Discrepancy Between Antihypertensive Effect and Angiotensin Converting Enzyme Inhibition by Captopril

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SUMMARY Captopril, an inhibitor of angiotensin converting enzyme, was administered twice daily to 13 hypertensive patients for a mean period of 9 weeks. Continuous blood pressure control in the ambulatory patients was established with a portable blood pressure recorder. Notwithstanding, in eight patients with normal renal function, plasma converting enzyme was found to resume normal activity before administration of the morning dose of captopril. Only in 5 patients with impaired renal function did some blockade of plasma converting enzyme persist for more than 12 hours. Measured plasma converting enzyme activity seemed to reflect total conversion of angiotensin I, including conversion in the pulmonary vascular bed, since changes in its activity were closely paralleled by changes in plasma aldosterone levels. Bradykinin accumulation seems unlikely when converting enzyme and thus, presumably, kininase II has resumed normal activity. Captopril administration does not seem to alter plasma epinephrine or norepinephrine levels. Blood pressure reduction in the face of normal angiotensin converting enzyme activity is probably due to hyporesponsiveness of the arterioles to pressor hormones, which may be due to specific renin-related and/or nonspecific effects of captopril.

KEYWORDS • captopril • converting enzyme activity • angiotensin • bradykinin • renin-angiotensin-aldosterone system • plasma catecholamines

CAPTOPRIL has been shown to be effective in lowering blood pressure of hypertensive patients. Despite the rather short half-life of this new antihypertensive agent, twice-daily administration appears sufficient to keep blood pressure under control throughout the day. This notion is based on some sporadic checks in several patients, however, but not on continuous blood pressure profiles established under investigational conditions. It is generally assumed that the mechanism by which captopril reduces blood pressure is closely related to its blocking effect on angiotensin II generation by inhibiting angiotensin converting enzyme. Nevertheless, a renin-independent action of captopril has not been ruled out so far. It therefore seemed appropriate to take a closer look at the longitudinal behavior of the renin-angiotensin-aldosterone system of patients treated chronically with captopril to evaluate whether their blood pressure throughout the day closely relates to the degree of blockade of the renin system.

In the present study, blood pressure profiles were obtained, with a portable blood pressure recorder (Remler Corp., San Francisco, CA), in hypertensive patients treated chronically by twice-daily administration of captopril. Furthermore, plasma renin activity, plasma angiotensin converting enzyme activity, and plasma aldosterone levels were measured before and after the morning dose of captopril and related to blood pressure. The results suggest that twice-daily administration of captopril is sufficient to keep blood pressure under control continuously. In patients with normal renal function, however, blood pressure remained low despite intermittent resumption of normal angiotensin converting enzyme activity.

Methods

Patients

Thirteen hypertensive patients, 10 men and three women, aged 23 to 51 years, were included in the study. None of the subjects had clinical signs or symptoms of congestive heart failure. Five patients had essential hypertension, three renovascular hypertension, and five hypertension associated with chronic renal
failure due to primary renal disease. Diagnostic work-up included physical examination; routine laboratory measurements; intravenous pyelography; and plasma determinations of renin activity and aldosterone, norepinephrine, and epinephrine levels. In addition, renal arteriography or percutaneous renal biopsy were performed when indicated. All patients were fully informed of the experimental nature and potential risks of the study. The protocol had previously been approved by the institutional human studies committee.

Procedures

The protocol used to initiate captopril treatment has been described previously. In short, antihypertensive medication was discontinued, whenever possible, 3 weeks prior to the study. In a few patients with severe hypertension, antihypertensive therapy was withdrawn only 1 week before administration of the investigational drug. The patients were hospitalized and maintained on a constant sodium and potassium intake of 100 mEq and 60 to 80 mEq per day respectively; then captopril was started after a placebo period of 2 to 3 days. Blood samples for the measurements of plasma renin and angiotensin converting enzyme activity and plasma aldosterone and catecholamine levels were drawn on the last day of placebo treatment and on Days 4 to 6 after starting captopril, 1 hour after the morning dose.

