TREATMENT OF HYPERTENSION WITH NIFEDIPINE, A CALCIUM ANTAGONISTIC AGENT

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SUMMARY Hemodynamic monitoring after a single dose (10 mg) of nifedipine in 27 primary hypertensive subjects (diastolic pressure > 110 mm Hg) documented that this calcium antagonistic agent exerts a potent arteriolar vasodilating action, which results in prompt (−21% of control at 30 minutes) and persistent (−16% of control at 120 minutes) fall in mean arterial pressure associated with a rise in cardiac output and pulse rate. The same patients received oral treatment for 3 weeks. Hourly pressure readings showed that 1) the antihypertensive response to each dose lasts 8–12 hours; and 2) nifedipine every 6 hours significantly reduced blood pressure throughout the 24 hours, without postural hypotension.

Side effects were short-lasting (headache in five patients, palpitation without arrhythmias in eight patients, burning sensation in the face and legs in five patients and sporadic extrasystoles in five patients) and tended to disappear with continued treatment.

Development of drug resistance, sodium retention, plasma volume expansion, renin release or angina pectoris were not observed during the study. Although these findings seem to differentiate nifedipine from other vasodilators currently used in the treatment of hypertension, broader experience and more prolonged trials with nifedipine as an antihypertensive agent will be needed before conclusions can be drawn on these particular aspects.

HIGH VASCULAR RESISTANCE is the proximate cause of elevated arterial pressure in most patients with chronic hypertension. Blood pressure can be normalized either by decreasing cardiac output or by lowering vascular resistance. The former, however, makes circulation doubly abnormal, since vascular resistance remains excessive and cardiac output becomes abnormally low. This situation may be associated with tissue hypoperfusion, involving kidneys, heart and brain. The desired hemodynamic effect in antihypertensive therapy is dilatation of constricted arterioles by a compound that acts directly on the smooth muscle, relaxes arterioles independently of the vasoconstrictor mechanism, and does not affect the heart or decrease the venous return.

Hydralazine, dazoxide, minoxidil and guancydine act directly on vascular smooth muscle to produce vasodilatation, and were introduced with variable degrees of success in the chronic treatment of hypertension. These agents share several common side effects, including an exaggeration of cardiac action that may precipitate angina pectoris in patients with coronary disease and the promotion of renin release, sodium retention and plasma volume expansion. In most circumstances β-blockers and diuretics should be added to counteract these effects.

The cellular mechanism of vasodilatation is not yet understood, but the capacity to chelate certain trace metals required for smooth-muscle contraction has been suggested as the vasodilating mechanism of dazoxide and hydralazine. A distinct group of compounds, the so-called calcium antagonists, specifically inhibit the penetration of extracellular calcium through the cell membrane and the inflow of Ca²⁺ ions from the binding sites of the sarcoplasmatic reticulum into the cell plasma, where the ATPase of the myofibrils is located. This enzyme needs Ca²⁺ ions to be activated and to split ATP for the energy-delivering process of muscle contraction. The reduction of the contractile activity of the heart as well as the coronary and systemic vasodilatation brought about by the calcium antagonistic compounds provide the rationale for their use in the management of angina pectoris. Since systemic vasodilatation can be expected to lower elevated blood pressure, during the last few years interest has been focused on calcium antagonists in the medical treatment of hypertension.

Recently, we reported that the profound vasodilating action of nifedipine [4-(2' nitrophenyl)-2, 6-dimethyl-3, 5-dicarbomethoxy-1, 4-dihydropyridine], (fig. 1), a calcium antagonist agent, has a considerable antihypertensive effect. In view of the promptness and the magnitude of the hypertensive reaction, we proposed its use for treating emergencies of severe hypertension.

The present study evaluates the chronic use of nifedipine in the therapeutic management of sustained hypertension. The well-documented antianginal action seems to offer a desirable advantage.

