Acute and Chronic Effect of Captopril in Hypertensive Patients

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SUMMARY Acute and chronic antihypertensive effects of the angiotensin converting enzyme inhibitor, captopril (SQ 14,225), was assessed in 29 consecutively-studied patients with hypertension. (Mean arterial pressure, 110-160 mm Hg). Eighteen patients had essential hypertension (three with high plasma renin activity (PRA), 11 with normal PRA, four with low PRA); eight had renovascular hypertension (four with high PRA and four with normal PRA); two had end-stage renal parenchymal disease, and one had primary aldosteronism due to bilateral adrenal hyperplasia. Antihypertensive drugs were discontinued approximately 1 month prior to being studied. Patients were studied on the metabolic unit and received a constant 100 mEq sodium and 60 mEq potassium/day diet. Control data were obtained for 3 days with placebo treatment. Captopril was then begun at 10 or 25 mg and increased to a maximum of 100 or 150 mg four times per day. During the first 3-10 days of treatment, 16 patients (55%) achieved normal blood pressure (BP) on captopril alone, and six patients (21%) achieved it with the addition of a diuretic. Six patients (21%) exhibited a fall in diastolic blood pressure (DBP) greater than 10 mm Hg, but did reach normal. Captopril was ineffective in lowering BP in one patient (low PRA, essential hypertension). Of the 22 patients who achieved normal BP, all but one (normal PRA) exhibited a rise in PRA, and all exhibited a fall in plasma aldosterone concentration (PAC). Blood pressure, PRA, and PAC responses were independent of either etiologic classification or renin subtype. The mean effective daily dose of captopril was 261 mg. Nineteen patients were followed from 1-18 months on maintenance captopril therapy. Blood pressure remained well controlled, without evidence of toxicity, in all patients, although medication adjustment (either a dose increase or a diuretic) was required in all but five patients by the fifth outpatient month. The PRA remained elevated in 12 patients up to 6 months after discharge. The BP response was not predicted by control PRA, PAC, or BP, although there was a correlation between acute renin rise and BP reduction. These results indicate that captopril is an effective, well-tolerated agent for the long-term treatment of hypertension of multiple etiologies. These results are consistent with captopril's known ability to block angiotensin II formation and perhaps to prevent bradykinin degradation, although the primary mechanism responsible for BP reduction remains to be elucidated. (Hypertension 2: 567-575, 1980)

KEY WORDS • angiotensin converting enzyme inhibition • blood pressure • plasma renin activity • plasma aldosterone concentration • captopril • essential hypertension • renovascular hypertension

HYPERTENSION is a multifactorial disease. The mechanisms leading to elevation of blood pressure (BP) differ from patient to patient, and the factors responsible for the initiation of hypertension may differ from those that maintain it. Treatment considerations must include recognition of those variations and an awareness of the possible stimulation of mechanisms that compensate for a falling BP.

Although the role of the renin-angiotensin system in the pathophysiology of hypertension is controversial, suppression of that system has led to effective BP reduction, primarily by the use of one of three classes of compounds: renin inhibitors, angiotensin I converting enzyme blockers, or angiotensin II antagonists. Inhibition of renin release has been observed with most sympatholytic agents and may account for at least part of their antihypertensive action. Interference with the interaction of renin with its substrate has been reported with antirenin antibody, synthetic phospholipids, prostaglandins, and several synthetic peptides, but none of these has been
evaluated in humans. The most widely used angiotensin II antagonist, [Sar\(^1\), ala\(^9\)]-angiotensin II (saralasin), has been effective in reducing BP in hypertensive patients but its clinical use has been limited by its partial agonistic properties and by the need for parenteral administration.\(^8\)\(^9\) Recent evidence has suggested that substances that inhibit angiotensin II formation by blockade of angiotensin I converting enzyme may be clinically useful antihypertensive agents.\(^1\)

A nonapeptide, teprotide (SQ 20,881, BPF e\(_2\)), has been synthesized using extract of Bothrops jararaca venom as a prototype.\(^1\) Teprotide competitively inhibited the hydrolysis of angiotensin I and bradykinin\(^9\)\(^1\) and decreased BP in hypertensive rats\(^1\)\(^4\) and dogs\(^1\)\(^8\) with renal artery stenosis.

