Calcium-channel blockade with nifedipine and angiotensin converting–enzyme inhibition with captopril in the therapy of patients with severe primary hypertension

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ABSTRACT Nifedipine (10 mg qid) and captopril (25 mg qid) were tested alone and in combination in 14 patients suffering from severe primary hypertension. Each study period was of 1 week’s duration. Circulatory response was evaluated through hourly pressure and pulse rate readings. The fall in pressure after oral nifedipine was maximal within 1 hr or less and was generally accompanied by palpitation and increase in pulse rate; with a six hourly dosing regimen the tendency of blood pressure to recover after each dose was interrupted by the next dose, so that values remained significantly reduced throughout the 24 hr, although pressure fluctuations were evident. Promptness of the antihypertensive action of captopril was similar, but the magnitude and the duration of the fall in pressure were less pronounced. When the converting–enzyme inhibitor was combined with the calcium-channel blocker, pressure fluctuations were not abolished, but the antihypertensive response was definitely enhanced, so that normal blood pressure was maintained for several hours during the day. Additional positive effects of captopril were mitigation of the heart rate reaction and prevention of the ankle pitting or edema elicited by nifedipine. A balance in arteriolar and venular dilatation promoted by captopril is the suggested mechanism for these effects. With the two-drug combination the function of the left ventricle was not reduced and possibly improved; blood urea nitrogen and serum electrolyte and creatinine concentration were not affected. Plasma renin activity increased with captopril and reverted toward baseline with the addition of nifedipine, suggesting an interference of the calcium-channel blocker with the release of renin.


Calcium antagonists block transmembrane Ca supply and reduce the contractile vascular muscle activity in a dose-related manner. However, the higher the wall tension is elevated above normal, the more relaxation is induced by a given concentration of Ca antagonist.1 Because of this, the use of these compounds has been proposed in the management of hypertensive crises2 as well as in the treatment of essential hypertension.3 The hypotensive response to oral nifedipine is prompt, and a dosing regimen every 6 hr significantly lowers blood pressure over the 24 hr, although fluctuations are recorded owing to the rate of decay of the vasodilating effect.4 The reaction of pulse rate at the nadir of the hypotensive response to each dose and development of ankle edema in about 25% of the patients are additional unwanted effects. Combination with methyldopa5 or propranolol6 potentiates the efficacy of nifedipine and reduces tachycardia and pressure fluctuations, but does not prevent ankle edema. In addition, although it has been proved that nifedipine does not depress the performance of the heart in an important way when the autonomic nervous system is intact, combination with a β-blocker may expose the patient to the potential hazard of excessive depression in contractility7 when the baseline heart function is impaired.8

Captopril lowers blood pressure9 without eliciting tachycardia and also improves the function of the failing heart.10 In two severely hypertensive patients whose disease responded poorly to nifedipine, the addition of captopril potentiated the hypotensive efficacy of the former and remarkably diminished ankle edema; this incidental observation suggested to us that the

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nifedipine-captopril combination might be worthy of trial in patients with severe hypertension.

Material and methods

Patient population. Fourteen hospitalized patients (eight men and six women, average age 48 years) were admitted to the trial because they fulfilled the following selection criteria: untreated or poorly treated essential hypertension with diastolic blood pressure of 120 mm Hg or greater 1 week after discontinuing antihypertensive medications or any other cardiovascular therapy; no history or evidence of renal insufficiency, major cardiac arrhythmias, or conduction abnormalities.

Study design. After it was determined that they were not suffering from secondary forms of hypertension, all patients received placebo, in preparations identical in shape and color to the active compounds, at regular 6 hr intervals for 7 days. Patients were then separated into two groups in a prospective randomized way and treated with two regimens that included three subsequent 7 day periods. In group 1 (seven subjects) treatment was started with nifedipine (10 mg doses) and placebo administered every 6 hr (period A, days 8 to 14). During the next period (period B, days 15 to 21) nifedipine was continued and captopril (25 mg each dose) was substituted for placebo. In the third phase captopril was continued and nifedipine was replaced by placebo (period C, days 22 to 28). In group 2 (seven subjects) the sequence of administration of the two compounds was inverted: captopril and placebo were given during period A, the two active preparations were given at period B, and nifedipine plus placebo were given during period C. Readings of blood pressure and pulse rate were taken hourly from 8 A.M. to 7 P.M. by the same observer throughout hospitalization. Blood pressure was measured with a standard mercury sphygmomanometer according to the recommendations of the American Heart Association.\(^\text{13}\) All blood pressures were measured three times at 1 min intervals in patients in the supine position and, subsequently, in the standing position, at least 5 min after the change in posture. Results of the three determinations were averaged. Pulse rate was counted after the last pressure measurement in each position. Patients were on a standard 100 meq sodium diet throughout hospitalization. Body weight, urinary output, and the water volume of the right foot ("foot volume"), determined by the method of water displacement,\(^\text{12}\) were checked daily for the duration of the study.

