Practical Efficacy of Telmisartan for Decreasing Morning Home Blood Pressure and Pulse Wave Velocity in Patients with Mild-to-Moderate Hypertension

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The current guideline-recommended blood pressure values are difficult to maintain in general practice, partly due to the lack of ideal anti-hypertensive agents. Since morning hypertension has a high correlation with cardiovascular events, expectations that telmisartan, a long-acting angiotensin-II type-1 receptor blocker (ARB), can improve cardiovascular mortality are high. In this study, the efficiency of telmisartan in reducing morning hypertension and pulse wave velocity (PWV) as a practical surrogate endpoint was investigated. Seventeen unsupervised and 7 untreated hypertensive patients were prescribed telmisartan 40 mg/day for 3 months. Medication already prescribed upon enrollment in this study was continued, with the exception of ARBs (all of which turned out to be losartan 50 mg/day), which were discontinued and replaced with telmisartan. Morning home blood pressure (MHBP), office blood pressure (OBP), and brachial-ankle PWV (baPWV) were investigated in a prospective fashion. A stratified analysis was performed regarding previous use (group L) or non-use (group N) of losartan. Over a 3-month period, telmisartan was found to significantly reduce both OBP (from 153 ± 13/85 ± 9 to 141 ± 17/80 ± 7 mmHg (p < 0.01)) and MHBP (from 153 ± 23/93 ± 11 to 137 ± 22/82 ± 10 mmHg (p < 0.001)). Surprisingly, 7 patients (70%) from group L achieved an OBP of less than 140/90 mmHg by simply changing their medication to telmisartan. Furthermore, baPWV fell significantly from 1,892 ± 334 cm/s to 1,672 ± 324 cm/s (p < 0.01), which was greater than the change in baPWV estimated by OBP reduction. Here it must be mentioned that there were no significant differences between group L and group N in the courses of blood pressures and baPWV. In conclusion, telmisartan 40 mg/day was found to be effective for reducing MHBP and arterial wall stiffness in patients with mild-to-moderate hypertension, and thus may also be effective for improving cerebrocardiovascular mortality.


Key Words: angiotensin-II type-1 receptor blocker, arterial wall stiffness, ankle-brachial pressure index, uric acid, losartan

Introduction

Hypertension is one of the primary risk factors for diseases of the brain, heart, and kidneys, as well as for other vascular events or dysfunction. In order to inhibit the onset of such events and to preserve organ function, mounting evidence indicates that blood pressure must be reduced to below target levels, which vary according to the presence or absence of risk factors and complications (1, 2). Although the relationship between cerebrocardiovascular events and early-morning hypertension, the so-called “morning surge,” has previ
ously received attention (3–6), it was not until recently that antihypertensive therapies based on early-morning home blood pressure became possible due to the prevalence of electronically-automated manometers. Management of morning surges requires antihypertensive agents that are both stable and effective over 24-h periods. Telmisartan was registered as the fourth angiotensin-II type-1 (AT1) receptor blocker (ARB) in Japan at the end of 2002. With its high selectivity for the AT1 receptor, and its ability to continuously bind to the receptor, telmisartan claims a longer period of sustained suppressor action compared to other ARBs, and is thereby expected to improve cardiovascular mortality. Currently, pulse wave velocity (PWV) and ankle-brachial pressure index (ABI) are being reviewed not only as indicators of arteriosclerosis, but also as independent predictors for cardiovascular mortality (7–9). Owing to the recent development of an easy-to-use, non-invasive device, Form ABI/PWV (Nihon Colin, Aichi, Japan), brachial-ankle PWV (baPWV) is rapidly spreading as a useful parameter to evaluate antihypertensive efficacy (10). In the present study, we examined the efficacy of telmisartan at reducing early-morning home blood pressure (MHBP) and baPWV in patients with mild-to-moderate hypertension but no serious target-organ dysfunction.

Methods

Subjects

The present study was performed prospectively at the hypertension clinics of Himeji Central Hospital and Okayama University Hospital. The following protocol was approved by the local Ethics Committee and informed consent was obtained from every participant. Between February and March 2003, 24 patients fulfilling the following conditions were enrolled in the present study: 1) an office blood pressure (OBP) >140 and/or 90 mmHg; 2) ability and willingness to take MHBP measurements; and 3) lack of any serious complications, such as cerebrovascular damage, cardiac infarction, or kidney dysfunction ≥Cr 2.0 mg/dl. Patients with secondary hypertension were excluded.

