Administration Time–Dependent Effects of Valsartan on Ambulatory Blood Pressure in Hypertensive Subjects

Ramón C. Hermida, Carlos Calvo, Diana E. Ayala, María J. Domínguez, Manuel Covel, José R. Fernández, Artemio Mojón, José E. López

Abstract—This study investigated the administration time–dependent antihypertensive efficacy of valsartan, an angiotensin II receptor blocker. We studied 90 subjects (30 men and 60 women), 49.0±14.3 (mean±SD) years of age with stage 1 to 2 essential hypertension; they were randomly assigned to receive valsartan (160 mg/d) as a monotherapy either on awakening or at bedtime. Blood pressure was measured by ambulatory monitoring every 20 minutes during the day and every 30 minutes at night for 48 consecutive hours before and after 3 months of treatment. Physical activity was simultaneously monitored every minute by wrist actigraphy to accurately calculate the diurnal and nocturnal means of blood pressure on a per-subject basis. The highly significant blood pressure reduction after 3 months of treatment with valsartan (P<0.001) was similar for both treatment times (17.0 and 11.3 mm Hg reduction in the 24-hour mean of systolic and diastolic blood pressure with morning administration and 14.6 and 11.4 mm Hg reduction with bedtime administration; P>0.174 for treatment time effect). Valsartan administration at bedtime as opposed to on waking resulted in a highly significant average increase by 6% (P<0.001) in the diurnal-nocturnal ratio of blood pressure; this corresponded to a 73% relative reduction in the number of nondipper patients. The findings confirm that valsartan efficiently reduces blood pressure throughout the entire 24 hours, independent of treatment time. They also suggest that time of treatment can be chosen according to the dipper status of a patient to optimize the effect of antihypertensive therapy, an issue that deserves further investigation. (Hypertension. 2003;42:283-290.)

Key Words: antihypertensive agents ■ blood pressure monitoring, ambulatory ■ receptors, angiotensin ■ circadian rhythm

Angiotensin II receptor blockers (ARBs) are a relatively new class of antihypertensive medications that selectively and specifically antagonize the action of angiotensin II, a potent vasoconstrictor that influences blood pressure (BP) regulation. ARBs are becoming increasingly popular because they are effective and well tolerated.1

Valsartan is an orally active, specific and selective ARB.2 After a single oral morning dose, the onset of its BP-lowering action is within 2 hours, with peak effect occurring within 4 to 6 hours. Morning once-a-day dosing ranging from 80 to 320 mg/d results in BP reduction throughout the entire 24 hours.3,4 The trough-to-peak ratio (T:P; the average BP reduction during the last 2 hours of the dosing interval compared with the average of the maximal reduction in BP over 2 consecutive hours)5 has been demonstrated to be >75%,4 confirming that a single morning dose of valsartan provides effective BP control throughout the day without alteration of the circadian pattern of BP variation.3

This circadian variation in BP represents, on the one hand, the influence of internal factors such as ethnicity, gender, autonomic nervous system tone, vasoactive hormones, and hematologic and renal variables.6 BP is also affected by a variety of external factors, including ambient temperature/humidity, physical activity, emotional state, alcohol or caffeine consumption, meal composition, and sleep/wake routine.7,8 Because the main steps in the mechanisms regulating BP are circadian-stage dependent,7 it is not surprising that antihypertensive medications might display a circadian time dependency in their pharmacokinetics and effects.6 Despite the great number of published evaluations of antihypertensive drug efficacy, rarely has the time of day of drug administration been a specific focus of investigation.6

Previous studies have demonstrated, for instance, a different effect of the angiotensin-converting enzyme inhibitors benazepril,9 enalapril,10 quinapril,11 ramipril,12 and perindopril13 when dosed in the morning versus the evening. In the HOPE (Heart Outcomes Prevention Evaluation) substudy on ambulatory BP monitoring (ABPM), subjects treated with ramipril at bedtime showed a marked BP reduction particularly during nighttime sleep,14 which was associated with a reduction in the prevalence of nondippers (patients with <10% decline in the nocturnal relative to the diurnal BP

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Similar findings were reported for the nondipper BP profile of patients with chronic renal failure; the BP could be normalized with evening but not morning dosing of isradipine. Other studies, for instance those involving amlodipine and nifedipine, however, reported no dosing time–dependent effect on the circadian pattern of BP. A search of the literature revealed that no ARB had yet been studied for potential dosing-time differences in effects. This study evaluated by 48-hour ABPM the antihypertensive efficacy of valsartan monotherapy when dosed either in the morning after awakening from nighttime sleep or at bedtime for a 3-month span.

