Hypotensive Action and Increased Plasma Renin Activity by Ca\(^{2+}\) Antagonist (Nifedipine) in Hypertensive Patients

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**Summary**

The Ca\(^{2+}\) antagonistic coronary vasodilator, Nifedipine, was sublingually administered by a dose of 30 mg to 19 patients with hypertension. Blood pressure of patients with essential hypertension (n=14) decreased from 177±24 to 123±13 mmHg systolic and from 108±12 to 80±11 mmHg diastolic (mean±SD) (p<0.01). Heart rate increased significantly from 73±11 to 85±10 beats/min (p<0.01). Plasma renin activity (PRA) increased significantly from 0.73±0.62 to 1.50±1.02 ng/ml/h (p<0.05). The same tendency was observed in malignant and renovascular hypertension. In primary aldosteronism (n=2), blood pressure decreased but PRA did not increase.

Hypotensive action and increased plasma renin activity by Ca\(^{2+}\) antagonist, Nifedipine, were clearly demonstrated in patients with hypertension.

**Additional Indexing Words:**

Hypotensive action  Ca\(^{2+}\) antagonist  Nifedipine  Hypertension  Plasma renin activity

Ca\(^{2+}\) antagonistic substance, Nifedipine, chemically designated as 4-(2'-nitrophenyl)-2, 6-dimethyl-1, 4-dihydropyridine-3, 5-dicarboxy-dimethyleneester was found by Bossert and Vater in 1971.\(^1\) It has vasodilating action, useful for treatment of ischemic heart diseases in view of its Ca\(^{2+}\) antagonistic action.\(^2\) Nifedipine interferes with transmembrane Ca\(^{2+}\) influx, preventing increase of intracellular free Ca\(^{2+}\) concentration, upon depolarization of the cell membrane.\(^3\),\(^4\) Since the activity of contractile element in vascular smooth muscle is controlled by intracellular Ca\(^{2+}\), the peripheral vascular resistance which seems to be regulated by vascular activity is reduced by Ca\(^{2+}\) antagonist. Therefore, this agent should reduced the tonus of cardiovascular muscle in hypertension, because of its Ca\(^{2+}\) antagonistic effect.
In such views, in this study, Nifedipine is administered to patients with hypertension and its hypotensive action is investigated for control of blood pressure in hypertension.

**METHODS**

Nineteen patients with established hypertension whose blood pressure over 150 mmHg systolic or over 90 mmHg diastolic in the supine position after 30 min bed rest were the subjects. Fourteen out of 19 patients (39 to 63 years of age, mean = 47) were the essential hypertension at the stage I or II, according to the classification of WHO. Two patients (42 and 33 years) were the malignant hypertension with blood pressure over 130 mmHg (diastolic), Scheie H4 (funduscopic examination) and decreased renal function. One patient (29 years) was accompanied by left renal arterial stenosis. And 2 patients (58 and 62 years) were diagnosed as primary aldosteronism by the presence of hypertension, hypokalemia, increased serum aldosterone, suppression of plasma renin activity, and normal urinary excretion of 17 OHCS and 17 KS.

Nifedipine (Bay a 1,040) was given sublingually in a dose of 30 mg. All medication was free at least 4 weeks before this study. Blood pressures were measured on the right forearm in the supine position at bed rest by auscultatory method with mercury manometer, and heart rate was monitored by electrocardiograms or counted from radial artery by palpation. These parameters were recorded before and after administration of the agent.

Blood samples were collected in cooled ethylene diamine tetraacetic acid solution, before and at 1, 2, and 4 hours after the administration. The plasma was separated at 2°C, 2,000 × g for 10 min and frozen at −20°C for the measurement of plasma renin activity by radioimmunoassay of the angiotensin I, which generated during 2 hours’ incubation at pH 7.4 and 37°C (Dainabot kit, in Japan). The plasma renin activity was expressed as ng of angiotensin I generated per ml of plasma per hour.

The values were expressed mean ± standard deviation and statistical significance of the difference was checked by the t-test.

**RESULTS**

Blood pressure: The blood pressure of the essential hypertension (177 ± 24 mmHg systolic, and 108 ± 12 mmHg diastolic) decreased drastically to (145 ± 21 and 91 ± 11 mmHg, respectively) at 15 min after the administration of Nifedipine as shown in Fig. 1 and Table I. The decrease of blood pressure continued, and at 2 hours after it reduced to 123 and 80 mmHg, systolic and diastolic, respectively. Fall in the blood pressure was significant (p < 0.01). The hypotensive effect of Nifedipine was quite evident in all hypertensive patients and its action continued for more than 4 hours.

With the effect of Nifedipine on patients with malignant hypertension
Fig. 1. Time course of blood pressure, systolic (○) and diastolic (●), heart rate (×) in essential hypertension after 30 mg of Nifedipine sublingual administration. Values are mean ± standard deviation.

or primary aldosteronism blood pressures were reduced significantly, as shown in Table I.

Heart rate: Heart rate in the essential hypertension was significantly increased by Nifedipine from 73 ± 11 to 86 ± 10 beats/min at 1 hour, and to 85 ± 11 beats/min at 2 hours (p < 0.01) (Fig. 1 and Table I). In malignant hypertension, renovascular hypertension and the patients with primary aldosteronism, heart rate was significantly increased after 1 hour of administration as shown in Table I.