In normotensive patients with normal sodium balance, teprotide had no effect on BP, whereas it led to a significant fall in BP in sodium-depleted normal subjects.\(^1\) Gavras and colleagues\(^1\)\(^9\) showed that enhancement of teprotide induced BP reduction in hypertensive patients by sodium depletion. The antihypertensive effectiveness of teprotide has been confirmed in the clinical treatment of patients with various types of hypertension.\(^1\)\(^1\)\(^1\)

Teprotide is a straight-chained peptide\(^2\)\(^4\) that must be given intravenously, thereby limiting its therapeutic usefulness. In 1977, Ondetti and coworkers\(^2\)\(^6\) synthesized an orally active agent, captopril (SQ 14,225), which competitively inhibited angiotensin converting enzyme without acting as a substrate. Captopril has been found effective in reducing arterial hypertension in rats\(^5\)\(^6\) and rabbits,\(^2\)\(^7\)\(^8\) with renovascular hypertension and in dogs\(^2\)\(^9\),\(^3\)\(^0\) cats,\(^3\)\(^1\) and man.\(^3\)\(^2\)\(^3\)

The following is a report of our experience with 29 consecutively treated hypertensive patients who have been treated by inhibition of angiotensin converting enzyme by captopril. Nineteen patients have been treated chronically from 1 to 18 months.

**Methods**

**Patient Profile**

Twenty-nine hypertensive patients, 16 men and 13 women aged 24–64 years, underwent treatment with the oral converting enzyme inhibitor, captopril (SQ 14,225, 2D methyl-3 mercaptopropanoyl-l-proline). The duration of their hypertension prior to captopril treatment was 10.5 ± 1 years (range, 1.5 to 38 years), and the mean arterial pressure (MAP) ranged from 110–162 mm Hg. Eighteen patients had essential hypertension, eight had renovascular hypertension, two had renal parenchymal disease, and one had primary aldosteronism with idiopathic bilateral adrenal hyperplasia. Two of the eight patients with renovascular hypertension had undergone successful surgical correction of the stenotic renal artery, with subsequent reocclusion of the graft manifested by recurrence of hypertension.

All patients had been treated previously in the University of Virginia Hypertension Unit and had been receiving combination antihypertensive therapy which included a diuretic and a sympatholytic agent, and in many cases a vasodilator. Adequate BP control (DBP less than 90 mm Hg) had been achieved in only three of the 29 patients.

**Experimental Design**

The patients were admitted over an 18-month period to the University of Virginia Clinical Research Center for initiation of captopril therapy. Antihypertensive medications had been discontinued in 28 patients from 3 days to 6 weeks (mean, 4 weeks) prior to admission. Propranolol and nitrates were continued in one patient with severe angina.

On admission to the hospital, the patients were maintained on an isocaloric diet containing 100 mEq of sodium and 60 mEq/day of potassium. A placebo was administered during the first 3 days while control measurements were obtained. On the fourth hospital day, captopril treatment was begun, initially at 10 mg and later at 25 mg every 6 hours. Doses were raised successively to 50, 100, and 150 mg every 6 hours if supine DBP was not lowered by more than 10 mm Hg or if a DBP less than 90 mm Hg had not been reached. The maximal daily dose was 600 mg at the beginning of the study and subsequently was reduced to 400 mg. The addition of a diuretic was allowed at the discretion of the investigator. Patients were discharged after BP remained stable for 1 to 4 days. Thus, the duration of hospitalization ranged from 3 to 13 days (mean, 6 ± 0.5 days). Nineteen of the 29 patients were placed on maintenance captopril therapy at the time of discharge from the hospital and were evaluated in the outpatient clinic weekly for the first 4 weeks and then monthly.