After discharge from the hospital, all patients continued treatment with captopril, 200 mg twice daily. Diuretics were added in Patients 4 to 13 (table 1) to further reduce their blood pressure. Twelve to 176 days (63 ± 12, mean ± SEM) after starting captopril, the patients came to the outpatient clinic where blood pressure was recorded with the patient seated, before taking the morning dose of captopril — i.e., 14 hours after the last dose — and again 1 hour after the morning dose. Simultaneously, blood samples for determination of plasma renin activity, plasma aldosterone levels, and plasma angiotensin converting enzyme activity were drawn. Within 1 week of these determinations, a portable blood pressure recorder was used to obtain a blood pressure profile in each ambulatory patient. With this device, an average of 25 blood pressure measurements were recorded in each patient throughout the day between 8 a.m. and 8 p.m.

Analytical Methods

Plasma renin activity and plasma aldosterone levels were measured by radioimmunoassay. The patient's renin activity was classified as "low," "normal," or "high" according to the method described previously. Plasma converting enzyme activity was determined by the radioenzymatic method with a radiolabelled acylated tripeptide as substrate (Ventrex Corp., Portland, ME).* Plasma catecholamines were

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**Table 1. Clinical Data of Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/Age</th>
<th>Clinical diagnosis</th>
<th>Serum creatinine (mg/100 ml)</th>
<th>Renin subgroup</th>
<th>Previous therapy (mg/day)</th>
<th>Captopril treatment</th>
</tr>
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<tbody>
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<td></td>
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<tr>
<td>Group I</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>M/51</td>
<td>RH</td>
<td>1.2</td>
<td>Hi</td>
<td>--</td>
<td>--</td>
</tr>
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<td>Nl</td>
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<tr>
<td>4</td>
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<td></td>
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<td>9</td>
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<td>FU 40 13</td>
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<td>* SEM</td>
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</table>

**Abbreviations:** RH = renovascular hypertension; EH = essential hypertension; CRF = hypertension associated with chronic renal failure; Nl = normal; Lo = low; Hi = high; AT = atenolol; CH = chlortalidone; FU = furosemide; HY = dihydralazine; ME = methyldopa; OX = oxprenolol; PI = pindolol; PR = propranolol; SP = spironolactone.
also quantitated by a radioenzymatic method. The Remler blood pressure recorder was used according to the recommendations established previously. Data were analyzed using the Student's t test for paired data.

Results

Patients 1, 2, and 3 had normal renal function and needed no diuretics to obtain a satisfactory blood pressure control (Group I). Patients 4 to 8 also had normal renal function, but a satisfactory control of their blood pressure was obtained only after adding a diuretic (Group II). Finally, Patients 9 to 13 had variable degrees of chronic renal failure, and all needed diuretics to control their blood pressure adequately (Group III). The clinical data of all patients are summarized in table 1.

The results obtained in patients of Group I are summarized in figure 1. When the patients were initially hospitalized, administration of captopril lowered blood pressure from 180/113 ± 17/2 to 132/91 ± 7/3 mm Hg and reduced plasma converting enzyme activity from 70 ± 9 to 20 ± 16 nmol/ml/min. Plasma renin activity increased from 24.1 ± 15.6 to 51 ± 13 ng/ml/hr, and plasma aldosterone fell from 18.3 ± 0.8 to 6.9 ± 3.7 ng/dl. During chronic captopril therapy of 109 ± 34 days, blood pressure before the morning dose of captopril averaged 150/86 ± 13/11 mm Hg. Surprisingly, this markedly reduced blood pressure level was obtained in the face of a plasma angiotensin converting enzyme that had resumed its normal activity of 86 ± 15 nmol/ml/min and despite a moderate increase in plasma renin activity to 39.3 ± 9 ng/ml/hr. Blood pressure fell to 127/84 ± 9/11 mm Hg 1 hour after the morning dose of captopril, and plasma converting enzyme activity to 27 ± 10 nmol/ml/min. Simultaneously, plasma renin activity rose further and plasma aldosterone levels fell from 29.5 ± 5.5 to 14.6 ± 3.6 ng/dl.