Methods

Subjects

We studied 90 white subjects (30 men and 60 women), 49.0 ±14.3 years of age, with stage 1 or stage 2 essential hypertension according to criteria of the report of the Joint National Committee VI, based on conventional BP measurements (systolic BP [SBP] between 140 and 179 mm Hg 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 24-hour mean SBP/DBP be >130/80 mm Hg, the diurnal mean be >135/85 mm Hg, or the nocturnal mean be >120/70 mm Hg.

All of the subjects received their routine medical care at the Hypertension and Vascular Risk Unit, Hospital Clínico Universitario, Santiago de Compostela, Spain. Shift workers, heavy drinkers (alcohol intake >80 g/d), smokers (>20 cigarettes/d), and heavy exercisers were excluded, as were individuals with either severe arterial hypertension (stage 3; i.e., SBP >180/110 mm Hg) or secondary arterial hypertension and cardiovascular disorders, including angina, heart failure, stroke, nephropathy, and retinopathy or prior myocardial infarction or coronary revascularization, as revealed by thorough clinical evaluation according to the standardized protocol at the unit.

After providing informed consent to participate in this open-label, randomized, chronotherapy trial and after a 2- to 4-week washout period when required (62% of the participants were previously never treated for hypertension and an additional 20% were untreated for at least 6 months), subjects were randomly assigned to receive single treatment periods when required (62% of the participants were previously never treated for hypertension and an additional 20% were untreated for at least 6 months), subjects were randomly assigned to receive single

BP Assessment

The SBP, DBP, and heart rate (HR) of each participant were automatically measured every 20 minutes during the day (7 AM to 11 PM) and every 30 minutes during the night for 48 consecutive hours with a validated device (SpaceLabs 90207, SpaceLabs Inc). Subjects were studied by ABPM under baseline conditions when they were free of medication (after washout for previously treated subjects) before and again after 3 months of timed treatment. They were assessed while adhering to their usual diurnal activity (8 AM to 11 PM for most) and nocturnal sleep routines. Participants were instructed to go about their usual activities with minimal restrictions but to follow a similar schedule during the 2 days of ABPM. No one was hospitalized during monitoring. ABPM always began between 10 AM and noon. BP series were eliminated from analysis when >30% of the measurements were lacking, when they had missing data for >3-hour spans, or when they were collected from subjects while they were 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 90 subjects. BP profiles of 6 subjects were eliminated because of missing ABPM data and from another 3 subjects because they either discontinued timed treatment or because they failed to return for the second ABPM at the end of treatment.

Actigraphy

During 48-hour ABPM, each participant wore an actigraph (MiniMotionLogger, Ambulatory Monitoring Inc) on the dominant wrist to monitor physical activity every minute. This compact device (about half the size of a wristwatch) functions as an accelerometer. The internal clocks 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 on circadian variability of activity, according to previous studies in this area.

Statistical Methods

Each individual’s clock-hour BP and HR values were first referenced from clock time to hours after awakening from nocturnal sleep, according to the information obtained from wrist actigraphy. This transformation avoided the introduction of bias due to differences among subjects in their sleep/activity routine. BP and HR time series were then edited according to conventional criteria to remove measurement errors and outliers. The circadian rhythm of BP and HR before and after 3 months of timed therapy was assessed by population multiple-component analysis, a method applicable to nonsinusoidally shaped hybrid time series data (time series data collected from a group of subjects) consisting of values distributed at equal or unequal intervals.

This method produces estimates of the 24-hour rhythm-adjusted time series mean, or MESOR (midline estimating statistic of rhythm; an average value of the rhythmic function fitted to the data), as well as the amplitude (one half the extent of change explainable by rhythmicity) and acrophase (crest time expressed as a lag in time from a designated reference; here, the time of awakening from nocturnal sleep) for every fitted component of a given period; for this study, 24 and 12 hours. When the shape of the rhythm is best approximated by a complex model composed of 2 or more cosine curves that are harmonics of the fundamental period (here, 24 hours), the method of multiple components provides 3 additional summary parameters: the overall amplitude (one half the difference between the maximum and minimum values of the best-fit curve), orthophase, and baphase (peak and trough times, respectively, expressed as a lag from the time of awakening from nocturnal sleep).

