Effects of the Angiotensin II Receptor Blockers Telmisartan Versus Valsartan on the Circadian Variation of Blood Pressure

Impact on the Early Morning Period

William B. White, Yves Lacourciere, and Giora Davidai

Background: Ambulatory blood pressure (BP) monitoring has shown that BP typically declines by 10% to 20% during sleep and increases fairly rapidly in the early morning period. Because the early morning period has been associated with both loss of hypertension control and increased rates of myocardial infarction and stroke, there has been interest in evaluating the effects of antihypertensive therapy at this particular time of the day. The purpose of this study was to assess the effects of a long half-life (telmisartan, 24 h) versus intermediate half-life (valsartan, 6 to 9 h) on early morning BP in two scenarios: after an active dose and after a missed dose of each agent.

Methods: The study was a double-blind, randomized trial that compared telmisartan (40 to 80 mg once daily) versus valsartan (80 to 160 mg once daily) on early morning BP in 490 patients with hypertension. Ambulatory BP recordings were performed at baseline after a placebo period and again after 6 and 8 weeks of double-blind therapy in a randomized cross-over design. The monitoring patients received either an active dose or a placebo dose (to mimic a “missed” dose). The primary study end point was reduction in the BP in the early morning period (last 6 h of the dosing period).

Results: After the active dose, telmisartan reduced the BP during the last 6 h of the dosing period by $-11/-7.6 \pm 0.8/0.6$ mm Hg compared to $-8.7/-5.8 \pm 0.8/0.6$ mm Hg on valsartan ($P = 0.02$ for systolic BP and .01 for diastolic BP). On the day of the missed dose, telmisartan reduced the early morning BP by $-9.0/-6.3 \pm 0.7/0.6$ mm Hg versus $-7.4/-5.1 \pm 0.7/0.4$ mm Hg on valsartan ($P = 0.09$ for systolic BP and .06 for diastolic BP). On the day of the missed dose, reductions in 24-h average BP for the two antihypertensive agents were $-10.3/-6.9$ mm Hg for telmisartan versus $-8.7/-5.9$ mm Hg for valsartan ($P = 0.06$ for systolic BP and .056 for diastolic BP).

Conclusions: On a day of active therapy, telmisartan lowered both systolic and diastolic BP to a greater extent than valsartan for the last 6 h of the dosing interval. On a day in which a dose was missed, there was a notable trend for greater BP reduction during the latter part of the dosing interval on telmisartan versus valsartan. These results demonstrate that telmisartan achieved a greater effect than valsartan on BP during the early morning period in patients with hypertension. Am J Hypertens 2004;17: 347–353 © 2004 American Journal of Hypertension, Ltd.

Key Words: Angiotensin receptor blockers, telmisartan, ambulatory blood pressure, early morning period.

In patients with hypertension, blood pressure (BP) follows a highly reproducible circadian pattern characterized by higher values while awake and active and lower values during rest and sleep.\(^1\)\(^2\)\(^3\) Epidemiologic studies have also shown that there is a substantial increase in the rate of acute myocardial infarction, ischemic stroke, and sudden death in the early morning period—especially during the first 4 to 6 h after awakening.\(^4\)\(^5\)\(^6\) Recent studies of Japanese patients with systolic hypertension have associated steep increases in the postawakening early...
morning BP with an increase in prevalence of stroke and ischemic brain lesions. These chronobiologic findings in hypertension have suggested a need for attenuating the increases in the BP in the early morning period with longer acting antihypertensive therapies or therapies directed at peak pharmacodynamic effects in the early morning period.

In the present study, we investigated the effects of two angiotensin II receptor blockers of varying plasma half-lives on the BP during the last 6 h of the dosing period of the drugs in men and women with hypertension. Telmisartan has peak plasma levels about 1 h after oral drug administration and a terminal elimination half-life of approximately 24 h. Valsartan has peak plasma concentrations about 2 h after oral administration followed by a biexponential decline in concentration with a half-life of 7 h. Using ambulatory monitoring of the BP, our study evaluated whether chronic therapy with telmisartan had greater effects on the BP during the last 6 h of the dosing interval compared to chronic therapy with valsartan. In addition, as there is often concern about patient compliance regarding consistent administration of once daily antihypertensive therapy, the effects of these angiotensin II receptor blockers were also evaluated on a day when the dose was “missed,” thereby evaluating the effects from 24 to 48 h after actual dosing of the medications.

