Original Article

Effects of Benidipine on Glomerular Hemodynamics and Proteinuria in Patients with Nondiabetic Nephropathy

Takashi MORIKAWA, Michiaki OKUMURA, Yoshio KONISHI, Noriyuki OKADA, and Masahito IMANISHI

Experimental studies suggest that some long-acting calcium antagonists decrease glomerular hypertension and suppress the progression of nephropathy, but clinical evidence is lacking. To investigate clinically whether a long-acting calcium antagonist, benidipine, lowers glomerular capillary hydraulic pressure via a decrease in efferent arteriolar resistance and decreases proteinuria, we examined hypertensive patients with nondiabetic nephropathy. The subjects were 7 patients with chronic glomerulonephritis or glomerulosclerosis. Before and during the administration of benidipine (4 mg/day), systemic pressure, glomerular hemodynamics, the sodium sensitivity index (reciprocal of the pressure-natriuresis curve), and urinary excretion of proteins (total protein, albumin, and immunoglobulin G) were investigated. The glomerular hemodynamics in terms of glomerular capillary hydraulic pressure and resistance of afferent and efferent arterioles were calculated from the renal clearance, plasma total protein concentration, and pressure-natriuresis relationship. Benidipine lowered the mean arterial pressure from 105 ± 5 to 99 ± 4 mm Hg (p ≤ 0.002; mean ± SD) and glomerular pressure from 48 ± 8 to 39 ± 5 mmHg (p = 0.006) by decreasing the resistance of efferent arterioles. Benidipine made the pressure-natriuresis curve steeper and decreased the median sodium sensitivity index from 0.099 (0.084 and 0.117; 25th and 75th percentiles) to 0.048 (0.017 and 0.058; p = 0.018). Urinary excretion of proteins did not change. Our clinical study showed that benidipine lowered the glomerular pressure by decreasing the resistance of efferent arterioles and decreased the sodium sensitivity of blood pressure, but did not affect proteinuria in patients with nondiabetic nephropathy. (Hypertens Res 2002; 25: 571–576)

Key Words: calcium antagonist, glomerular hemodynamics, sodium

Introduction

Hypertension, especially glomerular hypertension, is a risk factor for the progression of renal diseases (both glomerular and interstitial). For progression to be slowed, the glomerular capillary hydraulic pressure, $P_{GC}$, must be lowered. Calcium antagonists are widely used as antihypertensive drugs, but at least one of them, nifedipine, has little effect on the $P_{GC}$ in spite of lowering systemic pressure, because it decreases the resistance of afferent arterioles but not that of efferent arterioles (1, 2). Angiotensin-converting enzyme inhibitors lower $P_{GC}$ by decreasing the resistance of efferent arterioles (3–5). Still, calcium antagonists lower systemic blood pressure more effectively than angiotensin-converting enzyme inhibitors, except in patients with renin-dependent hypertension. For patients whose renin-angiotensin system is not involved in their hypertension, a calcium antagonist that decreases the resistance of efferent arterioles might be useful. A long-acting calcium antagonist, benidipine, decreases the resistance of efferent arterioles as well as afferent and lowers the $P_{GC}$, according to results of direct measurement of the glomerular hemodynamics in rats (2, 6). Unfortunately, such measurements are difficult in humans. A method for the clinical assessment of glomerular hemodynamics in terms of pressure-natriuresis curves has been published (7–9). Here,
using the method, we examined hypertensive patients with non-diabetic nephropathy and low-to-normal plasma renin activity to investigate whether benidipine lowers the PGC (via decreases in efferent arteriolar resistance) and lowers proteinuria. In addition, the effects of benidipine on the sodium sensitivity of blood pressure were investigated.

**Methods**

**Patients**

Seven Japanese inpatients with chronic glomerulonephritis and glomerulosclerosis but without diabetic nephropathy were studied at our hospital; the three men and four women were aged 49 to 77 years. Patients’ characteristics are shown in Table 1. Histological diagnosis of specimens obtained by renal biopsies was done for 5 patients. For the 2 other patients, the diagnosis was established from the clinical history and results of laboratory tests. The study was approved by the ethical review committee of Osaka City General Hospital. Informed consent was obtained from all patients.

