Original Article

Differential Effects of a Long-Acting Angiotensin Converting Enzyme Inhibitor (Temocapril) and a Long-Acting Calcium Antagonist (Amlodipine) on Ventricular Ectopic Beats in Older Hypertensive Patients

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We studied differences in the effects of a long-acting angiotensin-converting enzyme (ACE) inhibitor (temocapril) and a long-acting calcium channel blocker (amlodipine) on ventricular ectopic beats (VEB) in relation to sympathetic nerve activity in 46 patients with essential hypertension. We performed 24-h Holter electrocardiography and ambulatory blood pressure (BP) monitoring simultaneously, and examined blood samples during the baseline, temocapril and amlodipine treatment periods. The ambulatory BP was lower in the amlodipine period than in the temocapril period. However, the number of VEB was significantly increased in the amlodipine period compared to that in the baseline period (11.9 vs. 7.4/day, $p < 0.05$). In the temocapril period, the number of VEB was not significantly increased compared to that in the baseline period (8.6 vs. 7.4/day, $p = 0.30$). Ambulatory heart rate (HR) was significantly increased in the amlodipine period compared to that in the baseline period (24-h HR: 70 vs. 66 bpm, $p < 0.001$; daytime HR: 75 vs. 71 bpm, $p < 0.001$; nocturnal HR: 60 vs. 58 bpm, $p < 0.05$). Plasma norepinephrine (NE) also was significantly increased in the amlodipine period compared to that in the baseline period (457 vs. 369 pg/ml, $p < 0.001$). However, when patients receiving amlodipine were divided into a high dose group (8.6 ± 1.2 mg/day) and a low dose group (4.6 ± 1.2 mg/day), increases in HR and plasma NE levels were found only in the high dose group. These results indicate that amlodipine is effective at lowering BP in older hypertensives, although it may increase VEB, especially when given at a high dose. (*Hypertens Res* 2002; 25: 329–333)

Key Words: amlodipine, temocapril, ventricular ectopic beats, catecholamine

Introduction

Long-acting dihydropyridine (DHP) calcium channel blockers (CCBs), and long-acting angiotensin-converting enzyme (ACE) inhibitors are the most common antihypertensive drugs prescribed in Japan. It remains controversial whether long-acting CCBs activate sympathetic activity in essential hypertensive patients. A proarrhythmic effect has been reported with a short-acting DHP (1). Even with long-acting DHPs, there is mild sympathetic activation (2). However,

long-acting CCBs lower blood pressure (BP) without causing reflex sympathetic activation or tachycardia (3). On the other hand, ACE inhibitors provide cardioprotection and do not cause sympathetic activation (4, 5). A recent trial comparing ACE inhibitors and CCBs in older patients with hypertension concluded that the former drugs were more beneficial to the cardiovascular prognosis (6). However, a Japanese trial using CCB and ACE inhibitors concluded that the cardiovascular prognosis was equal between the two drug therapies (7). To clarify the difference in the effects on BP and sympathetic activity between long-acting CCB and ACE

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Fig. 1. Study design

inhibitors, we conducted a cross-over trial using a long-acting ACE inhibitor (temocapril) and a long-acting CCB (amlodipine), and examined the effects on ambulatory BP, the number of ventricular ectopic beats (VEB) and the plasma catecholamine levels in 46 older hypertensive patients.

Patients and Methods

Study Design

The study was a randomized prospective cross-over study. After a 2-week washout and run-in period, initial ambulatory BP monitoring (ABPM) and Holter ECG were performed. The patients were then randomized into two groups, a group receiving temocapril or a group receiving amlodipine for 4 to 8 weeks, and a second ABPM and Holter ECG were performed at the end of this treatment period (Fig. 1). The drugs were then switched, with the temocapril group receiving amlodipine and the amlodipine group receiving temocapril for 4 to 8 weeks, followed by a third ABPM and Holter ECG. Blood samples were taken at the time of each ABPM and Holter ECG recording. At the first part of the two 4~8 week treatment periods, all patients were treated with temocapril (2 to 4 mg) or amlodipine (2.5 to 5 mg) once daily. After 2 or 4 weeks, the temocapril dose was increased by 2 mg or amlodipine by 2.5 mg or by 4 mg or 5 mg, respectively, for 2 weeks up to twice the maximal reference dose recommended in Japan (*i.e.*, to 8 mg for temocapril and 10 mg for amlodipine) to achieve the office BP < 150/90 mmHg.

