Comparison of effects of cilnidipine and azelnidipine on blood pressure, heart rate and albuminuria in type 2 diabetics with hypertension: A pilot study

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ABSTRACT

Previous studies reported that both cilnidipine and azelnidipine have a renoprotective effect compared with amlodipine. The aim of this study was to compare the effects of cilnidipine and azelnidipine on blood pressure, heart rate and albuminuria. An open-label prospective crossover trial was carried out. We recruited 19 type 2 diabetics treated with amlodipine (5 mg/day) at least for 12 weeks. At study entry, amlodipine was changed to cilnidipine (10 mg/day) or azelnidipine (16 mg/day) and each administered for 16 weeks. Then, the drugs were switched and the treatment was continued for another 16 weeks. Despite no differences in 24-h blood pressure and heart rate between cilnidipine and azelnidipine, treatment with cilnidipine resulted in a greater reduction in urinary albumin:creatinine ratio than azelnidipine. Our results suggested that cilnidipine is more efficient in reducing albuminuria than azelnidipine independent of its blood pressure lowering effect in type 2 diabetic patients with hypertension. This trial was registered with UMIN (no. 000007201). (*J Diabetes Invest*, doi: 10.1111/jdi.12003, 2013)

KEY WORDS: Albuminuria, Calcium channel blocker, Diabetes

INTRODUCTION

Hypertension is common in patients with type 2 diabetes and contributes to the progression of diabetic nephropathy and the incidence of cardiovascular disease¹. Several studies have suggested that the use of blockers of the renin-angiotensin system (RAS) slows the progression of diabetic nephropathy^{2,3}, and they are recommended as the primary antihypertensive drugs⁴. However, the use of only one type of antihypertensive agents is inadequate to achieve the target blood pressure level, and might not be sufficient to reduce albuminuria or proteinuria.

The most frequently used calcium channel blocker (CCB) in Japan is amlodipine. Amlodipine belongs to the L-type calcium channel blockers, and has a potent blood pressure lowering effect and few adverse effects. The CCB-induced drop in blood pressure often stimulates sympathetic nerve activity, leading to tachycardia.

Cilnidipine is a CCB that inhibits not only the L-type calcium channel, but also the N-type calcium channel. As the N-type calcium channel is abundantly expressed in peripheral sympathetic nerve endings⁵, cilnidipine reduces excessive release of catecholamine and suppresses reflective tachycardia compared with amlodipine in hypertensive patients^{6,7}. In addition, a recent study showed that the L-type CCB inhibitors dilate the afferent, but not the efferent, arteries of glomeruli; whereas cilnidipine dilates both the afferent and efferent arteries, suggesting that N-type calcium channel inhibition seems to attenuate glomerular hypertension and prevent proteinuria⁸. Indeed, cilnidipine was shown to have a superior effect to amlodipine in preventing the progression of proteinuria in hypertensive patients^{8,9}.

Azelnidipine is also a unique long-acting L-type calcium channel inhibitor that decreases heart rate and proteinuria by suppressing sympathetic nerve activity^{10,11}. Clinical studies also confirmed that azelnidipine significantly reduced heart rate and proteinuria in hypertensive patients^{12,13}.

Thus, among the available CCBs, both cilnidipine and azelnidipine seem to have better renoprotective effects; however, there are no comparative data on the renoprotective effects of cilnidipine and azelnidipine in patients with type 2 diabetes.

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METHODS

Patients

All patients with type 2 diabetes mellitus who visited Juntendo University Hospital (Tokyo, Japan) between January 2009 and November 2010 were asked to participate. The inclusion criteria were patients with type 2 diabetes mellitus and hypertension treated with amlodipine 5 mg once daily for at least 12 weeks. Patients with severe renal or hepatic disease, overt cardiovascular disease, malignancy and macroalbuminuria (defined as ≥ 300 mg/g creatinine by examination of a spot urine sample at a screening point) were excluded. The hospital ethics committee approved the study protocol and informed consent was obtained from each patient.

