Captopril and Nifedipine in Combination for Moderate to Severe Essential Hypertension

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SUMMARY The effects of the addition of a calcium entry antagonist, nifedipine (20-mg tablet twice a day), to an angiotensin converting enzyme inhibitor, captopril (25 mg three times a day), and the addition of captopril to nifedipine were observed in two separate studies in patients with essential hypertension: After 4 weeks of captopril therapy alone, mean arterial pressure fell by 12 mm Hg, and with the addition of nifedipine to captopril for a further month, blood pressure fell by an additional 10 mm Hg. In a separate group of patients treated with the same doses, mean arterial pressure fell by 17 mm Hg with nifedipine treatment alone; when captopril was added to the nifedipine therapy for an additional month, mean arterial pressure fell by a further 11 mm Hg. These blood pressures were measured 2 hours after the last dose; however, there was less of a fall in blood pressure when it was measured 12 hours after the last dose. This study confirms that captopril and nifedipine have a marked additive effect on blood pressure in whichever order they are given, but it shows that the combination is relatively short-acting. (Hypertension 9: 629-633, 1987)

KEY WORDS • angiotensin converting enzyme inhibition • calcium entry antagonism • drug synergism • essential hypertension • renin-angiotensin system

THE calcium entry antagonist nifedipine and the angiotensin converting enzyme inhibitor captopril2 are well established as effective blood pressure-lowering agents on their own in patients with mild to moderate essential hypertension. However, neither of these drugs invariably lowers blood pressure into the normal or desired range, and we have found that the combination of nifedipine tablets and captopril was particularly useful in getting good control of blood pressure in patients with treatment-resistant hypertension. Therefore, we decided to perform a randomized study of the effect of the two drugs alone and in combination in patients with moderate essential hypertension who were receiving no other treatment.

Patients and Methods

All patients were referred by local general practitioners to the blood pressure unit and were included in the study if their supine diastolic pressure was between 100 and 120 mm Hg after at least 2 weeks off all treatment. All patients had been seen previously in the blood pressure unit for at least 2 months before the start of this study and had had their blood pressures measured every fortnight so that they were well used to having their blood pressure measured under standard conditions. Patients who had renal failure (plasma creatinine > 120 μmol/L), ischemic heart disease, or cerebrovascular disease or who were taking an oral contraceptive pill or any other drug were excluded from the study, which was approved by the hospital ethical committee.

Nineteen patients who gave their informed consent entered and completed the study. There were 12 men and 7 women, of whom 13 were white and 6 were black; mean age was 53 years (range, 35-69 years). Average supine blood pressure at entry was 168/107 ± 6.3/3.3 mm Hg. Subjects were randomly assigned to receive either a 1-month treatment with...
captopril (Capoten, Squibb), 25 mg three times a day (n = 10), or nifedipine tablets (Adalat Retard, Bayer), 20 mg twice a day (n = 9). After the 1-month treatment with either captopril or nifedipine alone, all patients received the combination of captopril (25 mg three times a day) and nifedipine (20 mg twice a day).

All blood pressures were measured every 2 weeks; each patient was seen on the same day of the week at the same time of day by the same nurse in the same room. Blood pressure was measured in the same arm by nurses using semiautomatic ultrasound sphygmomanometers (Arteriosonde; Roche, Cranbury, NJ, USA) with attached recorders. Measurements were therefore free from observer bias. The diastolic pressure measured by the Arteriosonde is between Phase IV and Phase V. Supine and standing blood pressures were taken as the mean of five readings taken at 1- to 2-minute intervals. Pulse was measured by a pulse monitor (Cambridge 3030; Kent Cambridge Instrument Company, Ossining, NY, USA).

At the end of each 1-month treatment, patients were seen before they had taken their usual morning dose of tablets; they had taken their evening dose the night before. Blood pressure was then measured 12 hours after their last evening dose, and blood was taken for the measurement of urea, creatinine, electrolytes, and plasma renin activity and aldosterone. After these measurements were made, the patients were then given their usual tablets. Blood pressure was measured again 2 hours later, when blood was also taken for estimation of plasma renin activity and aldosterone. All blood samples were taken without stasis between 0900 and 1200 after the patient had been sitting upright for 10 minutes. In patients who were given nifedipine first and then given captopril, the effect of the first dose of captopril was studied by measuring blood pressure 2 hours after the first 25 mg of captopril. No dietary advice was given to the patients.