Materials and Methods

Twenty-seven hospitalized men, average age 52 years, were admitted to the study after fulfilling the
following criteria: untreated or poorly treated essential hypertension with diastolic pressure > 110 mm Hg on admission; free consent to the investigation after detailed explanations of the procedures and of the possible clinical benefits; persistence of a diastolic pressure > 110 mm Hg after withdrawal of antihypertensive therapy and any other treatment that could interfere with cardiovascular function; no history or evidence of stroke, cardiac decompensation, heart block or major arrhythmias, asthma or renal failure.

After the diagnosis of essential hypertension was established by clinical and laboratory evaluation, all patients were given placebo in capsules identical in shape and color to the active compound, at regular, 6-hour intervals for 10 days. At the end of this period, hemodynamic measurements were performed, consisting of continuous systemic and pulmonary arterial pressure recording (for 30 minutes before and 120 minutes after a 10-mg oral dose of nifedipine) and cardiac output determination (in the control state and 30, 60 and 120 minutes after the drug). Then, patients were separated randomly into two groups and treated by the following regimens. In 14 patients (group 1) nifedipine (10 mg) and placebo were alternated at regular, 6-hour periods (nifedipine was administered at 8 a.m. and 8 p.m., placebo at 2 a.m. and 2 p.m.) for 3 weeks; 13 patients (group 2) received nifedipine only every 6 hours for 3 weeks. At the end of the trial (4 hours after the last dose of nifedipine), a hemodynamic evaluation was repeated in each subject, and placebo was substituted for the active drug for 3 days.

Readings of blood pressure and pulse rate were taken hourly by the same observer, from 8 a.m. to 9 p.m., throughout hospitalization. Blood pressure was measured with a standard mercury sphygmomanometer according to the recommendations of the American Heart Association. All blood pressures were taken three times at 1-minute intervals in the supine position and, subsequently, in the standing position, at least 5 minutes after the change in posture. Results of the three determinations were averaged. Pulse rate was counted after the last pressure recording in each position. Body weight and urinary output were checked daily. Blood urea nitrogen, serum creatinine and electrolyte concentration, glomerular filtration rate, plasma volume (dilution of T-1824) and plasma renin activity, both in the supine and, after 2 hours, standing positions, were determined at the end of the run-in and trial periods. The patients were on a standard 100 mEq sodium diet. Plasma renin activity was measured by radioimmunoassay of angiotensin I in plasma venous samples and calculated as the difference between immunoreactive angiotensin I formed during 3-hour plasma incubation at 37°C and that present in an incubated plasma sample at 4°C. It was expressed as nanograms of angiotensin I formed per milliliter of plasma per hour.

For the hemodynamic measurements a 5 flow-directed Swan-Ganz catheter was inserted percutaneously, under local anesthesia, into an antecubital vein and floated, under fluoroscopy, to the pulmonary artery or advanced to the wedge position. A polyethylene radiopaque catheter, introduced percutaneously into a brachial artery and advanced to the thoracic aorta, was used to monitor arterial pressure and to sample blood for cardiac output. Reproducible dye dilution curves were obtained by a Gilford densitometer after rapid injection of indocyanine green dye (5 mg) into the main pulmonary artery just beyond the pulmonary valve. Pressures were determined with Statham P23De and P23Db strain gauge transducers and recorded on a Gould-Brush eight-channel ink recorder, model 480. The zero reference level for pressure recording was 5 cm below the sternal angle. The mean pressures were obtained by electronic damping. Systemic vascular resistance (SVR) and pulmonary arteriolar resistance (PAR), in dyn-sec-cm⁻⁵, were calculated from the following formulas:

$$SVR = \frac{\bar{AP} - RAP \times 1332 \times 60}{CO (ml/min)},$$

$$PAR = \frac{PAP - PWP \times 1332 \times 60}{CO (ml/min)},$$

where $\bar{AP}$ is mean systemic arterial pressure, $\bar{PAP}$ is mean pulmonary arterial pressure, $RAP$ is mean right atrial pressure, $PWP$ is mean pulmonary wedge pressure and CO is cardiac output.

For the analysis of the circulatory data, differences were assessed through the analysis of variance, with an Olivetti desk-top computer.

