Cilnidipine Is As Effective As Benazepril for Control of Blood Pressure and Proteinuria in Hypertensive Patients with Benign Nephrosclerosis

Gregory W. ROSE, Yoshihiko KANNO, Hironori IKEBUKURO, Masaharu KANEKO, Keiko KANEKO, Tatsuhiko KANNO, Yuji ISHIDA, and Hiromichi SUZUKI

To investigate the beneficial effects of cilnidipine, a calcium channel blocker that shows high selectivity for N-type receptors, on the progression of chronic renal insufficiency, we compared the efficacy of cilnidipine to that of benazepril, an angiotensin-converting enzyme (ACE) inhibitor with known renal protective effects, in a one-year trial evaluating hypertensive control, serum creatinine, and albuminuria in a cohort of patients. Given the seeming importance of the etiology of chronic renal insufficiency in determining drug efficacy, we limited our study to 20 patients with a single common condition, benign nephrosclerosis. The average age of the patients was 62±4 years old. The changes in systolic and diastolic blood pressure over the course of the study year revealed a similar reduction with cilnidipine and benazepril. Both cilnidipine and benazepril induced similar reductions in systolic and diastolic blood pressure over the course of the study year. The baseline levels of serum creatinine were 1.40±0.2 mg/dl and urinary excretion of albumin was 168±10 mg daily. The levels of serum creatinine were not significantly changed throughout the study in either group, although the levels of urinary excretion of albumin were significantly decreased in both groups. There were no significant differences in either of these values between the two groups. In conclusion, both cilnidipine and benazepril equally and effectively reduced blood pressure and albuminuria in hypertensive patients with benign nephrosclerosis in a one-year trial. (Hypertens Res 2001; 24: 377–383)

Key Words: chronic renal insufficiency, ACE inhibitor, calcium channel blocker, benign nephrosclerosis

Introduction

Accumulating data have demonstrated that angiotensin converting enzyme (ACE)-inhibitor (I) therapy exerts renoprotective effects in both hypertension (I) and a host of other diseases (2–5). Control of hypertension can attenuate the progression of renal disease, especially in patients with more marked proteinuria (6, 7), but the renoprotective effect of ACE-I cannot be explained by hypertensive control alone, and thus these drugs are also useful for treatment of more moderate diseases (2, 3, 5).

Implicit in this statement is the idea that ACE-I are superior to other antihypertensive medications in slowing the progression of chronic renal insufficiency (CRI), and indeed they have been demonstrated to be superior to a number of treatment regimens, including β-blockers, diuretics, and calcium channel blockers (CCB), in treating a variety of CRI-related disorders including essential hypertension (8, 9), hypertension with diabetes mellitus type 2 (DM2) (10) and various nondiabetic renal diseases (11).

Whereas ACE-I are a relatively homogeneous group of drugs, CCB exert a wider range of actions, and thus it is possible that certain CCB may be as useful as ACE-I for the
treatment of chronic renal disease (12). In fact, one study comparing the effects of nifedipine and enalapril in elderly patients found that the rate of decline in renal function (as measured by the decline in creatinine clearance) was greater in the enalapril group (13). Based on this and several subsequent studies, it is clear that there is a subgroup of dihydropyridine CCB that lack the unwarranted reflex sympathetic activation plaguing older CCB (14–16). This sub group of long-acting dihydropyridines with increased N-type channel affinity includes amlodipine and cilnidipine (15, 17). A number of studies have provided evidence that amlodipine may be as useful as ACE-I in some CRI-related disorders, including 5/6 nephrectomy rat models (18, 19), human autosomal dominant polycystic kidney disease (4), and hypertension with DM2 (either as a monotherapy (20) or in combination with ACE-I (21)), or a variety of nondiabetic renal diseases (22, 23). Given the greater selectivity of cilnidipine for N-type receptors (15), as well as cilnidipine’s greater avoidance of sympathetic stimulation in both rat models and human studies (26, 24), it is reasonable to hypothesize that cilnidipine may be as effective as ACE-I in the treatment of certain CRI-related disorders. To investigate this hypothesis, we here compared the efficacy of cilnidipine to that of benazepril, an ACE-I with known renal protective effects (3, 25), in a one-year trial evaluating hypertensive control, serum creatinine, and albuminuria in a cohort of patients. Given the seeming importance of the etiology of CRI in determining drug efficacy (26, 27), we limited our study to patients with benign nephrosclerosis, a condition which has recently come under scrutiny due to its clinical severity, and for which amlodipine treatment may not be as beneficial as ACE-I (22).