Mean arterial pressure was calculated as diastolic pressure plus one third of the pulse pressure. All results are reported as means ± SEM. Statistical analysis was by Student's t test and Pearson's correlation analysis using the University of London computer and Northwestern University's Statistical Package for Social Sciences.

Results

Blood Pressure

In Group 1 (n = 10), captopril treatment was followed by the addition of nifedipine. After 4 weeks of captopril therapy alone, there was a significant fall in supine systolic and diastolic blood pressure 2 hours after the last dose (Figure 1). Mean arterial pressure at this time fell by 12 mm Hg (9.5%). Twelve hours after the last dose of the 1-month captopril treatment, however, no significant fall was observed in blood pressure (Table 1). After a further 1-month treatment with the combination of nifedipine and captopril, there was a further significant fall 2 hours after the last dose, as compared with that seen with captopril alone, in supine systolic and diastolic blood pressure (see Figure 1). Mean arterial pressure fell by 22 mm Hg (17.3%) compared with the pretreatment blood pressure. However, 12 hours after the last dose of the combined treatment, the fall in blood pressure had decreased (see Table 1), and the mean fall in blood pressure was 8 mm Hg (6.4%). Changes in standing blood pressure were similar to those in supine blood pressure (see Table 1).

In Group 2 (n = 9), nifedipine treatment was followed by the addition of captopril. After a 1-month treatment with nifedipine alone, there was a significant fall in supine systolic and diastolic pressure 2 hours after the last dose (Figure 2). Mean arterial pressure fell by 17 mm Hg (13.4%). Twelve hours after the last dose of the 1-month treatment with nifedipine, the fall in blood pressure was less but still significant (Table 2). The mean arterial pressure fall was 10 mm Hg (7.8%). After a further month of treatment with the combination of captopril and nifedipine, there was a further significant fall in both systolic and diastolic pressure (see Figure 2). Mean arterial pressure fell by 28 mm Hg (22%) compared with pretreatment values. However, 12 hours after the last dose of the combined treatment, the fall in both systolic and diastolic pressure had decreased (see Table 2), and the mean arterial pressure fall was 11 mm Hg (8.3%).

Blood pressure was also measured 2 hours after the first dose of captopril in the patients who were already...
receiving nifedipine (having taken the nifedipine 2 hours before the captopril). No patient became hypertensive or experienced postural hypotension with the addition of captopril to nifedipine. The mean fall in supine systolic blood pressure was 10 mm Hg and in diastolic pressure, 9 mm Hg. The maximum fall that occurred in an individual patient in either systolic or diastolic pressure was 29 mm Hg.

The effect of the combined treatment with captopril and nifedipine, in whichever order it was given, was significantly greater than that seen with either drug alone 2 hours after the last dose. However, when assessed 12 hours after the last dose, captopril appeared to have little blood pressure-lowering effect either alone or when combined with nifedipine.

As can be seen in Tables 1 and 2, there was little difference between the two groups either in initial pressures or in the other measurements that were made. Blood pressures that were measured at Weeks 2 and 6 of the study during routine visits, approximately 2 to 4 hours after the last dose of either captopril or nifedipine alone or in combination, showed similar changes to those measured at Week 4 of treatment 2 hours after the last dose.

Pulse Rate

There was no significant change in the supine pulse rate in Group 1 during the study (see Table 1), but there was a small but significant fall in standing pulse rate from 2 to 12 hours after 4 weeks of the combined treatment of captopril and nifedipine (mean fall in pulse rate, 4.7 beats/min; \( p < 0.02 \)). Similarly, during nifedipine treatment alone, Group 2 showed no significant change in supine pulse rate during the study compared with pretreatment values. However, with combined treatment, supine and standing heart rates were significantly higher 2 hours after the combination of nifedipine and captopril compared with 12 hours after the last dose (see Table 2).

Weight

With captopril treatment alone, Group 1 had no significant change in weight, but with the addition of nifedipine to captopril, Group 1 had a significant increase of 0.49 ± 2.99 kg.