**Study Protocol**

The patients were put on a diet with a low NaCl level (approximately 3 g/day) or what we call here an ordinary NaCl level (approximately 10 g/day) for 1 week at each level, in random order, with no time intervening. The diet contained the same amount of protein (1.2 g/kg of body weight per day) and the same calories (35 kcal/kg of body weight per day) throughout the study. Compliance to the fixed protein intake was confirmed by measurements of 24-h urinary urea nitrogen. Patients were asked to maintain their usual level of physical activity and to refrain from taking any drugs, including antihypertensive agents, 1 week before and during the 2 weeks of the study. On each of the last 3 days of the diet, 24-h urine collection was done and the urine was assayed for sodium, total protein, albumin, and immunoglobulin G.

On the last day of each diet, a 24-h record of blood pressure was taken with an automatic monitor by oscillometry (Ambulatory Blood Pressure Monitoring System, A&D Co., Ltd., Tokyo, Japan) with measurement each hour. The mean arterial pressure both final days was calculated by addition of one-third of the pulse pressure to the diastolic pressure. On the last day of each diet, the hematocrit and plasma total protein concentration were measured, and the effective renal plasma flow and glomerular filtration rate as creatinine clearance were calculated by the standard clearance technique with para-aminohippurate and endogenous creatinine, respectively, as markers. Such measurement of creatinine clearance does not give an exact glomerular filtration rate, but results can be used as a substitute for this rate in the clinical assessment of glomerular hemodynamics (10).

After the first 2-week study, another 2-week study was done with oral administration of benidipine (4 mg/day). The renal clearance tests were done under the same conditions before and during the administration of benidipine.

**Laboratory Procedures**

The urinary albumin concentration was measured by immuno-turbidimetry (Wako Pure Chemical Industries, Osaka, Japan) (11). The urinary immunoglobulin G concentration was measured by an enzyme-linked immunosorbent assay. Serum and urinary concentrations of creatinine were measured enzymatically with a kit from Kainosu (Tokyo) (12). Urinary sodium was measured with a flame photometer. Plasma renin activity was measured by radioimmunoassay of angiotensin I, which is produced by renin.

**Assessment of Glomerular Hemodynamics**

The method for the assessment of glomerular hemodynamics was described elsewhere (5, 9). Pressure-natriuresis curves (7, 13) were constructed by plotting of the urinary sodium excretion rate as a function of mean arterial pressure, and

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Body mass index (kg/m²)</th>
<th>BP, syst/diast (mmHg)</th>
<th>BUN/serum Cr (mg/dl)</th>
<th>PRA (ng/ml per h)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>49</td>
<td>23.6</td>
<td>160/90</td>
<td>14.7/0.6</td>
<td>0.2</td>
<td>Mesangial proliferative nephritis</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>77</td>
<td>24.0</td>
<td>160/90</td>
<td>23.8/1.9</td>
<td>0.8</td>
<td>Glomerulosclerosis</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>68</td>
<td>23.1</td>
<td>160/80</td>
<td>22.5/1.4</td>
<td>0.6</td>
<td>CGN</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>54</td>
<td>23.2</td>
<td>148/82</td>
<td>15.6/0.5</td>
<td>0.1</td>
<td>IgA nephropathy</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>58</td>
<td>25.5</td>
<td>146/98</td>
<td>8.4/0.6</td>
<td>0.4</td>
<td>Glomerulosclerosis</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>58</td>
<td>24.2</td>
<td>140/86</td>
<td>33.5/1.3</td>
<td>0.8</td>
<td>CGN</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>62</td>
<td>22.5</td>
<td>154/90</td>
<td>16.9/0.7</td>
<td>0.6</td>
<td>IgA nephropathy</td>
</tr>
</tbody>
</table>

Mean ± SD 61 ± 9 23.7 ± 0.9 155 ± 7/88 ± 7 19.3 ± 7.5/1.0 ± 0.5 0.5 ± 0.3
Table 2. Hemodynamic and Other Changes Caused by Benidipine in Patients with Nephropathy on a Diet with an Ordinary Sodium Level ($n = 7$)