Methods
Twenty patients (12 males and 8 females; average age 62±4 years) with benign nephrosclerosis demonstrated by renal biopsy were enrolled in this study. Enrollment criteria included hypertension diagnosed by an in-office blood pressure of at least 140/90 mmHg, and albuminuria of at least 130 mg/day. Prior to the start of the study, previously treated and untreated patients were asked to observe a drug-free regimen for 3 and 4 weeks, respectively.

Thereafter, patients were randomly assigned to either a benazepril group (5–10 mg/day) or a cilnidipine group (10–20 mg/day). In addition, dietary salt intake was reduced to 7 g/day, in order to reduce the detrimental impact of the higher average salt content of the Japanese diet.

Clinical blood pressure was measured in each clinic between 9 and 11 AM using a mercury sphygmomanometer; the first and fifth Korotkoff sounds were used to identify systolic and diastolic values, respectively. Two measurements were collected with the patient in the sitting position for 5 and 10 min, respectively, and the average of the 2 values was taken as the clinical blood pressure for inclusion in the study and for determination of the efficacy of treatment.

Patients were shown how to measure their own sitting blood pressure and instructed to do so at home at least twice weekly; on each of these 2 days of home measurement, they were to measure their blood pressure once in the morning before breakfast within 30 min after waking, and again in the evening before going to bed. Patients purchased their own semiautomatic home blood pressure devices (HEM 401C; Omron Life Science Co., Ltd., Tokyo, Japan) for this purpose; the HEM 401C is based on a cuff-oscillometric principle and generates a digital display of systolic and diastolic blood pressure and pulse rate. The accuracy of blood pressure self-monitoring was checked by nurses. A standard arm cuff was used to obtain the clinical and home blood pressure measurements, since the circumferences of the arms of patients were less than 14 cm in all cases.

 Adequacy of hypertensive control was monitored by both home blood pressure measurement and in-office measurement. If blood pressure control was not satisfactory, αβ-blocker (arotinolol; 10–20 mg daily) was added to the drug regimen of patients receiving cilnidipine and a loop diuretic (furosemide; 20–60 mg daily) was added for the patients receiving benazepril. These combination therapies were adopted because it has been reported that they are effective for reduction of blood pressure in patients with hypertension (28).

Serum creatinine levels were measured at 3 month intervals over the course of one year, while albuminuria was measured over 6 month intervals. Other serum biochemical values (uric acid, cholesterol, liver enzymes, and electrolytes) and complete blood count were measured at 6 month intervals. Twenty-four-hour urine samples were collected for measurements of sodium, creatinine and albumin. Urinary albumin concentration was measured by the TAC-2 test (MBL, Nagoya, Japan), which is based on the color shift of a monoclonal antibody (IgG) to human albumin labeled with colloidal gold, a shift that occurs after IgG binds with urinary albumin.

All patients gave their informed consent and the study was performed in accordance with the Declaration of Helsinki.

Statistics
All values were expressed as the means±SE. Statistical significance was determined using the paired Student’s t-test, unpaired Student’s t-test or multiple comparison test (Bonferroni). P values less than 0.05 were considered to indicate statistical significance.