Patients

Forty-six older patients with uncomplicated essential hypertension (aged 68 ± 9 years) were enrolled in this study. All patients were ambulatory. The results of physical and laboratory examinations, including blood and urine tests, chest X-

rays, and ECG at rest, were normal. Exclusion criteria included possible diabetes mellitus (fasting glucose > 100 mg/dl and/or hemoglobin A1c > 6.2%), secondary or malignant hypertension, history of myocardial infarction, angina pectoris, stroke, transient ischemic attack, and renal failure (serum creatinine ≥ 2 mg/dl). The reason for the exclusion criteria of fasting glucose > 100 mg/dl was to completely exclude possible diabetes. Written informed consent was obtained from all subjects. This study was approved by the Research Ethics Committee, Department of Cardiology, Jichi Medical School, Japan.

Twenty-Four-Hour Ambulatory BP Monitoring

Measurements of office systolic BP and diastolic BP were made by a single physician with a standard mercury sphygmomanometer at each clinical visit, 24 ± 4 h after previous intake of medication (*i.e.*, at trough). Pulse rate (PR) was measured by pulse palpation for 30 s immediately after the BP measurements. These measurements were obtained in the sitting position after at least 5 min of seated rest. An automatic ABPM with electric-powered cuff inflation (TM2421; A&D, Tokyo, Japan), which recorded BP and PR every 30 min for 24 h, was used. The accuracy of this device was previously validated (8). The ambulatory BP data was obtained by the oscillometric method. Each subject recorded his or her own daily activities. Subjects with documented sleep disturbance (frequent waking during sleep) due to ABPM were not included in the present study. The nocturnal BP was defined as the mean BP for the interval from the time the patient went to bed until he or she awoke.

Twenty-Four-Hour Holter Electrocardiogram

We performed 24-h Holter ECG during the run-in period, temocapril therapy and amlodipine therapy and recorded the

Table 1. Comparison of Blood Pressure and Heart Rate between Baseline and Each Therapy

		Baseline	Temocapril	Amlodipine
Office	SBP (mmHg)	168 (26)	146 (12)***	139 (7.7)***.††
	DBP (mmHg)	92 (17)	83 (9.5)***	82 (7.0)***
	PR (beats/min)	70 (17)	64 (13)**	68 (12)†
24-h	SBP (mmHg)	147 (14)	139 (13)***	132 (11)***.†††
	DBP (mmHg)	83 (7.8)	79 (8.7)***	77 (7.8)***.†
	HR (beats/min)	66 (7.6)	67 (8.4)	70 (7.3)***.††
Daytime	SBP (mmHg)	155 (15)	145 (15)***	140 (13)***.†
	DBP (mmHg)	88 (9.2)	82 (9.4)***	81 (8.8)***
	HR (beats/min)	71 (9.0)	72 (9.6)	75 (8.3)***.††
Nocturnal	SBP (mmHg)	132 (17)	129 (16)	117 (12)***.†††
	DBP (mmHg)	74 (8.7)	72 (9.9)*	68 (8.2)***.†††
	HR (beats/min)	58 (6.1)	58 (7.2)	60 (6.9)*.†

SBP, systolic blood pressure (BP); DBP, diastolic BP; PR, pulse rate; HR, heart rate. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. baseline; † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ vs. temocapril. Data are shown as mean (SD).

Table 2. Comparison of the Number of VEB and Neurohumoral Factors between Baseline and Each Treatment

	Baseline	Temocapril	Amlodipine
24-h total VEBs (/day)	7.4 (0.9–63)	8.6 (1.0–77)	11.9 (1.2–117)*
VEB (/h) Day	0.3 (0.0–3.0)	0.4 (0.0–3.8)	0.5 (0.0–5.5)*
Night	0.2 (0.0–1.4)	0.2 (0.0–1.8)	0.3 (0.0–2.6)*
PRA (ng/ml/h)	0.8 (0.9)	1.2 (1.0)*	1.2 (0.8)**
Adrenaline (pg/ml)	33.9 (25.3)	31.9 (23.7)	28.7 (18.2)
Noradrenaline (pg/ml)	368.5 (145)	367.5 (149)	456.9 (143)***.†

VEB, ventricular ectopic beat; PRA, plasma renin activity. * $p < 0.05$, ** $p < 0.01$ vs. baseline. † $p < 0.001$ vs. temocapril. Geometric mean (SD range) was used to calculate the number of VEB. Data are shown as mean (SD) in PRA, adrenaline, noradrenaline.

