Telmisartan Improves Endothelial Function in Patients With Essential Hypertension

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INTRODUCTION

Essential hypertension, a major cardiovascular risk factor, is a pathophysiology commonly associated with endothelial dysfunction and increased renal vascular resistance. Angiotensin receptor blockers (ARBs) may beneficially affect these parameters via antagonism of angiotensin type 1 (AT1) receptor-mediated vasoconstriction and vascular superoxide production. We therefore investigated whether the new ARB telmisartan improves endothelial function and renal vascular resistance in patients with essential hypertension.

Methods: Thirty-seven patients with essential hypertension were randomized to receive telmisartan, the calcium channel blocker nisoldipine, or their combination for 6 weeks in a prospective, parallel group study. Brachial artery flow-mediated (endothelium-dependent) dilation (FMD) and renal vascular resistance index (RVRI) were evaluated using high-resolution ultrasound before, at 3 weeks (low dose), and at 6 weeks (high dose) after initiation of treatment.

Results: At baseline, FMD and RVRI did not significantly differ between treatment groups. After 3 weeks of treatment neither treatment significantly changed FMD or RVRI. After 6 weeks of treatment, patients randomized to receive telmisartan alone or the combination, but not those treated with nisoldipine alone, displayed a significantly improved FMD, whereas RVRI values again were not significantly different as compared to those at baseline.

Conclusion: In our study cohort of patients with essential hypertension, treatment with telmisartan improved FMD but did not change RVRI. Future studies will demonstrate whether this telmisartan-induced effect may contribute to a blood pressure–independent reduction in cardiovascular morbidity.

Key Words: hypertension, telmisartan, nisoldipine, endothelial dysfunction, renal vascular resistance

single-blind study. The study design was approved by the local Ethics Committee, and the study was conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki.

Patients were included in the study if they had been diagnosed with essential hypertension and had given informed written consent. Main exclusion criteria were liver or renal dysfunction, severe heart failure, diabetes mellitus, acute or unstable coronary artery disease, and the use of lipid-lowering drugs (e.g., statins). The enrolled patients were subsequently randomized to receive telmisartan, nisoldipine, or the combination of both drugs, and all patients with previous antihypertensive treatment underwent a 2-week washout phase before the beginning of the study. Because the reduction of blood pressure was not a major endpoint of this study, hydrochlorothiazide alone or in combination with clonidine was available as rescue medication for patients to prevent uncontrolled blood pressure increases during the washout period.

Baseline examinations were performed on day 1 of the study period. These included fasting blood sampling, physical examinations, ultrasound measurements of brachial artery flow-mediated (endothelium-dependent) dilation (FMD), measurements of the RVRI, and 24-hour blood pressure monitoring. On the following day, patients returned blood pressure recorders and received their study medication. Medication was either once-daily telmisartan (40 mg), nisoldipine (10 mg), or a combination of telmisartan and nisoldipine (40/10 mg) for 3 weeks. After 3 weeks, patients returned to the clinic for the next examination round, which was performed as previously described. For the next 3 weeks, antihypertensive treatment was increased to once-daily telmisartan (80 mg), nisoldipine (20 mg), and telmisartan/nisoldipine (80/10 mg). After 6 weeks, the last examination round was performed as previously mentioned. Thereafter, patients returned to their previous blood pressure–lowering regimen and were closely monitored until their blood pressure was on the same level as before the study.

Ultrasound Measurements
Measurement of brachial artery vasodilation was performed in fasting individuals between 9:00 and 11:00 AM in a temperature-controlled room (22°C) using high-resolution ultrasound (12 MHz linear array transducer; Siena, Siemens, Germany), as previously described by Corretti and colleagues. The brachial artery in the volunteers’ right arm was visualized in the longitudinal plane approximately 5 cm proximal of the antecubital fossa, setting the transmit focus zone at the depth of the anterior wall. Anatomic landmarks and snapshot images were used to assess the FMD in the exact same vessel section on each study day and at each time point. Thirty-second periods were recorded at baseline and before and during peak (1 minute) reactive hyperaemia, which was induced by inflating a blood pressure cuff placed around the forearm to 50 mm Hg higher than the volunteer’s systolic blood pressure for 5 minutes. Each recording was subsequently digitalized (Vascular Imager 4.1.3, Medical Imaging Applications LLC, Iowa) at a rate of 10 frames per second using a specialized software (Brachial Analyzer 4.1.3, Medical Imaging Applications LLC, Iowa). Data based on mean vessel diameters are presented because these gave the best reproducibility. FMD was calculated as the percent change in diameter 1 minute after cuff release relative to the baseline diameter before cuff release. Ultrasound studies and image analyses were performed separately by independent investigators in an observer-blinded fashion.