### Table 1. Characteristics of Group I, Treated with 1 Month of Captopril Followed by the Addition of Nifedipine for 1 Month

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Pretreatment</th>
<th>Captopril 2 hr</th>
<th>Captopril 12 hr</th>
<th>Captopril + Nifedipine 2 hr</th>
<th>Captopril + Nifedipine 12 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine blood pressure (mm Hg)</td>
<td>166/108 ±5.3/2.5</td>
<td>154<em>95</em> ±5.3/3.3</td>
<td>170/107 ±6.0/3.2</td>
<td>139<em>88</em> ±5.6/4.5</td>
<td>155†101† ±5.4/2.8</td>
</tr>
<tr>
<td>Standing blood pressure (mm Hg)</td>
<td>164/115 ±3.8/2.9</td>
<td>157<em>103</em> ±5.3/3.9</td>
<td>168/115 ±5.0/3.2</td>
<td>137<em>93</em> ±5.4/4.3</td>
<td>153†105‡ ±5.1/3.6</td>
</tr>
<tr>
<td>Supine pulse (beats/min)</td>
<td>81 ± 3.7</td>
<td>81 ± 4.2</td>
<td>79 ± 3.4</td>
<td>82 ± 4.5</td>
<td>79 ± 3.4</td>
</tr>
<tr>
<td>Standing pulse (beats/min)</td>
<td>91 ± 2.8</td>
<td>93 ± 4.3</td>
<td>89 ± 2.9</td>
<td>94 ± 5.3</td>
<td>89 ± 4.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.00 ± 3.05</td>
<td>—</td>
<td>81.09 ± 2.87</td>
<td>—</td>
<td>80.49 ± 2.99</td>
</tr>
<tr>
<td>Plasma renin activity (ng ANG I/ml/hr)</td>
<td>0.75 ± 0.22</td>
<td>6.46 ± 2.4†</td>
<td>6.32 ± 3.7</td>
<td>11.36 ± 3.6†</td>
<td>3.63 ± 0.87‡</td>
</tr>
<tr>
<td>Aldosterone (pmol/L)</td>
<td>282 ± 70</td>
<td>150 ± 29</td>
<td>267 ± 26</td>
<td>187 ± 26</td>
<td>365 ± 74</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>138 ± 0.6</td>
<td>—</td>
<td>137.5 ± 0.7</td>
<td>—</td>
<td>137.9 ± 0.85</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.86 ± 0.13</td>
<td>—</td>
<td>3.85 ± 0.07</td>
<td>—</td>
<td>4.05 ± 0.06</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>103.1 ± 0.46</td>
<td>—</td>
<td>103.5 ± 0.81</td>
<td>—</td>
<td>101.5 ± 0.06†</td>
</tr>
</tbody>
</table>

Values are means ± SEM of 10 subjects. ANG I = angiotensin I. *p < 0.001, †p < 0.05, ‡p < 0.01, compared with pretreatment values.
weight loss of 0.6 kg (p < 0.05; see Table 1). In Group 2, who were treated with nifedipine first, there was a significant weight loss with nifedipine treatment alone (mean weight loss, 1 kg; p < 0.05) but no further fall in weight occurred when captopril was added to nifedipine (see Table 2).

### Plasma Renin Activity and Aldosterone

As expected, Group 1 had a significant increase in plasma renin activity after the last dose of the 1-month treatment with captopril, and this was still significantly raised 12 hours after the last dose. Two hours after the last dose there was a fall in plasma aldosterone that just failed to reach statistical significance; at 12 hours, aldosterone level had returned to pretreatment values. The combination of captopril and nifedipine produced a further increase in plasma renin activity 2 hours after the last dose, but a reduction at 12 hours. The combined treatment induced a fall in aldosterone 2 hours after the last dose, which just failed to reach statistical significance; aldosterone rose above pretreatment levels 12 hours after the last dose, although this change was not significant.

In Group 2, during nifedipine treatment alone, there was a significant increase in plasma renin activity 2 hours after the last dose, but at 12 hours, it fell toward pretreatment levels. Plasma aldosterone showed a slight but nonsignificant increase at both 2 and 12 hours after the last dose of the 1-month treatment with nifedipine alone. The combination of nifedipine and captopril produced a significant increase in plasma renin activity 2 hours after the last dose, an effect that was somewhat diminished but still significant compared with pretreatment levels 12 hours after the last dose. Plasma aldosterone fell 2 hours after the last dose of the combined therapy and rose above pretreatment levels 12 hours after the last dose.

### Other Measurements

There was no significant change in either group in plasma levels of sodium, potassium, or urea during the study. After 4 weeks of the combination of nifedipine and captopril, where nifedipine was administered first (Group 2), there was a small but significant increase in plasma creatinine (see Table 2), but in the group treated with captopril first, followed by nifedipine (Group 1), there was no significant increase in creatinine.

