Captopril, an orally active inhibitor of angiotensin-converting enzyme, seems to exert its hemodynamic and humoral effect mainly by reducing angiotensin II formation. Since both vascular and hormonal actions of angiotensin II seem to be calcium-mediated, there is at least a theoretical basis for a possible interaction between captopril and nifedipine, a calcium channel inhibitor with proved antihypertensive effect. Furthermore, besides any theoretical consideration, practical information could be derived on the usefulness of associating these two drugs in the treatment of hypertensive patients.

**Methods**

Nine outpatients, five men and four women aged 36 to 59 years, with mild to moderate uncomplicated essential hypertension, gave informed consent to the study. After all drugs were discontinued for at least 3 weeks, patients received, according to a randomized sequence, captopril (25 mg t.i.d.), nifedipine (10 mg t.i.d.) and both drugs for 1 week, each active treatment period being preceded by 1 week of placebo administration. At the end of each period and at the same time of the day, 1 hour after the last dosing, body weight was measured, venous blood samples were obtained for measurement of plasma renin activity (PRA), sodium, potassium, and aldosterone, while blood pressure and heart rate were monitored every 10 minutes over a 2-hour period using an automatic device (Dinamap) while patients were seated.

PRA and aldosterone were measured by radioimmunoassay. Mean blood pressure, calculated as diastolic blood pressure plus one-third of pulse pressure, and heart rate were reported as averages of all values recorded.

Means, standard errors of the mean (SEM), and correlation coefficients were calculated according to standard methods, while the significance of differences between mean values was tested by two-way analysis of variance for randomized blocks.

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**SUMMARY** Nine patients with uncomplicated essential hypertension received, according to a randomized sequence, captopril (25 mg three times daily), nifedipine (10 mg three times daily), and both drugs for 1 week, each treatment period separated by a 1-week interval during which a placebo was given. Captopril significantly reduced blood pressure and plasma aldosterone, increased plasma renin activity (PRA), and did not change heart rate. Nifedipine exerted a similar effect on blood pressure and PRA, but it increased heart rate and did not change aldosterone. Captopril plus nifedipine further reduced blood pressure and increased PRA, did not change heart rate, and reduced aldosterone to values similar to those after captopril alone. The hypotensive effect of captopril was highly predictable by basal PRA values, and that of nifedipine by age, while PRA increments induced by captopril were unrelated to those induced by nifedipine. These data indicate that: 1) captopril and nifedipine exert an additive effect on blood pressure and renin; 2) captopril counteracts the heart rate increase induced by nifedipine; 3) nifedipine does not influence the aldosterone inhibition induced by captopril. It is suggested that the association of the two drugs can be usefully employed in the treatment of hypertension. (Hypertension 5 (supp III): III-154-III-156, 1983)

**KEY WORDS** • hypertension • renin-aldosterone • calcium antagonists
Results

No difference in clinical data and variables was evident among patients who underwent different treatment sequences; for this reason, all data were analyzed irrespective of treatment periods. Plasma sodium and potassium and body weight did not change significantly. As shown in Table 1, mean blood pressure (MAP), heart rate, PRA, and plasma aldosterone showed similar values at the end of the three placebo periods. A direct significant correlation was found between placebo PRA and aldosterone values (r = 0.80, p < 0.001).

Captopril alone significantly reduced MAP (p < 0.02) and plasma aldosterone (p < 0.005), increased PRA (p < 0.05), and did not change heart rate. Nifedipine reduced MAP significantly (p < 0.02); and to a similar extent as captopril, it increased heart rate (p < 0.02) and PRA (p < 0.05) but did not change plasma aldosterone. The combination of the two drugs further reduced blood pressure (p < 0.005), decreased plasma aldosterone (p < 0.02) to values similar to those after captopril alone, increased PRA (p < 0.05), and did not change heart rate. Decrements of mean blood pressure induced by the combined treatment were significantly (p < 0.01) greater than those induced by single drugs, while PRA values, although three times greater, did not differ significantly from those after single drugs.