Study Design

After completion of run in period (amlodipine 5 mg once-daily), blood pressure was monitored continuously over a 24-h time period using an ambulatory blood pressure monitoring (ABPM) device (A&D Company, Tokyo, Japan), followed by collection of fasting blood samples. Then, the participants were randomized into one of two treatment groups; the 10 mg cilnidipine group and the 16 mg azelnidipine group, once daily in the morning instead of amlodipine. After 16 weeks of cilnidipine or azelnidipine treatment, blood pressure was again monitored with ABPM and fasting blood samples were collected. Then, the patients on cilnidipine were switched to azelnidipine, and the patients on azelnidipine were switched to cilnidipine, and each group continued the treatment for 16 weeks, after which another ABPM was carried out followed by fasting blood sampling. During the study period, except for CCBs, no changes were made to the types and doses of other drugs used before the study.

Biochemical Tests

Blood samples were obtained between 08.00 h and 10.00 h after overnight fast. The value of glycated hemoglobin (HbA_{1c}%; To-sho, Tokyo, Japan) was estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%)¹⁴. Urinary albumin excretion:creatinine ratio (UACR; DENKA SEI KE CO. Ltd. Tokyo, Japan; KAINOS Laboratories, Inc, Tokyo, Japan) was measured by latex agglutination assay using a spot urine sample.

Blood Pressure Evaluation

The ABPM device was used for blood pressure measurement, as reported previously by our group^{15,16}.

Statistical Analysis

Differences between groups were examined for statistical significance using the two-tailed paired Student's *t*-test or Wilcoxon signed-rank test. A *P*-value less than 0.05 denoted the presence of a statistically significant difference.

RESULTS

A total of 23 diabetic patients with hypertension were randomly assigned to the first cilnidipine group (*n* = 12) and the first azelnidipine group (*n* = 11). Of these, 19 patients

completed the first arm of the trial. Four patients dropped out (one lost to follow up, one refusal to use ABPM, one acute myocardial infarction, one traffic accident). No serious adverse effects were observed in all study patients including the four drop-out cases. The demographic characteristics and mean baseline data are shown in Tables 1 and 2.

Table 2 shows the systolic and diastolic blood pressures analyzed by 24-h ABPM. There were no significant differences in these parameters between cilnidipine and azelnidipine. The heart rate was also similar in both groups. In contrast, compared with the cilnidipine treatment, azelnidipine significantly reduced UACR and uric acid levels. Other metabolic and renal function tests were comparable between the two treatment groups.

DISCUSSION

In the present study, heart rate tended to decrease under both cilnidipine and azelnidipine treatments, compared with baseline (amlodipine), suggesting similar beneficial effects on the sympathetic nerve activity. Nevertheless, we found that cilnidipine reduced UACR more than azelnidipine despite the similar blood pressure level. The exact reason for the better effect of cilnidipine on albuminuria relative to azelnidipine is not clear. However, it is possible that cilnidipine reduced proteinuria through the inhibition of N-type calcium channel in the podocytes¹⁷. Podocytes play a pivotal role in glomerular filtration barrier¹⁸, and are known to express N-type calcium channel¹⁷. Inhibition of this channel in podocytes by cilnidipine might prevent podocyte injury, leading to protection of glomerular filtration¹⁷.

In the present study, cilnidipine significantly reduced uric acid compared with azelnidipine, but the mechanism of this

Table 1 | Baseline characteristics of study participants

<i>n</i>	19
Age (years)*	63.7 ± 6.9
Sex (male/female)	13/6
Bodyweight (kg)*	68.3 ± 8.7
Mean duration of diabetes (years)*	14.7 ± 3.9
Current smokers (<i>n</i>)	3
Medications	
Other antihypertensive medications	
Angiotensin II type I receptor blockers (<i>n</i>)	12
Others (<i>n</i>)	4
Glucose lowering agents	
Sulfonylurea (<i>n</i>)	10
Glinide (<i>n</i>)	3
α -Glucosidase (<i>n</i>)	6
Thiazolidinedione (<i>n</i>)	4
Metformin (<i>n</i>)	8
Statins (<i>n</i>)	7
Anti-platelet agents (<i>n</i>)	7

*Data are mean ± standard deviation or number of participants.

