nocturnal mean of BP when telmisartan was ingested on awakening (Figure 2 and Table 2). Morning telmisartan treatment exerted no effect on the 24-hour mean HR (decrease of 0.5 bpm; $P=0.354$; Table 2). The circadian pattern of physical activity monitored before and after 3 months of treatment also remained unchanged ($P=0.213$ for comparison of 24-hour mean activity before and after treatment). The average duration of nocturnal rest was not statistically different for the profiles obtained before and after treatment ($P=0.469$; Table 2).

Telmisartan at Bedtime

The right panels in Figure 1 show the 24-hour pattern of SBP and DBP before and after bedtime telmisartan ingestion. This timed treatment resulted in significant reduction in the 24-hour mean of SBP/DBP from baseline, by 11.7/8.3 mm Hg ($P<0.001$; Table 2). In keeping with the ABPM criteria mentioned above, 64.8% of the patients in this group evidenced controlled BP after treatment. Despite the significant effect on BP, HR remained unchanged after treatment (decrease of 0.5 bpm in the 24-hour mean of HR; $P=0.644$). The circadian pattern of activity was also similar before and after therapy ($P=0.703$). The average duration of nocturnal rest was comparable for the profiles obtained before and after intervention ($P=0.082$; Table 2). The BP reduction after treatment was statistically significant ($P<0.001$ after correcting for multiple testing) in all of the 24-hour intervals, as shown by the asterisks above the lower horizontal axis in the right panels of Figure 1. The circadian amplitude of BP was significantly increased after treatment ($P<0.018$; Figure 1), corroborating that the effects of treatment were greater on the nocturnal than on the diurnal mean of BP when telmisartan was ingested at bedtime (Figure 2 and Table 2).

Table 2. Ambulatory BP Characteristics of Subjects Investigated

Variable*	Telmisartan on Awakening	Telmisartan at Bedtime	*P* for Group Comparison
Patients, n	107	108	
Before treatment			
Nocturnal rest, h	8.6±1.2	8.4±1.0	0.175
Diurnal mean of SBP, mm Hg	138.1±10.9	137.7±10.0	0.791
Nocturnal mean of SBP, mm Hg	120.4±11.1	122.0±11.4	0.289
24-h mean of SBP, mm Hg	132.6±10.0	133.0±9.7	0.747
Diurnal/nocturnal ratio of SBP, %	12.7±5.7	11.4±6.2	0.088
Morning surge of SBP, mm Hg	21.8±11.4	20.2±10.4	0.279
Diurnal mean of DBP, mm Hg	89.7±7.7	87.4±8.6	0.138
Nocturnal mean of DBP, mm Hg	73.7±8.2	73.1±8.4	0.595
24-h mean of DBP, mm Hg	84.8±7.4	83.2±8.0	0.213
Diurnal/nocturnal ratio of DBP, %	17.5±6.5	16.1±6.6	0.093
Morning surge of DBP, mm Hg	19.8±7.7	18.1±8.0	0.061
Diurnal mean of HR, bpm	78.3±6.8	79.6±9.6	0.260
Nocturnal mean of HR, bpm	64.9±6.4	67.8±8.2	0.033
24-h mean of HR, bpm	74.2±6.5	76.0±8.8	0.074
Nondippers, %	29.9	34.2	0.494
After treatment			
Nocturnal rest, h	8.5±1.1 (0.469)	8.2±1.0 (0.082)	0.061
Diurnal mean of SBP, mm Hg	126.4±11.5 (<0.001)	126.5±11.0 (<0.001)	0.972
Nocturnal mean of SBP, mm Hg	112.2±11.2 (<0.001)	108.3±11.1 (<0.001)	0.011
24-h mean of SBP, mm Hg	122.1±10.9 (<0.001)	121.3±10.7 (<0.001)	0.629
Diurnal/nocturnal ratio of SBP, %	11.2±5.3 (0.010)	14.4±4.2 (<0.001)	<0.001
Morning surge of SBP, mm Hg	19.8±8.9 (0.102)	20.6±7.4 (0.718)	0.457
Diurnal mean of DBP, mm Hg	80.9±8.4 (<0.001)	79.2±8.2 (<0.001)	0.133
Nocturnal mean of DBP, mm Hg	67.3±8.9 (<0.001)	63.4±8.2 (<0.001)	<0.001
24-h mean of DBP, mm Hg	76.9±8.3 (<0.001)	74.8±8.1 (<0.001)	0.069
Diurnal/nocturnal ratio of DBP, %	16.6±6.6 (0.157)	19.9±5.6 (<0.001)	<0.001
Morning surge of DBP, mm Hg	18.3±8.3 (0.101)	18.7±5.6 (0.370)	0.429
Diurnal mean of HR, bpm	77.5±8.2 (0.156)	79.4±8.7 (0.765)	0.089
Nocturnal mean of HR, bpm	65.0±7.7 (0.852)	66.6±7.3 (0.242)	0.112
24-h mean of HR, bpm	73.7±7.7 (0.354)	75.5±8.1 (0.644)	0.097
Nondippers, %	36.5 (0.309)	8.3 (<0.001)	<0.001
Average percentage reduction from baseline			
Diurnal mean of SBP	8.3±6.7	8.1±7.0	0.773
Nocturnal mean of SBP	6.5±8.6	11.1±7.0	<0.001
24-h mean of SBP	7.8±6.6	8.7±6.4	0.327
Diurnal mean of DBP	9.6±7.0	9.1±7.4	0.562
Nocturnal mean of DBP	8.3±10.5	13.0±8.3	<0.001
24-h mean of DBP	9.2±7.1	9.8±6.9	0.554