**Methods**

**Study Design**

This was a multicenter, double-blind, double-dummy, randomized, parallel group, forced titration study that compared the efficacy and safety of telmisartan versus valsartan. The study was conducted at 34 clinical sites in the United States and Canada. The purpose of the study was to determine whether the administration of telmisartan (80 mg once daily) was superior to valsartan (160 mg once daily) for the control of ambulatory BP during the final 6 h of the dosing period as well as during the period between 6 AM and noon. These end points were evaluated during steady-state active therapy (6 to 8 weeks) and after having missed one dose of medication on the day of ambulatory BP monitoring.

There were three periods during the study (Fig. 1): 1) a 1-week screening period for patients who were currently receiving antihypertensive therapy; 2) a 2- to 4-week single-blind placebo period to establish baseline ambulatory BP values; and 3) an 8-week double-blind treatment period during which patients took either telmisartan or valsartan in a 1:1 randomization scheme and were force-titrated to higher doses at 2 weeks. At the end of this treatment period ambulatory BP measurements were performed after a dose of active medication or after a dose of placebo to mimic a missed dose of medication. This latter
phase was performed in a randomized crossover design to maintain the blind. The patients were examined at 2-week intervals in the clinic between 7 and 9 AM for clinical evaluation. At every visit, adverse events were also assessed by nonleading questions.

**Patient Population**

Men and women with systemic hypertension were included in the study if their average seated diastolic BP was \( \geq 95 \) mm Hg but \( <110 \) mm Hg during 2 consecutive weeks of the single-blind placebo treatment period. Furthermore, at the end of the placebo period it was required that the 24-h ambulatory diastolic BP was \( \geq 85 \) mm Hg. These additional ambulatory BP criteria were used to ensure inclusion of patients with sustained hypertension into the trial.13

Patients with known coronary disease, stroke, congestive heart failure, secondary hypertension, poorly controlled diabetes mellitus, chronic renal failure, and night shift workers were excluded from the study.

**Measurements of Clinic and Ambulatory BP and Heart Rate**

The office (or clinic) BP was measured by mercury column sphygmomanometry in triplicate in the seated position. The heart rate was measured in duplicate. Ambulatory BP and heart rate measurements were obtained with the SpaceLabs 90207 monitor (Richmond, WA) as previously described.14 Quality criteria used for an acceptable ambulatory BP recording included 1) a minimum of 75% valid readings obtained within 24 h after monitor hookup, 2) no more than 2 consecutive h of missing data, and 3) a minimum of six valid readings during the last 6 h of the ambulatory BP recording. If these criteria were not met at baseline, the patient was asked to repeat the study within 3 days. If the repeat study failed to meet the quality control criteria, the ambulatory BP data were considered nonevaluable. Repeat studies were not feasible during the randomization period.

During the 24-h ambulatory monitoring study, BP and heart rate were measured every 20 min. Monitoring hookup was initiated before 9 AM. Study coordinators recorded times of sleep, awakening, medication dosing, and monitor hookup in the case report forms.

**Statistical Analyses**

The comparability of patients in the two treatment groups was determined from the demographic data and baseline BP values. The primary end points for assessing efficacy were the changes from baseline in diastolic BP during the last 6 h after dosing after an active dose of medication and after a missed dose of medication. The statistical analyses were performed on an intention-to-treat basis. All patients randomized to the study who took at least one dose of double-blind medication and who had a successful ambulatory BP study at baseline and after an active/missed dose of medication were included in the analyses. Treatment group effects were compared with respect to change from baseline to the two efficacy end points using an analysis of covariance (ANCOVA) that included treatment, center, and baseline measures as the covariate in the model. Treatment comparisons were based on the least square means obtained with a SAS general linear model procedure (SAS version 8 VMS operating system, Cary, NC).

Other efficacy analyses evaluated the change from baseline in the systolic BP during the final 6-h period postdosing, as well as the changes from baseline in these BP for the morning (6 AM to noon), and the entire 24-h period of monitoring.

Sample size calculations were based on ability to detect a 3 mm Hg difference between the telmisartan and valsartan treatment groups (active dose study) during the last 6 h of the 24-h dosing interval. It was determined that a sample size of 180 patients per active treatment group would give 90% power to detect a 3 mm Hg difference between the treatment groups assuming a standard deviation of 8 mm Hg and a two-tailed \( \alpha \) of 0.025. Assuming that 15% of the patients randomized would not meet all ambulatory BP criteria or finish the trial, a total of 420 patients (210 patients per treatment arm) were required for randomization to attain the 360 patients with successful ambulatory BP monitoring studies.

**Evaluation of Safety**

All reported adverse events were categorized by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).15 The incidence of treatment-emergent adverse effects in each treatment group was tabulated by severity and by relationship to study drug (as ascertained by the site study personnel).