The circadian rhythm parameters of MESOR, overall amplitude, and orthophase obtained for each timed-therapy group obtained at baseline and after 3 months of treatment were compared with a paired nonparametric test developed to assess differences in parameters derived from population multiple-components analysis. Hourly BP means obtained before and after treatment were compared by t test and corrected for multiple testing with the Holm procedure. Additionally, the demographic and clinical characteristics in the Table were compared between groups by ANOVA (quantitative variables) or nonparametric χ² before and after 3 months of treatment within each group by paired t test.
Demographic and Analytical Characteristics of Subjects Investigated

<table>
<thead>
<tr>
<th>Variable</th>
<th>Valsartan After Awakening</th>
<th>Valsartan Before Bedtime</th>
<th>P for Group Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>46</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Previously treated with, n</td>
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<td></td>
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<tr>
<td>α-Blockers</td>
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<tr>
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<td></td>
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<td>ARB</td>
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<td>4</td>
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</tr>
<tr>
<td>ACEI</td>
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<td>4</td>
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</tr>
<tr>
<td>CCB</td>
<td>3</td>
<td>3</td>
<td></td>
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<tr>
<td>Gender, % men</td>
<td>30.4</td>
<td>36.4</td>
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<tr>
<td>Age, y</td>
<td>49.3±12.3</td>
<td>48.7±16.2</td>
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</tr>
<tr>
<td>Height, cm</td>
<td>159.0±8.9</td>
<td>162.1±9.4</td>
<td>0.108</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72.7±13.7</td>
<td>74.3±14.0</td>
<td>0.576</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.6±4.0</td>
<td>28.3±4.7</td>
<td>0.700</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>91.0±10.3</td>
<td>91.2±12.5</td>
<td>0.940</td>
</tr>
<tr>
<td>Hip, cm</td>
<td>103.4±8.2</td>
<td>106.6±9.1</td>
<td>0.130</td>
</tr>
<tr>
<td>SBP, mm Hg*</td>
<td>157.0±14.2</td>
<td>158.3±19.3</td>
<td>0.696</td>
</tr>
<tr>
<td>DBP, mm Hg*</td>
<td>92.0±10.1</td>
<td>91.6±11.5</td>
<td>0.841</td>
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<tr>
<td>Nondippers, %</td>
<td>52.2</td>
<td>59.1</td>
<td>0.509</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>93.2±14.1</td>
<td>94.9±17.0</td>
<td>0.711</td>
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<tr>
<td>Creatinine, mg/dL</td>
<td>0.83±0.18</td>
<td>0.89±0.16</td>
<td>0.181</td>
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<tr>
<td>Cholesterol, mg/dL</td>
<td>206.1±37.8</td>
<td>205.0±26.2</td>
<td>0.890</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>109.8±54.6</td>
<td>100.1±53.0</td>
<td>0.442</td>
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<td>Uric acid, mg/dL</td>
<td>5.5±2.0</td>
<td>5.0±1.6</td>
<td>0.200</td>
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<td>Fibrinogen, mg/dL</td>
<td>310.7±60.4</td>
<td>319.0±102.1</td>
<td>0.695</td>
</tr>
<tr>
<td>After treatment (P vs values before treatment)</td>
<td></td>
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<tr>
<td>Weight, kg</td>
<td>72.9±13.3 (0.948)</td>
<td>74.8±14.2 (0.881)</td>
<td>0.512</td>
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<tr>
<td>BMI, kg/m²</td>
<td>28.7±3.9 (0.923)</td>
<td>28.4±4.8 (0.867)</td>
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<tr>
<td>Waist, cm</td>
<td>91.0±10.5 (0.999)</td>
<td>92.1±12.1 (0.723)</td>
<td>0.641</td>
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<tr>
<td>Hip, cm</td>
<td>104.9±7.9 (0.341)</td>
<td>106.7±10.2 (0.800)</td>
<td>0.375</td>
</tr>
<tr>
<td>SBP, mm Hg*</td>
<td>143.7±19.2 (&lt;0.001)</td>
<td>144.6±18.5 (&lt;0.001)</td>
<td>0.805</td>
</tr>
<tr>
<td>DBP, mm Hg*</td>
<td>83.4±12.7 (&lt;0.001)</td>
<td>82.4±9.3 (&lt;0.001)</td>
<td>0.671</td>
</tr>
<tr>
<td>Nondippers, %</td>
<td>45.7 (0.532)</td>
<td>15.9 (&lt;0.001)</td>
<td>0.002</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>96.9±13.9 (0.320)</td>
<td>94.3±11.4 (0.882)</td>
<td>0.463</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.83±0.16 (0.897)</td>
<td>0.88±0.15 (0.643)</td>
<td>0.293</td>
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<tr>
<td>Cholesterol, mg/dL</td>
<td>203.2±50.0 (0.776)</td>
<td>212.4±32.1 (0.324)</td>
<td>0.404</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>112.8±64.5 (0.829)</td>
<td>98.2±56.0 (0.894)</td>
<td>0.363</td>
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<tr>
<td>Uric acid, mg/dL</td>
<td>5.4±1.7 (0.672)</td>
<td>5.1±1.3 (0.740)</td>
<td>0.532</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>283.0±63.4 (0.114)</td>
<td>316.6±61.4 (0.806)</td>
<td>0.373</td>
</tr>
</tbody>
</table>

