Long-Term Therapy with an ACE Inhibitor, Temocapril, Reduces Microalbuminuria in Essential Hypertension


The present study was conducted to prospectively evaluate whether a new ACE inhibitor, temocapril, could modify urinary microalbumin excretion rate (UAE) in a group of hypertensive outpatients who had no evidence of renal impairment. Sixty-three outpatients (32 men and 31 women; mean age, 59.9 ± 1.5 yr) with essential hypertension entered the study, all having been treated for at least 6 mo with dihydropyridine calcium-channel blockers (CCBs: nitrendipine, nisoldipine, or amlodipine). Their blood pressures (BPs) had been controlled to adequate levels with the CCBs. None had overt proteinuria (determined by Albustix) or abnormal serum creatinine levels. After 3 mo of baseline observation under the previous treatment, the subjects were randomly divided into two groups. In group A (n = 31), the previously used CCBs were switched to temocapril, 2 to 4 mg once daily for 12 mo, and BP was controlled at a level equivalent to that during CCB treatment. In group B (n = 32), the subjects were maintained on their previous treatment for a further 12 mo. The effect of temocapril on BP appeared to be clinically similar to that of the previously used CCBs, but it significantly decreased UAE as compared with the previous therapy. In group A, UAE decreased significantly (p < 0.01) from the baseline value of 38.9 ± 5.1 mg/g creatinine (Cr) to 22.2 ± 4.2 and 25.3 ± 5.6 mg/g Cr at the 6th and 12th months of temocapril therapy, respectively. In contrast, in group B UAE was unchanged (baseline 39.8 ± 6.6 mg/g Cr; 6 mo, 44.6 ± 6.8; 12 mo, 45.9 ± 7.7). In group A, 17 of 31 patients (54.8%) had abnormal UAE levels (> 29.5 mg/g Cr) during previous therapy with CCBs, but 6 mo after switching to temocapril 25 of these patients (80.6%) had normal UAE (< 29.5 mg/g Cr). In group B, 15 of 32 patients (46.9%) had abnormal UAE levels during the observation period, and these abnormal UAE levels remained unchanged; 17 of the 32 patients (53.1%) had abnormal UAE levels after a further 6 mo of continued CCBs therapy. We conclude that long-term therapy with temocapril may provide renal protection by reducing UAE even in hypertensive patients with no evidence of renal impairment. (Hypertens Res 1998; 21: 81-87)

Key Words: microalbuminuria, essential hypertension, ACE inhibition, temocapril, calcium-channel blockers

Microalbuminuria occurs in 5% to 40% of patients with mild-to-moderate essential hypertension (1-3). The presence of albuminuria and microalbuminuria may be an independent predictor of cardiovascular morbidity and mortality in patients with essential hypertension (4, 5). Antihypertensive therapy has been shown to actively decrease urinary albumin excretion in patients with essential hypertension (1, 2, 6), but it was also reported that insufficiently treated hypertensive patients have elevated urinary albumin excretion (1).

The ability to decrease urinary albumin excretion beyond that due to BP reduction has recently been claimed for drugs such as dihydropyridine calcium-channel blockers (CCBs) and ACE inhibitors (7-10). The influence of ACE inhibition therapy on urinary microalbumin excretion rate (UAE) is controversial. Several investigators have reported that ACE inhibitors, but not other agents, significantly reduce UAE (8, 9), but other investigators have reported that UAE remains unchanged during ACE inhibitor therapy (11-13). The reasons for the different reported effects of ACE inhibition on UAE are not clear, but may involve different demographic characteristics of the subjects in each study or the use of ACE inhibitors with different chemical struc-
tures and properties.

The long-term effects of antihypertensive agents on UAE in patients with essential hypertension are controversial. Unresolved problems include whether the effects of different agents on UAE differ, despite similar antihypertensive effects. Temocapril is a long-acting ACE inhibitor without a sulfhydryl group in its molecular structure (14, 15). After oral administration, temocapril, a prodrug, is rapidly and completely hydrolyzed to yield the pharmacologically active diacid temocaprilat, which is excreted by the dual elimination routes of hepatobiliary and renal clearance (15).

Thus, we conducted the present study to determine whether long-term treatment with this unique ACE inhibitor, temocapril, can reduce UAE in a group of outpatients with mild to moderate essential hypertension who have no evidence of renal impairment.

