Reduction of the morning blood pressure surge treated with Olmesartan in Chinese patients with mild to moderate essential hypertension – a multicenter, open-label, single treatment group clinical study

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Conclusions: Olmesartan effectively reduces blood pressure in patients with essential hypertension, and olmesartan especially reduces the MBPS in MBPS-prone patients.

Key Words: Olmesartan, Essential hypertension, Morning blood pressure surge.

Introduction

In some hypertensive patients, changes in neuroendocrine factors, for example, may influence the first peak of the day (i.e., the morning peak) and may even lead to it being the highest blood pressure level of the 24 hour period. This phenomenon is called the morning blood pressure surge (MBPS). Matsui et al reported that morning hypertension is closely related to left ventricular remodeling. In recent years, an increasing number of clinical studies have linked the MBPS to the occurrence of cardiovascular and cerebrovascular events. About 40% of the myocardial infarction and 29% of sudden cardiac death occurred in this stage which is referred to as “early morning risk.” Thus, effective treatment of hypertension involves not only the reduction of the mean 24 hour blood pressure but also the reduction of blood pressure 18 to 24 hours after the dose to avoid the MBPS.
hours after dosing (i.e., the final 6 hours of the dosing interval) and the range of the MBPS, which is the optimal method to reduce “early morning risk.”

Olmesartan is a new angiotensin II receptor antagonist for the treatment of hypertension. Numerous published studies have investigated the effects on 24 hour blood pressure, and several of these have provided evidence of effects on MBPS. However, our study utilized a protocol that involves a long-term administration of olmesartan (24 weeks) compared to that of several other studies (e.g., 8 weeks), and examined the anti-hypertensive effect on the MBPS in a Chinese population according to ABPM dataset.

**Study Methods**

**Main Outcome Measures**

Two outcomes were measured: 1, the changes of mean 24 hour blood pressure and the last 6 hours of the dosing interval prior to the next dose of olmesartan (i.e., 18 to 24 hours after dosing); 2, the changes of MBPS before and after olmesartan therapy. Quantitative analysis of the MBPS was performed using the method commonly cited in the literature, in which the MBPS range is equal to the mean SBP within 2 hours of rising minus the minimum SBP value during
sleep at night (the mean hourly SBP value including the lowest SBP value). We defined MBPS exceeding the 50th percentile of our dataset (≥23 mmHg) as the MBPS group.

**Statistical Analysis**

SPSS 16.0 statistical analysis software was used for statistical analysis. Measurement data were expressed as mean value ± standard deviation (x ± SD) and were compared with baseline values at screening using independent t-test, paired t-test. For controlled affective factors such as baseline blood pressure level in the morning, analysis of covariance was used. The two-sided test was used for all significance tests, and p < 0.05 was considered statistically significant.

**Results**

**Baseline Characteristics**

A total of 120 patients were screened for this trial. As 24 patients did not have ABPM results both before and after treatment, 96 patients were eligible for analysis. Of these, 9 patients did not meet the criteria for ABPM data validity (≥80% of the data were legible and monitoring time ≥22 hours), so the final ambulatory blood pressure data set consisted of 87 patients. Baseline mean clinical SBP and DBP were 149.39 ± 11.79 mmHg and 98.52 ± 4.55 mmHg, respectively, and the average heart rate was 73.86 ± 8.85 beats per minute.

At baseline, patients with an MBPS ≥23 mmHg were classified as the MBPS group (n = 41), and all other patients were classified as the non-MBPS group (n = 46). Figure 1 and Table I show the baseline characteristics of the study participants.

**Ambulatory Blood Pressure During 24 Hours and the Last 6 Hours of the Dosing Interval**

There was a significant reduction in the mean 24 hour ambulatory blood pressure following treatment with olmesartan 20 mg/d for 24 weeks. Prior to treatment, the mean 24 hour blood pressure was 141.78 ± 12.8/91.17 ± 7.34 mmHg,
whereas following treatment it was 128.35 ± 15.86/83.58 ± 9.53 mmHg. The average reduction in mean 24 hour blood pressure was 13.34/7.59 mmHg, which was statistically significant \((p < 0.01)\). The mean blood pressure in the final 6 hours of the dosing interval dropped from 135.75 ± 5.84/87.29 ± 4.80 mmHg to 122.98 ± 6.46/80.49±4.31 mmHg. This represented a mean reduction in blood pressure of 12.77/6.80 mmHg, which was statistically significant \((p < 0.01)\) compared with pre-treatment values.