Echocardiographic evaluations. Influences of the drugs, alone and in combination, on the contractile activity of the heart were evaluated noninvasively on echocardiograms recorded at the end of each period (3 hr after the last doses). Left ventricular end-systolic wall stress was calculated through the angiographically validated equation of Grossman et al.,\(^\text{13}\) as modified by Reichek et al.\(^\text{14}\):

\[
\text{c.s. CWS} = \frac{0.334 \times \text{Ps/LVVIDS}}{\text{PWTs} \times (1 + \frac{\text{PWTs}}{\text{LVVIDS}})}
\]

where Ps, LVVIDS, and PWTs are systolic cuff arterial pressure, left ventricular minor dimension (cm), and posterior wall thickness (cm), respectively, at end systole. For these calculations pressure was measured by an independent observer three times consecutively (with 5 min intervals between each measurement) with the patient at rest, after 15 min of recumbency. Readings were averaged to obtain a more accurate value. For the echocardiographic measurements, a Hewlett-Packard ultrasound unit, model 77020A, was used. End-systolic dimension of the endocardial surface was determined by the shortest distance between the septal and posterior internal walls during systole. End-systolic posterior wall thickness was measured as the point of maximal anterior motion with the leading edge-to-leading edge method. Data analyzed were the means of three to five consecutive cycles. The end-systolic stress–left ventricular end-systolic diameter relationship was taken as an index of the end-systolic force-length relationship.

Humoral measurements. Blood urea nitrogen, serum creatinine and electrolyte concentrations, glomerular filtration rate, and plasma renin activity were determined both in the supine patients and after 2 hr in the standing position at the end of the run-in period and of each treatment period. Plasma renin activity was measured by radioimmunoassay\(^\text{15}\) of angiotensin I in venous plasma samples. Each sample was assayed in triplicate and expressed as the difference between samples incubated at 37° and 4° C in ng·ml⁻¹·hr⁻¹.

Statistical evaluation. For the analysis of the circulatory and hemodural data, differences were assessed through the analysis of variance with a Kontron computer, model Cardio 80.

Results

Figure 1 illustrates the averages of the daily systolic and diastolic pressure and heart rate readings in subjects in groups 1 and 2 while in the supine position during the run-in and trial periods. Blood pressure was comparable in the two groups at control (days 1 to 7), without significant fluctuations during the day. In group 1 the single value derived from the average of all supine determinations on day 7 was 178/114 mm Hg. Nifedipine (day 8) was promptly effective and, within 1 hr or less, lowered systolic and diastolic values by 19.5% and 18.4%, respectively. Although a trend toward increase was then observed, pressure remained significantly lower than at the end of the run-in period (day 7) up to the time of the second dose, which reduced blood pressure to the level attained after the first. A similar pattern to this was observed throughout period A (days 8 to 14). The single value of all pressure readings averaged 160/105 and 152/103 mm Hg by days 8 and 14, respectively; both of these values were significantly (p < .01) lower than that on the last pretreatment placebo day (day 7). During period A blood pressure ranged from an average of 161/111 mm Hg to an average of 146/95 mm Hg over a 12 hr period (systolic fluctuation 15 mm Hg, diastolic fluctuation 16 mm Hg). Heart rate was significantly augmented (by 17 beats/min; p < .01) for about an hour after each dose. Pressure and heart rate fluctuations were qualitatively and quantitatively similar in subjects in the standing position. When captopril was added to nifedipine therapy (period B, days 15 to 21) hypotension was still maximal within 1 hr; systolic and diastolic values
FIGURE 1. Mean ± SEM hourly supine systolic and diastolic arterial pressure (AP) and heart rate (HR) readings during run-in (days 1 to 7) period and periods A (days 8 to 14), B (days 15 to 21), and C (days 22 to 28) in groups 1 and 2. Open arrows indicate the time of the day at which the drugs were administered. ▲ = differences from the corresponding value on day 7 significant at p < .05; * = differences from the corresponding value on day 7 significant at p < .01.