**Results**

**Patient Enrollment and Disposition**

A total of 877 patients were screened for the study; 387 failed to meet the double-blind inclusion criteria and 490 patients were randomized to receive the following treatment: 244 patients to telmisartan and 246 patients to valsartan. Two hundred thirty (94%) of the telmisartan patients completed the study compared to 224 (91%) in the valsartan treatment group. The most common reasons for discontinuing the study in both groups were adverse events (6 of 36 patients), lack of efficacy (13 patients), and withdrawal of consent (10 patients).

**Baseline Characteristics of the Study Population**

The baseline demographics of all randomized patients in the four treatment groups are listed in Table 1. The mean age of the entire patient population was 54.5 years and was predominantly male and non-African American. With regard to
Changes from baseline in ambulatory blood pressures on active and missed dose studies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Telmisartan (40/80 mg)</th>
<th>Valsartan (80/160 mg)</th>
<th>Difference Between Treatment Groups</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active dose study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last 6-hour systolic BP (mm Hg)</td>
<td>−11.0 ± 0.8</td>
<td>−8.7 ± 0.8</td>
<td>−2.4 ± 1.0</td>
<td>−4.3, −0.4</td>
<td>0.02*</td>
</tr>
<tr>
<td>Last 6-hour diastolic BP (mm Hg)</td>
<td>−7.6 ± 0.6</td>
<td>−5.8 ± 0.6</td>
<td>−1.8 ± 0.7</td>
<td>−3.2, −0.4</td>
<td>0.01*</td>
</tr>
<tr>
<td>24-hour systolic BP (mm Hg)</td>
<td>−11.8 ± 0.7</td>
<td>−10.6 ± 0.7</td>
<td>−1.2 ± 0.9</td>
<td>−3.0, 0.6</td>
<td>0.18</td>
</tr>
<tr>
<td>24-hour diastolic BP (mm Hg)</td>
<td>−7.9 ± 0.5</td>
<td>−7.0 ± 0.5</td>
<td>−0.9 ± 0.6</td>
<td>−2.1, 0.4</td>
<td>0.16</td>
</tr>
<tr>
<td>6 AM to noon systolic BP (mm Hg)</td>
<td>−12.0 ± 0.8</td>
<td>−9.7 ± 0.8</td>
<td>−2.3 ± 1.0</td>
<td>−4.3, −0.3</td>
<td>0.03*</td>
</tr>
<tr>
<td>6 AM to noon diastolic BP (mm Hg)</td>
<td>−8.0 ± 0.5</td>
<td>−6.6 ± 0.5</td>
<td>−1.3 ± 0.7</td>
<td>−2.7, 0.0</td>
<td>0.05*</td>
</tr>
<tr>
<td>Missed dose study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last 6-hour systolic BP (mm Hg)</td>
<td>−9.0 ± 0.7</td>
<td>−7.4 ± 0.7</td>
<td>−1.6 ± 0.9</td>
<td>−3.5, 0.3</td>
<td>0.09</td>
</tr>
<tr>
<td>Last 6-hour diastolic BP (mm Hg)</td>
<td>−6.3 ± 0.6</td>
<td>−5.1 ± 0.4</td>
<td>−1.2 ± 0.7</td>
<td>−2.6, 0.1</td>
<td>0.06</td>
</tr>
<tr>
<td>24-hour systolic BP (mm Hg)</td>
<td>−10.3 ± 0.6</td>
<td>−8.7 ± 0.6</td>
<td>−1.6 ± 0.8</td>
<td>−3.2, 0.1</td>
<td>0.06</td>
</tr>
<tr>
<td>24-hour diastolic BP (mm Hg)</td>
<td>−6.9 ± 0.4</td>
<td>−5.9 ± 0.4</td>
<td>−1.1 ± 0.6</td>
<td>−2.2, 0.0</td>
<td>0.056</td>
</tr>
<tr>
<td>6 AM to noon systolic BP (mm Hg)</td>
<td>−10.8 ± 0.7</td>
<td>−8.9 ± 0.7</td>
<td>−1.9 ± 0.9</td>
<td>−3.7, 0.0</td>
<td>0.05*</td>
</tr>
<tr>
<td>6 AM to noon diastolic BP (mm Hg)</td>
<td>−7.5 ± 0.5</td>
<td>−6.5 ± 0.5</td>
<td>−1.0 ± 0.6</td>
<td>−2.3, 0.2</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SE.