Similar trends were observed in the MBPS group and the non-MBPS group (see Figures 2 and 3). The mean SBP/DBP over 24 hours in the MBPS group were reduced from 143.32 ± 14.47/92.76 ± 7.58 to 130.00 ± 18.11/81.67 ± 9.61 mmHg \((p < 0.01)\). The mean blood pressure in the final 6 hours of the dosing interval in the MBPS group dropped from 139.09 ± 15.85/91.11 ±10.34 mmHg to 127.54 ± 17.72/81.09 ± 9.21 mmHg \((p < 0.01)\). The 24 hour mean SBP/DBP and the mean SBP/DBP over the last 6 hours in the non-MBPS group were significantly reduced after treatment (see Table II). However, no statistically significant differences were found between the two groups.

### MBPS Changes

#### Changes in MBPS range

There was a significant reduction in the MBPS range for the MBPS group after 24 weeks of treatment with olmesartan; the MBPS ranges for SBP dropped significantly from 35.68 ± 8.85 mmHg to 28.62 ± 15.08 mmHg \((p = 0.01)\). There was also a significant reduction in the DBP MBPS range from 29.77±17.19 mmHg to 19.08 ± 11.01 mmHg \((p < 0.01)\). In contrast, there was a slight increase in the MBPS range for SBP \((p = 0.02)\) and DBP \((p = 0.93)\) in the non-MBPS group (Figure 4).

### Intergroup Comparison of MBPS Range After Treatment

Following 24 weeks of treatment with olmesartan, the MBPS ranges for SBP and DBP in the MBPS group decreased by 7.07 ± 16.39 mmHg and 10.69 ± 19.17 mmHg, respectively, compared with pre-treatment values, but in the non-MBPS group the corresponding changes were increased of 4.20 ± 11.58 mmHg and 0.08 ± 22.62 mmHg, respectively. After adjusting for the mean SBP over the final 2 hours of the dose interval, statistically significant differences were observed between the two groups \((p < 0.01)\).

### Discussion

Olmesartan medoxomil is a highly selective non-peptide angiotensin II receptor blocker that has a high affinity for the AT1 receptor and can selectively prevent angiotensin II (AII) binding...
to AT1 on vascular smooth muscle; it, therefore, limits the undesired effects of AII and consequently reduces blood pressure. Olmesartan is absorbed rapidly after oral administration. Peak plasma concentration is reached after 1-3 hours and stabilizes after 3 to 5 days. The elimination half life (t1/2) of olmesartan is 10-15 hours. The advantages of high efficacy, high safety, long-lasting action and favorable tolerability make olmesartan a new antihypertensive drug with outstanding competitive strength. This study has examined the anti-hypertensive effect in Chinese patients treated with long-term administration of olmesartan according to ambulatory blood pressure monitoring.

Our study showed that after treatment with olmesartan for 24 weeks, the mean reduction of 24 hour blood pressure was 13.34/7.59 mmHg, and the mean blood pressure during the final 6 hours of the dosing interval was also significantly lower than the blood pressure during the same period before treatment (mean reduction of 12.77/6.80 mmHg). Compared with pre-treatment values, these are statistically significant differences. Treatment effectively reduced the blood pressure over 24 hours as well as over the final 6 hours of the dosing interval in both the MBPS group and the non-MBPS group. These findings demonstrate that olmesartan is capable of not only reducing the 24 hour mean blood pressure but

### Table II. Changes (x ± s) in mean ambulatory blood pressure over 24 hours and for the last 6 hours of the dosing interval before and after treatment with olmesartan.

