Acute Antihypertensive Effects of Calcium Channel Blockers Are not Affected by Calcium Supplementation in Patients with Essential Hypertension

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SUMMARY

The study was designed to investigate whether the acute antihypertensive effects of calcium channel blockers are affected by calcium supplementation in patients with essential hypertension. The antihypertensive effects of calcium channel blockers (oral manidipine or intravenous nicardipine) were studied before and during calcium supplementation (1200 mg/day for 8 weeks) in 30 hospitalized patients with essential hypertension. The averages of systolic and diastolic blood pressure during a 24-hour period were not decreased by calcium supplementation. The acute antihypertensive effects of the calcium channel blockers nicardipine (0.25, 0.5, 1.5, 2.0 $\mu\text{g/kg/min}$, intravenous infusion) or manidipine (20 mg, once a day, orally) were not enhanced by calcium supplementation. Thus, calcium channel blockers can be safely combined with calcium supplementation in terms of blood pressure. (*Jpn Heart J* 1998; 39: 347–353)

Key words: Blood pressure, Calcium supplementation, Calcium channel blocker, Essential hypertension, Treatment

IN Japan, many people usually have taken calcium for prophylaxis of osteoporosis and many hypertensive patients have taken calcium channel blocker as a main antihypertensive treatment.^{1,2)} Many people with hypertension take a calcium channel blocker in combination with calcium supplementation. Investigators in our division have previously demonstrated that the infusion of calcium increases total peripheral resistance and blood pressure by inhibiting the infusion of calcium channel blocker.^{3,4)} However, there are no reports of the acute antihypertensive effects of calcium channel blockers on the long-term treatment of calcium supplementation. It is necessary to investigate whether the acute antihypertensive effects of calcium channel blockers are affected by calcium

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supplementation in patients with essential hypertension.

METHODS

Subjects: Thirty patients with essential hypertension (16 males and 14 females), 30 to 64 years of age, participated in the study (Table I). All had been treated for essential hypertension for at least 5 years and had mean diastolic blood pressure >95 mmHg and mean systolic blood pressure >160 mmHg before the medication. All medication, including antihypertensive drugs, were discontinued for at least 4 weeks before the study.

Procedure: Effects of calcium supplementation on antihypertensive effects induced by (1) oral manidipine or (2) intravenous nicardipine were studied.

All patients were admitted to our hospital and placed on a diet containing NaCl 8 g/day and calcium 600 mg/day. Ambulatory blood pressure (ABPM-90207, Nihon Kohden Ltd., Tokyo, Japan) (every hour for 24 hours) was measured twice at 3-day intervals; on the day of the second measurement, manidipine (20 mg) was administered orally at 8 AM. Three days later, the effects of intravenous nicardipine were evaluated by direct measurement of arterial pressure. The patients were allowed to rest in a supine position into a quiet, comfortable room (22–25°C) and a polyethylene catheter was introduced in the left radial artery under local anesthesia to monitor arterial blood pressure with a

Table I. Characteristics of 30 Hypertensive Subjects

Age (years)	50 ± 9
Body height (cm)	158 ± 6
Body weight, (kg)	57 ± 5
SBP (mmHg)	178 ± 10
DBP (mmHg)	107 ± 5
Heart rate (beats/min)	72 ± 9
Fundus oculi	H1:18, H2:12 S0:13, S1:10, S2:7
CTR (%)	51 ± 2
RV _s , (mV)	2.5 ± 0.7
RV _s + SV _i (mV)	4.1 ± 1.0
ST, T change (+/-)	11/19
Urinalysis	
proteinuria, (+/-)	0/30
glucosuria, (+/-)	0/30
BUN (mg/dl)	14 ± 1
Cr (mg/dl)	0.7 ± 0.2
Ca (mg/dl)	9.5 ± 0.3
PTH (ng/ml)	0.34 ± 0.07
PRA (ng/ml/hr)	1.9 ± 0.4

SBP = systolic blood pressure; DBP = diastolic blood pressure; CTR = cardio-thoracic ratio; BUN = blood urine nitrogen; Cr = creatinine; PTH = parathyroid hormone; PRA = plasma renin activity.

polygraph system (AP641G, Nihon Kohden Ltd.). Blood pressure was continuously recorded with a thermal array recorder. Heart rate was measured using a continuously monitored electrocardiogram. Increasing doses of nicardipine (0.25, 0.5, 1.0, 2.0 $\mu\text{g/kg/min}$ for 10 min, respectively) diluted with 5% glucose solution (0.2 mg/ml) were infused through the right antecubital vein with an infusion pump (model 2620; Harvard Apparatus, South Natick, MA, USA). Three days later, the antihypertensive effects of intravenous hydralazine (10 mg for 40 min, 1 mg/ml) were studied.

The same procedures were performed 8 weeks after calcium supplementation (1200 mg elemental calcium in the form of a calcium carbonate) was started.

Manidipine was used because it is long-lasting and possesses highly selective vascular action with an extremely weak cardiodepressant action. Nicardipine was chosen for intravenous infusion since both manidipine and nicardipine are 1,4 dihydropyridine derivatives.