Plasma renin activity (PRA): PRA was significantly increased in the patients of essential, malignant and renovascular hypertension by Nifedipine (Fig. 1, Table I). The increased PRA returned to the control level about 4 hours after the administration. In patients with primary aldosteronism, PRA was not increased by the drug.

Subjective symptoms: A few patients complained of mild palpitation and slight warm sensation in the extremities but neither heart failure nor angina pectoris developed by Nifedipine. Side effects observed were headache, facial flushing and heating. These side effects were temporary and not severe, and well tolerated by the patients.

**DISCUSSION**

The results clearly demonstrate that the administration of coronary vasodilator, Nifedipine, decreases high blood pressure to nearly normotensive
Table I. Blood Pressure, Heart Rate, and Plasma Renin Activity after Nifedipine Administration

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age &amp; Sex</th>
<th>BUN mg/100 ml</th>
<th>Blood Pressure mmHg</th>
<th>Heart Rate/min</th>
<th>PRA ng/ml/h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Before</td>
<td>2 hours</td>
<td>Before</td>
</tr>
</tbody>
</table>

Essential Hypertension

1  39 M  16  166  106  120  80  68  76  0.65  2.41
2  63 M  19  190  120  120  84  76  92  0.75  2.08
3  49 F  13  180  100  114  70  64  86  0.48  1.86
4  41 M  17  160  110  138  98  84  88  1.92  2.21
5  52 F  10  180  100  138  88  64  74  0.15  0.41
6  49 F  13  154  90  110  60  52  64  1.49  3.52
7  43 M  15  184  124  124  88  88  98  0.98  0.98
8  40 M  10  148  98  102  70  66  72  0.72  0.72
9  50 F  15  240  130  150  100  92  102  0.92  1.02
10 45 M  13  200  120  130  80  71  90  0.24  0.41
11 42 F  7  180  110  110  70  80  90  0.16  0.58
12 51 M  11  190  100  130  86  74  90  0.09  0.41
13 53 M  11  160  100  110  70  74  82  1.37  1.53
14 44 M  15  150  110  120  80  68  88  0.76  1.08
Mean 47.2 13.2 177.3 108.4 122.6 80.3 72.9 85.1 0.73 1.50
S.D. 6.5 3.2 24.4 11.5 13.4 11.4 10.6 10.1 0.62 1.02
P values <0.01 <0.01 <0.01 <0.01 <0.05

Malignant Hypertension

15 42 M  71  230  140  150  100  66  102  8.31 21.59
16 33 M  20  240  160  150  100  76  88  6.10 10.25

Renovascular Hypertension

17 29 M  10  150  90  100  68  63  67  1.47 3.46

Primary Aldosteronism

18 58 F  17  160  100  120  88  92  96  0.21  0.25
19 62 F  23  150  90  120  88  68  68  0.25  0.31


levels, and increases both the heart rate and PRA in the patients with essential, malignant, and renovascular hypertension. Decrease of blood pressure by Nifedipine has been reported by Murakami et al. in hypertensive patients and by Vater et al. in rats. The mechanism of the anti-hypertensive action of the drug in hypertensive patients has been attributed to the reduction of
vascular resistance due to the vasodilatation induced by this drug. It is apparent that vasodilatation is caused by relaxation of vascular smooth muscle—lowering intracellular Ca\(^{2+}\) concentration by blocking of Ca\(^{2+}\) influx.

An increase in heart rate after Nifedipine might be due to increased sympathetic discharge caused reflexly by peripheral vasodilating action of this agent, as described by Page and McCubbin\(^6\) in the case of hydralazine. Ueda et al\(^7\) suggested that the renin release by hydralazine was associated with increased renal sympathetic activity. Increased PRA by Nifedipine might result from both increased sympathetic discharge and decreased renal perfusion pressure by vasodilatation.\(^8\)

It has been reported that the most common side effect observed was the effect on the cutaneous vessels, headache 4.5%, facial flushing 3.1%, heating 1.7%, and giddiness 1.7%. The local vascular effect of the agent causes an increased circulation in the different regions of the body, such as the myocardium, muscles, skin, kidneys and liver. This, depending on the intensity of the local effect, produces a higher arterial blood intake and redistribution of the blood.

Administration of Nifedipine seemed to be quite useful for management of hypertension, because side effects were not severe and not high frequency.\(^9\) The combined therapy of this agent with sympathetic beta blocking agent may be advisable, because beta-blockers may inhibit both increase of heart rate and of PRA by Nifedipine. In addition, combined administration of this agent with diuretics would be also useful for management of volume hypertension. On the mechanism of inhibition of transmembrane Ca\(^{2+}\) influx by Nifedipine, the further investigation is necessary to elucidate the mechanism of hypotensive action of this new type of drug.

References

6-dimethyl-1, 4-dihydropyridine-3, 5-dicarboxic acid dimethylester (Nifedipine, Bay-a 1040), a new coronary dilator. Jap Heart J 13: 128, 1972


