Effects of Bedtime vs. Morning Administration of the Long-Acting Lipophilic Angiotensin-Converting Enzyme Inhibitor Trandolapril on Morning Blood Pressure in Hypertensive Patients

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Cardiovascular events occur most frequently in the morning. To study the effects of the long-acting lipophilic angiotensin-converting enzyme (ACE) inhibitor trandolapril on morning blood pressure (BP), we performed ambulatory BP monitoring (ABPM) before and after administration of trandolapril just before going to bed (bedtime-administered group: n = 17) or in the morning (morning-administered group: n = 20) in 37 hypertensive patients. Both sets of ABPM data were available in 30 patients. The 24-h systolic BP (SBP) levels were significantly decreased by 7.2 mmHg in the morning-administered group (p = 0.02) and by 5.2 mmHg in the bedtime-administered group (p = 0.04). In the bedtime-administered group, prewaking SBP (the average of the 2-h SBP values just before waking) and morning SBP (the average of the 2-h SBP values just after waking) were significantly decreased by 11 mmHg (p = 0.005) and by 8.4 mmHg (p = 0.03), respectively. On the other hand, in the morning-administered group, the reduction of prewaking SBP (3.9 mmHg, n.s.) and morning SBP (6.6 mmHg, n.s.) did not reach the level of statistical significance. However, the differences in the reductions of prewaking and morning SBPs between the two groups were not statistically significant. There was no additional reduction of the nighttime lowest BP in either administration group. In conclusion, bedtime administration of the long-acting ACE inhibitor trandolapril seems to be a safe and effective means of controlling morning BP in hypertensive patients without an excessive fall in nocturnal BP.

(Hypertens Res 2004; 27: 15–20)

Key Words: angiotensin-converting enzyme inhibitor, hypertension, morning blood pressure surge, morning hypertension, nocturnal blood pressure

Introduction

Clinical cardiovascular events and subclinical target organ damage are closely associated with blood pressure (BP) variation independent of BP level (1–10). Diurnal BP variation is determined by various genetic (11, 12), and environmental factors, including psychological and physical activities (13–27). Cardiovascular events occur more frequently in the morning, and BP also exhibits diurnal variation with increases in the morning (morning surge) (28–30). Previously, morning BP surge was reported to be associated with cardiac hypertrophy in hypertensive patients (31). Recently, we showed that the morning BP surge was significantly associated with clinical stroke risk in hypertensive patients (32). This association was independent of age and 24-h BP level.
Thus, an antihypertensive medication that was more specific for morning BP surge would be useful for the prevention of cardiovascular events in hypertensive patients.

The renin-angiotensin-aldosterone system is activated in the morning, and may contribute to morning BP surge (29) and morning increase in cardiovascular risk. Long-acting angiotensin-converting enzyme (ACE) inhibitors have been reported to lower the ambulatory BP without disruption of its diurnal variation (33). However, a specifically timed administration of the long-acting lipophilic ACE inhibitor trandolapril just before going to bed may achieve a greater reduction of morning BP in hypertensives.

**Methods**

**Patient Selection**

This study was a multicenter open-label randomized study of the effects of morning vs. evening administration of trandolapril on ambulatory BP. The subjects included older Japanese hypertensive patients at four Japanese hospital clinics. The entry period was February 2001 to January 2003. A total of 37 patients were recruited for this study (Fig. 1). The entry BP criteria were as follows: 1) average seated clinic systolic BP (SBP) ≥ 140 and < 180 mmHg and/or diastolic BP (DBP) ≥ 90 and < 110 mmHg during the follow-up period (3–5 weeks); and 2) 24-h SBP ≥ 130 mmHg and/or 24-h DBP ≥ 80 mmHg as shown by baseline first ambulatory BP monitoring (ABPM). To be included in the study, patients had to be ≥ 40 years of age, had to have been diagnosed with essential hypertension, and had to have no history of other significant medical disorders, including diabetes, renal failure (serum creatinine ≥ 2.0 mg/dl), atrial fibrillation, or any clinically overt cardiovascular disease. They were all fully ambulant. The body mass index was calculated as weight (kg)/[height (m)]².

![Fig. 1. Selection of study subjects.](image)

**Study Design**

Each patient was studied for a maximum of 12 weeks, with an observation period of 2–4 weeks, and a treatment period of up to 8 weeks. After the observation period, patients were started on 1 mg of trandolapril, taken at bedtime (bedtime-administration group), or just after breakfast (morning-administration group). After 4 weeks of treatment the dosage was increased to 2 mg of trandolapril unless the patient’s BP had already been reduced to below 150 mmHg in systole and 90 mmHg in diastole, or side effects had occurred. Following this dosage adjustment, patients remained on treatment for another 4 weeks. Informed consent was obtained, and the study was approved by the Research Ethics Committee of the Department of Cardiology, Jichi Medical School.

We excluded seven patients for whom the second ABPM recordings were not obtained: four of these patients refused the second ABPM, two developed cough, and one developed dizziness during the titration period (Fig. 1).