<table>
<thead>
<tr>
<th></th>
<th>Control values</th>
<th>Values with benidipine (4 mg)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>143 ± 14</td>
<td>134 ± 11</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>86 ± 5</td>
<td>81 ± 7</td>
<td>0.0065</td>
</tr>
<tr>
<td>Mean</td>
<td>105 ± 5</td>
<td>99 ± 4</td>
<td>0.002</td>
</tr>
<tr>
<td>Glomerular capillary pressure, $P_{GC}$ (mmHg)</td>
<td>48 ± 8</td>
<td>39 ± 5</td>
<td>0.0064</td>
</tr>
<tr>
<td>$Rs$ (dynes · s · cm$^{-5}$)</td>
<td>8,400 ± 3,960</td>
<td>7,350 ± 3,160</td>
<td>0.10</td>
</tr>
<tr>
<td>$Re$ (dynes · s · cm$^{-5}$)</td>
<td>7,070 ± 3,340</td>
<td>4,780 ± 2,340</td>
<td>0.0082</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min per 1.73 m$^2$)</td>
<td>96 ± 38</td>
<td>92 ± 33</td>
<td>0.39</td>
</tr>
<tr>
<td>Renal plasma flow (ml/min per 1.73 m$^2$)</td>
<td>410 (244, 537)</td>
<td>434 (303, 590)</td>
<td>0.028</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>0.24 ± 0.05</td>
<td>0.19 ± 0.05</td>
<td>0.010</td>
</tr>
<tr>
<td>$K_e$</td>
<td>0.097 (0.074, 0.226)</td>
<td>0.239 (0.111, 0.843)</td>
<td>0.018</td>
</tr>
<tr>
<td>FE Na (%)</td>
<td>1.02 (0.066, 0.149)</td>
<td>1.05 (0.062, 0.153)</td>
<td>0.31</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml per h)</td>
<td>0.2 (0.2, 0.6)</td>
<td>0.1 (0.1, 0.4)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

$Rs$, resistance of afferent arterioles; $Re$, resistance of efferent arterioles; $K_e$, gross filtration coefficient of the glomerular capillaries; FE Na, fractional excretion of sodium. All hemodynamics values other than renal plasma flow are expressed as means ± SD. Other values (from renal plasma flow and $K_e$ to end of table) are expressed as medians (with 25th and 75th percentiles) because data were not in a normal distribution. Differences in values expressed as means before and during the administration of benidipine were evaluated by Student’s $t$-test for paired samples, and differences in values expressed as medians were evaluated by the Wilcoxon signed-rank test.

**Sodium Sensitivity of Blood Pressure**

To assess the sodium sensitivity of blood pressure, we used the sodium sensitivity index, which is the reciprocal of the slope of the pressure-natriuresis curve ($I^4$). Assuming a linear relation between mean arterial pressure and the urinary excretion of sodium, a pressure-natriuresis curve for a subject can be drawn by linkage of two datum points obtained when the subject’s sodium balance is in a steady state during diets with different amounts of sodium. This curve is linear for individuals with a daily sodium intake of 1–18 g of NaCl (18–308 mmol of sodium) when three sodium levels are examined ($I^6$). The reciprocal of the slope of the curve reflects the sodium sensitivity of the blood pressure and used as the sodium sensitivity index.

**Statistical Analysis**

All hemodynamics values other than renal plasma flow are expressed as means ± SD. For renal plasma flow, the gross filtration coefficient ($K_e$), fractional excretion of sodium, plasma renin activity, urinary excretion of proteins, and the sodium sensitivity index, the values are given as medians with the 25th and 75th percentiles, because these values were not in a normal distribution. The significance of differences with the administration of benidipine was examined by Student’s $t$-test for paired samples except for the values expressed as medians, for which the Wilcoxon signed-rank test was used. StatView (ver. 5.0) software was used.

**Results**

Changes in systemic and renal hemodynamics and other effects of benidipine during the diet with an ordinary sodium level are shown in Table 2. Benidipine lowered systemic blood pressure (both systolic and diastolic). Benidipine also lowered $P_{GC}$ and decreased the resistance of efferent arterioles, but did not decrease the resistance of afferent arterioles significantly. However, the drug did decrease the resistance of afferent arterioles in the 2 patients with glomerulosclerosis. Of the 5 patients with glomerulonephritis, 2 had an afferent arteriolar resistance of more than 8,400 dynes · s · cm$^{-5}$. 