All values are mean±SD. ARB indicates angiotensin II receptor blocker; ACEI, ACE inhibitor; CCB, calcium channel blocker. Nondippers: <10% decline in nocturnal mean vs the diurnal mean of SBP using data sampled by ambulatory monitoring for 48 consecutive hours.

*Values provided correspond to the average of 6 conventional BP measurements obtained for each subject before starting ambulatory BP monitoring.

Results

Demographic Characteristics and Serum Parameters

The baseline characteristics of the 2 groups of subjects (Table) were similar in age, height, weight, body mass index, waist and hip perimeters, SBP; and DBP (average of the 6 conventional morning measurements obtained just before ABPM). Moreover, there were no statistically significant changes in weight, body mass index, and waist and hip perimeters in either group after 3 months of timed treatment. Conventional BP measurements were highly reduced and by a comparable amount from baseline (P<0.001) after 3 months of once-a-day valsartan monotherapy, independent of dosing time (Table). The serum values of glucose, creatinine, cholesterol, triglycerides, uric acid, fibrinogen (Table), and
other laboratory chemistry variables of the 2 treatment groups were comparable at baseline and were unchanged after 3 months of treatment.

**Valsartan on Awakening**

The circadian rhythm of SBP and DBP measured by 48-hour ABPM before and after 3 months of 160 mg/d valsartan on awakening is depicted in Figure 1. Hours of nocturnal rest (average across all patients) are indicated by the dark bar on the lower horizontal axis of the graphs. Morning valsartan treatment resulted in a highly statistically significant reduction in BP from baseline after 3 months of treatment (17.0 and 11.3 mm Hg reduction in the 24-hour mean of SBP and DBP, respectively; \( P < 0.001 \)). After treatment, ABPM showed that 56.3% of the subjects had diurnal, nocturnal, and 24-hour means of SBP and DBP below the respective threshold for a diagnosis of hypertension.\(^2^0\) Moreover, 69.6% of the subjects underwent a reduction \( > 10\% \) in their baseline 24-hour BP mean. There was also a highly significant reduction (\( P < 0.001 \)) of 5.8 mm Hg in the 24-hour mean of pulse pressure (difference between SBP and DBP) when valsartan was administered on awakening.