Administration of Telmisartan

All patients were administered telmisartan 40 mg orally once daily after breakfast. As a rule, patients continued any prior drug regimens, including antihypertensive agents. However, prescribed ARBs were discontinued, and switched to telmisartan 40 mg. Telmisartan was discontinued immediately in the case of any adverse reactions.

Blood Pressure Measurement

Home blood pressure was measured once daily between 6:00 and 7:00 AM, within half an hour of getting up, by the subjects themselves using an electronically automated manometer. It was taken after urination and before breakfast, with the patient resting for 5 min in a sitting position before measuring. The average value taken over 3 consecutive days prior to each monthly visit was employed as the patient’s monthly MHBP. Patients were asked to visit the doctor’s office between 9:00 and 11:00 AM every month, where conventional “office blood pressure” was measured after 5 min resting in a sitting position.

PWV Measurement

baPWV and ABI were simultaneously measured by a trained

Table 1. Patients Baseline Characteristics; Age, Sex, BMI, Smoking, Diabetes, Hyperlipidemia, Blood Pressures, ABI, baPWV and Uric Acid

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 22)</th>
<th>Group-N (n = 12)</th>
<th>Group-L (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.9 ± 9.5</td>
<td>60.8 ± 10.1</td>
<td>63.2 ± 8.9</td>
</tr>
<tr>
<td>Female/male (n)</td>
<td>8/14</td>
<td>4/8</td>
<td>4/6</td>
</tr>
<tr>
<td>BMI</td>
<td>25.0 ± 2.8</td>
<td>24.8 ± 2.5</td>
<td>25.2 ± 3.3</td>
</tr>
<tr>
<td>Smoking (n (%))</td>
<td>13 (59)</td>
<td>6 (27)</td>
<td>7 (32)</td>
</tr>
<tr>
<td>Diabetes (n (%))</td>
<td>12 (55)</td>
<td>8 (67)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Hyperlipidemia (n (%))</td>
<td>13 (59)</td>
<td>7 (58)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>Office SBP (mmHg)</td>
<td>153.4 ± 12.7</td>
<td>150.8 ± 10.3</td>
<td>156.5 ± 15.0</td>
</tr>
<tr>
<td>Office DBP (mmHg)</td>
<td>85.1 ± 8.9</td>
<td>81.5 ± 8.3</td>
<td>89.4 ± 8.0</td>
</tr>
<tr>
<td>Home SBP (mmHg)</td>
<td>153.0 ± 22.7</td>
<td>151.1 ± 17.7</td>
<td>155.2 ± 29.2</td>
</tr>
<tr>
<td>Home DBP (mmHg)</td>
<td>92.5 ± 10.9</td>
<td>95.6 ± 10.6</td>
<td>88.8 ± 10.9</td>
</tr>
<tr>
<td>ABI</td>
<td>1.154 ± 0.084</td>
<td>1.159 ± 0.056</td>
<td>1.147 ± 0.111</td>
</tr>
<tr>
<td>baPWV (cm/s)</td>
<td>1.892 ± 334</td>
<td>1.870 ± 358</td>
<td>1.918 ± 319</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.05 ± 1.02</td>
<td>5.11 ± 1.10</td>
<td>4.97 ± 0.98</td>
</tr>
</tbody>
</table>

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ABI, ankle brachial pressure index; baPWV, brachial-ankle pulse wave velocity; n, number of subjects. Data presented as mean ± SD.
technician in a separate room, using Form ABI/PWV, after 5 min resting in a lying position, prior to, as well as 3 months after, administration of telmisartan.

Adverse Effects

Subjective symptoms immediately after getting up and adverse reactions to telmisartan were assessed with reference to the patients’ “treatment diary.” Laboratory tests, including cell counts, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA) and K were conducted every month, and any abnormal data were assessed as adverse effects of telmisartan.

Statistics

The results are presented as the mean ± SD. Changes in values were analyzed using the paired t-test, while ANOVA with Scheffe’s test was used for repeated measurements to test for differences in blood pressures. A difference of \( p < 0.05 \) was considered to be statistically significant.