Both variables were measured after a steady-state sodium balance had been reached on both diets. We expressed the systemic blood pressure as the mean of the 24 values from 24-h monitoring, and calculated the mean urinary sodium excretion rate for each of the last 3 days of each diet period. Glomerular hemodynamics were evaluated by analysis of the pressure-natriuresis curve, with the assumption that the difference between the mean arterial pressure on the diet with ordinary sodium levels and the extrapolated intercept on the x axis of the pressure-natriuresis curve corresponded to the effective filtration pressure across the glomerular basement membrane ($I^7$, $I^4$). $P_{GC}$ can be represented as the sum of the mean oncotic pressure within glomerular capillaries, the effective filtration pressure, and the hydrostatic pressure in Bowman’s space. The same method was used for calculation of the resistance of both efferent and afferent arterioles ($I^5$, $I^5$).
The mean for all 7 patients, and this resistance was decreased by benidipine. Creatinine clearance was not changed, but the renal plasma flow increased and the filtration fraction decreased. The gross filtration coefficient increased, but the fractional excretion of sodium did not change. Benidipine did not change plasma renin activity significantly.

Table 3 shows changes in the urinary excretion of protein, albumin, and immunoglobulin G. These three parameters were not decreased significantly by benidipine during the diet with ordinary or low sodium levels. However, in the 2 patients with glomerulosclerosis, the urinary excretion of proteins decreased with the drug.

Table 3. Changes in Urinary Excretion of Proteins Caused by Benidipine in Patients with Nephropathy on a Diet with an Ordinary or Low Sodium Level (n = 7)

<table>
<thead>
<tr>
<th>Sodium level</th>
<th>Control values</th>
<th>Values with benidipine (4 mg)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary excretion of protein (mg/day)</td>
<td>Ordinary</td>
<td>795 (163, 1,240)</td>
<td>675 (152, 1,030)</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>675 (152, 1,028)</td>
<td>634 (126, 676)</td>
</tr>
<tr>
<td>Urinary excretion of albumin (mg/day)</td>
<td>Ordinary</td>
<td>381 (41, 631)</td>
<td>354 (56, 779)</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>332 (29, 563)</td>
<td>265 (37, 432)</td>
</tr>
<tr>
<td>Urinary excretion of IgG (mg/day)</td>
<td>Ordinary</td>
<td>43.9 (33.8, 91.8)</td>
<td>41.9 (30.0, 94.3)</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>31.6 (27.6, 46.5)</td>
<td>26.2 (16.3, 37.1)</td>
</tr>
</tbody>
</table>

All values are expressed as medians (with 25th and 75th percentiles) because data were not in a normal distribution. Differences were evaluated by the Wilcoxon signed-rank test.

Discussion

We found that benidipine lowered the glomerular pressure with a decrease in the resistance of efferent arterioles and decreased the sodium sensitivity of blood pressure, but did not decrease proteinuria significantly in patients with nondiabetic nephropathy. Clinical evidence of these effects has been lacking.

The method we used here for clinical investigation of glomerular hemodynamics has been described elsewhere (7) and examined in detail (8, 14, 17). Using this method, we earlier investigated the intraglomerular hemodynamics, including Pgc, in patients with diabetic nephropathy (5, 15) or immunoglobulin A nephropathy (9). The method has been criticized; we gave further details about its utility at that time (17). For subjects with completely normal kidneys, our method may underestimate the Pgc, but for subjects with nephropathy, the estimate obtained by our method is close to the actual measured value (8). There is no direct way to assess the Pgc in humans. We believe that the method used here is the best way to investigate the Pgc clinically until a more appropriate method is developed.

A preliminary clinical study with manidipine, another long-acting calcium antagonist, in three patients with essential hypertension was done earlier by this same method (18). For our clinical study of another long-acting calcium antagonist, benidipine, we set out to increase the number of subjects. We selected subjects with glomerulonephritis or glomerulosclerosis so that effects of the drug on protein excretion would be observable. The number of our subjects, 7, was still small, because at least 5 weeks of hospitalization and adherence to two diets with fixed sodium intakes were necessary. However, our results showed clinical evidence of the effects of a long-acting calcium antagonist on glomerular hemodynamics.