Results
Table 1 shows the basic clinical characteristics of all patients. There were no significant differences in the characteristics between the two groups.
Table 1. Baseline Demographic Data

<table>
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<tr>
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<th>ACE inhibitor</th>
<th>Cilnidipine</th>
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<tr>
<td>Age</td>
<td>62.4±4.2</td>
<td>62.5±3.6</td>
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<tr>
<td>Gender (male/female)</td>
<td>6/4</td>
<td>6/4</td>
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<td>Blood pressure at the beginning of the study</td>
<td>150/97±2/1</td>
<td>159/95±2/2</td>
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<td>Hemoglobin (g/dl)</td>
<td>12.1±0.5</td>
<td>12.2±0.4</td>
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<td>Serum potassium (mEq/l)</td>
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<td></td>
<td>5.0±0.2</td>
<td>4.9±0.2</td>
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<td>Serum cholesterol (mg/dl)</td>
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<td></td>
<td>216±8</td>
<td>204±12</td>
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<td>Serum uric acid (mg/dl)</td>
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<td>7.0±0.8</td>
<td>7.0±0.7</td>
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Fig. 1. Effects of cilnidipine and benazepril on blood pressure. The symbols ○ and ● represent benazepril and cilnidipine, respectively. *p<0.05 and **p<0.01 compared to the basal values.

Fig. 2. Effects of cilnidipine and benazepril on urinary excretion of albumin. The symbols ○ and ● represent benazepril and cilnidipine, respectively. *p<0.05 compared to the basal values.

Fig. 3. Effects of cilnidipine and benazepril on serum creatinine. The symbols ○ and ● represent benazepril and cilnidipine, respectively.

Effects of Cilnidipine and Benazepril on Blood Pressure

Figure 1 demonstrates the changes in systolic and diastolic blood pressure over the course of the study year. Despite the seeming trend toward higher average systolic blood pressure on initial examination in the group randomized to receive cilnidipine, there was no significant difference in average blood pressures between the two groups at any of the four measurement intervals. The cilnidipine group had an average blood pressure of 159±2/95±2 mmHg at study outset and an average of 128±3/75±3 at conclusion, while the benazepril group had an average blood pressure of 150±2/97±1 mmHg at study outset and an average of 130±3/73±2 mmHg at conclusion. The reduction in systolic and diastolic blood pressure from study outset to conclusion was significant for both treatment groups (p<0.01).

Effects of Cilnidipine and Benazepril on Urinary Excretion of Albumin

Figure 2 shows the changes in measured albuminuria for
both treatment groups. The benazepril group had an average of 168 ± 10 mg/day at study outset and an average of 110 ± 11 mg/day at study conclusion, while the cilnidipine group had an average of 169 ± 18 mg/day at study outset and an average of 118 ± 56 mg/day at study conclusion. There was no significant difference between the two groups at any measurement interval, and both agents significantly reduced albuminuria equally over the course of the study period (p < 0.01). In addition, 3 patients of both groups (30%) showed a normalization of albuminuria less than 135 mg/day in our hospital.

Effects of Cilnidipine and Benazepril on Serum Creatinine

Figure 3 shows the changes in serum creatinine for both treatment groups. The benazepril group had an average of 1.48 ± 0.15 mg/dl at study outset and an average of 1.45 ± 0.12 mg/dl at study conclusion, while the cilnidipine group had an average of 1.42 ± 0.21 mg/dl at study outset and an average of 1.46 ± 0.24 mg/dl at study conclusion. There was again no significant difference between the two groups at any measurement interval, and no significant change in serum creatinine was observed in either treatment group.

Effects of Cilnidipine and Benazepril on GFR

GFR was determined using the renal clearance of endogenous creatinine over a 24-h period. The benazepril group had an average of 67 ± 7 ml/min at study outset and an average of 62 ± 9 ml/min at study conclusion, while the cilnidipine group had an average of 68 ± 8 ml/min at study outset and an average of 63 ± 8 ml/min at study conclusion. There was again no significant difference between the two groups at any measurement interval, and no significant change in serum creatinine was observed in either treatment group.