* Values are statistically significant (P ≤ .05).
Telmisartan reduced the final 6-h BP (9/6.3 mm Hg) to a greater extent than valsartan (7.4/5.1 mm Hg), but this failed to achieve statistical significance (P = .09 for systolic BP, P = .06 for diastolic BP). Similar results were seen when the 6-h period of 6 AM to noon was evaluated, although in that instance, the reductions in systolic BP by telmisartan (-10.8 mm Hg) was significantly greater than for valsartan (-8.9 mm Hg) (P = .05) (Table 2). The 24-h profiles of the changes in ambulatory BP after a missed dose showed consistent separation in the hourly reductions of both systolic and diastolic BP between hours 15 and 24 as well as for hours 0 to 5 postdosing (Fig. 3).

The mean changes from baseline in the 24-h mean BPs after missed doses of telmisartan and valsartan are also listed in Table 2. The mean 24-h BP reductions on telmisartan versus those on valsartan were quite close to meeting statistical significance (telmisartan: -10.3/-6.9 mm Hg v valsartan: -8.7/-5.9 mm Hg, P = .06 and .056, respectively).

**Changes in the Clinic BPs and Heart Rates**

After active doses, telmisartan reduced the seated clinic BP by -14/-9 ± 0.9/0.5 mm Hg, whereas valsartan reduced the seated clinic BP by -12.5/-8 mm Hg (P = .22/.16). After a missed dose, telmisartan reduced the seated clinic BP by -10/-7 mm Hg, whereas valsartan reduced the seated clinic BP by -9/-6 mm Hg (P = .20/.13) (data not shown).

**Adverse Experiences**

The overall occurrence of adverse events during the 8-week double-blind treatment period was 93 of 244
(38%) of telmisartan patients and 76 of 246 (31%) of valsartan patients. The most common adverse events were infections (telmisartan, 13% and valsartan, 12%) and headache (telmisartan, 7% and valsartan, 5%).

Discussion

Principal Findings

The angiotensin II receptor antagonist telmisartan lowered the early morning systolic and diastolic BP to a greater extent than once daily dosing of the angiotensin receptor blocker valsartan (Table 2 and Fig. 2). These findings were predictable, in part, considering the pharmacokinetic profile of telmisartan, which is characterized by an inherently longer half-life than valsartan.9,12 In our study, we also had a unique study design (Fig. 1) that allowed for a missed dose at either 6 or 8 weeks into the treatment period while maintaining the study blind. After a missed dose, telmisartan also had a larger effect at the end of the dosing period compared to valsartan on systolic BP (Table 2 and Fig. 3). Thus, patients who may forget to take their antihypertensive therapy would still have a relatively good maintenance of BP control.

Importance of the Effects of Telmisartan Versus Valsartan During the Early Morning Period

The incidence for acute myocardial infarction and ischemic stroke has been shown to be the greatest during the first 3 to 4 h after awakening. During the early morning, the post-awakening period, several neurohormonal and hematologic changes occur that may contribute to the
enhanced risk of acute myocardial infarction and stroke. Sudden increases in the levels of epinephrine upon awakening and norepinephrine levels on arising combined with enhanced platelet aggregation may increase the risk for coronary thromboses and small vessel cerebral artery occlusions. The enhanced activity of the sympathetic nervous system typically translate into increases in early morning BP as well as the heart rate–pressure product, direct correlates of myocardial work. As noted above, Kario and colleagues recently demonstrated that patients who have a surge in early morning BP (peak awake early morning BP—preawakening BP in the top quintile of the population) have a threefold increase in the development of ischemic stroke compared to the patients who lacked a substantial morning BP surge. Thus, in addition to prevention of coronary events, stroke has become another target for improved antihypertensive coverage in the early morning period.

Through ambulatory monitoring of the BP, we have been able to capture significant differences in these parameters on telmisartan versus valsartan. As shown in Table 2, valsartan had a lesser effect on the reduction in the early morning BP even with doses as high as 160 mg in all patients (Fig. 2). In a previous study by Littlejohn and coworkers, treatment with telmisartan was also associated with larger reductions in ambulatory diastolic BP during the last 6 h of the dosing period compared to valsartan but at doses of 80 mg once daily. In addition, Mallion et al recently showed that telmisartan at 40 mg once daily induced significantly larger reductions in early morning BP (last 6 h of the dosing period) compared to losartan 50 mg once daily. Lacourciere and Asmar performed a study comparing the efficacy and duration of action of candesartan versus losartan using a somewhat similar design to the present study and demonstrated superior efficacy of candesartan over losartan on the day of a missed dose. Taken together, these studies do suggest that the pharmacology of the angiotensin II receptor blockers, whether associated with a tissue-based half-life difference or a plasma half-life difference (or both), play an important role in the pharmacodynamic effects of these agents during the latter portion of the dosing interval.

Acknowledgments
The authors express their sincere appreciation for the input of Patricia Norman, Project Manager for the MICADO 2 trial and Stephen Kovel, Statistician for the MICADO 2 trial.

References