Beneficial effect of calcium channel blockers on home blood pressure variability in the morning in patients with type 2 diabetes

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ABSTRACT

Aims/Introduction: Recent studies have shown the association between blood pressure variability and cardiovascular events. The present study was designed to investigate the relationship between antihypertensive drug class and home blood pressure variability in patients with type 2 diabetes.

Materials and Methods: We compared home blood pressure variability among patients treated with calcium channel blockers (n = 44), with angiotensin II receptor blockers and/or angiotensin-converting enzyme inhibitors (n = 159), and with calcium channel blockers combined with angiotensin II receptor blockers and/or angiotensin-converting enzyme inhibitors (n = 183). Next, we analyzed the effect of calcium channel blockers on morning blood pressure variability using multiple linear regression analysis.

Results: Coefficient variation of morning systolic blood pressure in patients treated with calcium channel blockers was significantly lower than that in patients treated with angiotensin II receptor blockers and/or angiotensin-converting enzyme inhibitors (P = 0.036). Multivariate linear regression analyses showed that treatment with calcium channel blockers was significantly correlated with coefficient variation of morning systolic blood pressure (β = –0.264, P = 0.001).

Conclusions: The present study implies a possibility for validity on selecting calcium channel blockers in hypertensive patients with type 2 diabetes to reduce home blood pressure variability. (J Diabetes Invest, doi: 10.1111/jdi.12052, 2013)

KEY WORDS: Blood pressure variability, Home blood pressure monitoring, Type 2 diabetes mellitus

INTRODUCTION

An increased average blood pressure (BP) is an important cause of cardiovascular disease (CVD)[1,2]. Furthermore, several studies have shown that blood pressure variability (BPV) also plays an important role in the progression of organ damage, and in the trigger for vascular events[3–5]. In this way, BPV has been considered to be a novel risk factor for CVD in hypertensive patients, and clinicians are recommended to make attempts to reduce BPV as well as average BP.

Recently, several meta-analyses of randomized controlled trials of antihypertensive drugs have shown that there are drug-class differences on BPV[6,7]. Webb *et al.*[6] reported that BPV was reduced by calcium channel blockers (CCB) and non-loop diuretic drugs, and that BPV was increased by angiotensin-converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers (ARB) and beta blockers. They also reported that BPV was reduced the most by CCB compared with a placebo.

In contrast, strict control of BP, not only in the clinic but also at home, is important for the prevention of development and progression of microvascular and macrovascular complications in patients with type 2 diabetes. ARB or ACE-I is recommended as a first-line therapy for hypertensive patients with type 2 diabetes[8,9]. However, to our knowledge, no reports provided the relationship between antihypertensive-drug class and home blood pressure (HBP) variability (HBPV) in patients with type 2 diabetes. Therefore, we compared HBPV among patients with type 2 diabetes treated with CCB, with ARB and/or ACE-I, and with CCB combined with ARB and/or ACE-I.

MATERIALS AND METHODS

Patients

HBP measurements were carried out in patients with type 2 diabetes who had regularly attended the diabetes outpatient clinic at the Hospital of Kyoto Prefectual University of Medicine and the other four general hospitals. The details of this study have been reported elsewhere[10,11]. There was no BP level criterion for the study inclusion.

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A total of 954 patients with type 2 diabetes agreed to participate in the present study. We excluded patients who did not adequately measure their HBP (n = 31) and who had advanced renal dysfunction (serum creatinine equal to or more than 2.0 mg/dL; n = 10).

Additionally, because we intended to compare HBPV among patients treated with CCB and that treated with ARB and/or ACE-I, patients who received antihypertensive drugs except for CCB, ACE-I or ARB (n = 132), or who did not receive antihypertensive drugs (n = 395) were excluded from the analyses. We included patients who received only CCB, only ARB and/or ACE-I, and CCB combined with ARB and/or ACE-I. Finally, 386 patients comprised the study population (222 male, 164 female). The diagnosis of type 2 diabetes mellitus was based on the American Diabetes Association criteria[12].