The T:P was 88% and 84% for SBP and DBP, respectively, when valsartan was dosed on awakening. The overall smoothness index (SI; the average of hourly mean BP reductions divided by the standard deviation of the average\(^2^6\)) was also very high—8.79 and 7.47 for SBP and DBP, respectively—indicating a similar BP reduction during the 24 hours, as shown in Figure 1. The circadian amplitude of BP remained unchanged after treatment, further indication of the full and smooth 24-hour coverage of valsartan when dosed in the morning. Figure 1 further indicates that the mean reduction in BP at each clock time during the 24-hour dosing interval was statistically significant (\( P \) always \( < 0.005 \) after correcting for multiple testing), as designated by the asterisks above the lower horizontal axis. Despite the highly significant reduction in BP, there was no effect of valsartan on HR (increase in the 24-hour mean was 0.06 beat per minute; \( P = 0.973 \) compared with baseline; not shown). The circadian pattern of physical activity monitored before and after 3 months of treatment also remained unchanged (24-hour mean of 132 and 123 counts/min before and after treatment, respectively; \( P > 0.05 \) for 24-hour mean comparison and \( P > 0.146 \) for each of the 24 before- and after-treatment hourly comparisons). Thus, the BP reduction after treatment with valsartan shown in Figure 1 was independent of any significant change in physical activity. Finally, the average sleep time of subjects was not statistically different (\( P = 0.354 \)) for the profiles obtained before (8.5 ± 0.9 hours) and after (8.8 ± 0.9 hours) 3 months of morning treatment.

**Valsartan at Bedtime**

Figure 2 shows the significant reduction compared with baseline of 14.6 and 11.4 mm Hg in the 24-hour mean of SBP and DBP, respectively (\( P < 0.001 \)) after 3 months of 160 mg/d valsartan taken at bedtime. The percentage of subjects with controlled BP with bedtime treatment according to ABPM criteria was 65.9%. A total of 68.2% of the subjects showed...
a reduction >10% in the 24-hour mean BP. The 24-hour mean of pulse pressure was also significantly reduced from baseline, by 3.2 mm Hg ($P<0.001$) with bedtime valsartan. Despite the significant effect on BP, HR remained unchanged after 3 months of treatment (increase in the 24-hour mean was 0.08 beat per minute; $P=0.908$; not shown). The circadian pattern of activity measured by wrist actigraphy was also similar before and after 3 months of therapy (24-hour mean of 127 and 129 counts/min before and after treatment; $P=0.460$ and $P=0.297$ for each of the before and after clock-time hourly mean comparisons). Average sleep time of the subjects was not statistically different ($P=0.732$) for the profiles obtained before (8.6±1.1 hours) and after (8.7±1.2 hours) bedtime treatment.

The BP reduction was statistically significant ($P$ always $<0.005$, after correcting for multiple testing) at each of the 24-hour clock times, as shown in Figure 2, indicating a BP-lowering effect throughout the entire 24-hour dosing interval when valsartan was administered at bedtime. The T:P, however, was less than that when valsartan was administered on awakening (72% and 74% for SBP and DBP, respectively). The SI was also less when valsartan was administered at bedtime (5.12 and 5.47 for SBP and DBP, respectively). Figure 2 also shows that there was a significant increase, by 4.5 mm Hg ($P<0.001$) and 2.2 mm Hg ($P=0.006$), in the circadian amplitude of SBP and DBP, respectively, when valsartan was taken at bedtime. This increase in amplitude was due to a greater effect of treatment on the nocturnal than diurnal BP means.

### Comparison Between Groups

The comparison of results shown in Figures 1 and 2 reveals lack of statistically significant differences in ambulatory BP at baseline between the 2 treatment groups ($P=0.876$ for comparison of 24-hour mean of SBP; $P=0.946$ for DBP). After 3 months of timed treatment, the 24-hour mean BP was also statistically similar ($P=0.466$ for SBP; $P=0.873$ for DBP); accordingly, the treatment efficacy of valsartan on the 24-hour BP was comparable and independent of the time of its administration. The 24-hour, diurnal, and nocturnal means of activity at baseline and after treatment were also similar between the treatment groups ($P=0.212$ in all cases). Thus, the changes in BP after treatment with valsartan were independent of any modification in the 24-hour level and pattern of physical activity.