Results

The time course of the circulatory response to a 10-mg oral dose of nifedipine in the whole hypertensive group is shown in figure 2. Average changes from control of mean systemic and pulmonary arterial...
pressure, cardiac index, systemic and pulmonary vascular resistance, pulse rate and stroke index are reported. At 30 minutes after administration of the drug, the average decrease in supine mean arterial pressure was 28 mm Hg (−21% of control). This was associated with a 17% increase in heart rate, a 13% increase in stroke index, a 35% increase in cardiac index, and a 39% reduction in systemic vascular resistance. At 60 minutes after nifedipine, some tendency to recover was observed: Blood pressure and peripheral vascular resistance were reduced by 19% and 33%, respectively, and cardiac index was increased 28% from control. At 120 minutes after nifedipine, this trend was more pronounced; in fact, peripheral resistance decreased 29% from control, cardiac index increased 16% and mean arterial pressure decreased 16%. The rise in cardiac index was caused by a higher pulse rate and larger stroke index at 30 and 60 minutes after administration of nifedipine, and exclusively by a larger stroke index after 120 minutes, as the pulse rate reverted to the control level at this point. In spite of the great changes in flow, pulmonary arterial pressure did not vary significantly from control throughout the study.

A significant correlation was detected between systemic vascular resistance in the control state and systolic and diastolic pressure reduction at 30 minutes after the drug (fig. 3).

Figure 4 reports the averages of the daily sphygmomanometric systolic and diastolic readings in groups 1 and 2 during placebo (days 1–10, and again after day 29) and trial (days 11–29). Open arrows indicate placebo, solid arrows indicate the active compound. In both groups supine and standing pressures were comparable in the control state, without significant fluctuations during the day. In group 1 the single value derived from the average of all daily determinations was 190/117 mm Hg on day 1 and 181/114 mm Hg on day 10. Administration of nifedipine (day 11) was promptly effective and, within 1 hour, lowered supine systolic and diastolic pressure by 21% and 19%, respectively. Subsequent measurements of blood pressure showed a slow, progressive increase and approached the control levels at about 12 hours after the drug. Placebo did not interfere with this trend; on the contrary, a second dose of nifedipine duplicated the hypotensive effect of the first. The pattern was similar throughout the trial. The average of all daily determinations was 165/100 mm Hg on day 11, 160/97 mm Hg on day 12, and 158/97 mm Hg on day 29. The differences from day 10 were significant (p < 0.01). When nifedipine was discontinued after day 29, pressure rose promptly and stabilized by day 31 at the same levels recorded on day 10, the last pretreatment placebo day. Heart rate was slightly, but significantly (p < 0.01) increased only for about an hour after each
dose of the active compound; placebo was ineffective on pulse rate.

In group 2, the single value of all daily supine determinations averaged 205/118 mm Hg on day 1 and 198/122 mm Hg on day 10. Nifedipine (day 11) induced prompt systolic and diastolic pressure fall which at the first hour averaged 22% and 21% of control, respectively. Then, although some trend to increase was seen, pressure remained significantly lower than control up to the second dose, which brought blood pressure to the level attained after the first. The pattern was similar throughout the trial. The single value of all daily pressure readings averaged 166/102, 164/98 and 165/97 mm Hg by days 11, 12 and 29, respectively; each of these was significantly ($p < 0.01$) lower than by the last pretreatment placebo day (day 10). Heart rate increased for about an hour following each dose. When placebo was substituted for the active compound, pressure rose promptly and stabilized by day 31 at the same levels recorded on the last pretreatment placebo day.

In both groups pressure variations at the various periods were qualitatively and quantitatively similar in the supine and standing positions.

Hemodynamic measurements carried out before and at the end of trial in the whole hypertensive population are reported in table 1. Systolic and diastolic systemic arterial pressures and vascular resistance were significantly reduced and cardiac index significantly increased after treatment; systolic and diastolic pulmonary pressure and plasma volume remained almost unchanged. As shown in table 2, blood urea nitrogen, serum electrolyte and creatinine concentrations, glomerular filtration rate and plasma renin activity did not vary consistently. Body weight was steady, and urinary output increased by an average of 600 ml on day 11 and reverted to the control value in the subsequent days.