The mean intra-individual coefficient of variation of the baseline measurements obtained on the three separate study days (representing the cumulative intra-individual day-to-day variation and the intraobserver and interobserver variation in measurement) was 4.2%.

Renal resistance index was assessed in an investigator-blinded fashion with Doppler sonography at baseline and at 3 and 6 weeks after treatment using a Sonoline Elegra (Siemens, Germany). In brief, intrarenal Doppler signals were obtained from 3 representative proximal segmental arteries. The peak systolic velocity (Vmax) and the minimal diastolic velocity (Vmin) were determined, and the renal segmental arterial resistance index was calculated as $100 \times \left(1 - \frac{V_{\text{min}}}{V_{\text{max}}}\right)$. The values from the 3 measurements were averaged.

Sample Size Estimation and Statistical Analyses
Given the rather unclear clinical significance of drug-mediated improvement of endothelial-dependent vasodilation (FMD), we anticipated that only a considerable induction of FMD (at least 35%) would be of clinical relevance. Based on observations from our laboratory we estimated a within-group standard deviation of 20%–40%. We assumed relative differences of the means of at least 35% to be clinically significant. For a power of 80% and an alpha of 5%, this corresponds to a minimal sample size of 6–12 patients per group.

Distribution of data was tested with the Kolmogorov-Smirnov test. Continuous variables were expressed as arithmetic mean ± standard deviation (SD) if normally distributed or otherwise as median with 25% and 75% percentiles (interquartile range). Differences in baseline characteristics among groups were tested with one-way analysis of variance (ANOVA) if normally distributed, whereas baseline differences of variables with skewed distribution were tested using the Kruskal Wallis H test or the Mann-Whitney U test. Changes during treatment within different treatment groups were tested using the repeated-measures ANOVA followed by Dunnett’s test. Bivariate correlations were analyzed using either Spearman’s rho or Pearson’s r. Probability values less than 0.05 were considered significant. For all statistical analyses, SPSS version 13.0 was used.

RESULTS
Patients’ Characteristics and Blood Pressure–Lowering Effect of Antihypertensive Treatment
Baseline characteristics of patients in the study are shown in Table 1. In the study population, patients randomized to receive nisoldipine had a significantly higher body mass index (BMI) as compared with patients randomized to receive telmisartan (27.1 ± 4.1 versus 23.0 ± 3.0; $P < 0.05$). Except for this observation, baseline characteristics showed no
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Telmisartan (n = 12)</th>
<th>Nisoldipine (n = 13)</th>
<th>Combination (n = 12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>7/5</td>
<td>6/7</td>
<td>7/5</td>
<td>ns.</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.0 ± 7</td>
<td>56.9 ± 8</td>
<td>59.6 ± 8</td>
<td>ns.</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>103.6 ± 8.7</td>
<td>108.6 ± 12.5</td>
<td>99.8 ± 7.5</td>
<td>ns.</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>23.0 ± 3.0*</td>
<td>27.1 ± 4.1*</td>
<td>24.5 ± 4.2</td>
<td>*0.043</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>244 ± 32</td>
<td>236 ± 48</td>
<td>254 ± 46</td>
<td>ns.</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>63 ± 13</td>
<td>56 ± 11</td>
<td>58 ± 16</td>
<td>ns.</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>158 ± 25</td>
<td>150 ± 41</td>
<td>164 ± 28</td>
<td>ns.</td>
</tr>
<tr>
<td>C-reactive protein high sensitive (mg/L)</td>
<td>0.95 (0.7–1.925)</td>
<td>2.1 (1.25–3.7)</td>
<td>1.9 (1.125–3.15)</td>
<td>ns.</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.95 ± 0.17</td>
<td>0.95 ± 0.15</td>
<td>0.93 ± 0.18</td>
<td>ns.</td>
</tr>
<tr>
<td>Current smokers</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>ns.</td>
</tr>
<tr>
<td>Wash-out medication</td>
<td>Hydrochlorothiazide</td>
<td>6</td>
<td>8</td>
<td>ns.</td>
</tr>
<tr>
<td>Clonidine</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>ns.</td>
</tr>
</tbody>
</table>