Subjects and Methods

Patients
Men and women 40 to 80 yr of age who had essential hypertension and had been treated with CCBs were eligible for the study if they met following criteria: a serum creatinine (s-Cr) concentration of less than 1.5 mg/dl (133 mmol/l) and no overt proteinuria detected by Albustix during a 3-mo screening period. After oral informed consent was obtained from all subjects, they were enrolled in the study.

The exclusion criteria were secondary hypertension; treatment with corticosteroids or non-steroidal anti-inflammatory drugs; myocardial infarction or cerebrovascular accidents during the 6 mo preceding the study; congestive heart failure; insulin dependent or non-insulin dependent diabetes mellitus; elevated serum aminotransferase concentrations; collagen diseases; chronic cough; a history of allergy to an ACE inhibitor; cancer; drug or alcohol abuse; and pregnancy. Secondary causes of hypertension were excluded by a detailed medical history, thorough physical evaluation, determination of renal function and serum electrolytes, urine analysis and, when necessary, by endocrinological and radiological examinations, including renoscintigraphy, adrenoscintigraphy, and computed tomography.

Study Design

All eligible hypertensive patients who were receiving monotherapy with CCBs visited the hospital monthly and were screened for 3 mo. Sitting BP, s-Cr concentration, urinary microalbumin excretion, urinary creatinine (u-Cr) excretion, and other serum biochemical variables (uric acid, alanine aminotransferase, and aspartate aminotransferase) were measured. S-Cr and u-Cr concentrations were measured with an autoanalyzer.

The patients were asked to void urine when they arrived at the hospital, and then an approximately 90-min urine sample was collected. The urinary microalbumin concentration was determined by a turbidimetric immunoassay (Nippon DPC Co., Chiba, Japan) on a Hitachi 7150 autoanalyzer. The assay sensitivity was 1 µg/ml of urine, and the intra- and inter-assay coefficients of variation at a concentration of 30 mg/g Cr of urine were 3.4% and 4.4%, respectively, similar to previously reported values (16).

The urinary-microalbumin-to-u-Cr ratio (mg albumin/g Cr) was used as an estimate of urinary albumin excretion rate (UAE), according to methods described elsewhere (17, 18). In our earlier study, the mean UAE in casual urine was 9.1 ± 6.8 mg/g Cr (mean ± SD) in healthy subjects (n = 36; mean age, 36.4 ± 4.2 yr, mean ± SE) and 13.3 ± 4.6 mg/g Cr in normotensive subjects (n = 24; mean age, 56.1 ± 3.8 yr).

After 3-mo of observation, during which all subjects received CCBs, the subjects were randomly divided into two groups (Table 1). In group A (n = 31), the previously used CCBs were switched to temocapril, 2 to 4 mg once daily for 12 mo, and BP was controlled at a level equivalent to that during CCB treatment. In group B (n = 32), the same CCBs were continued for a further 12 mo. The BP of each patient was checked monthly, and the dose of temocapril or CCBs was adjusted as necessary to adequately control the BP.

The data were analyzed statistically by repeated-measures analysis of variance. Paired Student’s t-tests were used for comparisons within the groups and unpaired Student’s t-tests were used for comparisons between the groups. Pearson coefficients of correlation between the UAE level during the previous treatment and the change in UAE either after switching to temocapril treatment or after continuing CCBs were calculated. Differences were considered significant at the 0.05 probability level. The results are expressed as means ± SEM.

Results

Sixty-three outpatients (32 men and 31 women; mean age, 59.9 ± 1.5 yr) with essential hypertension who had been treated with CCBs (nitrendipine, nisoldipine, or amlodipine) were enrolled in the study. The mean UAE level in the patients with adequately controlled BP during treatment with CCBs was 39.4 ± 6.2 mg/g Cr (n = 63). The patients were randomly allocated to two groups. In group A (n = 31) the previously used CCBs were switched to temocapril, 2 to 4 mg once daily, and in group B (n = 32) the patients were given the same CCBs for a further 12 mo.

Two patients assigned to temocapril were withdrawn from the study because of the side effect of coughing, and three patients who continued CCBs were withdrawn because of the side effects of rash, flushing, and edema, respectively.

No significant differences were found in any study variable between the two groups during the baseline observation period (Table 1).

