Antihypertensive and Metabolic Effects of Diltiazem and Nifedipine

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SUMMARY The antihypertensive effect of diltiazem (180–270 mg/day) and nifedipine (40–60 mg/day) in slow-release forms was assessed over 8 weeks in a double-blind parallel study in 40 subjects with essential hypertension at rest and during exercise. Blood pressure was comparably reduced in both groups at rest as well as during exercise. The responder rates (≥10% reduction in diastolic blood pressure) after 8 weeks of therapy were 53% at rest and 75% during exercise in the diltiazem group and 78% and 50%, respectively, in the nifedipine group. Diltiazem decreased heart rate by 8% (p<0.01), while nifedipine did not affect it. As a consequence, myocardial oxygen consumption, as judged by the pressure-rate product, was reduced by diltiazem. Resting plasma norepinephrine levels were increased significantly after 8 weeks of diltiazem therapy. Plasma epinephrine, renin, aldosterone, glucose, insulin, and lactate and routine laboratory parameters were unchanged at the end of the study. No significant changes in total cholesterol and triglyceride levels were observed after 8 weeks. Whereas therapy with diltiazem resulted in an 8% fall in low density lipoprotein cholesterol after 8 weeks (p<0.05), nifedipine induced a drop in very low density lipoprotein cholesterol (p<0.05) after 8 weeks of therapy. We conclude that both diltiazem and nifedipine are effective antihypertensive agents lacking undesirable metabolic side effects. Diltiazem, however, had the advantage of lowering heart rate and myocardial oxygen consumption. (Hypertension 8: 859–865, 1986)

KEY WORDS • diltiazem • nifedipine • blood pressure • exercise • plasma catecholamines • plasma renin activity • carbohydrate metabolism • serum lipoproteins

AN elevated peripheral vascular resistance is the hallmark of chronic essential hypertension. Therefore, the use of drugs with a direct dilating effect on the arterial wall is a logical treatment approach. As demonstrated more than 15 years ago by Bender and Brittinger et al., calcium entry blockers have an antihypertensive effect. All calcium entry blockers decrease the influx of extracellular Ca2+ and promote systemic vasodilation. The effects on myocardium, cardiac cells, and vascular smooth muscle differ depending on the drug used. While verapamil and diltiazem act on myocardium, pacemaker cells, and vascular smooth muscle, nifedipine and its derivatives act mostly at the vascular site rather than on the cardiac pacemaker.


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Recent reports have dealt with the antihypertensive effect of calcium entry blockers in patients with mild to moderate essential hypertension. The effects of calcium entry blockers on catecholamines, plasma renin, aldosterone, lipoproteins, and carbohydrate metabolism have also been examined, but only a few studies comparing different calcium entry blockers have been performed during chronic therapy.

The aim of our study was to evaluate the effect of the calcium entry blockers diltiazem and nifedipine in slow-release forms on blood pressure and heart rate at rest and during exercise as well as on plasma renin activity, aldosterone, catecholamines, serum lipoproteins, and carbohydrate metabolism in essential hypertension during 2 months of treatment.

Subjects and Methods

The study group comprised 40 subjects, 12 women and 28 men, 18 to 55 (mean, 52) years of age, who gave informed consent (Table 1). All subjects had grade I to II essential hypertension according to World
Blood pressure was measured by sphygmomanometry in triplicate at rest, after 5 minutes in the supine position, and after 2 minutes of standing. Heart rate was recorded by electrocardiogram. Repeat measurements were done at the same time of day between 2 and 3 hours after dosing and by a single observer at biweekly intervals. The exercise test after 2 weeks of placebo treatment as well as after 4 and 8 weeks of therapy was conducted in a semireclining position on a bicycle ergometer (ERG 301 R, Robert Bosch, Berlin, West Germany) at 50 cycles/min, starting at 50 W and increasing by a 10-W increment every minute to a work load of 100 W before and after 4 and 8 weeks of therapy. Fifteen patients receiving diltiazem and 14 receiving nifedipine required dose adjustments; however, increasing the doses by half did not cause any further decrease in blood pressure. The overall responder rates (≥10% reduction in diastolic blood pressure) after 8 weeks of treatment were comparable for both groups: in the supine position, 53% receiving diltiazem and 78% receiving nifedipine; in the standing position, 63% and 78%, respectively. The differences between groups were not significant. There was no significant correlation between pretreatment blood pressure and percentage fall in blood pressure, regardless of whether the two groups were evaluated separately or together.