Data are given as mean ± SD (parametric data) or median with interquartile range (non-parametric data). ns., not significant.

clinically relevant differences among treatment groups. Antihypertensive treatment with hydrochlorothiazide alone or in combination with clonidine during washout was taken by 6, 8, and 7 patients in the telmisartan, nisoldipine, and combination groups, respectively. As shown in Table 2, mean blood pressure was reduced in patients after 6 weeks of antihypertensive treatment with telmisartan (−7.0 mm Hg; P < 0.05) and the combination of both substances (−8.2 mm Hg; P < 0.05). In patients treated with nisoldipine alone, a trend toward lower blood pressure values was also observed, but values failed to reach statistical significance during the study period (−3.9 mm Hg; P = 0.090). It is important to note that no significant associations between blood pressure and FMD at baseline (r = 0.065; P = 0.704) or blood pressure reduction and change in FMD (r = 0.061; P = 0.749) were detected. Furthermore, BMI did not significantly correlate with FMD at baseline (r = 0.015; P = 0.932) or change in FMD during treatment (r = 0.032; P = 0.854).

Effects of Telmisartan and Nisoldipine on Brachial Artery FMD and Renal Vascular Resistance

As shown in Figure 1, values of FMD at baseline did not significantly differ between treatment groups. Moreover, no significant changes in FMD values as compared with those obtained at baseline were observed after 3 weeks of treatment in patients randomized to receive telmisartan, nisoldipine, or the combination of both substances. Patients who received telmisartan or the combination of telmisartan and nisoldipine displayed a significantly improved FMD after 6 weeks of treatment [telmisartan (mean ± SD): 5.47 ± 3.38% versus 10.91 ± 4.69%, P < 0.05; combination: 4.56 ± 1.65% versus 10.83 ± 4.77%, P < 0.05]. In contrast, in patients randomized to receive nisoldipine no change regarding FMD (6.61 ± 3.37% versus 5.93 ± 3.74%, P = 0.635) was discernible.

To investigate whether antihypertensive treatment significantly influences the renal vascular tone, we performed ultrasound measurements of the RVRI. As shown in Table 2, none of the antihypertensive regimens significantly affected RVRI during the course of the study.

DISCUSSION

The present study shows that (1) treatment with telmisartan significantly improved brachial artery flow-mediated vasodilation in patients with essential hypertension and that (2) antihypertensive treatment did not significantly affect the renal vascular resistance index in the individuals who were studied.

TABLE 2. Effects of Antihypertensive Treatment on Blood Pressure and Renovascular Resistance Index (RVRI)

<table>
<thead>
<tr>
<th></th>
<th>Telmisartan</th>
<th>Nisoldipine</th>
<th>Combination</th>
</tr>
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<tbody>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>103.6 ± 8.7</td>
<td>108.6 ± 12.5</td>
<td>99.8 ± 7.5</td>
</tr>
<tr>
<td>RVRI</td>
<td>0.65 ± 0.06</td>
<td>0.65 ± 0.06</td>
<td>0.64 ± 0.05</td>
</tr>
</tbody>
</table>

Data are given as mean ± SD (parametric data) or as median (IQR) (non-parametric data). L, left kidney; R, right kidney; ns., not significant.
Several groups have convincingly demonstrated that essential hypertension is associated with endothelial dysfunction, probably as a result of increased oxidative stress in individuals affected. In this regard, angiotensin II, the main effector peptide of the renin–angiotensin system, may play a major pathophysiologic role primarily via an AT1 receptor-mediated increased in superoxide production and consecutive decrease in endothelial nitric-oxide bioavailability. On the prognostic level, endothelial dysfunction represents an important early event in the development of atherosclerosis and may serve as a useful independent predictor of cardiovascular events. It is interesting that reduction of blood pressure alone is not associated with improved endothelial function in patients with hypertension, although the clinical impact of these findings remains largely obscure. Nevertheless, certain antihypertensive drugs (eg, ARBs and ACE inhibitors) have been shown to ameliorate endothelial dysfunction in patients with cardiovascular diseases. Hence, the aim of this study was to investigate the effect of the ARB telmisartan on endothelial function in patients with essential hypertension.