Data in parenthesis are *P* values from comparison with values before treatment. The diurnal/nocturnal ratio, an index of BP dipping, is defined as the percentage decline in BP during the hours of nocturnal rest relative to the mean BP obtained during the hours of diurnal activity and calculated as the [(awake BP mean−sleep time BP mean)/awake BP mean]×100. The morning BP surge is defined as the difference between the average BP during the first 2 hours after awakening and the hourly average centered on the lowest nighttime BP reading. Nondippers are patients with diurnal/nocturnal SBP ratio <10%, using data sampled by ABPM for 48 consecutive hours.

*All of the values are shown as mean±SD.

Comparison in Efficacy Between Treatment Groups

Comparison of the results shown in Figure 1 reveals a lack of statistically significant differences in ambulatory BP at baseline among the treatment-time groups ($P=0.747$ for comparison of 24-hour mean SBP and $P=0.213$ for comparison of 24-hour mean DBP; Table 2). After 12 weeks of timed treatment, the 24-hour mean BP was also similar for both

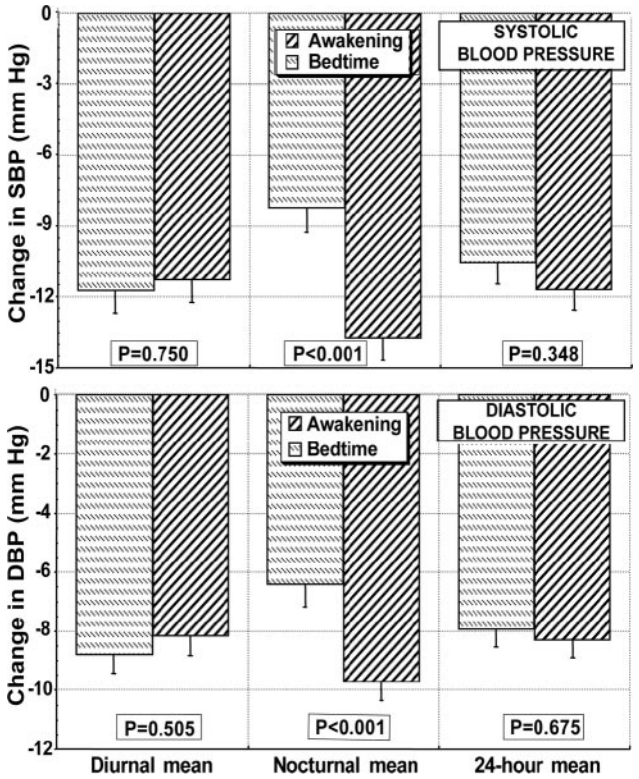

Figure 2. Changes (in units of mm Hg) in the diurnal (active hours), nocturnal (sleep time), and 24-hour mean of SBP (top) and DBP (bottom) with telmisartan (80 mg/d) ingested on awakening or at bedtime in patients with grade 1 or 2 essential hypertension studied by 48-hour ABPM before and after 12 weeks of timed treatment. *P* values are shown for comparison of the effects between the 2 groups of subjects by ANOVA.

treatment-time groups ($P=0.629$ for SBP; $P=0.069$ for DBP; Table 2); thus, the efficacy of telmisartan on the 24-hour BP mean was comparable independent of the time of treatment.