Adverse Effects

No patients complained of symptoms or showed physical findings suggesting side effects of ACE inhibitors in benazepril or calcium antagonists in the benidipine-treated groups.

Discussion

Our focus on the effect of cilnidipine on the progression of benign nephrosclerosis in hypertensive patients is a reflection of current trends in research in Japan. In this country, CCB are of clinical relevance in as much as they comprise 52%–69% of the initial drugs used by Japanese physicians for treatment of hypertension (29). In particular, cilnidipine is of relevance because of the similarity of its pharmacokinetic profile to that of amlopidine, as discussed above. However, despite the favorable information gathered from in vitro and animal models, there have been very few human studies performed on cilnidipine during its 11 year lifetime, and none outside of Japan where cilnidipine was developed. This paper is, to our knowledge, the first report in the English literature to address the effects of cilnidipine on CRI in humans.

In 1997, Takahara et al. (30) published a report of experiments in which anesthetized dogs were subjected to direct stimulation of the renal nerve. With high frequency stimulation they demonstrated a reduction in renal blood flow (RBF) and with low frequency stimulation they demonstrated both a reduction in absolute and fractional excretion of sodium, as well as an increase in norepinephrine secretion. They then went on to demonstrate reversal of all of these effects by infusion of cilnidipine into the renal artery, indicating that cilnidipine can alter renal function to improve solute excretion, likely through a sympatholytic increase in RBF. Three years later, in 2000, Sugiura et al. (31) demonstrated that induction of the growth factors such as transforming growth factor β and fibronectin, and the cell proliferation regulator activator protein 1, were all induced in rat mesangial cells by fetal calf serum. These markers of cell proliferation were inhibited by cilnidipine and also nifedipine, indicating that cilnidipine possesses the antiproliferative renoprotective effects thought to be a main component of CCB renoprotection (12). Taken together, these two papers (30, 31) indicate that cilnidipine may combine the antiproliferative effects common to the CCB, with the improvements in renal microvascular hemodynamics classically associated with ACE-I (12).

Until our present study, human studies on cilnidipine have been lacking, and reference to prior reports comparing ACE inhibitors to amlopidine, the close cousin of cilnidipine, has been somewhat less than satisfactory, given cilnidipine’s superior blockade of N-type calcium channels (14) and more consistent sympatholytic activity (23), as well as the variable efficacy of amlopidine in differing etiologies of CRI as
discussed above. We therefore deem it prudent to make reference to studies comparing ACE inhibitors to dihydropyridines, in cohorts of essential hypertension/benign nephrosclerosis, with comment on the differing pharmacokinetics of the dihydropyridine CCB used.

Our study showed that both cilnidipine and benazepril were effective in reducing blood pressure in patients with benign nephrosclerosis. This is an expected result, given the known antihypertensive effects of the two drugs (25, 32).

Furthermore, we demonstrated a significant and equal reduction in albuminuria level by both agents. Again, such anti-proteinuric effects have already been demonstrated for benazepril (3), but no data have previously been made available for cilnidipine. Bianchi et al. conducted an important trial comparing antihypertensive medications, including a dihydropyridine CCB, in terms of their attenuation of renal insufficiency in essential hypertension (8). The investigators found that all four treatment modalities (ACE-I, CCB, diuretic, or β-blocker) significantly and equally reduced systolic and diastolic blood pressures, that no treatment regimen altered sodium excretion or creatinine clearance, and that only enalapril reduced albuminuria during the study period. The patient group studied by Bianchi et al. was similar to our patient group with respect to disease etiology and age, and the entrance requirements between the two groups were also equivalent, although we entered patients with lower diastolic pressures and did not screen for creatinine clearance. It is thus interesting that in the study by Bianchi et al. (8) the solely L-type channel selective dihydropyridine, nitrrendipine, did not have a significant anti-proteinuric effect, while in the present study we did observe such an effect by the L-type, N-type antagonist cilnidipine.