Table 2 | Blood pressure (mmHg) recorded by 24-h ambulatory blood pressure monitoring and biochemical measurements during each treatment

Variable	Baseline (amlodipine)	Cilnidipine	Azelnidipine	P-value*
24-h data				
Systolic BP (mmHg)	131.4 ± 9.1	134.4 ± 14.0	134.8 ± 13.0	NS
Diastolic BP (mmHg)	77.6 ± 5.4	78.6 ± 6.7	78.0 ± 7.1	NS
Heart rate (b.p.m.)	73.6 ± 10.2	70.3 ± 8.8	69.0 ± 8.2	NS
Daytime				
Systolic BP (mmHg)	136.2 ± 9.5	138.6 ± 14.0	138.3 ± 11.2	NS
Diastolic BP (mmHg)	80.5 ± 6.2	81.3 ± 6.7	81.1 ± 7.3	NS
Heart rate (b.p.m.)	77.1 ± 10.6	74.2 ± 9.5	72.1 ± 9.4	NS
Nighttime				
Systolic BP (mmHg)	119.8 ± 12.1	124.8 ± 17.9	125.7 ± 18.9	NS
Diastolic BP (mmHg)	70.0 ± 6.3	72.1 ± 8.7	71.2 ± 9.4	NS
Heart rate (b.p.m.)	64.6 ± 9.0	63.5 ± 9.2	62.4 ± 10.3	NS
Body mass index (kg/m ²)	25.5 ± 4.1	25.6 ± 4.2	25.8 ± 4.4	NS
Clinic systolic BP (mmHg)	128.1 ± 10.0	129.8 ± 11.3	129.3 ± 18.3	NS
Clinic diastolic BP (mmHg)	71.7 ± 10.0	72.1 ± 9.7	72.0 ± 11.7	NS
HbA _{1c} (%) (NGSP)	7.26 ± 0.99	7.22 ± 1.21	7.26 ± 1.02	NS
High-density lipoprotein (mmol)	1.39 ± 0.32	1.39 ± 0.35	1.40 ± 0.38	NS
Low-density lipoprotein (mmol)	2.99 ± 0.66	3.02 ± 0.72	3.03 ± 0.77	NS
Triglyceride (mmol)	1.56 ± 0.72	1.51 ± 0.70	1.45 ± 0.62	NS
Cre (μmol)	71.8 ± 14.3	74.5 ± 17.0	76.4 ± 18.7	NS
Uric acid (mmol)	0.34 ± 0.08	0.33 ± 0.08	0.35 ± 0.09	<0.05
Log UACR (mg/mmol)	9.47 ± 10.9	8.60 ± 9.9	12.3 ± 17.3	<0.05

Data are mean ± standard deviation or number of participants.

*Comparison between cilnidipine and azelnidipine groups by two-tailed Student's *t*-test or Wilcoxon signed-rank test. Night-time was defined as the period between the time when the patients retired to their beds and the time when they woke up the next morning. BP, blood pressure; Cre, creatinine; HbA_{1c}, glycated hemoglobin; NGSP, National Glycohemoglobin Standardization Program; NS, not significant; UACR, Urinary albumin excretion/creatinine ratio. [Correction added on 7 Feb 2013, after first online publication: The cilnidipine and azelnidipine values for uric acid were changed to 0.33 ± 0.08 and 0.35 ± 0.09 respectively.]

action is unknown at this stage. However, it was shown that skeletal muscles in patients with hypertension might be an important source of uric acid, because activation of muscle-type adenosine monophosphate deaminase by hypoxia increased hypoxanthine, the precursor of uric acid¹⁹. Cilnidipine was shown to decrease these productions of uric acid precursor in skeletal muscles²⁰. Epidemiological studies suggest that uric acid concentration correlates with urinary albumin excretion and subclinical atherosclerosis in patients with type 2 diabetes²¹, and lowering uric acid could slow the progression of renal disease in non-diabetic patients²². Thus, the reduction of uric acid by cilnidipine seems to be beneficial for renoprotection and prevention of atherosclerosis.

The limitation of the present pilot study is the small number of patients studied over a short period of time, although the crossover design is statistically efficient and thus requires fewer participants than non-crossover designs. In addition, we could not set up a washout period for reasons related to ethical standards and clinical management of patients^{15,21,23}. However, further studies that are set up with a washout period or a third period with amlodipine treatment between cilnidipine and azelnidipine treatments, considering ethical problems, are required to clarify the differential effects more clearly in the future. Although we measured UACR only once using a spot urine sample, the accuracy will improve by measuring UACR more than twice or albuminuria using urine collection for a day.

In conclusion, our data suggest that cilnidipine can be considered a unique CCB that can prevent the progression of diabetic nephropathy in type 2 diabetic patients with hypertension.

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