VEB on magnetic tape. Each patient underwent 24-h monitoring 3 times (once while taking placebo with subsequent recordings at the end of each drug therapy). Monitoring was performed using a double channel recorder (SM-50; Fukuda Denshi Co., Ltd., Tokyo, Japan) and analysis was performed on a 2-channel cardioscanner (MARS 8000; Marquette, USA). All tapes were analyzed by automatic analysis report and findings were confirmed by an experienced doctor.

Other Measurements

We collected fasting blood samples in the morning just before the start of 24-h ambulatory ECG and ABPM for each patient in each period after the patients had reclined for at least 15 min in a semi-dark and silent room. Blood samples were taken *via* a butterfly needle previously inserted in the forearm vein to exclude the effect of pain stress. Plasma catecholamines were measured by the high performance liquid chromatography method. Plasma renin activity (PRA) was measured by the radio immunoassay method.

Statistical Analysis

The SAS statistical program (SAS Institute, Cary, USA) was

used to perform all statistical analyses. Two-tailed, paired Student's *t*-test was used for comparison of the mean values before and after each drug therapy. These data are expressed as the mean ($\pm$ SD) or prevalence. The geometric mean ($\pm$ SD range) was calculated to compare the number of VEB. We used analysis of covariance (ANCOVA) to detect the independence of the norepinephrine (NE) level in relation to the 24-h BP level. Values of $p < 0.05$ were considered to indicate statistical significance.

Results

Table 1 shows the BP and heart rate (HR) parameters of the 46 patients studied. Although each drug significantly reduced BP compared to that with placebo, the BP reduction was greater with amlodipine than with temocapril. Although it caused a greater reduction in BP, amlodipine caused an increase in HR parameters (24-h, daytime and nocturnal), as well as an increase in plasma NE levels accompanied by an increased number of VEB compared to placebo (Table 2). The difference in the plasma NE level after temocapril administration compared to that after amlodipine therapy was independent of the post-treatment 24-h ambulatory BP ($p = 0.04$, by ANCOVA). There were no differences between the

NE levels before and those after temocapril therapy. Office PR was more decreased by temocapril therapy than by placebo. VEB occurring during the daytime and nighttime were both increased with amlodipine therapy but not with temocapril therapy (Table 2). However, the Lown grade of VEB was not altered by the administration of amlodipine.

We subanalyzed the data according to the dose of each drug: the low dose group vs. high dose group. The low doses were 2–4 mg (mean $\pm$ SD: 3.2 ± 1.6 mg) temocapril or 2.5–5 mg (4.6 ± 1.2 mg) amlodipine, and the high doses were 6–10 mg (8.8 ± 1.7 mg) temocapril or 7.5–10 mg (8.6 ± 1.2 mg) amlodipine. There were no significant differences in BP levels between the low- and high-dose groups for either drug. There were no differences in the number of VEB, plasma catecholamine level or HR between the low- and high-dose temocapril groups. By contrast, 24-h HR (70 vs. 67 bpm, $p < 0.001$), and plasma NE (461 vs. 333 pg/ml, $p < 0.001$) were significantly greater in the high-dose amlodipine group ($n = 22$) compared to the baseline levels. In the low-dose amlodipine group ($n = 24$), though there were also significant increases in VEB (6.5 vs. 4.3/day, $p < 0.05$ vs. placebo), but there were no differences in the plasma NE level (453 vs. 407 pg/ml) or 24-h HR (68 vs. 66 bpm).

Discussion

The main finding in this study was that even a long-acting CCB, amlodipine, increased the plasma NE level and number of VEB. This increase was more potent when amlodipine was administered at a higher dose. However, an ACE inhibitor, temocapril, did not increase the plasma NE level or the number of VEB at either low or high doses.

Plasma NE, Sympathetic Activity and VEBs

Vasoactive substances in circulation, especially NE, angiotensin II (AII) and endothelin-1, are indicators of sympathetic activity (9). The most common type of VEB, which is triggered by sympathetic activation, increases with HR (10). The higher sympathetic drive associated with periods of increased HR might accentuate phase 4 diastolic depolarization and permit more frequent emergence of VEB due to enhanced automaticity (10).