<table>
<thead>
<tr>
<th>Blood pressure (mmHg)</th>
<th>MBPS group (n = 41)</th>
<th>non-MBPS group (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment (0w)</td>
<td>After treatment (24w)</td>
</tr>
<tr>
<td>24hs SBP</td>
<td>143.32 ± 14.47</td>
<td>130.00 ± 18.11*</td>
</tr>
<tr>
<td>24hs DBP</td>
<td>92.76 ± 7.58</td>
<td>81.67 ± 9.61*</td>
</tr>
<tr>
<td>Last 6hs SBP</td>
<td>139.09 ± 15.85</td>
<td>127.54 ± 17.72*</td>
</tr>
<tr>
<td>Last 6hs DBP</td>
<td>91.11 ± 10.34</td>
<td>81.09 ± 9.21*</td>
</tr>
</tbody>
</table>

Note: Indicator differences followed a normal distribution based on normality testing with paired t test.*24W versus 0W, p < 0.001; †24W versus 0W, p < 0.01; ‡24W versus 0W, p < 0.05.
also effectively lowering the ambulatory blood pressure in the early morning and of controlling nocturnal blood pressure in patients with mild to moderate hypertension.

Recent studies have shown that, compared with clinically measured blood pressure, the range of the MBPS are more closely associated with hypertensive target-organ damage and cardiovascular and cerebrovascular events, and that the range of the MBPS is independent of the 24 hour mean blood pressure9. Many mechanisms have been proposed for the MBPS, including sympathetic nervous system disorders, renin-angiotensin-aldosterone system (RAAS) activation10, vascular endothelial dysfunction, decreased morning arterial baroreceptor sensitivity, age, smoking, and alcohol use. A rapid increase in sympathetic outflow, RAAS overactivation, and an excessive release of catecholamines can lead to an increase in heart rate, peripheral vascular resistance, and cardiac output, and can lead indirectly to increased water and sodium retention. These factors produce a rapid rise in blood pressure and the occurrence of the MBPS, and they may contribute to the development of cardiovascular and cerebrovascular disease. Thus, in hypertensive patients who exhibit an MBPS, both the 24 hour blood pressure as well as early morning blood pressure should be controlled effectively, and the range of the MBPS should also be limited.

The J-MORE study and the ACAMPA study showed that most routine antihypertensive drugs fail to effectively curtail the MBPS11,12. With respect to the selection of antihypertensive medication, the consensus in the field is that long-lasting drugs administered once daily and maintain continuous action over 24 hours, are preferable, such as the long-acting calcium-channel antagonists, diuretics, and long-acting angiotensin II receptor blockers. Since the activation of RAAS is associated with MBPS, angiotensin converting enzyme inhibitors and angiotensin receptor blockers would control MBPS effectively13. Comparing telmisartan (80 mg/d) with ramipril (10 mg/d) given once each morning, PRISMA14 found that the former performed significantly better in controlling the MBPS.

The results of our study suggest that the MBPS range of SBP and DBP in the MBPS group can be reduced significantly treated with olmesartan compared to pre-treatment. Although reductions in mean 24 hour blood pressure and mean blood pressure in last 6 hours of the dosing interval were also observed in the non-MBPS group, the MBPS range of SBP and DBP were increased after treatment. Differences between groups were statistically significant. This indicates that the inhibitory effect of olmesartan on the MBPS range was better in MBPS group. The reason may be that renin-angiotensin-aldosterone system (RAAS) activity is strongest in the early morning. The MBPS range of the MBPS group was higher, thus the blocking effect of olmesartan on the RAAS was more effective, and the inhibitory effect on MBPS was stronger. The range of MBPS in non-MBPS group increased after treatment with olmesartan, which may have been caused by excessive reduction of nocturnal blood pressure resulting from the drug.

Figure 4. Changes in the MBPS range before and after treatment with olmesartan for the MBPS group and non-MBPS group.
Smith et al15 performed a study comparing the antihypertensive efficacy of olmesartan (20 mg/d), losartan potassium (50 mg/d), and valsartan (80 mg/d) and found that olmesartan was superior for lowering both the mean blood pressure over 24 hours and blood pressure in the final 4 hours of the dosing interval. Furthermore, long-term treatment of hypertensive patients with olmesartan resulted in a reduction of the plasma Ang II level compared with other ARBs16. Tsutamoto et al17 demonstrated that olmesartan significantly decreased LVM in patients with essential hypertension over the 12 month observation period.

Conclusions

Olmesartan is capable of not only lowering mean blood pressure over 24 hours and in the last 6 hours of the dosing interval but also effectively diminishes the range of the MBPS. Thus, olmesartan might reduce cardiovascular and cerebrovascular events more effectively.

Acknowledgements

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