Drugs: Commercially available racemic solutions of nicardipine hydrochloride (Yamanouchi Pharmaceutical Co. Ltd., Tokyo), hydralazine hydrochloride (Ciba-Geigy, Takarazuka, Japan), manidipine hydrochloride (Takeda Pharmaceutical Co. Ltd., Tokyo), and calcium carbonate (Kenei Co. Ltd., Osaka, Japan) were used.

Ethics: The objectives and methods of the study were explained in detail to the patients and informed consent was obtained before the start of the study. The protocol was approved by the Ethics Committee of Nagoya City University Hospital.

Statistics: Values are expressed as mean (SD). Statistical comparisons were made by Student's paired *t*-test and the Bonferroni method when analysis of variance for repeated measurements demonstrated significant differences. Statistical significance was assumed when $p < 0.05$.

RESULTS

24-hour blood pressure: Calcium supplementation (1200 mg/day, 8 weeks) did not alter mean systolic or mean diastolic blood pressure, or mean heart rate (Figure 1, Table II). Manidipine decreased the mean of 24-hour blood pressure and increased that of heart rate before and during calcium supplementation (Figure 1, Table II). Neither the decrease in systolic or diastolic blood pressure nor the increase in heart rate were affected by calcium supplementation (Table II).

Intravenous nicardipine and hydralazine: Nicardipine (0.25, 0.5, 1.0 or 2.0 $\mu\text{g/kg/min}$ for 10 min) decreased blood pressure and increased heart rate dose-dependently before and during calcium supplementation (Figure 2). The decrease

Figure 1. Line graphs showing effects of manidipine (20 mg) on 24-hour blood pressure and heart rate before and during calcium supplementation (1,200 mg). ○: control, ●: manidipine 20 mg, □: calcium supplementation, ■: manidipine 20 mg with calcium supplementation. Arrow indicates the administration of manidipine. Values are mean $\pm$ SD.

Table II. Comparison of Averages in Blood Pressure and Heart Rate Measured for 24 Hours before and after Treatment with Manidipine and/or Calcium Supplementation

	Control		Calcium supplementation period	
	Baseline	Manidipine	Baseline	Manidipine
24-hr SBP (mmHg)	150 $\pm$ 34	135 $\pm$ 31**	151 $\pm$ 35	135 $\pm$ 31**
24-hr DBP (mmHg)	91 $\pm$ 21	82 $\pm$ 19**	91 $\pm$ 20	82 $\pm$ 18**
24-hr HR (bpm)	61 $\pm$ 15	66 $\pm$ 17**	59 $\pm$ 15	67 $\pm$ 17*

Data are mean $\pm$ SD. * p < 0.01, ** p < 0.001 vs. respective baseline values. SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

Figure 2. Line graphs showing effects of nicardipine (left) and hydralazine (right) on blood pressure and heart rate before (○) and during calcium supplementation (●). Values are mean $\pm$ SD. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. values obtained before the infusion.

in blood pressure or the increase in heart rate were not affected by calcium supplementation. Similar results were obtained using hydralazine (Figure 2).

DISCUSSION

Calcium supplementation did not decrease blood pressure in this study. In most epidemiologic studies, low dietary calcium intake is associated with an increased prevalence of hypertension.⁵⁻⁷ Previously some studies shown that an increased calcium intake lowers blood pressure.⁸ However, the overall effect of an increased calcium intake is minimal.^{9,10} Our results confirm the negative re-

ports. We used 1200 mg of elemental calcium in the form of calcium carbonate for 8 weeks as calcium supplementation. McCarron and Morris demonstrated that 1000 mg/day of oral calcium for 8 weeks represents a safe and well-tolerated, and non-pharmacologic intervention.⁸⁾ Thus, the dose, form and duration of calcium supplementation must be adequate for evaluation of the effects of calcium supplementation.

The present study demonstrates that the acute antihypertensive effects of calcium channel blockers are not enhanced by calcium supplementation in patients with essential hypertension. An additive effect of calcium intake during pharmacological treatment with calcium channel blockers has been reported in SHR.¹¹⁾ Although the reason for the discrepancy between the results obtained in the present clinical study and this previous experimental study is not certain, there are some possible explanations. First, an increase in extracellular calcium due to the increased calcium intake may have attenuated the action of calcium channel blockers which inhibit calcium influx through voltage-sensitive calcium channels. However, this is not likely since the other vasodilator, hydralazine, decreased during calcium supplementation the blood pressure to the same extent as did the calcium channel blocker, nicardipine. Second, we investigated the acute, but not the long-term, antihypertensive effects of the calcium channel blockers. It is possible that calcium supplementation enhances the effects of long-term treatment with calcium channel blockers. Indeed, in the previous study using SHR, nifedipine or verapamil was administered for 8 weeks.¹¹⁾ Third, high doses of calcium (1–4 g/day) and calcium channel blockers (two- to five-fold) might have an additive effect.¹¹⁾ Fourth, in patients whose blood pressure decreases in response to calcium supplementation, this combination may evoke a synergistic effect. In our patients, calcium supplementation failed to reduce the blood pressure.

There were no adverse effects on hemodynamics induced by calcium channel blockers in the long-term treatment with calcium supplementation. Thus, it is safe to use the combination.

In conclusion, calcium supplementation had no effect on the acute antihypertensive effects of calcium channel blockers.

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