Placebo MAP values were directly related to their decrements induced by captopril (r = 0.93, p < 0.001), nifedipine (r = 0.79, p < 0.01), and by both drugs (r = 0.95, p < 0.001). Decrements of MAP induced by captopril were directly related to their corresponding placebo PRA values (r = 0.81, p < 0.001), while those induced by nifedipine were directly related to age (r = 0.82, p < 0.001) and to heart rate increments (r = 0.56, p < 0.05). Increments of PRA induced by captopril were unrelated to those induced by nifedipine.

Discussion

Our data show that captopril and nifedipine, at the dose we used, caused a significant reduction in blood pressure of similar magnitude, probably by acting on different mechanism. In fact, even if the hypotensive action of both drugs was related to basal blood pressure values, that of captopril was highly predictable by basal renin values and that of nifedipine by age. These findings confirmed that captopril exerts its hypotensive action mainly by inhibiting the renin-angiotensin system, while nifedipine, like verapamil, seems to act by reversing an age-related calcium-entry-dependent vasconstriction.

In spite of the similar reductions in blood pressure, only nifedipine increased heart rate, an effect that seems mediated by reflex activation of the sympathetic nervous system (SNS). When the two drugs were combined, a further and significant reduction of blood pressure was obtained without any increase in heart rate. These findings suggest that the two drugs exert an additive hypotensive action, which can tentatively be explained by the fact that captopril can either reduce SNS activation or block the cardiovascular effect of renin stimulation induced by nifedipine. Captopril and nifedipine stimulated renin probably through different mechanisms, the effect of captopril probably being mediated by the removal of the negative feedback of angiotensin II or by the activation of prostaglandin synthesis, and that of nifedipine by the reduction of systemic blood pressure and the reflex activation of SNS. In fact the findings that both drugs combined further increased renin (an effect that can also be partially due to the greater decrease of blood pressure during the combined treatment period) and that renin increments induced by the two drugs were unrelated, tend to suggest that the two drugs act through different mechanisms and suggest that the effect of angiotensin II on renin is largely independent of cellular calcium transport or that captopril stimulates renin through other mechanisms.

In our patients, whose basal PRA and aldosterone values were directly related, captopril reduced aldosterone, an effect that is well explained by antiantiogenin II inhibition either in the presence or in the absence of nifedipine. Nifedipine, in turn, did not increase aldosterone in spite of significant renin stimulation. Taken together, these data suggest that extracellular

<table>
<thead>
<tr>
<th>Variable measured</th>
<th>Captopril</th>
<th>Nifedipine</th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>129.7 ± 2.1</td>
<td>118.2 ± 2.2†</td>
<td>130.8 ± 1.9</td>
<td>120.0 ± 1.7†</td>
<td>129.7 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>(11.5 ± 1.6)</td>
<td>(11.5 ± 1.6)</td>
<td>(10.0 ± 2.2)</td>
<td>(10.0 ± 2.2)</td>
<td>(10.0 ± 2.2)</td>
</tr>
<tr>
<td>HR (b/min)</td>
<td>66.3 ± 2.0</td>
<td>66.0 ± 1.6</td>
<td>67.6 ± 1.9</td>
<td>83.3 ± 6.3†</td>
<td>69.1 ± 2.1</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>PRA (ng·m⁻¹·hr⁻¹)</td>
<td>0.57 ± 0.12</td>
<td>2.04 ± 0.60*</td>
<td>0.53 ± 0.14</td>
<td>1.54 ± 0.41*</td>
<td>0.61 ± 0.15</td>
</tr>
<tr>
<td>PA (ng/dl)</td>
<td>14.1 ± 1.3</td>
<td>9.5 ± 0.8†</td>
<td>14.7 ± 1.2</td>
<td>12.8 ± 1.2</td>
<td>14.0 ± 1.1</td>
</tr>
</tbody>
</table>

Numbers in parentheses show percentage decrements from placebo values.

*p < 0.05; †p < 0.02; ‡p < 0.005, compared to corresponding placebo values.

§p < 0.01, compared to captopril and nifedipine values.
calcium is in some way involved in the aldosterone-stimulating action of angiotensin II, although other factors may be involved.

Finally, besides any theoretical consideration, the findings that captopril and nifedipine exert an additive hypotensive effect, indicate that these two drugs can be usefully combined in the treatment of hypertensive patients.

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