Similar results were obtained in Group II (fig. 2), except that the blood pressures measured after discharge from the hospital cannot be directly compared to those obtained in the hospital, since diuretics were added to the captopril treatment. To get a better parameter for comparison, blood pressures of ambulatory patients measured during 3 months on previous therapy (table 1) are depicted. In this group also, blood pressure decreased in the hospital, with captopril therapy alone, from 172/116 ± 5/6 to 143/92 ± 6/5 mm Hg (p < 0.01), while plasma converting enzyme activity fell from 72 ± 12 to 23 ± 10 nmol/ml/min. After an average of 42 ± 11 days of treatment with captopril and diuretics, however, 14 hours after the evening dose of captopril, blood pressure was still reduced at 138/93 ± 6/3 mm Hg despite resumption of normal plasma converting enzyme activity of 61 ± 9 nmol/ml/min and in the face of plasma renin activity of 19.7 ± 4.7 ng/ml/hr. Blood pressure decreased slightly to 131/87 ± 4/6 mm Hg (p > 0.05) 1 hour after the morning dose of captopril, while plasma renin activity rose. It is important to note that the dose of diuretics added to captopril was the same or less than that used with previous therapy. It is striking, therefore, that 14 hours after the evening dose of captopril, with normal plasma converting enzyme activity and high plasma renin activity, blood pressure was significantly lower than with previous therapy, having decreased from 171/116 ± 4/4 to 138/93 ± 6/3 mm Hg (p < 0.02).

The results obtained in Group III are depicted in similar fashion in figure 3. They are quite comparable.
to those of the other two groups with one notable exception: 14 hours after the evening dose of captopril, plasma angiotensin converting enzyme activity was still reduced to $26 \pm 7 \text{ nmol/ml/min} (p < 0.005)$, and it decreased only slightly after the morning dose of captopril to $15 \pm 7 \text{ nmol/ml/min} (p < 0.05)$. Thus, in contrast to the patients with normal renal function, plasma angiotensin converting enzyme activity of patients with chronic renal failure remained partially inhibited 14 hours after the last administration of captopril.

Figure 4 relates, for each of the 13 patients, the captopril-induced decrease in plasma converting enzyme activity to the concomitant fall in plasma aldosterone levels that are thought to reflect changes in angiotensin II. There was a significant positive correlation between the two parameters with an $r$ value of 0.65 ($p < 0.025$).

Determinations of circulating catecholamines were obtained in seven patients (Patients 1, 4–6, 11–13).
During the placebo-treatment period, plasma norepinephrine was $0.39 \pm 0.12$ ng/ml and plasma epinephrine $0.06 \pm 0.01$ ng/ml. These pressor hormones were not significantly changed by 4 to 6 days of captopril therapy alone, since they remained at $0.38 \pm 0.11$ and $0.12 \pm 0.04$ ng/ml respectively.

The mean of all blood pressure profiles obtained in 12 of the 13 patients is shown in figure 5. Blood pressure 14 hours after the previous evening dose of captopril and immediately preceding the morning dose averaged $139/88 \pm 6/4$ mm Hg. After the morning dose, it fell further to a low of $126/84 \pm 4/3$ mm Hg ($p > 0.05$). During the day it rose again and reached $138/92 \pm 5/4$ mm Hg before the evening dose. Readministration of captopril induced a new, slight, blood pressure drop. Despite these small blood pressure changes related to the readministration of the drug, blood pressures remained controlled throughout the day. Of the 305 systolic blood pressure recordings obtained in the 12 patients, 82% were equal to or below 160 mm Hg. As to the diastolic blood pressures, approximately two-thirds were below 90 mm Hg and 73% below 95 mm Hg. This degree of blood pressure control was obtained while the patients were pursuing their usual daily activities.

**Discussion**

So far, it has been generally assumed that captopril has to be administered three or four times daily in order to obtain continuous blood pressure control, because its biological half life seems to be less than 2 hours. We have been using twice-daily administration of captopril for more than a year, since this seemed sufficient to keep blood pressure low throughout the day. The present blood pressure profiles established with a portable recorder document that blood pressure constantly remains well controlled even when captopril is administered twice daily. In patients with normal renal function, however, continuous blood pressure control occurs, despite periodic resumption of normal plasma converting enzyme activity, before the next dose of captopril is administered. Only in patients with impaired renal function does partial blockade of converting enzyme persist for 14 hours after captopril administration. It is surprising that in the eight patients with normal renal function, blood pressure remained low for up to 14 hours after the last dose of captopril despite resumption of normal converting enzyme activity. One might argue that measured plasma angiotensin converting enzyme activity does not reflect total conversion of angiotensin that takes place mainly in the pulmonary vascular bed. Thus, pulmonary angiotensin converting enzyme could remain blocked while plasma angiotensin converting enzyme has resumed normal activity. That this is not so is suggested by the observation that changes in plasma angiotensin converting enzyme are closely paralleled by changes in plasma aldosterone levels (fig. 4). Since plasma potassium levels do not decrease with captopril administration, it seems reasonable to assume that the fall in aldosterone levels after each captopril administration reflects a decrease in circulating angiotensin II.