Headache in five patients, palpitation without arrhythmias in eight patients, sporadic premature ventricular contractions in five patients, burning sensation in the face and legs in five patients were reported 30-60 minutes after nifedipine. All these symptoms tended to disappear with continued treatment. In no case did side effects require interruption of the trial. Cardiac rhythm was normalized in six patients who had ventricular extrasystoles in the control period.

**Discussion**

Continuous hemodynamic monitoring provided further evidence that nifedipine exerts a rapid, profound and persistent antihypertensive action. Mean arterial pressure, in fact, was lowered by 21% of control at 30 minutes (average fall 28 mm Hg) and by 16% at 120 minutes after the drug. The hemodynamics of the antihypertensive effect were characterized by a diminished peripheral resistance associated with simultaneous rise of cardiac output.

The magnitude and the promptness of the fall in peripheral vascular resistance suggest that the calcium antagonistic action of nifedipine produces a direct dilating effect on the resistance vessels. Venous capacitance vessels do not seem to be involved, since cardiac output increased and pressures in the right side of the heart remained unchanged. Increase of cardiac output could be caused by reflex sympathetic activation or by left ventricular afterload reduction consequent to decreased peripheral vascular resistance, or to both. The beneficial effects of a lowered cardiac load probably were predominant 120 minutes after nifedipine, since at this point the pulse rate had
reverted to control values, while the cardiac output remained elevated.

No correlation was found between cardiac output, during either baseline or hypotensive phases, and the magnitude of the blood pressure fall. There was, however, a correlation between vascular resistance in the control state and hypotensive response to nifedipine, suggesting that, within certain limits, the greater the vasoconstriction the greater the hypotensive effect of the drug, and also that modulation of this effect depends not so much upon the cardiac output reaction as upon the degree of vasodilatation.

In spite of the augmented flow, pulmonary pressure did not increase. Whether this was a consequence of a direct vasodilating effect of the compound or of the high compliance of the pulmonary vascular bed, is not known.

Throughout chronic treatment nifedipine maintained its ability to lower blood pressure, as it did during acute hemodynamic monitoring in both groups.
Although this would suggest that repeated doses are not associated with development of drug resistance or tachyphylaxis, more prolonged trials will be necessary to clarify this point. The analysis of the pressure readings at the various times provides an approximate idea on the rate of decay of the hypotensive effect as well as on blood pressure fluctuation with the two regimens. In group 1 (nifedipine every 12 hours) pressure remained reduced significantly for 7-8 hours after nifedipine and approached the control levels in the next 3-4 hours; at 12 hours the hypotensive effect was almost completely lost in each case. Average blood pressure ranged from 172/104 mm Hg to 147/89 mm Hg over a 12-hour period (systolic fluctuation was 25 mm Hg, diastolic fluctuation was 15 mm Hg). As was expected from these findings, nifedipine every 6 hours (group 2) maintained arterial pressure significantly lower than control throughout the day; it also held the average systolic and diastolic fluctuation to 17 and 11 mm Hg, respectively.

Circulatory measurements repeated at the end of the trial documented that the hypotensive effect after a 3-week treatment was still mediated through reduction of the peripheral vascular resistance associated with increase in cardiac output, which indicates that the hemodynamics of the hypotensive effect did not vary during that time. However, no circulatory readjustment seems to have occurred during this period. In fact, when placebo was substituted for nifedipine, arterial pressure rose again and stabilized at pre-treatment levels within 2 days.