Treatment with diltiazem resulted in significantly (p < 0.01) decreased heart rates both at rest and during exercise (8% reduction) after 8 weeks of therapy (Figure 3; see Table 2). Heart rate was not significantly changed in the nifedipine group. Comparison of the groups showed a significant difference (p < 0.01). The two drugs had significantly different effects (p < 0.05) on the pressure-rate product (systolic blood pressure × heart rate) as an indirect index of myocardial oxygen consumption (see Table 2).27 There was a distinctly greater decrease with diltiazem after 8 weeks of therapy: by 20% (p < 0.001) at rest in the supine position and by 15% (p < 0.001) during exercise. The pressure-rate product was not changed significantly in the nifedipine group.

Only diltiazem produced an increase (82% at rest) in plasma norepinephrine after 8 weeks of treatment (p < 0.01; Table 3). However, the difference between
TABLE 2. Blood Pressure, Heart Rate, and Pressure-Rate Product of Subjects Before and After 4 and 8 Weeks of Treatment with Diltiazem and Nifedipine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diltiazem (n = 19)</th>
<th>Nifedipine (n = 18)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Pretreatment</td>
<td>4 wk</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine (5 min)</td>
<td>111 ± 3</td>
<td>102 ± 3†</td>
</tr>
<tr>
<td>Standing (2 min)</td>
<td>116 ± 2</td>
<td>102 ± 3†</td>
</tr>
<tr>
<td>Exercise (100 W)</td>
<td>126 ± 4</td>
<td>113 ± 5†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine (5 min)</td>
<td>72 ± 2</td>
<td>69 ± 3</td>
</tr>
<tr>
<td>Standing (2 min)</td>
<td>78 ± 2</td>
<td>75 ± 4</td>
</tr>
<tr>
<td>Exercise (100 W)</td>
<td>129 ± 2</td>
<td>119 ± 3*</td>
</tr>
<tr>
<td>Pressure-rate product (mm Hg/min × 10^3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine (5 min)</td>
<td>12.1 ± 0.5</td>
<td>10.6 ± 0.6*</td>
</tr>
<tr>
<td>Standing (2 min)</td>
<td>13 ± 0.5</td>
<td>11.4 ± 0.7†</td>
</tr>
<tr>
<td>Exercise (100 W)</td>
<td>30 ± 1.1</td>
<td>25.5 ± 1.2†</td>
</tr>
<tr>
<td>Values are means ± SEM.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| *p<0.01, †p<0.001, ‡p<0.05, compared with pretreatment values; §p<0.01, ||p<0.05, ‡‡p<0.001, compared with values for diltiazem.

**HYPERTENSION AND CALCIUM ANTAGONISTS/Schulte et al.**

groups was not significant. Plasma epinephrine, renin activity, and aldosterone remained unchanged at the end of treatment.

Therapy did not significantly alter glucose and insulin levels either at rest or during exercise (see Table 3).

Nifedipine induced a 33% drop in very low density lipoprotein cholesterol after 8 weeks of treatment (p<0.05). Divergent (p<0.05) alterations after 8 weeks were only seen in low density lipoprotein cholesterol, which decreased after 8 weeks of diltiazem.

![Figure 1. Systolic and diastolic blood pressure at rest (5 minutes supine) before and after 4 and 8 weeks of therapy with calcium entry blockers.](http://hyper.ahajournals.org/)

- mean values ** p<0.01 ***p<0.001
therapy ($p < 0.05$). Total serum cholesterol and triglycerides, high density lipoprotein cholesterol and triglycerides, very low density and low density lipoprotein triglycerides, and the other laboratory parameters did not vary significantly after 8 weeks of treatment with either drug.

Adverse reactions were reported by 10 subjects receiving diltiazem and 11 receiving nifedipine (Table 4). These side effects disappeared after 1 to 2 weeks of therapy. One subject receiving diltiazem and two receiving nifedipine had to be dropped from the study because of side effects (agitation with diltiazem, flush and palpitation with nifedipine) during the first treatment period.

Discussion

Therapy with the calcium entry blockers diltiazem and nifedipine in slow-release forms resulted in a marked blood pressure reduction at rest and during exercise in our subjects with mild to moderate essential hypertension. The decrease in diastolic blood pressure at rest was significantly more pronounced after 8 weeks than after 4 weeks of treatment with both kinds of drugs. A similar time-dependent effect has also been observed with nifedipine and verapamil.