were diminished by 19% and 22.5%, respectively, and the absolute levels attained were consistently lower than with nifedipine alone. Because the slope of recovery remained essentially unchanged, at the moment of administration of the subsequent dose pressure was less elevated than before the captopril combination and after dosing it fell again to the level attained after the first dose. Persistence of this pattern throughout period B resulted in a potentiation of the antihypertensive action; in fact, the mean blood pressure readings had declined to 147/96 and 141/91 mm Hg by days 15 and 21, respectively, and the blood pressure range was from an average of 152/102 mm Hg to 129/85 mm Hg over a 12 hr period (systolic fluctuation 23 mm Hg, diastolic fluctuation 16 mm Hg; neither significantly different from those recorded during the nifedipine period). No potentiation of the decrease in pressure in the vertical position, as compared with in the horizontal position, was seen after the addition of captopril. While on this regimen, phasic changes in heart rate,
FIGURE 2. Shift from baseline (solid square) with treatment (open squares) of the relationship between left ventricular end-systolic circumferential wall stress (es CWS) and end-systolic internal diameter (es ID). Symbols represent means ± SEM. * = p value of <.01 for differences in wall stress and diameter between baseline and treatment.

both supine and standing, were much less pronounced and statistical significance of differences from baseline was lost. When placebo was substituted for nifedipine and captopril was continued (period C, day 22 to 28), supine and standing systolic and diastolic fluctuations were basically unchanged, but the range was displaced upwards (from 167/114 to 155/99 mm Hg over a 12 hr period) to levels somewhat higher than with nifedipine alone (period A). Average heart rate was reduced and phasic tachycardia was fully abolished.

In group 2, findings at periods A, B, and C were similar to those in group 1 at periods C, B, and A, respectively. The quality and the quantity of the circulatory response to each regimen, therefore, did not appear to be influenced by the sequence of drug administration.

The left ventricular end-systolic stress—end-systolic diameter relationship illustrated in figure 2 (data of the two groups at the various periods were pooled together) was shifted to the left by each type of treatment.

Blood urea nitrogen, serum sodium, chloride and creatinine concentrations, glomerular filtration rate, body weight, and urinary output did not vary consistently (table 1); serum potassium concentration was slightly, but significantly, augmented after captopril. Foot volume was significantly augmented by nifedipine but not by the converting enzyme inhibitor; the latter, when combined with nifedipine, brought foot volume back to baseline levels. It is worth noting that foot volume increased during calcium-channel blockade concomitant with some increase in the urinary output and reduction in body weight, and was reduced

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Laboratory data (mean ± SEM) at baseline and after treatments</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Blood urea concentration (mg/100 ml)</td>
<td>31</td>
</tr>
<tr>
<td>Serum creatinine concentration (mg %)</td>
<td>1.21</td>
</tr>
<tr>
<td>Serum sodium concentration (meq/l)</td>
<td>147.7</td>
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<tr>
<td>Serum potassium concentration (meq/l)</td>
<td>4.02</td>
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<tr>
<td>Serum chloride concentration (meq/l)</td>
<td>100.5</td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min)</td>
<td>81.8</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>(5.6)</td>
</tr>
<tr>
<td>Supine</td>
<td>(1.28)</td>
</tr>
<tr>
<td>Standing</td>
<td>(2.08)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>77.6</td>
</tr>
<tr>
<td>Foot volume (ml)</td>
<td>1245.8</td>
</tr>
<tr>
<td>Urinary output (ml/24 hr)</td>
<td>1042.8</td>
</tr>
</tbody>
</table>

* indicates differences from baseline significant at p < .01.
by the converting-enzyme inhibitor compared with during the nifedipine period without associated changes in body weight and urinary output. Plasma renin activity in subjects in the supine and standing positions did not differ significantly from control after nifedipine, was remarkably increased after captopril, and reverted toward baseline after the combination of the drugs.

No noticeable side effect of captopril was observed or reported.