Figure 2 provides additional information regarding the comparison of changes in the diurnal (ie, specific to the daytime activity span as determined by wrist actigraphy), nocturnal (ie, specific to the sleep span as determined by actigraphy), and 24-hour mean BP values after 12 weeks of 80 mg/d telmisartan treatment. Results, as a complement to those shown in Figure 1, reveal the significant differences among the treatment-time groups in the effect of telmisartan on BP, specifically, a greater efficacy after bedtime dosing in regulating nighttime BP.

These differing effects on nocturnal BP are reflected in changes in the sleep time–relative BP decline or diurnal/nocturnal BP ratio (an index of BP dipping[21]), defined as the percentage of decline in BP during the hours of nocturnal rest relative to the mean BP obtained during the hours of diurnal activity (Table 2). Figure 3 shows a significant increase in the diurnal/nocturnal BP ratio when telmisartan was consistently ingested at bedtime and a decrease when the drug was ingested on awakening ($P<0.001$ between treatment groups). The number of patients with a nondipper BP pattern at baseline was unaltered after ingestion of the 80 mg/d telmisartan dose on awakening, but nondipping was significantly reduced from 34% to 8% when the same dose was ingested at bedtime ($P<0.001$; Table 2).

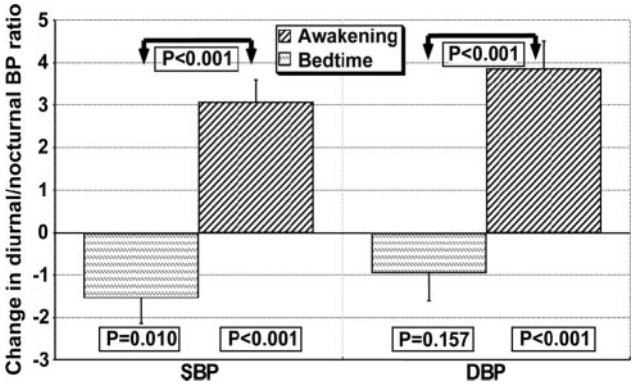

Figure 3. Changes in the nocturnal BP decline relative to the diurnal mean (diurnal/nocturnal ratio) with telmisartan (80 mg/d) ingested on awakening or at bedtime in subjects with grade 1 or 2 essential hypertension studied by 48-hour ABPM before and after 12 weeks of timed treatment. *P* values on top are shown for comparison of the effects between the 2 treatment time groups of subjects by ANOVA. *P* values on the bottom are shown for the change after the timed treatment in the diurnal/nocturnal BP ratio per treatment time group and by variable determined by paired *t* test.

Other parameters derived from ABPM have also been related to cardiovascular risk. For example, the morning BP rate of rise coincident with the commencement of diurnal activity has been verified to be an independent risk factor of stroke in older Japanese patients with hypertension.[22] Accordingly, we also tested the potential administration time–dependent effects of telmisartan on the morning BP surge, calculated as the difference between the average BP during the first 2 hours after wake-up time and the hourly average centered on the lowest nighttime BP reading.[22] The morning BP surge was slightly but not significantly decreased after telmisartan on awakening (2.0/1.5 mm Hg for SBP/DBP; $P>0.101$). When telmisartan was taken at bedtime, there was also no change in the morning surge (increase of 0.4/0.6 mm Hg for SBP/DBP; $P>0.370$). There were no differences in morning BP surge between timed-treatment groups either before or after treatment (Table 2).