The T:P and SI differed according to valsartan dosing time. Figure 3 provides additional information on the comparison between the treatment groups of the changes in diurnal, nocturnal, and 24-hour mean BP values after 3 months of therapy. Results comparable to those shown in Figures 1 and 2 reveal a borderline difference between the treatment groups in the effect of valsartan on the diurnal mean of SBP, but not on the diurnal mean of DBP. The effect of valsartan on the nocturnal and 24-hour means of SBP and DBP was similar and independent of treatment time. Figure 3 also shows that when valsartan was taken on awakening, the mean reduction in the diurnal and nocturnal BP means was similar (17.1 vs 16.0 mm Hg reduction in SBP, $P=0.604$; 11.1 vs 10.8 mm Hg reduction in DBP, $P=0.855$). However, when
valsartan was taken at bedtime, the mean reduction in nocturnal BP was significantly greater than the mean reduction in diurnal BP (12.0 vs 17.9 mm Hg reduction in the diurnal and nocturnal mean SBP, respectively, \( P < 0.009 \); 9.8 vs 13.3 mm Hg in the diurnal and nocturnal mean DBP, respectively, \( P < 0.015 \)). Accordingly, there was a highly significant average increase (\( P < 0.001 \)), by 5.5% and 6.3%, in the nocturnal decline in BP relative to the diurnal mean (an index of BP dipping\(^{15} \)) only when valsartan was taken at bedtime (Figure 4). Thus, the reduction in the frequency of subjects who at baseline were nondippers by treatment with 160 mg/d valsartan daily for 3 months in the morning was only 12.5% (\( P = 0.532 \)); however, the reduction in the frequency of subjects who at baseline were nondippers was highly significant at 73.1% (\( P = 0.001 \)) when the same dose of valsartan was taken for 3 months at bedtime (Table).

Because there is a linear correlation between the night-to-day ratio of BP and the slope of morning rise, we also evaluated the effect of treatment time on this variable. We calculated the morning rise in BP, for comparative purposes, as the slope of the straight line connecting the average of all BP data sampled between 2.5 and 0.5 hours before awakening and the average of data sampled between 0.5 and 2.5 hours after awakening,\(^{8} \) where time of awakening was individually obtained from the actigraphy profile of each patient. A similar approach was also used to calculate the slope of the BP decrease at bedtime. We found no significant change in the slope of the morning rise or nocturnal decline in both SBP and DBP (\( P > 0.112 \) in all cases) when valsartan was taken on awakening. When valsartan was taken at bedtime, there was no significant change in the slope of the morning rise and evening decline in DBP (\( P > 0.090 \)); however, there was a significant increase of 1.6 mm Hg/h in the slopes of the morning rise and nocturnal decline of SBP (\( P = 0.012 \)). However, the actual slope of the morning BP rise obtained after 3 months of treatment was similar in subjects treated either on awakening (4.56 and 4.12 mm Hg/h for SBP and DBP) or at bedtime (4.79 and 4.21 mm Hg/h for SBP and DBP; \( P > 0.218 \) for comparison between treatment times). Despite the changes in night-to-day ratio or slope of morning BP rise, the prevalence of extreme dippers (decline in nocturnal mean \( >20\% \) relative to the diurnal mean of SBP) remained unchanged after valsartan treatment (from 10% to 8% with morning treatment; from 5% to 7% with bedtime dosing).

**Discussion**

Our results indicate that doses of 160 mg/d valsartan are equally effective for BP control when taken once daily either on awakening or at bedtime. Both dosing times provide 24-hour coverage and a highly significant BP reduction after 3 months of treatment, with an associated high percentage (\( \approx 70\% \)) of responders (participants with a decline \( >10\% \) of the baseline 24-hour BP mean) and a high percentage of subjects with controlled BP (56% with the morning dose and 66% with the night dose). The BP reduction after valsartan was statistically significant during both the span of diurnal activity and nocturnal rest. Valsartan, no matter the treatment time, significantly reduced pulse pressure during the 24 hours. Valsartan dosing on awakening and at bedtime similarly reduced BP during the 24 hours; however, valsartan when administered at bedtime was especially efficient in reducing nocturnal BP and thus, significantly increasing the day-night ratio of BP (Figure 4).
Lack of a nocturnal decline in BP (nondipping\textsuperscript{15}) has been related to an increase in end-organ injury and cardiovascular events.\textsuperscript{27–29} Although the mechanism underlying this phenomenon is unclear,\textsuperscript{30} O’Brien et al\textsuperscript{15} reported that nondipper hypertensive subjects are significantly more likely to suffer a stroke than are dippers. Verdecchia et al\textsuperscript{27} also showed that, after an average follow-up period of 3.2 years, nondipper hypertensive patients experienced nearly 3 times as many adverse cardiovascular events as dippers. More recently, Staessen et al\textsuperscript{28} presented results from a subgroup of 808 persons who underwent ABPM at baseline in the Syst-Eur trial. Nondippers experienced a greater incidence of stroke and myocardial infarction than did the group of persons who had a normal dipping pattern. The last evaluation of the data from the Ohasama study indicated that, after an average follow-up of 9.2 years, a 5% decrease in the decline of nocturnal SBP in hypertensive patients was associated with a 31% increased risk of cardiovascular mortality.\textsuperscript{29} What is even more relevant, dipper hypertensives had a relative hazard of cardiovascular mortality (2.37) similar to that of nondipper normotensives (2.16).\textsuperscript{29} These results indicate that cardiovascular risk could be influenced not by BP elevation alone but also by the magnitude of the circadian BP variability, although further study of the latter is required. Thus, there is increasing interest in how to tailor the treatment of nondippers.\textsuperscript{29}