The values of systolic and diastolic BP (SBP, DBP), s-Cr concentration, serum uric acid (s-UA) concentration, and UAE after switching to temocapril or continuing CCBs are shown in Table 2.
The effects of temocapril on BP appeared to be clinically similar to those obtained with the previously used CCBs, but the decrease in SBP at 12 mo was statistically significant (−3 mmHg, p < 0.05). In group A, temocapril significantly decreased UAE, s-Cr concentration, and s-UA concentration as compared with the previous therapy, but in group B, there were no significant changes in SBP, DBP, s-Cr concentration, or s-UA concentration. In group A, UAE decreased significantly (p < 0.01) from the baseline value of 38.9 ± 5.1 mg/g Cr to 22.2 ± 4.2 and 25.3 ± 5.6 at 6 and 12 mo, respectively. In contrast, in group B, UAE remained unchanged (baseline, 39.8 ± 6.6 mg/g Cr; 6 mo, 44.6 ± 6.8; 12 mo, 45.9 ± 7.7). There were no significant differences in the baseline levels of UAE between the two groups, but the UAE levels in group A at 6 mo and 12 mo were significantly (p < 0.01) lower than the corresponding values in group B (Table 2).

In our earlier study, the mean value of UAE in casual urine was 9.1 ± 6.8 mg/g Cr (mean ± SD) in young healthy subjects (n = 36; mean age, 36.4 ± 4.2 yr, mean ± SE), and 13.3 ± 4.6 mg/g Cr in middle-aged normotensive subjects (n = 24; mean age, 56.1 ± 3.8 yr). When abnormal UAE was considered higher than the normal value +3SD, the upper limit of normal was calculated as 29.5 mg/g Cr (9.1 + 20.4 mg/g Cr) in young healthy subjects and 27.1 mg/g Cr (13.3 + 13.8 mg/g Cr) in middle-aged normotensives. When abnormal UAE was defined as higher than 29.5 mg/g Cr, as in the present study, 17 of 31 patients (54.8%) in group A had

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### Table 1. Demographic Characteristics of the Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Sex (males/females)</th>
<th>Body mass index (kg/m²)</th>
<th>Blood pressure (mmHg)</th>
<th>Duration of hypertension (yr)</th>
<th>Fasting plasma glucose (mg/dl)</th>
<th>Serum creatinine (mg/dl)</th>
<th>Serum uric acid (mg/dl)</th>
<th>UAE* (mg albumin/g Cr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>59.9±1.5</td>
<td>15/16</td>
<td>23.8±0.6</td>
<td>151.3±1.3</td>
<td>8.1±2.3</td>
<td>89.4±2.4</td>
<td>0.85±0.04</td>
<td>5.67±0.19</td>
<td>38.9±5.1</td>
</tr>
<tr>
<td>B</td>
<td>59.8±1.4</td>
<td>17/15</td>
<td>23.8±0.4</td>
<td>151.3±0.9</td>
<td>7.8±2.4</td>
<td>91.3±2.8</td>
<td>0.85±0.02</td>
<td>5.75±0.14</td>
<td>39.8±6.6</td>
</tr>
</tbody>
</table>

Data are means±SEM. *UAE, urinary-microalbumin-to-urinary-creatinine ratio (mg albumin/g Cr); CCBs, calcium-channel blockers. There were no significant differences in the clinical variables between the groups.

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### Table 2. Responses of Clinical Variables and Urinary Albumin Excretion Rate in Hypertensive Patients Who Were Switched from Calcium-Channel Blockers to Temocapril (Group A) or Who Continued to Receive Calcium-Channel Blockers (Group B)

<table>
<thead>
<tr>
<th>Group</th>
<th>During treatment with CCBs</th>
<th>After 6 mo of temocapril therapy</th>
<th>After 12 mo of temocapril therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>151.3±1.3</td>
<td>149.5±0.6</td>
<td>148.3±0.7*</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>87.8±1.1</td>
<td>87.4±0.5</td>
<td>86.6±0.6</td>
</tr>
<tr>
<td>S-Cr (mg/dl)</td>
<td>0.85±0.04</td>
<td>0.80±0.04**</td>
<td>0.78±0.04**</td>
</tr>
<tr>
<td>S-UA (mg/dl)</td>
<td>5.67±0.19</td>
<td>5.34±0.24**</td>
<td>5.27±0.22**</td>
</tr>
<tr>
<td>UAE*** (mg albumin/g Cr)</td>
<td>38.9±5.1</td>
<td>22.2±4.2**</td>
<td>25.3±5.6**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>During treatment with CCBs</th>
<th>After 6 mo of continuing CCBs</th>
<th>After 12 mo of continuing CCBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>151.3±0.9</td>
<td>150.2±1.1</td>
<td>149.9±0.8</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>87.1±0.7</td>
<td>86.8±0.8</td>
<td>86.5±0.7</td>
</tr>
<tr>
<td>S-Cr (mg/dl)</td>
<td>0.85±0.02</td>
<td>0.87±0.02</td>
<td>0.88±0.03†</td>
</tr>
<tr>
<td>S-UA (mg/dl)</td>
<td>5.75±0.14</td>
<td>5.83±0.15†</td>
<td>5.77±0.16†</td>
</tr>
<tr>
<td>UAE*** (mg albumin/g Cr)</td>
<td>39.8±6.6</td>
<td>44.6±6.8†</td>
<td>45.9±7.7†</td>
</tr>
</tbody>
</table>