Although nifedipine did not significantly change the heart rate after 8 weeks of therapy, diltiazem led to a significant reduction at rest and during ergometric work load. This decrease may reflect a negative chronotropic effect of diltiazem by direct action on the sinus node. Similarly, the pressure-rate product, a well-documented parameter of myocardial oxygen consumption, was significantly reduced by diltiazem only through a decrease in heart rate. Comparable results have been reported by Klein et al.

Bühler et al. described a significantly more pronounced verapamil-induced reduction of mean and diastolic arterial blood pressure in older and low renin patients with essential hypertension. MacGregor et al. were not able to confirm such a correlation in a short-term study with nifedipine in young and old normotensive and hypertensive subjects. Hallin et al., who treated mildly to moderately hypertensive patients with nifedipine for 24 weeks, were likewise unable to find a greater blood pressure reduction in older patients. In a 6-week study of nifedipine and verapamil, Midtbø et al. found no relation between blood pressure reduction and age. In our study as well, no correlation was detected between age or plasma renin activity before therapy and arterial blood pressure reduction.

A number of the studies reported that the higher the initial blood pressure values, the greater the mean and diastolic blood pressure decreases detected. This could not be confirmed either in the study of Midtbø et al. or in our own. As to correlations between pretreatment blood pressure and decrease of blood pressure during therapy, Gill et al. have shown that such positive correlations are mathematically inevitable and may thus not be valid.

The treatment was well tolerated. A total of 21 subjects in both groups complained of side effects, which disappeared in most instances within 1 or 2 weeks, as reported by others. Side effects related to peripheral vasodilation (e.g., flush and palpitations) were observed more frequently during nifedipine therapy, resulting in two dropouts (see Table 4).

Resting norepinephrine level increased significantly with diltiazem treatment after 8 weeks, but the difference between the groups was not significant. Inouye et al. reported a similar increase of norepinephrine with diltiazem treatment that they attributed to the inhibitory effect of diltiazem on the postsynaptic α-adrenergic receptors. However, Klein et al. found an increase in norepinephrine during nifedipine, but not diltiazem treatment, which they ascribed to a decrease in systemic vascular resistance. Lederballe-Pedersen et al. described a significantly more pronounced verapamil-induced reduction of mean and diastolic arterial blood pressure in older and low renin patients with essential hypertension.
et al. did not confirm such an increase during chronic therapy in contrast to their finding during acute therapy with nifedipine.

There was no change in plasma renin activity or aldosterone after 8 weeks of treatment with either drug. These findings are partially in contrast to acute studies demonstrating a rise in plasma renin but not in aldosterone. As with renin and aldosterone, there were no significant changes in sympathetic tone as judged from the plasma norepinephrine concentration. This finding was also demonstrated during long-term therapy with nifedipine.

Several experimental studies and case reports have described the occurrence of a reversible hyperglycemia with diminished insulin release during nifedipine therapy. Several patients treated with nifedipine, verapamil, or diltiazem or in diabetic subjects treated with nifedipine, verapamil, or diltiazem. We were also unable to find any significant changes in serum glucose or insulin; however, patients with diabetes were not included in our study.

Total serum cholesterol and triglyceride levels remained unchanged after 8 weeks of treatment in both groups, and there were no significant differences between the drug groups at any time point. There were no significant changes in serum triglycerides after 8 weeks of treatment in both groups. There were no significant changes in serum triglycerides after 8 weeks of treatment in both groups.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Diltiazem (n = 20)</th>
<th>Nifedipine (n = 20)</th>
</tr>
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<tbody>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Palpitation</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Flush</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>Leg edema</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Agitation</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
mained unchanged; however, there was a significant
decrease of the atherogenic low density lipoprotein
cholesterol after 8 weeks of diltiazem therapy as com-
pared with nifedipine therapy. Wada et al. found no
alteration of lipid metabolism in hypertensive patients
after 3 months of orally administered diltiazem.
Our results confirm that the calcium entry blockers
diltiazem and nifedipine are effective antihypertensive
agents, also in slow-release forms. Diltiazem, howev-
er, has the advantage of decreasing heart rate and myo-
cardial oxygen consumption at rest and during exer-
cise. The antihypertensive potency of the calcium
antagonists is similar to that of diuretics and β-adrener-
gic receptor blocking drugs. Calcium entry blockers
seem to be particularly useful in patients with
diabetes mellitus or lipid disturbances, since they do
not affect carbohydrate or lipid metabolism. 5, 7, 15, 16

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