If angiotensin I conversion does not need to remain inhibited throughout the day in order to control blood pressure, one has to consider possible alternate mechanisms by which captopril lowers blood pressure. Angiotensin converting enzyme is identical with kininase II, and its blockade may result in bradykinin accumulation that could contribute to the antihypertensive effect of captopril. Even assuming such accumulation, which has not been found by other investigators, it seems unlikely that the kininase II activity of the enzyme would remain inhibited longer than the angiotensin converting activity.

**Figure 5.** Blood pressure profiles measured with a portable recorder in 12 ambulatory, hypertensive patients on long-term, twice-daily administration of captopril. Blood pressure remained controlled throughout the day.
A decrease in sympathetic nerve activity induced by captopril could also explain the blood pressure reduction in the face of unobstructed activity of the renin system. Plasma norepinephrine and epinephrine levels have actually been measured in these patients before and 4 to 6 days after administration of captopril, and no significant change of these parameters was detected. Thus, so far there is no evidence that altered sympathetic activity is responsible for the observed blood pressure behavior.  

A decrease in sodium balance could explain reduced vascular sensitivity to angiotensin II. It is well known that blood pressure responsiveness to angiotensin II depends closely on the state of sodium balance and that salt depletion reduces blood pressure response to a given dose of angiotensin II.  

However, there is no evidence that a decrease in sodium balance occurred with the administration of captopril in the patients of Group I, who did not receive diuretics. No weight change was observed, and urinary sodium excretion actually increased, once the patients were discharged from the hospital, which presumably reflects a higher sodium intake. Moreover, previous balance studies have not provided any evidence for a captopril induced sodium diuresis.  

Conversely, in patients of Group II, diuretics administered after discharge must have decreased body sodium as compared to that of the hospital period, but the dose that was needed to normalize blood pressure was equal or less in each patient than the dose taken before admission, when blood pressure was poorly controlled. Accordingly, even in these patients, blood pressure remained reduced throughout the day when total body sodium apparently was not lower than before captopril administration. Thus a negative sodium balance does not appear to explain the blood pressure effect in the face of normal converting enzyme activity.  

Sodium balance should, however, not be considered without taking into account simultaneous changes that may be induced in other variables. There seems to exist a physiologic inverse relationship between blood volume and blood pressure such that an increase in blood pressure tends to reduce blood volume and vice versa. Moreover, it has been postulated that hypertensive patients have abnormally increased blood volume when related to blood pressure, though absolute values do not differ from those measured in normal subjects. Unlike most other antihypertensive drugs, with the exception of diuretics and propranolol, captopril does not induce sodium retention while lowering blood pressure, possibly because it simultaneously reduces aldosterone levels and increases renal blood flow. Since any blood pressure reduction may be expected to result in sodium retention, lack of such a retention in the face of blood pressure reduction may actually represent a relative decrease in sodium balance.  

High blood pressure per se has been shown to induce vascular ionic changes independently of humoral mechanisms and to increase the vascular wall thickness to lumen ratio that enhances vascular responsiveness to vasopressor hormones. These would be reversed by the captopril-induced blood pressure reduction. Such a nonspecific or only indirectly renin-related mechanism might also explain why the duration of the blood pressure lowering effect of the majority of antihypertensive agents exceeds their biological half life.  

Taken together, the data provide evidence that twice daily administration of captopril is a practical and efficient way to treat hypertensive patients. Continuous blood pressure control is achieved despite intermittent resumption of normal angiotensin converting enzyme activity. Only in patients with impaired renal function does a certain degree of blockade of angiotensin conversion persist for more than 12 hours, probably because of reduced renal elimination of the drug. Specific and nonspecific effects of chronic captopril administration may act together to reduce blood pressure in the face of an intermittently unblocked renin system.

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