The potential reduction in cardiovascular risk associated with normalization of the circadian variability of BP (converting a nondipper to dipper pattern) has not yet been clearly established. As indicated previously, results from the HOPE substudy, wherein patients were evaluated by ABPM, indicated a significant BP reduction mainly during the hours of nighttime sleep.\textsuperscript{14} The authors suggested that the beneficial effects on cardiovascular morbidity and mortality in the HOPE study might be related to the 8% increase in the night-day ratio of BP seen after ramipril was administered at bedtime. Unfortunately, the study did not provide any comparison with ramipril administered on awakening. Another relevant study in which the nondipper BP profile in patients with chronic renal failure was normalized after evening but not after morning 4-week dosing of isradipine\textsuperscript{16} did not conduct a follow-up to evaluate potential changes in cardiovascular risk, mainly because of the short period of active treatment. In the present trial, no surrogate measures of risk were determined, first, because we could not anticipate the results of this first dosing-time trial with an ARB and, second, because of the short follow-up period (3 months) of treatment. Evaluation of a potential decrease in cardiovascular risk as well as the impact of valsartan treatment on surrogate measures of risk, such as cardiac hypertrophy, microalbuminuria, intima-media thickness, etc, deserves further prospective investigation.

The definition of nocturnal hypertension on the basis of the dipper concept has been frequently criticized because of the inability to reproduce, over time, the classification of patients into dippers and nondippers.\textsuperscript{31} This might be due to the fact that most studies have relied on 24-hour monitoring. The advantages of 48-hour sampling, instead of the more common 24-hour ABPM, in terms of reproducibility of results and classification have been documented previously.\textsuperscript{22,31,32} The proper estimation of mean BP values is more dependent on monitoring span than on sampling rate. Therefore, a better definition of nondipping (comparing nocturnal and diurnal means) can be obtained by sampling for 48 hours, even when data are obtained at a lower rate, than for just 24 hours.\textsuperscript{32}

International guidelines recommend the use of long-acting, once-daily medications that provide 24-hour efficacy; they improve adherence to therapy and minimize BP variability with smoother and more consistent BP control.\textsuperscript{11,19} Use of a medication with a high SI is unlikely to affect the circadian profile of BP and might be the best choice for treatment of the dipper hypertensive patients. However, it might be an inappropriate choice to treat nondipper hypertensives. Corroborating early findings,\textsuperscript{3,4} results from this study indicate that a single daily dose of 160 mg/d of valsartan in the morning highly reduces BP smoothly over the 24 hours on the basis of high SI and T:P. The same dose of valsartan taken before bedtime resulted in comparable BP reduction during the 24 hours while highly improving the diurnal-nocturnal ratio of BP and thus, significantly reducing the incidence of nondippers. Whether this time-dependent effect is a class-related feature applicable to all ARBs or is specific to valsartan awaits future investigation.

**Perspectives**

The results of this study of subjects with stage 1 or 2 essential hypertension randomly assigned to receive the daily dose of valsartan either on awakening or at bedtime indicate that this ARB efficiently reduces BP for the entire 24 hours. The findings of this study further suggest that the dosing time of valsartan can be chosen in relation to dipper status to improve therapeutic benefit and reduce cardiovascular risk. This potential clinical significance of timed therapy for nondipper hypertension requires future assessment.

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Administration Time–Dependent Effects of Valsartan on Ambulatory Blood Pressure in Hypertensive Subjects
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