Results

Two of the 24 patients were omitted from the analysis due to adverse reactions such as hot flushes or systemic eruptions. The clinical backgrounds of the remaining 22 patients at the time of registration are shown in Table 1. Subjects’ ages ranged from 50 to 79 years. Five patients had never been treated for hypertension. The remaining 17 were being treated insufficiently with ARBs (\( n = 10 \); the ARB was losartan 50 mg/day in all 10 cases), an angiotensin converting enzyme inhibitor (\( n = 1 \)), or calcium-channel blockers (\( n = 11 \)). All patients with hyperlipidemia were receiving statin therapy, and 2 of the 12 patients with type-2 diabetes were undergoing insulin therapy.

With regard to OBP after telmisartan administration, systolic blood pressure (SBP) was significantly reduced at the 1-month measurement, and then reached a plateau at 2 months, while diastolic blood pressure (DBP) was significantly reduced at 3 months (\( p < 0.01 \), Fig. 1a). The mean OBP at 3 months was 141 ± 17/80 ± 7 mmHg, with more than 55% of participants having an OBP of below 140/90 mmHg. More importantly, MHBP was also significantly decreased in a parallel fashion, and at the 3-month measurement reached a level of 137 ± 22/82 ± 10 mmHg (\( p < 0.001 \), Fig. 1b), which is close to the normal MHBP value of 135/85 mmHg (11, 12). The average baPWV was as high as 1,892 ± 334 cm/s at commencement. However, 3 months after telmisartan administration, it fell significantly by 220 cm/s to 1,672 ± 324 cm/s (\( p < 0.01 \), Fig. 1c). No significant change was seen in ABI after 3 months.

A stratified analysis was performed according to previous use (group L, \( n = 10 \)) or non-use (group N, \( n = 12 \)) of losartan. It is worth mentioning that there was a significant OBP reduction in group L at 2 months, after the medication was switched from losartan to telmisartan (\( p < 0.05 \), Fig. 2a). There was no significant difference in OBP at any given time-point between groups L and N. A significant decrease was also observed in systolic and diastolic MHBP at the 3-month measurement (\( p < 0.05 \), Fig. 2b). Once again, there was no significant difference in the time-course of MHBP between the groups. Similarly, the reaction of baPWV to telmisartan was almost identical in both groups (Fig. 2c). The changes in ABI values were not significant in either group (\( p = 0.13 \), data not shown). Abnormal laboratory data included a significant increase in serum uric acid (\( + 0.5 \) mg/dl after 3 months, \( p < 0.01 \)). Since this increase occurred in group L, it was considered to be a result of losartan discontinuation, which is known to stimulate renal excretion of uric acid. Other laboratory test results were not significantly
Discussion

It is well known that the higher blood pressure results are, the higher cerebrocardiovascular disease mortality will be (13). Home blood pressure is superior to office blood pressure in predicting the risk of cerebrocardiovascular mortality (5, 14, 15), and since a large proportion of cerebrocardiovascular events occur in the early morning (4, 6, 16, 17), it is essential to adequately suppress the morning blood pressure (especially a morning surge). However, treatments rarely achieve this, partly due to the absence of effective antihypertensive agents that are sufficiently potent and long-lasting.

In the present study, telmisartan 40 mg produced significant reductions not only in OBP but also in MHBP, confirming the previous reports of its potency and sustained action (18, 19). Since 17 of the subjects were being treated, but treated insufficiently, it is significant that 53% of them (9 out of 17) experienced a reduction of blood pressure levels to below 140/90-mmHg when taking telmisartan. While 5 subjects were not being treated, 3 of them showed a reduction in blood pressure to the same level. More importantly, in terms of MHBP, as many as 82% of the subjects (18 out of 22) experienced a reduction in hypertension from the moderate-to-mild, to the mild-to-normal range. Since the study commenced between February and March, seasonal variations in blood pressures must also be taken into account. Minami et al. suggested that, in patients with essential hypertension, the winter–summer differences in home blood pressure were about 6/3 mmHg (20). Therefore, it can be said that the decrease of 16 mmHg in MHBP in the present study was largely attributable to the blood-pressure-lowering effect of telmisartan, and not to seasonal influences. Interestingly, the antihypertensive effects observed in group L were similar to those in group N. Since all patients in group L had received losartan at 50 mg/day, while those in group N had not, it may be justifiably argued that the losartan dosage was not high enough. While losartan was expected to have an insufficient suppressor effect due to its short half life, we never anticipated that there would be no difference between the two groups, even for OBP.