**ABPM**

Noninvasive ABPM was carried out two times on a weekday with one of two automatic ABPM devices (TM-2421 or TM-2425; A&D Co. Inc., Tokyo, Japan), which recorded BP and pulse rate by the oscillometric method every 30 min for 24 h. The first ABPM was performed at the end of the observation period, and the second ABPM at the end of the 8-week treatment period. The interval between the first and second ABPMs was 8 weeks.

Twenty-four hour BP was defined as the average of all BP readings over 24 h (34). The subjects were all ambulant during the day, and no subjects reported staying in bed after waking. Sleep BP was defined as the average of BPs from the time when the patient went to bed until the time he/she got out of bed, and awake BP as the average of BPs recorded during the rest of the day (4, 7). Morning BP was defined as the average of BPs during the first 2 h after the wakeup time (four BP readings) (32). The nighttime lowest BP was defined as the average BP of three readings centered on the lowest nighttime reading. Evening BP was defined as the average BP during the 2 h before going to bed (four BP readings) (32). Preawake BP was defined as the average BP during the 2 h just before wakeup time (four BP readings) (32). The morning BP surge (MBPS) was calculated as the morning SBP minus the nighttime lowest SBP (32). SBP were used for all these calculations.

**Statistical Analysis**

The analysis was conducted for the 30 patients for whom the first and second ambulatory BP recordings were successfully obtained. The changes from the baseline values were analyzed statistically using the paired Wilcoxon-test for each subgroup. Two-sided Mann-Whitney U-tests and χ²-tests...
were used to test differences between the two groups in the mean values of continuous measures and prevalence rates, respectively. The criterion for determining statistical significance was \( p < 0.05 \). The results are given as the mean \( \pm \) SD.

## Results

The baseline characteristics of the study subjects as well as the baseline BPs and BPs after trandolapril therapy were comparable between the morning- and bedtime-administration groups (Table 1). In addition, there were no significant differences in the baseline ABPM-derived BP parameters between the 2 groups. The 24-h BPs were reduced significantly in both groups, and the degrees of the reductions were also comparable between the two groups (Figs. 2, 3). There were no significant differences in the BP-lowering effects on ABPM parameters between subjects taking and those not taking additional antihypertensive medications.

In the morning-administration group, awake BPs were significantly reduced, but the reduction of sleep BPs, morning BPs and preawake BPs did not reach statistical significance (Fig. 2). In the bedtime-administration group, the reduction

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Morning administration group</th>
<th>Bedtime administration group</th>
<th>Total group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>((n = 16))</td>
<td>((n = 14))</td>
<td>((n = 30))</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68 ( \pm ) 9.0</td>
<td>66 ( \pm ) 13</td>
<td>67 ( \pm ) 11</td>
</tr>
<tr>
<td>Men/women ((n))</td>
<td>7/9</td>
<td>10/4</td>
<td>17/13</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>25.2 ( \pm ) 5.1</td>
<td>23.8 ( \pm ) 3.3</td>
<td>24.6 ( \pm ) 4.3</td>
</tr>
<tr>
<td>Other antihypertensives ((n))</td>
<td>7</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Calcium antagonist ((n))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Long-acting</td>
<td>5</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>(\alpha)-Blocker</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>(\beta)-Blocker</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dose of trandolapril (mg/day)</td>
<td>1.4 ( \pm ) 0.5</td>
<td>1.2 ( \pm ) 0.5</td>
<td>1.3 ( \pm ) 0.5</td>
</tr>
<tr>
<td>Clinic SBP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>158 ( \pm ) 8.7</td>
<td>161 ( \pm ) 12</td>
<td>160 ( \pm ) 10</td>
</tr>
<tr>
<td>After trandolapril</td>
<td>141 ( \pm ) 17</td>
<td>143 ( \pm ) 14</td>
<td>142 ( \pm ) 15</td>
</tr>
<tr>
<td>Reduction</td>
<td>17 ( \pm ) 16</td>
<td>19 ( \pm ) 16</td>
<td>18 ( \pm ) 16</td>
</tr>
<tr>
<td>Clinic DBP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>93 ( \pm ) 9.6</td>
<td>92 ( \pm ) 15</td>
<td>92 ( \pm ) 12</td>
</tr>
<tr>
<td>After trandolapril</td>
<td>83 ( \pm ) 7.6</td>
<td>84 ( \pm ) 13</td>
<td>83 ( \pm ) 11</td>
</tr>
<tr>
<td>Reduction</td>
<td>10 ( \pm ) 7.9</td>
<td>8.3 ( \pm ) 6.1</td>
<td>9.3 ( \pm ) 7.1</td>
</tr>
<tr>
<td>Sleep time (h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.9 ( \pm ) 1.2</td>
<td>8.7 ( \pm ) 1.3</td>
<td>8.8 ( \pm ) 1.2</td>
</tr>
<tr>
<td>After trandolapril</td>
<td>8.8 ( \pm ) 1.4</td>
<td>8.9 ( \pm ) 1.1</td>
<td>8.9 ( \pm ) 1.2</td>
</tr>
</tbody>
</table>

BP, blood pressure; SBP, systolic BP; DBP, diastolic BP. Data are shown as the means \( \pm \) SD or the number of patients.