Data are means±SEM. ***UAE, urinary-microalbumin-to-urinary-creatinine ratio (mg albumin/g Cr). *p < 0.05, **p < 0.01, comparing values during previous treatment (CCBs) with values during temocapril therapy. †p < 0.01, comparing values between the groups at the same times.
Table 3. Number of Patients with Abnormal Urinary Albumin Excretion Rate during Previous Treatment and after Switching to Temocapril Treatment (Group A) or Further Continuing Calcium Channel Blockers (CCBs; Group B)

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th></th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>During treatment with CCBs (n=31)</td>
<td>After 6 mo of temocapril therapy (n=31)</td>
<td>After 12 mo of temocapril therapy (n=29)</td>
</tr>
<tr>
<td>No. of patients with</td>
<td>17</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>abnormal UAE* ** ≥29.5 mg/g Cr</td>
<td>54.8%</td>
<td>19.4% *</td>
<td>6.9% *</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with</td>
<td>15</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>abnormal UAE* ** ≥29.5 mg/g Cr</td>
<td>46.9%</td>
<td>53.1% ‡</td>
<td>48.3% ‡</td>
</tr>
</tbody>
</table>

**UAE, urinary-microalbumin-to-urinary-creatinine ratio (mg albumin/g Cr). Abnormal UAE was considered any value higher than 29.5 mg/g Cr, which was the normal value (9.1 mg/g Cr) + 3SD (20.4 mg/g Cr) of UAE.

*p < 0.01, comparing values during previous treatment (CCBs) with values during temocapril therapy. ‡p < 0.01, comparing values between the groups at the same times.

Discussion

The present study clearly demonstrated that long-term therapy with a new ACE inhibitor, temocapril, decreased UAE in patients with mild-to-moderate essential hypertension and microalbuminuria who had no evidence of renal impairment.

The urinary albumin-to-creatinine ratio was used to estimate UAE in the present study. Several studies (17–20) have shown good agreement between albumin excretion measured in this fashion and direct measurement of short-term urinary albumin excretion or of overnight or 24-h urinary albumin.
excretion. The present study showed that the mean UAE level in hypertensive patients in whom BP was controlled by treatment with CCBs was 39.4 ± 6.2 mg/g Cr (n = 63). When abnormal UAE was defined as higher than 29.5 mg/g Cr, nearly half of the patients (32 of 63 patients, 50.8%) had abnormal UAE levels during treatment with CCBs. This abnormal UAE level is similar to the upper limit of normal UAE (30 mg/g Cr) in healthy Pima Indians (21). A significant correlation between UAE and casual BP has been reported in patients with essential hypertension (1, 2). Elevated BP is an independent risk factor for increased UAE (1, 2, 22), and lowering BP with antihypertensive agents reduces UAE (23). From the clinical point of view, it is particularly important to emphasize that in the present study ACE inhibition with temocapril significantly reduced UAE. Abnormal UAE was normalized in a high proportion of patients assigned to temocapril, whereas the incidence of abnormal UAE was unchanged in patients who continued to receive CCBs. These UAE-reducing effects of temocapril may occur independently of changes in BP, since the BP was similarly controlled in both groups. Unfortunately, we had no data on UAE in the patients before they received CCBs and therefore could not ascertain whether the CCBs used reduced UAE. In addition, a significant correlation was found between the UAE level during previous treatment with CCBs and the change in the UAE level after switching to temocapril, whereas no such correlation was seen in the patients who continued to receive CCBs. Taken together, the present results suggest that ACE inhibition with temocapril, but not with CCBs, may have an independent anti-proteinuric effect, despite similar antihypertensive effects in hypertensive patients.