Study Design

We accessed a database of our previous study[10] to evaluate the antihypertensive-drug class-specific effects on HBPV in patients with type 2 diabetes. We divided patients into three groups as follows: (i) patients treated with CCB; (ii) patients treated with ARB and/or ACE-I; and (iii) patients treated with CCB combined with ARB and/or ACE-I. We compared the clinical characteristics and coefficient variation (CV) of HBP of study patients among the three groups. Next, we applied a multivariate linear regression analysis for patients treated only with CCB and those treated only with ARB and/or ACE-I after adjustment for the following variables as confounding factors: duration of diabetes, body mass index, hemoglobin A_{1c}, low-density lipoprotein cholesterol, triglycerides, logarithm of urinary albumin excretion (UAE), estimated glomerular filtration rate, average morning systolic BP, smoking status, alcohol consumption status and antihypertensive medication[5]. Further information regarding the study design can be found in our previous report[10]. All procedures of the present study were approved by the local Research Ethics Committee and were carried out in accordance with the Declaration of Helsinki, and informed consent was obtained from all patients.

Data Collection

Blood samples for biochemical measurements were taken in the morning. Hemoglobin A_{1c}, serum lipid profile (low-density lipoprotein cholesterol, triglycerides and high-density lipoprotein cholesterol) and other biochemical data were determined by standard laboratory measurements. UAE was measured with an immunoturbidimetric assay. A mean value for UAE was determined from three urine collections. Hemoglobin A_{1c} was expressed as National Glycohemoglobin Standardization Program unit as recommended by the Japan Diabetes Society[13]. Information including age, duration of diabetes, smoking and alcohol consumption status, and antihypertensive medication were obtained at the time of the BP measurement. Alcohol consumption status (everyday, social or never) and smoking status (current, past or never) were assessed by interview.

HBP measurements were carried out using an automatic device, HEM-70801C (Omron Healthcare Co. Ltd, Kyoto, Japan), which uses the cuff-oscillometric method to generate a digital display of heart rate and systolic/diastolic BP value. HEM-70801C uses the identical components and blood pressure determining algorithm to those of another device, HEM-705IT, which was previously validated and satisfied the criteria of the British Hypertension Society protocol[14].

Coefficient of Variation

We used CV of HBP as an index of HBPV described previously[10]. Briefly, patients were instructed to carry out triplicate morning and evening BP measurements for 14 consecutive days. The mean of three measurements in the morning and in the evening for 14 consecutive days was taken as the home blood pressure in the present study. Measurements of morning BP were made within 1 h of waking, before breakfast or taking any drugs, with the patient seated and rested for at least 5 min[15]. Measurements of evening BP were obtained in a homologous way just before going to bed. The cuff was directly placed around their non-dominant arm and the position of cuff was maintained at the level of the heart. As an indicator of HBPV, we defined CV of HBP as standard deviation (SD) of HBP divided by average HBP in the morning and in the evening, respectively.

Statistical Analysis

Values were expressed as mean ± SD for continuous variables and as n for categorical variables. Because UAE showed a skewed distribution, logarithmic transformation was carried out before carrying out statistical analysis. One-way analysis of variance was carried out to detect differences between patients with different antihypertensive treatments. Pairwise comparisons were carried out using Tukey's test. The χ^2-test was used to compare categorical variables between patients with different antihypertensive treatments. Pearson's correlation analyses and multivariate linear regression analyses were used to investigate the relationship between CV of morning systolic BP and antihypertensive drug class or other variables. To adjust the effects of various factors on CV of morning systolic BP, the following factors were considered as covariates: duration of diabetes, body mass index, hemoglobin A_{1c}, low-density lipoprotein cholesterol, triglycerides, logarithm of UAE, estimated glomerular filtration rate, average morning systolic BP, smoking status, alcohol consumption status and antihypertensive medication[5]. Two-tailed values of $P < 0.05$ were considered to show statistical significance. All statistical analyses were carried out using SPSS version 11.0J (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical characteristics of patients among the three groups are shown in Table 1. There were no significant differences among the three groups, except for the distributions of sex and alcohol status.