Nifedipine, with its weak vasodilatory effects on efferent arterioles, seems not to protect renal function in diabetic rats (19), although it has a protective effect in rats with hypertension (20). In contrast, benidipine, with stronger effects on
such arterioles, may protect the kidneys in rats with hypertension (21). It is not known why nifedipine and benidipine have different effects on the efferent arterioles. Vascular cells have several subtypes (for example, L-type and T-type voltage-dependent) of calcium channels (22). The L type has been found in afferent but not in efferent arterioles (23). In contrast, the T type, especially a subunit of this type, has been found in both kinds of arterioles (24). Blocking of subtypes of calcium channels differs depending on the calcium antagonist (nifedipine, efonidipine, or nilvadipine) (25, 26). Efonidipine blocks T-type calcium channels (27) and dilates afferent and efferent arterioles in rats (1). Benidipine also may block only certain subtypes, as well; evidence about blocking specificity is not yet available.

In experimental studies, benidipine decreased the resistance of both afferent and efferent arterioles (6, 28). However, in our study, the decrease in resistance of afferent arterioles was not statistically significant. The reason is not clear, but our study was clinical, not experimental, and the renal damage was heterogeneous in our subjects. In some patients with glomerulopathy, before the study began, afferent arterioles might be already more dilated than efferent arterioles as part of the mechanism that maintains the glomerular filtration rate. In such patients, the dilation of efferent arterioles caused by benidipine may be greater than that of the afferent arterioles.

Many studies on the long-term effects of nifedipine have shown that it does not decrease proteinuria (29). Our study had only a 4-week observation period of the effects of benidipine. Its short-term effect was a decrease in the Poc. However, benidipine did not decrease proteinuria significantly in our patients. For patients with glomerulonephritis (immunoglobulin A nephropathy), we found earlier that Poc is not correlated with proteinuria (9); in other words, the Poc may not be a major determinant for the degree of proteinuria in subjects with glomerulonephritis. If so, the lack of a decrease in the proteinuria despite the decrease in Poc can be explained. However, in patients with diabetic nephropathy, one cause of proteinuria is an increase in the Poc (in other words, glomerular hypertension): a decrease in the Poc decreases the proteinuria (15). The diabetic nephropathy progresses to glomerulosclerosis. In our two patients with glomerulosclerosis, proteinuria was decreased by benidipine. Thus the mechanism of proteinuria in glomerulonephritis may differ from the mechanisms in diabetic nephropathy and glomerulosclerosis.

The slope of the pressure-natriuresis curve was made steeper with benidipine, as has been seen with diuretics (30): benidipine decreased the sodium sensitivity of blood pressure. The slope of the pressure-natriuresis curve is governed mainly by negative feedback of the renin-angiotensin system and in part by the glomerulotubular balance (31). The renin-angiotensin system is influenced by inhibitors of angiotensin-converting enzyme, but seems not to be influenced by the calcium antagonist benidipine, because this drug did not change plasma renin activity in our study. The glomerulotubular balance is controlled by the tubular reabsorption of sodium and the gross filtration coefficient (32). In sodium-sensitive states, whether the tubular reabsorption of sodium is increased or the gross filtration coefficient of the glomerular capillaries is reduced, Poc rises to compensate for the impairment in sodium excretion. In other words, both sodium sensitivity and glomerular hypertension reflect adaptations necessary to overcome defects in the capacity of the kidneys to excrete sodium (14, 33). In spontaneously hypertensive rats (21), benidipine increases the urinary and fractional excretion of sodium. In our clinical study, however, the fractional excretion of sodium did not increase with benidipine, although the gross filtration coefficient increased. The fractional excretion of sodium was unchanged, probably because measurements were made in the steady state after administration of the drug started and after the sodium intake changed: urine collection was done at least 4 days after administration started or the sodium intake changed. Within a few days after the administration of benidipine started, the fractional excretion of sodium was likely to increase. Therefore, the change in the slope of the pressure-natriuresis curve caused by benidipine seems to be associated with the glomerulotubular balance.

In conclusion, benidipine, a long-acting calcium antagonist, lowers Poc via a decrease in the resistance of efferent arterioles and decreases the sodium sensitivity of blood pressure in patients with nondiabetic nephropathy. However, in such patients, high Poc seems not to be the only determinant of proteinuria; the mechanisms of proteinuria are heterogeneous (especially in glomerulonephritis).

Acknowledgements

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References