Triplicate measurements of supine and standing brachial artery pressure were recorded with a mercury sphygmomanometer four times each day during waking hours. For 4 to 6 hours following the initial dose and following each dose increase, BP was measured every 5 minutes with an automatic ultrasonic BP recorder (Arteriosonde Model 1217, Roche, Cranberg, New Jersey). Heart rate (HR) was recorded simultaneously. Weights, respirations, and temperatures were recorded daily. Serum electrolytes, BUN, creatinine, and 24-hour urinary sodium, potassium, and creatinine excretion rates were obtained daily. Blood was obtained for determination of plasma cortisol levels, supine and upright plasma renin activity (PRA), and plasma aldosterone concentration (PAC), at appropriate times before and during treatment and stored at −20°C until assayed.

The average of at least 12 BP and HR measurements was determined for each hospital day. The pretreatment BP and HR values reported here represent the average of all placebo day values. The BP at 1 hour after treatment was determined by calculating the average of seven BP measurements between 30 and 90 minutes after the initial captopril dose and after each dose increase. Values reported here include the BP determined 1 hour after the first effective dose
(average of 7 values) and that determined on the last hospital day (average of 12 values). All BP measurements were obtained with the patient in the supine position unless otherwise stated. The effective dose (ED) of captopril was defined as the dose required to achieve a normal BP (DBP less than 90 mm Hg); such a response was defined as a complete response.

Plasma renin activity (PRA) was determined by measuring angiotensin I generated at 37°C and pH 5.7 according to the method of Sealey et al. Radioimmunoassay of plasma aldosterone concentration (PAC) was performed by the method of Buhler et al. Serum and urine sodium and potassium were determined by flame photometry. Plasma cortisol was determined by the fluorometric method of Mettingly. Classification of patients into low, normal, and high PRA subgroups was based on the concomitant 24-hour urine Na excretion as described by Laragh and colleagues. Upright PRA and PAC determinations on placebo and at 1 hour after the initial and effective doses of captopril were compared.

**Results**

**Acute Administration of Captopril**

**Complete Responders**

Table 1 illustrates the acute BP responses to captopril in 29 patients during 3 to 13 days of treatment. A complete response (a decrease in DBP to less than 90 mm Hg) was observed in 16 patients with captopril alone. Six patients required the addition of a diuretic to achieve a similar response. The length of time off diuretics prior to initiation of captopril did not predict the initial BP response.

Figure 1 illustrates the responses of all 22 patients who achieved a normal BP during the 3–13 day dosing period. The BP was 163 ± 4/103 ± 2 mm Hg on placebo and fell to 139 ± 5/89 ± 2 mm Hg (p < 0.05) on the last hospital day (fig. 1A). The PRA and PAC

<table>
<thead>
<tr>
<th>Complete response</th>
<th>Partial response</th>
<th>No response</th>
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<tbody>
<tr>
<td>Captopril alone</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Captopril &amp; diuretic</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Totals</td>
<td>22</td>
<td>6</td>
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(78%) (21%) (3%)
responses are depicted in figure 1B. The PRA increased from 11.7 ± 3.9 to 25.0 ± 7 ng/ml/hr (p < 0.05) at 1 hour after the effective dose, and PAC decreased from 25.2 ± 5 to 10.9 ± 3 ng/dl simultaneously (p < 0.05). The mean daily effective dose of captopril was 257 ± 37 mg.

Figure 2A compares the BP in 16 patients who achieved a complete response with captopril alone to the six patients (five normal PRA; one low PRA), who required the addition of a diuretic to achieve a similar response. Renal function was normal in five and impaired in one (BUN of 26 mg% and a serum creatinine concentration of 2.0 mg%). Pretreatment BP was higher in the group of patients requiring a diuretic (170 ± 6/110 ± 4 vs 160 ± 5/101 ± 1 mm Hg; p < 0.05) as was the BP determined 1 hour after the effective dose (149 ± 5/100 ± 6 vs 135 ± 2/86 ± 3 mm Hg; p < 0.05). Patients who achieved a complete response to captopril alone did so within 2.6 ± 0.5 days (range, 1-6 days), whereas those requiring a diuretic took 7.7 ± 1.3 days (range, 3-13 days; p < 0.05) to achieve a normal BP. Figure 2B depicts the change in PRA and PAC prior to the addition of a diuretic in all cases. The rise in PRA was greater in the group treated with captopril alone (from 10.3 ± 3 to 20.1 ± 4 ng/ml/hr; p < 0.05) than in patients requiring a diuretic (5.2 ± 1 to 10.1 ± 2 ng/ml/hr; p < 0.05), and the fall in PAC was also greater in the group treated with captopril alone (20.9 ± 4 to 6.2 ± 1 ng/dl; p < 0.05) compared to those requiring a diuretic (22.4 ± 4 to 13.2 ± 3 ng/dl; p < 0.05).