Table 1 | Clinical characteristics of patients

Characteristic	CCB	ARB/ACE-I	CCB + ARB/ACE-I	*P*-value
n	44	159	183	
Sex (male/female)	17/27	91/68	114/69	0.017
Age (years)	67.9 ± 8.6	65.8 ± 10.0	66.4 ± 8.3	0.414
Duration of diabetes mellitus (years)	12.3 ± 9.5	12.3 ± 9.1	13.0 ± 9.8	0.757
Body mass index (kg/m^2)	24.9 ± 4.3	24.4 ± 3.9	24.3 ± 3.5	0.647
Hemoglobin A_{1c} (%)	7.1 ± 1.2	7.1 ± 1.0	7.1 ± 0.9	0.886
Low-density lipoprotein cholesterol (mmol/L)	2.70 ± 0.85	2.75 ± 0.69	2.73 ± 0.76	0.930
High-density lipoprotein cholesterol (mmol/L)	1.51 ± 0.35	1.39 ± 0.38	1.44 ± 0.47	0.238
Triglycerides (mmol/L)	1.49 ± 0.78	1.51 ± 0.89	1.59 ± 1.06	0.701
Creatinine (mg/dL)	0.77 ± 0.22	0.79 ± 0.24	0.82 ± 0.22	0.280
eGFR (mL/min/1.73 m^2)	69.4 ± 19.5	72.6 ± 19.8	68.5 ± 16.5	0.119
Urinary albumin excretion (mg/g creatinine)	88.3 ± 146.6	110.0 ± 320.6	117.3 ± 232.5	0.817
Smoking (current/past/never)	6/12/26	27/42/90	51/43/89	0.056
Alcohol (everyday/social/never)	6/13/25	38/37/84	69/40/74	0.004
Morning systolic blood pressure (mmHg)	137.5 ± 13.7	138.1 ± 17.1	141.7 ± 18.0	0.103
Evening systolic blood pressure (mmHg)	133.1 ± 15.9	132.2 ± 16.6	134.5 ± 17.7	0.462
Morning diastolic blood pressure (mmHg)	73.4 ± 8.7	76.0 ± 10.8	76.8 ± 11.1	0.171
Evening diastolic blood pressure (mmHg)	68.7 ± 8.6	69.9 ± 10.1	70.1 ± 10.0	0.700
Morning heart rate (b.p.m.)	68.0 ± 9.4	68.4 ± 9.6	68.7 ± 10.5	0.924
Evening heart rate (b.p.m.)	71.8 ± 9.9	73.0 ± 10.1	72.2 ± 10.7	0.699

Data are means ± standard deviation or *n*. ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; eGFR, estimated glomerular filtration rate.

Table 2 | Home blood pressure variability among patients treated with calcium channel blockers, with angiotensin II receptor blockers and/or angiotensin-converting enzyme inhibitors, and with combined calcium channel blockers and angiotensin II receptor blockers and/or angiotensin-converting enzyme inhibitors

CV	CCB	ARB/ACE-I	CCB + ARB/ACE-I	*P*-value (CCB vs ARB/ACE-I)	*P*-value (CCB vs CCB + ARB/ACE-I)	*P*-value (ARB/ACE-I vs CCB + ARB/ACE-I)
CV of morning systolic blood pressure (%)	6.59 ± 1.62	7.45 ± 2.24	7.01 ± 1.97	0.036	0.439	0.113
CV of evening systolic blood pressure (%)	8.07 ± 2.55	8.53 ± 2.82	8.17 ± 2.84	0.600	0.974	0.471
CV of morning diastolic blood pressure (%)	6.20 ± 1.88	7.28 ± 2.95	7.28 ± 2.99	0.072	0.067	1.000
CV of evening diastolic blood pressure (%)	8.74 ± 4.22	9.06 ± 3.56	8.97 ± 3.95	0.876	0.974	0.933
CV of morning heart rate (%)	6.32 ± 2.02	6.49 ± 2.20	6.93 ± 2.65	0.911	0.288	0.209
CV of evening heart rate (%)	6.88 ± 1.98	7.23 ± 2.56	7.21 ± 2.72	0.706	0.723	0.998

Data are means ± standard deviation. CV, coefficient of variation; CCB, calcium channel blockers; ARB/ACE-I, angiotensin II receptor blockers and/or angiotensin-converting enzyme inhibitors.

Coefficient variation of morning systolic BP in patients treated with CCB (6.59 ± 1.62) was significantly lower than that in patients treated with ARB and/or ACE-I (7.45 ± 2.24, $P = 0.036$; Table 2).