The moderately N-type selective amlodipine has demonstrated efficacy in reducing proteinuria in both spontaneously hypertensive rats (SHR) (18, 33) and type 2 diabetic human models (20). However, it has been less successful at proteinuria reduction in other CRI etiologies, as discussed in the Introduction above. One study concentrating on essential hypertension was that of Ali et al. (22). This study was similar to ours in terms of patient population, structure, and degree of hypertension, but we required demonstrable microalbuminuria for study enrollment, whereas only half of the patients treated by Ali et al. had microalbuminuria. While this difference is partially due to the slightly different focus of their study, these investigators still demonstrated a curious variability in the effects of amlodipine on urinary albumin.

Previous animal studies on the antiproteinuric effects of CCB have shown varying results (34). In a study using two groups of rats, one consisting of Munich Wistar rats and the other of SHR, neither group demonstrated an anti-proteinuric effect for amlodipine, and neither demonstrated a reduction in glomerular pressure (35). This last point is in sharp contrast to the reduction in afferent and efferent glomerular arteriolar resistances seen in the study by Nakamura et al. using SHR (33); however, in this latter study amlodipine was not as effective in reducing arteriolar resistance as the T-type selective CCB nifedipinl. In fact, amlodipine has been found to be ineffective in reducing efferent arteriolar resistance (and therefore, presumably, glomerular pressure) in models of SHR and Sprague-Dawley rats (18, 36). It is believed that one mechanism of ACE-I renoprotection consists of the decrease in glomerular pressure by dilation of the efferent arterioles (12), and some CCB (e.g., mandipil, efondipine) have been shown to induce such a decrease effectively and consistently (2, 18). It has been postulated that such a mechanism may be responsible for some of the variable efficacy of CCB in reducing proteinuria. Amlodipine is therefore seen to have mixed results in terms of efferent arteriolar effects, and also anti-proteinuric effects. This is somewhat puzzling, and taken with the inefficacy of nitrrendipine for microalbuminuria in essential hypertension as demonstrated by Bianchi et al. (8), makes our demonstration of cilnidipine’s anti-proteinuric effects in benign nephrosclerosis seem exciting. These effects, and the previous study showing an increase in RBF with cilnidipine administration (30), lead one to suspect that cilnidipine may reduce efferent arteriolar resistance and glomerular pressure. In addition to the reduction of intraglomerular capillary pressure, through which calcium antagonists are able to reduce proteinuria, the modula
tion of macromolecular traffic across and entrapment within the mesangium and the tubulus might be involved (37). It is unfortunate that there have been no studies on mandipil or efondipine in humans with nephrosclerosis to which we may compare our clinical data, but in truth, micropuncture studies in animal models would first be required to demonstrate a definite efferent arteriolar dilative effect of cilnidipine before clinical comparison to efondipine or mandipil would be irrefutably relevant.

Proteinuria has long been used as a surrogate marker for renal function (7, 8), and higher levels have been demonstrated to be associated with a greater decline in creatinine clearance (6). The nature of the cause-effect relationship between proteinuria and renal function decline has not been fully explained, although it is strongly suspected that protein ultrafiltration is at least partly responsible for the process of CRI. It is therefore with great interest that we discovered a lack of reduction in serum creatinine in the setting of a reduction in albuminuria in our study. Moreover, especially in Japan, our study might support the Guidelines for Hypertension in the Elderly issued in 1999 (38).

Limitations

One clear limitation of the present study was the lack of a control group. We did not use a control group because the control conditions are considered dangerous for these patients. Another limitation was that the study was conducted using a relatively small number of patients, and thus some degree of type II error in the results cannot be denied.
Conclusions

In our one-year study comparing the ACE inhibitor benazepril to the L-type, N-type selective dihydropyridine calcium channel blocker cilnidipine, we demonstrated that both agents equally and effectively reduced hypertension and albuminuria in hypertensive patients with benign nephrosclerosis. However, we did not demonstrate a reduction in serum creatinine concentration with either agent, and we believe a longer study period of perhaps 3–4 years may be necessary.

References