Nifedipine did not reduce, and even tended to improve renal function, and did not interfere with sodium metabolism. The fact that no patient developed precordial symptoms consistent with angina pectoris is probably attributable to the well-documented efficacy of the compound on ischemic disorders of the myocardium.13-17

A precise definition of the effects of the drug on plasma renin activity obviously requires more detailed studies. It may be possible that variations in renin secretion parallel the time course of changes in arteriolar tone, blood pressure, cardiac output and sympathetic activation after each dose. It is interesting to note, however, that 3 hours (lying position) and 5 hours (standing position) after the last dose of nifedipine (day 30), plasma renin activity did not differ significantly from control (table 2), even though arterial pressure and vascular resistance were reduced and cardiac output increased (table 1) at the time of plasma renin activity determination. This may indicate that activation of renin secretion, if any, is of short duration, and also that the baseline level of renin is not elevated after 3 weeks of continued treatment.

Recently, it has been suggested that distal tubular calcium delivery is an important functional part of the macula densa-glomerular feedback mechanism;20,21 it has been documented that the calcium antagonistic agent, verapamil, is a complete inhibitor of the tubuloglomerular feedback operation.22 The hypothesis that nifedipine interferes with calcium availability at the level of the distal tubule might explain why, in spite of its vasodilating and hypotensive action, the compound does not seem to activate renin secretion.

For all these reasons nifedipine may be regarded as a promising pharmacological agent in the therapy of high blood pressure. Further clinical evaluation will be required to determine the persistence of the antihypertensive effect during long-term administration of the drug.

### Table 1. Hemodynamic Data (mean ± SEM) Before and After Treatment with Nifedipine

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Nifedipine</th>
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<tr>
<td>HR (beats/min)</td>
<td>75 ± 3.1</td>
<td>74 ± 1.9</td>
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<tr>
<td>MSAP (mm Hg)</td>
<td>140.4 ± 3.2</td>
<td>120 ± 2.6</td>
</tr>
<tr>
<td>CI (ml/min/m²)</td>
<td>3577 ± 162</td>
<td>4076 ± 210</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>49.2 ± 2.6</td>
<td>55 ± 2.7</td>
</tr>
<tr>
<td>SVR (dyn sec cm⁻²)</td>
<td>1766 ± 94.6</td>
<td>1281 ± 61.1</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>17.6 ± 1.4</td>
<td>15.2 ± 0.9</td>
</tr>
<tr>
<td>PAR (dyn sec cm⁻²)</td>
<td>113.5 ± 6.6</td>
<td>98.2 ± 5.7</td>
</tr>
<tr>
<td>PV (ml)</td>
<td>3149 ± 75.5</td>
<td>3094 ± 75.4</td>
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</tbody>
</table>

*Measurements carried out 4 hours after the last dose.
†Differences from control significant at p < 0.05.
‡Differences from control significant at p < 0.01.

**Abbreviations:** HR = heart rate; MSAP = mean systemic arterial pressure; CI = cardiac index; SI = stroke index; SVR = systemic vascular resistance; MPAP = mean pulmonary arterial pressure; PAR = pulmonary arterial resistance; PV = plasma volume.

### Table 2. Laboratory Data (mean ± SEM) Before and After Chronic Treatment with Nifedipine

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Nifedipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood urea concentration (mg/100 ml)</td>
<td>48 ± 3.2</td>
<td>43.6 ± 3.1</td>
</tr>
<tr>
<td>Serum creatinine concentration (mg%)</td>
<td>1.34 ± 0.07</td>
<td>1.32 ± 0.08</td>
</tr>
<tr>
<td>Serum potassium concentration (mEq/l)</td>
<td>3.75 ± 0.11</td>
<td>3.93 ± 0.13</td>
</tr>
<tr>
<td>Serum sodium concentration (mEq/l)</td>
<td>140.5 ± 0.78</td>
<td>140.2 ± 0.65</td>
</tr>
<tr>
<td>Serum chloride concentration (mEq/l)</td>
<td>104 ± 0.96</td>
<td>103 ± 0.87</td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min)</td>
<td>80.5 ± 5.09</td>
<td>81.8 ± 4.9</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>0.566 ± 0.14</td>
<td>*0.736 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>standing</td>
<td>1.007 ± 0.24</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>71 ± 2.3</td>
<td>70.5 ± 2.2</td>
</tr>
</tbody>
</table>

*The differences are not significant.
†Three hours after the last dose.
‡Six hours after the last dose.

**References**

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