Fig. 2. Change in ambulatory blood pressure levels in the morning-administration group.

Fig. 3. Change in ambulatory blood pressure levels in the bedtime-administration group.
of morning BPs and preawake BPs was significant (Fig. 3). Sleep BPs were significantly reduced, but the nighttime lowest BPs were not further decreased in the bedtime-administration group. However, the differences in the reductions of ABP parameters, including preawake SBP ($p = 0.186$), between the two groups were not statistically significant.

Although the morning BP surge was not significantly reduced in either group, the morning BP surge was reduced to less than 45 mmHg in all five hypertensives with exaggerated morning BP surge ≥ 45 mmHg (the highest tertile) in the bedtime-administration group. On the other hand, morning BP surge remained ≥ 45 mmHg in three of the five hypertensives with exaggerated morning BP surge in the morning-administration group.

**Discussion**

The present results indicate that bedtime administration of the long-acting lipophilic ACE inhibitor trandolapril is a safe and effective means of controlling morning BP in hypertensive patients without an excessive fall in nocturnal BP.

Recently, we showed that the morning BP surge was significantly associated with clinical stroke risk in hypertensive patients (32). This association was independent of age, 24-h BP level, and silent cerebral infarct (32), which is a powerful predictor of clinical stroke events (34, 35). In addition to the morning BP surge, the morning BP level is also an important predictor of stroke events in hypertensive patients (32). In this study, bedtime administration of trandolapril significantly reduced morning BP levels after waking. In addition, the prewaking BP was also significantly reduced by the bedtime administration. On the other hand, the morning administration of trandolapril significantly reduced awake BP, but the reduction of morning and preawake BPs was limited. Thus, the bedtime administration of trandolapril could be a specific treatment for reducing morning BP.

There have been several studies of antihypertensive medications specific for morning BP. Long-acting effects are the most important characteristic for sufficient morning BP control by once-daily use of antihypertensive medication (29, 36, 37). Antihypertensive therapy should provide the most effective protection at the time of the greatest risk, that is, in the morning hours. Pharmacokinetically, an extended-release form of verapamil was also reported to be highly effective for BP reduction (38). In addition, it may be possible to achieve more specific chronological treatment for morning BP surge by using an antihypertensive medication which reduces the pressor effect of neurohumoral factors potentiated in the morning, such as inhibitors of the sympathetic activity or the renin-angiotensin system. $\alpha$-Adrenergic blockers and $\alpha\beta$-blockers might be effective for reducing morning BP surge in hypertensive patients. Bedtime administration of $\alpha$-adrenergic blockers has the most marked BP-lowering effect in the morning (39). This study also demonstrated the potential benefit of bedtime ACE inhibitors for controlling morning BP in clinical practice for hypertensive patients.

Nighttime administration of the ACE inhibitor trandolapril appears to be more effective than morning administration for specifically controlling morning SBP. However, we cannot state this conclusively based on the present results. The differences in the reductions of ABP parameters, including preawake SBP, between the two groups did not reach the level of statistical significance. One of the limitations of this study was the lack of a control group. Thus, the reproducibility of each ABPM parameter was not sufficiently clear to render the results conclusive. Other, shorter-acting ACE inhibitors might increase the difference between the two groups due to the weaker BP-lowering effect of the morning administration.

Because of its lipophilic nature, trandolapril has the longest-acting ACE inhibitory activity and BP-lowering effect of all the ACE inhibitors (40). In fact, the 24-h BP-lowering effects were comparable among the two groups. However, awake BP was not significantly reduced in the bedtime-administration group. A longer-acting BP-lowering effect is the most important effect for an antihypertensive medication, and in addition, for those with higher morning BP level, bedtime administration seems an alternative or additional antihypertensive strategy.

Recently, it has been demonstrated that, in addition to circulatory factors, the tissue renin-angiotensin-aldosterone secretion of the cardiovascular system exhibits diurnal variation (41), possibly in relation to a clock gene (42, 43). In addition to the reduction of the morning BP level, the morning activation of the tissue renin-angiotensin-aldosterone system might be effectively suppressed by bedtime administration of an ACE inhibitor, leading to more effective protection against hypertensive target organ damage and cardiovascular events in hypertensive patients.

The bedtime administration of antihypertensive medication has the potential hazard of ischemia of target organs because of excessive nocturnal BP reduction. Extreme-dippers with marked nocturnal BP falls have increased potential risk for ischemic cardiovascular events when treated with strict antihypertensive medication or specific medication just before going to bed (10, 44). Since it has been reported that ACE inhibitor reduced normal BP levels further in white-coat hypertensive patients (45), we expected the nighttime lowest BP levels to be reduced further by bedtime administration of trandolapril. However, the nighttime lowest BP was not further decreased, although the average sleep BP decreased, particularly in the prewake period. Thus, bedtime administration of trandolapril can be considered safe with respect to ischemia of target organs during sleep.

In conclusion, bedtime administration of the long-acting ACE inhibitor trandolapril was effective for controlling morning BP and was suggested to be safe in the sense that it caused no marked nocturnal BP reduction in hypertensive patients.
References