Pearson's correlation analyses showed significant positive relationships between CV of morning systolic BP and duration of diabetes mellitus or average morning systolic BP (Table 3).

Multivariate linear regression analyses showed that average morning systolic BP ($\beta = -0.235$, $P = 0.011$) and antihypertensive medication ($\beta = -0.255$, $P = 0.003$) were significantly correlated with CV of morning systolic BP after adjustment for other potential cofactors.

DISCUSSION

In the present study of patients with type 2 diabetes, we found, for the first time, that HBPV in the morning is lower in patients with type 2 diabetes treated with CCB than that in those treated with ARB and/or ACE-I, and that treatment with CCB was significantly correlated with HBPV independent of other potential cofactors. The present findings implicated the

Table 3 | Simple correlation and multiple regression analysis on coefficient of variation of morning systolic blood pressure in patients with type 2 diabetes

	Univariate		Multivariate*	
	r	*P*	β	*P*
Duration of diabetes mellitus	0.159	0.026	0.084	0.380
Body mass index	–0.101	0.175	0.003	0.975
Hemoglobin A_{1c}	0.122	0.082	0.115	0.219
Low-density lipoprotein cholesterol	0.018	0.818	0.028	0.741
Triglycerides	–0.014	0.843	–0.074	0.392
Logarithm of urinary albumin excretion	0.127	0.083	0.147	0.107
Estimated glomerular filtration rate	0.014	0.841	–0.026	0.789
Average morning systolic BP	–0.150	0.032	–0.235	0.011
Smoking status	–	–	0.037	0.687
Alcohol consumption status	–	–	–0.098	0.279
Antihypertensive medication	–	–	–0.255	0.003

BP, blood pressure; CV, coefficient of variation. β indicates multiple linear regression coefficient. Sex (women = 0, men = 1), smoking status (never = 0, past = 1, current = 2), alcohol consumption status (never = 0, social = 1, everyday = 2) and antihypertensive medication (angiotensin II receptor blockers and/or angiotensin-converting enzyme inhibitors = 0, calcium channel blockers = 1). *Adjusted for all variables in this table.

possibility of the drug-class differences on HBPV in patients with type 2 diabetes.

The previous large-scale prospective studies[5,16] revealed evidence that increased BPV is a risk factor for cardiovascular events. This evidence suggests that BPV reduction is beneficial in terms of organ damage attenuation. Therefore, we should pay attention to drug-class specific effects on HBPV.

Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm[17] showed that short-term within-individual BPV was lower in the amlodipine group than that in the atenolol group at all follow-up visits ($P < 0.0001$). Frattola *et al.*[18] reported that lacidipine, compared with placebo, reduced BPV monitored by 24-h ambulatory BP in 10 diabetic hypertensive patients (double-blind crossover design; $P < 0.05$). Furthermore, in a meta-analysis, Webb *et al.*[6] reported that BPV was increased by ACE-I, ARB and beta blockers. Another meta-analysis reported that CCB appears superior to ACE-I for prevention of stroke over and beyond BP reduction[19].

In the present study, we compared HBPV with CCB and that with ARB and/or ACE-I, and revealed that morning systolic BPV in patients treated with CCB is lower than that with ARB and/or ACE-I in patients with type 2 diabetes, which is consistent with previous evidence in hypertensive patients.

Increased BPV depends mainly on sympathovagal imbalance and impaired baroreflex function[20]. Sympathovagal imbalance and insulin resistance are the common underlying disorders linking hypertension and diabetes[21]. It has been hypothesized that autonomic imbalance causes at first increased insulin sensitivity and reduced energy dissipation. However, the excess of energy stores and anabolic processes determine visceral obesity, which is the major cause of insulin resistance and hypertension. At this stage, both hypertension and insulin resistance can be further and directly worsened by autonomic imbalance, whereas compensatory hyperinsulinemia can worsen autonomic imbalance, creating a vicious cycle. Weck[22] recommended that antihypertensive treatment of patients with disturbed sympathovagal balance might include beta blockers, ACE-I, ARB and CCB of the verapamil or diltiazem type, as well as slow-release dihydropyridines and selective imidazoline-receptor agonists (moxonidine) from a pathophysiological point of view. It is also known that the main function of the arterial baroreflex is to maintain stable BP[23]. In hypertensive patients, baroreflex function is impaired and BPV is high. It was also reported that the most effective drugs for BPV reduction are those acting on the arterial baroreflex and calcium channel. Su[23] reported that nitrendipine significantly decreased BPV, and decreased end-organ damage score in spontaneously hypertensive rats. Many studies have shown that CCB are effective in reducing BPV[24,25].