The validity and reproducibility of baPWV measured by the non-invasive automated device, Form ABI/PWV, have recently been confirmed, and baPWV has been shown to be an acceptable marker of vascular damages, comparable to carotid-femoral PWV measured by previously established methods (21–23). Thus, baPWV can be introduced as a surrogate endpoint in the treatment of hypertension. While it is said that baPWV values are influenced by both blood pressure and ABI (24), in the present study, the reduction of baPWV after 3 months was not correlated with any changes in ABI. Therefore, the decrease in blood pressures must be associated with the drop in baPWV, because it seems unlikely that the arterial wall structure could change rapidly in as short a period as 3 months. The impact of OBP reduction on baPWV may vary among individuals; however, a 10-mmHg fall in SBP by an ARB is almost equivalent to a 90–100 cm/s reduction in baPWV (10). In the present study, telmisartan decreased the average office SBP by 12 mmHg, while the average baPWV was lowered by 220 cm/s; the latter change was greater than that estimated from the SBP reduction. With regard to MHBP, the reduction in mean MHBP tended to correlate with the decrease in baPWV, although the association was not statistically significant ($r = 0.396$, $p = 0.0835$). Several studies have suggested that ARBs have an effect on PWV beyond the mere lowering of blood pressure (25–27). Asmar et al. proposed that telmisartan has such an effect, based on their measurements of carotid-femoral PWV in patients with type-2 diabetes (28). Since angiotensin-II acts on hardening of the vascular wall.

Fig. 2. Systolic and diastolic office blood pressure plots of patients newly prescribed telmisartan (group N) and patients who were changed to telmisartan (group L) (a), systolic and diastolic early morning home blood pressure plots of group N and group L (b), and changes in baPWV after 3 months’ administration of telmisartan (c). Values are presented as the mean ± SEM. ⊙, group N: * $p < 0.05$ and ** $p < 0.01$ vs. pre-administration. ⊙, group L: * $p < 0.05$ and ** $p < 0.01$ vs. pre-administration.
by constricting the vascular smooth muscle and promoting vascular wall remodeling, ARBs may improve arterial stiffness independently of their blood pressure-lowering efficacy (10, 25). However, the present study failed to find any significant effect of losartan 50 mg on baPWV. Therefore, the dramatic reduction in baPWV induced by telmisartan cannot be attributed to the class effect of ARBs. In other words, in the present study, the strong and sustained reductions of MHBP levels can mainly be attributed to the decrease in baPWV, and thus it is difficult in this case to address the effects of telmisartan that are not related to blood pressure reduction.

The adequacy of the losartan dosage used in this study is uncertain. However, the cost-effectiveness of telmisartan is indisputably superior to that of losartan in Japan, given that the two are similarly priced (losartan costs 201 yen/50 mg, and telmisartan costs 184 yen/40 mg), but less telmisartan is needed. That is to say, if the dosages of losartan were to be doubled to 100 mg/day, it may be true that blood pressure levels could be brought to under 140/90 mmHg, but patients would have to pay twice the price. On the other hand, if losartan 50 mg/day were to be switched to telmisartan 40 mg/day, the patients would pay about the same price. Discontinuation of losartan raised serum uric acid levels marginally (by 0.5 mg/dl), but this change was within the normal range and the additional use of antihyperuricemic drugs was not necessary. It is worth mentioning that those patients who were administered losartan 50 mg/day and who had blood pressure levels under 140/90 mmHg were excluded from the present study. Thus the present study had a limitation in that the results of group L were from subjects who were administered losartan 50 mg/day and whose OBP was more than 140/90 mmHg.

Further study is required to investigate whether telmisartan exerts an effect on baPWV beyond its effect on blood pressure. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), a comparative trial with ramipril, may answer this question (29). In the present study, MHBP was lowered to a greater extent than OBP, and baPWV was decreased more than expected. These facts imply that it is necessary to employ MHBP and/or baPWV in clinical practice to evaluate the real efficiency of long-acting antihypertensive drugs such as telmisartan.

In conclusion, a 40 mg once daily administration of telmisartan achieved an efficient reduction in morning blood pressure and baPWV in patients with mild-to-moderate hypertension, but without serious complications.

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