Discussion

A number of previous publications revised elsewhere[23,24] have documented morning-evening dosing time differences in the pharmacokinetics and/or pharmacodynamics of several different classes of BP-lowering medications, including calcium channel blockers, angiotensin-converting enzyme inhibitors, α-blockers, and β-blockers. We also found that the once-daily evening, in comparison to morning, ingestion schedule of the ARB valsartan significantly improved the sleep time–relative BP decline,[5] especially in nondipper hypertensive subjects,[6] thus markedly modifying the circadian pattern of BP variation. This circadian variation is influenced, among many other factors, by the autonomic nervous system tone, vasoactive hormones, and hematologic and renal variables.[25] A prominent circadian variation has been demonstrated for plasma renin activity, angiotensin-converting enzyme inhibitors, angiotensin II, aldosterone, atrial natriuretic peptide, and catecholamines,[26] all reflecting the marked circadian structure of the renin-angiotensin-aldo-

sterone system. Possibly related to the circadian variation that characterizes the renin-angiotensin-aldosterone system, activated during the nocturnal sleep time cycle, clinical studies demonstrated different effects of the angiotensin-converting enzyme inhibitors benazepril, enalapril, imidapril, perindopril, quinapril, ramipril, spirapril, and trandolapril when dosed in the morning versus the evening.[23,24] In all cases, evening administration of these medications resulted in a higher effect on nocturnal BP and a significant modification of the circadian BP profile toward a more dipper pattern.[24] Thus, we hypothesized that the administration time-dependent effects of valsartan on BP[5] might also be somehow related to the circadian variation in the renin-angiotensin-aldosterone system and not just a consequence of a relatively low terminal half-life. Accordingly, we tested a potential similar dosing time difference in the effects of the ARB telmisartan.

Results of this randomized prospective trial indicate that 80 mg/d of telmisartan efficiently reduces BP for the entire 24 hours whether the once-daily ingestion is consistently in the morning on awakening from nighttime sleep or at bedtime at night (Figure 1). Telmisartan dosing on awakening and at bedtime similarly reduced BP during the 24 hours (Figure 2); however, telmisartan when administered at bedtime was especially efficient in reducing nocturnal BP and, thus, significantly increasing the sleep time–relative decline of BP (Figure 3). After 12 weeks of treatment, the number of controlled patients (in keeping with ABPM criteria) was significantly greater with bedtime than morning treatment ($P=0.023$). Moreover, the number of patients with a nondipper BP pattern at baseline was unaltered after ingestion of telmisartan on awakening but significantly reduced when the medication was ingested at bedtime ($P<0.001$; Table 2). This may be clinically relevant because, although the mechanism underlying the lack of nocturnal decline in BP is unclear, nondipping has been related to an increase in end-organ injury and cardiovascular events.[8,27,28] Moreover, nighttime BP seems to be a better predictor of cardiovascular mortality than the diurnal or 24-hour BP means.[8,9,10]

International guidelines for the treatment of hypertension recommend the use of long-acting, once-daily medications that exhibit 24-hour efficacy; they improve adherence to therapy and minimize BP variability with smoother and more consistent BP control.[1,2] Telmisartan has been approved for once-daily dosing but without specification of treatment time. Use of a medication with a high homogeneous efficacy, such as telmisartan administered on awakening, is unlikely to affect the circadian profile of BP and may be the best choice for the treatment of dipper hypertensive patients. However, it may not be the best time to treat nondipper hypertensive subjects. Results of this study indicate that a single daily 80-mg/d dose of telmisartan in the morning reduces BP smoothly over the entire 24 hours. The same dose of telmisartan taken before bedtime, however, improves BP control during the nocturnal resting hours without any loss in 24-hour efficacy and increases the sleep time–relative BP decline, thus significantly reducing the prevalence of the nondipping BP pattern, whereas also increasing the proportion of controlled patients after 3 months of this monotherapy. These results, similar to those documented previously for valsartan,[5] suggest that these administration time-dependent effects may be class-related features applicable to all ARBs, an issue that may need further investigation.

The potential reduction in cardiovascular risk associated with the normalization of the circadian variability of BP (converting a nondipper to dipper pattern) has not yet been clearly established. Apart from the Syst-Eur trial, where nitrendipine was dosed at bedtime,[8] results from the Heart Outcomes Prevention Evaluation substudy where patients were evaluated by ABPM indicated a significant BP reduction mainly during hours of nighttime sleep.[29] The authors suggested that the beneficial effects on cardiovascular morbidity and mortality in the Heart Outcomes Prevention Evaluation Study may be related to the 8% increase in the sleep time–relative BP decline seen after ramipril was administered at bedtime. On the other hand, we demonstrated recently that urinary albumin excretion was significantly reduced after bedtime, but not morning, treatment with valsartan.[30] This reduction was independent of the 24-hour BP decrease after treatment but highly correlated with the decrease in the nocturnal mean of BP and, mainly, with the increase in sleep time–relative BP decline associated to bedtime administration of valsartan.[30] Moreover, plasma fibrinogen has also been significantly reduced after bedtime treatment with valsartan in direct correlation with the increasing sleep time–relative BP decline resulting from the conversion of nondippers into dippers.[6,7]