CCB and VEB

The increase in VEB was observed not only in the high-dose but also in the low-dose amlodipine group. Therefore, the number of VEB in the low-dose group can be attributed to the CCB mechanism. Furberg and Psaty suggested that CCB might be proarrhythmic, increasing arrhythmia via several mechanisms (11). Dihydropyridine CCBs potentially and indirectly lead to myocardial Ca^{2+} overload and activation of cardiac β_1 receptors. This disturbance in myocardial Ca^{2+} regulation could lead ultimately to the development of after-

depolarizations, triggered activity, and arrhythmias (1). However, this increase in VEB would not always imply an increased risk for malignant arrhythmia and cardiac sudden death in hypertensive patients with relatively preserved cardiac function. In this study, the Lown grade of VEB was not altered by amlodipine administration despite the increase in VEB frequency.

Amlodipine and Sympathetic Nerve Activation

Plasma NE was increased by amlodipine therapy compared to that in the baseline period (457 vs. 369 pg/ml, $p < 0.001$). The report of Lopez *et al.* showed findings similar to ours: though a 4-week amlodipine treatment significantly reduced BP, plasma NE and 24-h PR were significantly increased (2). When we subanalyzed between high and low doses of amlodipine, increases in HR and NE were observed only in the high-dose (8.6 ± 1.2 mg) group. The extent of increase in NE by amlodipine was independent of the degree of 24-h BP reduction *per se*. The precise mechanism of NE increase is unclear, but a few studies have reported that amlodipine increased the plasma NE level (2, 12). Though plasma NE is significantly increased by CCB, this does not directly and completely explain the increased number of VEB observed in the present study. However, a possible explanation is that increased sympathetic activation indirectly increased VEB, and this increase was expressed as resulted in an increase in plasma NE.

On the other hand, some reports have indicated that long-acting CCBs effectively reduce the BP without causing reflex sympathetic activation or tachycardia (3). Hamada *et al.* reported that amlodipine does not stimulate sympathetic nerve activity in hypertensive patients (13). In comparison with our series, the mean subject age in their study was 8 years younger, the baseline BP was lower (143/83 mmHg in their series vs. 168/92 mmHg in ours) and the baseline plasma NE was lower (271 pg/ml in their series vs. 369 pg/ml in ours). Furthermore, in contrast to our series, a sufficient antihypertensive effect was obtained by amlodipine 5 mg/day. Therefore, their population was relatively young and showed mild hypertension. By contrast, our patients had relatively higher sympathetic activity and more than 5 mg was needed to lower BP sufficiently and to trigger sympathetic activation. Because the recommended dose of amlodipine is 5 mg/day in Japan, a dose of more than 5 mg is not practical, especially in older patients.

ACE Inhibitor

In contrast to CCB, temocapril induced no changes in plasma NE or the number of VEB. In addition to the BP-lowering effect, ACE inhibitors have cardioprotective effects shown by reduced morbidity and mortality due to heart failure (4). The reduced mortality is largely attributable to the reduction in sudden cardiac death attributable to ventricular

arrhythmia (5). In previous reports using ACE inhibitors, plasma catecholamine levels were unchanged in patients with essential hypertension (14), as in our results.

PRA was significantly increased in both the temocapril- and amlodipine-treatment groups after 4–8 weeks of therapy. An increase in PRA after temocapril therapy is expected due to a reduction in circulating angiotensin II levels (15). In some previous reports using sustained-release diltiazem (15) and nitrendipine (16), PRA has been reported to be increased. Our finding that PRA was increased by amlodipine therapy is in accordance with these reports. There are three possible mechanisms by which CCBs enhance PRA. First, the increased PRA during CCB treatment could be partly explained by reflex sympathetic activation (16). Second, increased PRA may reflect the direct action of the CCB on renal juxtaglomerular cells. Since the intracellular calcium concentration has been shown to inversely affect renin secretion, a CCB might thus enhance PRA (16). Third, slight natriuresis by the CCB may cause mild volume loss, resulting in an increase in PRA (15).

The present study has some limitations. First, the period of study was a relatively short 4 to 8 weeks, and the sample size was small ($n = 46$). Second, electrophysiological study was not performed. Third, the clinical significance of the increase in the small number of VEB is unknown.

In conclusion, the present study on older uncomplicated hypertensive patients showed that a long-acting CCB induced a greater increase in sympathetic activities, and thereby a greater increase in VEB, than did an ACE inhibitor, and these CCB-induced increases occurred in a dose-dependent manner. These effects were greater when a high dose of CCB was used. In contrast, sympathetic activation was not observed by ACE inhibitor therapy. These different cardiovascular and neurohumoral effects need to be considered in clinical practice.

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