Patients were asked at each visit whether they felt well and whether the tablets had upset them in any way. Symptoms were recorded both before and after drug therapy was started, either singly or in combination, for each of the study groups. Although a number of minor side effects were reported, no patient had to withdraw from the study. Of the group that received captopril first, three patients reported headaches before entering the study that did not increase with captopril treatment and two other patients reported occasional mild headaches with the combination of captopril and nifedipine. One patient reported flushing before entering the study. Three reported flushing with captopril alone, and three with captopril and nifedipine. Dyspepsia was noted by one patient before entry, four with captopril alone, and three with the combined treatment. Transient dizziness early in the study occurred in one patient with captopril alone and in two with the combination.

Of the group that received nifedipine first, none reported headaches before entry, three patients reported headaches with nifedipine as single therapy, and none reported headaches with the combined treatment. Flushing was reported by one patient in this group before entering the study and by three while on nifedipine alone. However, only one patient noted flushing with the combined treatment. Mild ankle swelling developed in one patient with nifedipine alone and in two with the combination.
patients with the combined treatment. Two patients had occasional mild tingling and noted warm extremities with both nifedipine and the combined treatment.

**Discussion**

This study clearly demonstrates that the combination of nifedipine and captopril is significantly more effective than either drug alone and confirms our previous impression in patients with resistant hypertension that this combination is effective. Two previous studies have demonstrated an additive effect between calcium entry antagonists and angiotensin converting enzyme inhibitors. In one study, six patients received verapamil and 10 received nifedipine, to which various doses of captopril later were added in a wide range of treatment periods. An additive effect was shown in 15 of the 16 patients. In another study, blood pressure was satisfactorily controlled in 12 patients with hypertension who were refractory to treatment with captopril and a diuretic but responded when nifedipine was added to this regimen. Interestingly, in 10 of those patients, the diuretic was withdrawn without loss of blood pressure control.

Neither of the two previous studies reported the timing of the blood pressure measurement after the last dose of the calcium entry antagonist or captopril. Our study clearly demonstrates that the additional effect of the two drugs is short-lived and that there is little additive effect 12 hours after the last dose. This finding again confirms our experience in treatment-resistant hypertensive subjects: the combination of nifedipine and captopril is effective when both drugs have their peak effect on blood pressure, but the combination must be given at least three and sometimes four times a day to gain adequate control of blood pressure throughout the day.

The mechanism of the additive effect of these two drugs is not clear. Nifedipine is known to cause an acute loss of sodium, and some circumstantial evidence suggests that it has a longer-lasting diuretic effect. It also causes a rise in plasma renin activity and angiotensin II immediately after a dose, as can be seen in the present study. This increase in angiotensin II is likely to offset, at least in part, the blood pressure-lowering effect of nifedipine. As captopril would block this rise in angiotensin II, this could partly explain the additive effect of captopril. However, studies in normotensive subjects have shown a reduced pressor effect of angiotensin II when subjects are pretreated with nifedipine. Further studies are needed to clarify the mechanism of the additive effect of these two drugs.

The treatment alone and in combination was well tolerated, and no major adverse effects were encountered. All subjects completed the study. Our longer-term experience with therapy in treatment-resistant hypertensive subjects has also been that this treatment is well tolerated, although the well-known side effects of nifedipine—facial flushing, tingling, and warmth in the hands and feet—are encountered occasionally. Interestingly, we could find no consistent change in heart rate in this study with either drug alone or in combination. When the first dose of captopril was added to nifedipine, there were no severe falls in blood pressure. This has also been our experience in a much larger number of patients with treatment-resistant hypertension who were treated with nifedipine alone followed by the addition of captopril.

Our study clearly confirms that the addition of a calcium entry antagonist, nifedipine, to a converting enzyme inhibitor, captopril, has an additive effect on blood pressure regardless of the order of administration. Because this marked additive effect is short-lived, multiple daily dosing is required for adequate maintenance of blood pressure control. However, the well-being of patients on this combination, as compared with older regimens, is such that many patients with more severe hypertension are prepared to undergo the inconvenience of multiple daily dosing. The combination of nifedipine and captopril may be particularly useful in those patients whose hypertension is not controlled on captopril and large doses of diuretics, as the addition of nifedipine reduces or may replace the need for diuretics, which can be associated with adverse metabolic side effects. Our results also indicate that a longer-acting converting enzyme inhibitor combined with a longer-acting calcium entry antagonist should be very effective in the treatment of moderate to severe essential hypertension.

**References**

Captopril and nifedipine in combination for moderate to severe essential hypertension.

D R Singer, N D Markandu, A C Shore and G A MacGregor

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