Common to all of the previous trials demonstrating the increased cardiovascular risk in nondippers as compared with dipper patients[8,21,27,28] is that the prognostic significance of ABPM has relied on a single baseline profile from each participant, without accounting for possible changes in the BP pattern, mainly associated with antihypertensive therapy and aging during follow-up. Along these lines, the Monitorización Ambulatoria de Presión arterial y Eventos Cardiovasculares Study was designed to investigate whether normalizing the circadian BP profile toward a more dipper pattern by chronotherapy reduces cardiovascular risk.[31] Recent preliminary findings from this prospective trial indicate that the probability of cardiovascular (stroke and myocardial infarction) event-free survival is strongly correlated with the sleep time–relative BP decline.[31] Most important, results suggest that an increase in this parameter toward a more dipper pattern is associated with a decrease in cardiovascular risk, whereas a decrease in the nocturnal BP decline is associated with an increase in morbidity and mortality. In light of these collective findings, evaluation of the potential decrease in cardiovascular risk from the proper modeling of the circadian BP profile by the timed administration of antihypertensive medication, beyond reduction of BP levels, deserves further prospective investigation.

Perspectives

The results of this ingestion time study on subjects with grade 1 or 2 essential hypertension randomly assigned to receive the 80-mg daily dose of telmisartan either on awakening or at bedtime demonstrate a normalization of the circadian BP profile toward a more dipper pattern only when telmisartan is

administered at bedtime. Results raise the possibility that the dosing time of telmisartan should be chosen in relation to the baseline dipper status of each patient to improve therapeutic benefit and to increase BP control, as defined by an adequate reduction in both diurnal and nocturnal means of BP. Whether converting a nondipper to dipper pattern with bedtime administration of telmisartan could also reduce cardiovascular risk is a hypothesis that merits investigation.

Sources of Funding

This investigator-promoted independent research was supported in part by grants from Dirección General de Investigación, Ministerio de Educación y Ciencia (SAF2006-6254); Xunta de Galicia (PGIDIT03-PXIB-32201PR); Hospital Clínico Universitario de Santiago; and Vicerrectorado de Investigación, University of Vigo.

Disclosures

None.