The present result showed statistically different alcohol consumption in the three groups ($P = 0.004$), and an almost statistic difference in smoking ($P = 0.056$). Johansson *et al.*[26] reported that excessive use of alcohol was an independent determinant of greater day-by-day home BP variability in the Finn-home study. There was no evidence of an association between HBPV and smoking. In the present study, there was no significant difference in alcohol consumption or smoking between patients treated with CCB and patients treated with ARB and/or ACE-I. CV of morning systolic BP in patients treated with CCB was significantly lower than that in patients treated with ARB and/or ACE-I ($P = 0.007$), even after adjustment for alcohol consumption. The relationship between HBPV and CCB in the present study might not be affected by alcohol consumption or smoking.

In the Natrilix SR vs Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) Study, the effect of different antihypertensive agents on BPV and the underlying mechanism were investigated[7]. It reported that the reduction in BPV by amlodipine was significantly associated with the reduction in BP and the reduction in heart rate variability, and that the mechanism of BPV reductions was possibly attributable to lowering BP and ameliorating the autonomic nervous system regulation. Nevertheless, there were no significant differences in heart rate and heart rate variability among the three groups in the present study.

Furthermore, the significant difference in home BPV between ARB and/or ACE-I and CCB was observed only in CV of morning systolic BP, but not in other the three indexes of home BPV in the present study. It was postulated that the presence of advanced atherosclerosis could lead to increased variability in systolic BP in diabetic patients[27]. In contrast,

it was reported that an inverse relationship was found between atherosclerosis and the absolute range of diastolic BPV[28]. Furthermore, of 203 patients treated with CCB (n = 44) or renin angiotensin system inhibitors (n = 159), 170 patients (83.7%) took antihypertensive medicine in the morning. Therefore, we speculate that the significant difference in home BPV between ARB and/or ACE-I and CCB was observed only in CV of morning systolic BP in the present study.

Because the timing of antihypertensive therapy could have influenced the results, we have added the timing of antihypertensive therapy for multiple regression analysis, and the result was not changed. Average morning systolic BP (β = –0.235, P = 0.011) and antihypertensive medication (β = –0.260, P = 0.003) were significantly correlated with CV of morning systolic BP.

There are some limitations in the present study. First, our cross-sectional data did not show the precise demonstration of the proper cause–effect nature of the relationships. It is not yet clear how CCB decreases BPV, or how ARB or ACE-I increases BPV in humans. It was postulated that BPV is controlled partly by the arterial baroreflex, and the effect of CCB on BPV is possibly mediated by improving the impaired baroreflex function[23]. Second, the present study included a relatively small number of patients; however, treatment with CCB was significantly correlated with HBPV independent of other potential cofactors. Finally, the adherence of antihypertensive drugs and what kinds of CCB, ARB and ACE-I were prescribed for patients is crucial in a study of morning hypertension; however, we do not have data for them.

The strengths of the present study included that we used a device that is equipped with a memory to store readings rather than trusting patients' logbooks, which is poor adherence[29], and that HBP measurements were carried out for a relatively long consecutive period.

Although ARB or ACE-I is recommended to be prescribed as a first-line of treatment for hypertensive patients with type 2 diabetes in the Japanese Society of Hypertension Guidelines 2009[30], CCB is more beneficial than ARB or ACE-I from the point of view of reducing HBPV. In the future, large prospective studies and intervention trials are required to confirm a causal relationship between antihypertensive-drug class and HBPV in patients with type 2 diabetes.

In conclusion, the present findings have shown a possibility for validity on selecting CCB for hypertensive patients with type 2 diabetes to reduce HBPV.

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None of the authors has any conflicts of interest to declare.

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