In our study cohort, 6 weeks of treatment with telmisartan alone or in combination with the dihydropyridine calcium channel blocker nisoldipine significantly induced FMD of the brachial artery. These data suggest that treatment with telmisartan is able to ameliorate endotheliopathy-dependent vasodilation in patients with essential hypertension. Our findings are in line with those of other interventional studies in which patients with coronary heart disease (CAD) or patients at high cardiovascular risk (eg, individuals with hypercholesterolemia) were treated with ARBs, such as losartan and candesartan. Mechanisms responsible for the observed effects may involve a telmisartan-induced reduction in AT1 receptor activation, which may result in a reduction of NADPH (nicotinamide adenine dinucleotide phosphate)-mediated superoxide formation. Moreover, a reduction in vascular tone through AT1 receptor antagonism may enhance endothelial shear stress leading to an activation of shear stress-activated signal transduction cascades (eg, PI3 kinase–Akt–eNOS) resulting in an increased endothelial NO bioavailability.27

In contrast to our findings, Ghiadoni and colleagues observed no effect of telmisartan on endothelial dysfunction in patients with essential hypertension, although telmisartan caused a significant reduction in oxidative stress in these patients [as assessed by plasmatic malonaldehyde (MDA) and linoleic acid hydroperoxide (LOOH) values]. The apparent discrepancy to our findings remains unclear but may result from differences in study design. In this context, our study was designed to reveal acute treatment-induced changes of FMD after 6 months of antihypertensive treatment. Nevertheless, a recent study demonstrated that telmisartan has the ability to induce flow-mediated vasodilation in patients with hypertension treated for as long as 24 weeks.29

In contrast to treatment with telmisartan, treatment with nisoldipine did not significantly affect FMD in our trial. Although we cannot exclude that the rather minor (and nonsignificant) effect of nisoldipine monotherapy on blood pressure observed in our study is responsible for this negative finding, no significant correlation between FMD and blood pressure at baseline or change in FMD and blood pressure reduction during treatment was discernible in our study. These data are supported by results from other clinical trials. Thus, insufficient blood pressure reduction is unlikely to account for the inability of nisoldipine to improve FMD in our study. Furthermore, patients randomized to receive nisoldipine had a significantly higher BMI than patients randomized to receive telmisartan. Again, correlation analysis revealed no association of BMI and FMD or change in FMD during treatment. Nonetheless, we cannot exclude that these factors may interfere with potential nisoldipine-induced effects on FMD. Angiotensin receptor blockers have proved to be a highly successful therapeutic strategy for treatment of patients with renal diseases. Furthermore, several controlled clinical trials indicate that these classes of drugs may exert renoprotective effects beyond mere blood pressure lowering, an effect that may involve an increase in renal blood flow through reduction of renal vascular resistance. Therefore, a clinical trial in which a decrease in renal vascular resistance induced by the ARB olmesartan was demonstrated has received great interest. Furthermore, very recent data from the TRENDY (Telmisartan versus Ramipril in renal ENdothelial Dysfunction) trial demonstrate a favorable effect of telmisartan on renal plasma flow and albuminuria in patients with diabetes and hypertension. However, in the present study the renal vascular resistance index remained remarkably stable during medical intervention in all treatment groups. In this regard, different outcomes may partly result from differences in renal pathophysiology of diabetes mellitus and essential hypertension.

CONCLUSIONS

Our study is limited by the small sample size, which led to relatively high interindividual variability in baseline blood
pressure and body mass index. Moreover, the blood pressure–lowering effect of nisoldipine was unexpectedly low and possibly affected by antihypertensive treatment requested by the patients during washout. Therefore, and despite the fact that formal statistical analysis for interaction between blood pressure and FMD was negative, we cannot exclude that differences in posttreatment blood pressure may have affected our results. Nonetheless, our study provides clinical evidence for a favorable effect of telmisartan on flow-mediated vasodilation in patients with essential hypertension, supporting and confirming previous evidence for beneficial effects of angiotensin receptor blockers on endothelial function. Further, larger controlled clinical trials will now be necessary to assess whether this telmisartan-induced effect may contribute to a blood pressure–independent reduction in cardiovascular morbidity.

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