References

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Rocella EJ. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–1252.
2. Guidelines Committee. 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens*. 2003;21:1011–1053.
3. Sharpe M, Jarvis B, Goa KL. Telmisartan: a review of its use in hypertension. *Drugs*. 2001;61:1501–1529.
4. Neutel JM, Smith DHG. Evaluation of angiotensin II receptor blockers for 24-hour blood pressure control: meta-analysis of a clinical database. *J Clin Hypertens*. 2003;1:58–63.
5. Hermida RC, Calvo C, Ayala DE, Domínguez MJ, Covelo M, Fernández JR, Mojón A, López JE. Administration-time-dependent effects of valsartan on ambulatory blood pressure in hypertensive subjects. *Hypertension*. 2003;42:283–290.
6. Hermida RC, Calvo C, Ayala DE, Fernández JR, Covelo M, Mojón A, López JE. Treatment of non-dipper hypertension with bedtime administration of valsartan. *J Hypertens*. 2005;23:1913–1922.
7. Hermida RC, Calvo C, Ayala DE, Mojón A, Rodríguez M, Chayán L, López JE, Fontao MJ, Soler R, Fernández JR. Administration time-dependent effects of valsartan on ambulatory blood pressure in elderly hypertensive subjects. *Chronobiol Int*. 2005;22:755–776.
8. Staessen JA, Thijs L, Fagard R, O′Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J, for the Systolic Hypertension in Europe (Syst-Eur) trial investigators. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA*. 1999;282:539–546.
9. Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA, O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension*. 2005;46:156–161.
10. Kikuya M, Ohkubo T, Asayama K, Metoki H, Obara T, Saito S, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Ambulatory blood pressure and 10-year risk of cardiovascular and noncardiovascular mortality. The Ohasama Study. *Hypertension*. 2005;45:240–245.
11. Oparil S. Newly emerging pharmacologic differences in angiotensin II receptor blockers. *Am J Hypertens*. 2000;13:18S–24S.
12. O'Brien A, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens*. 2003;21:821–848.
13. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ. Recommendations for blood pressure measurement in humans and experimental animals. Part 1: blood pressure measurement in humans. *Hypertension*. 2005;45:142–161.
14. Anwar YA, Giacco S, McCabe EJ, Tendler BE, White WB. Evaluation of the efficacy of the Omron HEM-737 Intellisense device for use on adults according to the recommendations of the Association for the Advancement of Medical Instrumentation. *Blood Press Monit*. 1998;3:261–265.
15. Hermida RC, Calvo C, Ayala DE, Mojón A, López JE. Relationship between physical activity and blood pressure in dipper and nondipper hypertensive patients. *J Hypertens*. 2002;20:1097–1104.
16. Mansoor GA, White WB, McCabe EJ, Giacco S. The relationship of electronically monitored physical activity to blood pressure, heart rate, and the circadian blood pressure profile. *Am J Hypertens*. 2000;13:262–267.
17. Staessen J, Fagard R, Lijnen P, Thijs L, Vaa Hoof R, Amery A. Ambulatory blood pressure monitoring in clinical trials. *J Hypertens*. 1991;9(suppl 1):s13–s19.
18. Fernández JR, Hermida RC. Inferential statistical method for analysis of nonsinusoidal hybrid time series with unequidistant observations. *Chronobiol Int*. 1998;15:191–204.
19. Fernández JR, Mojón A, Hermida RC. Comparison of parameters from rhythmometric models with multiple components on hybrid data. *Chronobiol Int*. 2004;21:467–482.
20. Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat*. 1979;6:65–70.
21. O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. *Lancet*. 1988;13:397. Letter.
22. Kario K, Pickering TG, Umeda Y, Hoshide S, Hoshide Y, Morinari M, Murata M, Kuroda T, Schwartz JE, Shimada K. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. *Circulation*. 2003;107:1401–1406.
23. Hermida RC, Smolensky MH. Chronotherapy of hypertension. *Curr Opin Nephrol Hypertens*. 2004;13:501–505.
24. Hermida RC, Ayala DE, Calvo C. Administration time-dependent effects of antihypertensive treatment on the circadian pattern of blood pressure. *Curr Opin Nephrol Hypertens*. 2005;14:453–459.
25. Lemmer B. Cardiovascular chronobiology and chronopharmacology. In: Touitou Y, Haus E, eds. *Biologic Rhythms in Clinical and Laboratory Medicine.* Berlin, Germany: Springer-Verlag; 1992:418–427.
26. Angeli A, Gatti G, Masera R. Chronobiology of the hypothalamic-pituitary-adrenal and renin-angiotensin-aldosterone systems. In: Touitou Y, Haus E, eds. *Biologic Rhythms in Clinical and Laboratory Medicine.* Berlin, Germany: Springer-Verlag; 1992:292–314.
27. Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistell M, Guerrieri M, Gatteschi C, Zampi I, Santucci A, Santucci C, Reboldi G. Ambulatory blood pressure: an independent predictor of prognosis in essential hypertension. *Hypertension*. 1994;24:793–801.
28. Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohmori K, Michimata M, Matsubara M, Hashimoto J, Hoshi H, Araki T, Tsuji I, Satoh H, Hisamichi S, Imai Y. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. *J Hypertens*. 2002;20:2183–2189.
29. Svensson P, de Faire U, Sleight P, Yusuf S, Östergren J. Comparative effects of ramipril on ambulatory and office blood pressures. A HOPE substudy. *Hypertension*. 2001;38:e28–e32.
30. Hermida RC, Calvo C, Ayala DE, López JE. Decrease in urinary albumin excretion associated to the normalization of nocturnal blood pressure in hypertensive subjects. *Hypertension*. 2005;46:960–968.
31. Hermida RC, Calvo C, Ayala DE, Soler R, Mojón A, López JE, Rodríguez M, Chayán L, Fontao MJ, Alonso I, Fernández JR. Prediction of cardiovascular events by ambulatory blood pressure and effects of chronotherapy: the MAPEC study. *J Hypertens*. 2006;24(suppl 4):S180. Abstract.