In patients with essential hypertension, however, the influence of ACE inhibition therapy on UAE is controversial. Some investigators have reported (8, 9, 24, 25) that ACE inhibitors reduced UAE after short-term treatment, whereas others (11) have found that the ACE inhibitor benazepril failed to decrease UAE, despite adequate control of BP. ACE inhibitors have also been reported to significantly reduce UAE, but this beneficial effect appeared to disappear or diminish, with UAE returning to the pretreatment level after long-term treatment (12, 13). In contrast, the ACE inhibitor quinapril has been shown to significantly reduce UAE over a period of 1 yr of treatment (26), and another long-term study has shown that ACE inhibition with enalapril prevents renal deterioration in patients with essential hypertension (27). Our present results with temocapril are consistent with the latter findings. Temocaprilat, the active moiety of temocapril, is unique in that it is excreted by dual elimination routes, i.e., hepatobiliary and renal clearance (15). The reasons for the different response of UAE to ACE inhibition are unclear, but may involve differences in demographic characteristics of the study groups or the use of ACE inhibitors with different chemical structures and properties. Thus, the dual elimination routes of temocapril may contribute to renal protection.

The mechanism for the beneficial effect of ACE inhibition on UAE is not well established. The reduction in UAE during treatment with ACE inhibitors may not be exclusively due to decreased BP, but may be mediated by intrarenal hemodynamic changes or by a direct effect of ACE inhibitors on the glomerular basement membrane. Agents that cause greater reductions in glomerular capillary pressure by inhibiting the effects of angiotensin II may cause greater reductions in UAE (28, 29). Reductions in glomerular capillary pressure may, in some circumstances, be associated with reduced filtration fraction and GFR. Unfortunately, the filtration fraction and GFR were not evaluated in the present study, but temocapril has been reported to significantly decrease both SBP and DBP and to increase both GFR and renal plasma flow in patients with essential hypertension (30). Thus, temocapril may not reduce glomerular capillary pressure. The decrease in UAE after temocapril treatment most likely involves other mechanisms.

Angiotensin II may have a role in the pathogenesis and development of glomerulosclerosis through mesangial cell growth and mesangial matrix synthesis (31-34). ACE inhibition may suppress mesangial cell proliferation and hypertrophy by decreasing angiotensin II generation (31, 35), thus, ACE inhibition might help to decrease albuminuria and prevent renal impairment.

Elevated UAE in hypertension could also be explained by different mechanisms (1, 2, 6, 36-38), such as changes in permeselectivity of the glomerular filter, insufficient tubular reabsorption of albumin, and structural damage to the glomeruli and arterioles. Experimental studies have reported that continuous infusion of angiotensin II induces a progressive, significant increase in urinary protein excretion in the rat isolated kidney, and that this effect of angiotensin II is completely prevented by pretreatment with a specific angiotensin II receptor antagonist (39). These observations may also support the hypothesis that ACE inhibition reduces UAE by decreasing angiotensin II generation.

In the present study, both s-Cr and s-UA concentrations decreased significantly after switching to temocapril from the previously given CCBs. A recent study (40) has shown that ACE inhibitors may have the potential to reduce both UAE and GFR in patients with diabetic nephropathy, whereas many clinical studies have found that therapy with ACE inhibitors decreases UAE and stabilizes s-Cr in a variety of renal diseases (7, 41-45). Increased renal excretion of urate after ACE inhibition has been demonstrated in hypertensive patients, and s-UA levels have been significantly reduced by ACE inhibition (46). Thus, our findings in hypertensive patients without renal impairment are, in part, consistent with those of earlier studies.

An increase in UAE may be an early sign of dysfunction of the glomeruli or of the intrarenal vasculature in patients with essential hypertension. Thus, a reduction in UAE during long-term ACE inhibition may indicate an improvement in functional and...
structural damage in the kidneys, but the clinical evidence supporting this claim in patients with essential hypertension is still limited.

This study had several limitations. Most important, it was an open-labeled study. Large, long-term prospective, double-blind studies are needed to address the many unsolved issues.

In conclusion, the present results indicate that long-term therapy with temocapril improves abnormal UAE in patients with essential hypertension and microalbuminuria without evidence of renal impairment.

References