Discussion

Both nifedipine¹ and captopril⁶ are basically vasodilators and they lower blood pressure²,⁷ through reduction of peripheral vascular resistance. As antihypertensive drugs, they seem best suited for treating patients with a high degree of vasoconstriction, who generally present with remarkable elevation of the diastolic blood pressure.³,⁵,¹⁸⁻²¹

A dosing regimen of 25 mg qid captopril has proved to possess definite antihypertensive efficacy with minimal side effects²⁰,²²,²³; no side effects of captopril were noted in the present trial. Comparing period A in group 1 and C in group 2 (nifedipine) with period A in group 2 and C in group 1 (captopril) we observed the following: the time for maximal pressure lowering was similar for captopril and oral nifedipine, nifedipine was more potent,²⁴ and the slopes of recovery of blood pressure and, consequently, the rates of decay of the vasodilatation were comparable, although the mechanism of the vasodilating action was likely very different. Because the two drugs are of disparate antihypertensive efficacy while there is a similar decay of their vasodilatory effects, 6 hr after each dose pressure reduction was invariably significant with nifedipine, while differences from control were only of borderline significance with captopril (group 2, period A). This suggests that with a three-times-daily dosing regimen, which is currently used for captopril, pressure may remain elevated for a certain span over the 24 hr. It also suggests that a single daily pressure measurement during the day may be adequate for a reliable evaluation of the antihypertensive response and that repeated measurements or ambulatory monitoring are needed for an appropriate institution of a drug regimen.

The combination of the two compounds resulted in potentiation of the antihypertensive efficacy (period B in either group) and in persistence of blood pressure variability during the day. However, at each hourly measurement, blood pressure was definitely lower than at baseline, and was totally normal during many hours of the day. Also, at least over a short-term period, both preparations maintained their efficacy; period C was characterized, in both group 1 and group 2, by a consistent increase in pressure compared with period B.

The mechanism through which vasodilatation is induced and blood pressure is lowered by captopril is not completely understood; inhibition of angiotensin II production, increase in the circulating levels of bradykinin, enhanced release of prostaglandins,¹⁶ and depression of α-adrenergic responsiveness in vascular smooth muscle²⁵ seem to be involved. Whatever the mechanisms are, they must be active in the presence of calcium-channel blockade. With regard to the relationship between calcium and the renin-angiotensin system, it is documented that the former is involved in the control of renin release²⁶ and that calcium antagonists, unlike other vasodilators, do not promote hyperreninemia.¹,⁴,²⁷ In this study, plasma renin activity was enhanced by the converting-enzyme inhibitor⁶ and was brought back toward baseline (table 1) by the addition of nifedipine, indicating a negative interference of this compound with the release of renin.

Captopril reduced the reaction of heart rate to nifedipine and exerted a beneficial effect on the ankle pitting or edema promoted by the calcium-channel blocker. The pulse rate restraint might have been due to withdrawal of the facilitating action of angiotensin II on the sympathetic neurotransmission; however, this interpretation is not supported by the changes that captopril, both alone and in combination, induced on the relationship of the end-systolic stress vs left ventricular end-systolic diameter,²⁸,²⁹ which was taken as an index of the end-systolic force-length relationship.¹⁴ The shift to the left of baseline (figure 2) in this relationship, in fact, rules out a negative inotropic influence, which would be expected if sympathetic neurotransmission were impaired. Other pharmacologic actions of the converting-enzyme inhibitor may be responsible, such as its modification of arterial baroreflexes³⁰ and the venodilatation it induces¹⁷ (if blood pressure falls from balanced arterial and venodilatation, resulting heart rate may not vary).

Changes from baseline that were observed in the force-length relationship may indicate either a shift to a different point in the same basal stress-length line (which would indicate no change in contractility) or a displacement to the left of the stress-length line itself (which would reflect improved contractility). It is worthwhile to note that the decrease in stress was comparable after the three different drug regimens, while reduction in ventricular end-systolic dimension was
greater when captopril was used alone or combined with nifedipine. This pattern favors the interpretation that the force-length line was shifted to the left by the converting-enzyme inhibitor and suggests that the nifedipine-captopril combination may also be used with a reasonable amount of confidence in patients with advanced hypertensive heart disease.

The tendency to ankle pitting or edema in patients on nifedipine is probably not related to the hypertensive state, since it may also appear in patients with normal blood pressure who are treated with nifedipine for angina pectoris. It has also been documented that the mechanism of this effect is independent of fluid retention or cardiac function depression. Perhaps arteriolar vasodilatation without venular dilatation increases capillary pressure, which adds to gravitational effects, resulting in edema. Possible explanations for the beneficial influence of captopril can only be speculative given the presently available data. Apart from the humoral actions of the compound that make it a useful remedy for idiopathic edema, the venodilatation it induces might substantially contribute to counteract this unwanted effect.

The combination of a calcium blocker and the converting-enzyme inhibitor, if properly used, appears to be more effective and better suited than each drug alone for treating patients with severe hypertension with high-level diastolic pressure and vasoconstriction. Persistence of efficacy is being evaluated through a long-term follow-up trial.

References

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