Five of the eight patients with renovascular hypertension and 15 of 18 patients with essential hypertension had complete responses (table 2). The BP in patients with renovascular hypertension decreased from 180 ± 8/105 ± 2 to 150 ± 6/89 ± 2 mm Hg (p < 0.05) 1 hour after the effective dose was reached and was 143 ± 4/89 ± 2 mm Hg on the last hospital day. In patients with essential hypertension, BP was lowered from 159 ± 4/104 ± 2 to 141 ± 5/92 ± 2 mm Hg (p < 0.05) and remained at approximately the same level on the last hospital day (136 ± 3/88 ± 2 mm Hg; p = NS). The BP response was similar in the two groups as was the mean daily effective dose of captopril.

The increase in PRA (table 2) was greater in the patients with renovascular hypertension than in those with essential hypertension (from 13.8 ± 7 to 31.1 ± 8 ng/ml/hr, p < 0.05; compared to 7.1 ± 1 to 11.9 ± 2 ng/ml/hr, p < 0.05 respectively), but there was no statistical difference between the two groups in PAC response (17.4 ± 3 to 6.9 ± 3 and 22.7 ± 3 to 8.6 ± 2 ng/dl respectively).

The BP-lowering effect of captopril according to renin classification was also analyzed (table 2). Six patients had high PRA (three with essential and three with renovascular hypertension), and 12 exhibited normal PRA. The two patients with low PRA and the two with renal parenchymal disease are not depicted. The BP in the high PRA group was reduced from 164 ± 4 to 6.2 ± 1 ng/dl; p < 0.05) compared to those requiring a diuretic (22.4 ± 4 to 13.2 ± 3 ng/dl; p < 0.05).

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**Figure 2.** A. Comparison of blood pressure (BP) responses in 16 patients who achieved a normal BP on captopril alone with six patients who required the addition of a diuretic by the last hospital day (mean, 6 days) (mean ± 1 se). Clear bar = control BP; striped bar = BP 1 hour after the effective dose of captopril; dotted bar = BP after 6 days; horizontal bar = MAP; interrupted line = normal BP. B. The PRA and PAC responses in each group before and 1 hour after captopril. Diuretics had not been given at the time of these measurements.
receiving the effective dose of captopril. The BP on the
last hospital day was 138 ± 4/85 ± 1 mm Hg in those
with high PRA and 130 ± 8/88 ± 3 mm Hg in
patients with normal PRA. There was no difference in
BP reduction between the two groups, but patients
with high PRA achieved a normal DBP initially on a
lower dose of captopril, 148 ± 8 mg daily, whereas
those with normal PRA required 300 ± 8 mg daily for
a similar response (p < 0.05). The PRA rose from
16.2 ± 5 to 27.3 ± 7 ng/ml/hr (p < 0.05) in patients
with high PRA and from 6.1 ± 0.8 to 13.2 ± 3
ng/ml/hr (p < 0.05) in patients with normal PRA
(table 2). The increase in PRA with captopril was not
different in the two groups. The PAC fell
simultaneously from 23.5 to 7.4 ± 2 ng/dl (p < 0.05)
in the patients with high PRA, and similarly from 22.6
± 3 to 8.9 ± 2 ng/dl (p < 0.05) in those with normal
PRA. Not depicted are two patients with a low PRA
who had achieved a normal BP.

Supine heart rate (HR) did not change with cap-
topril therapy. Baroreceptor reflexes were intact, as
demonstrated by an increase in HR with upright
posture. Serum sodium, potassium, BUN, creatinine,
and plasma cortisol concentrations were normal and
remained unchanged after treatment. An analysis of
variance of daily weights and 24-hour urinary excre-
tion of sodium, potassium, and creatinine for 2 to 3
days before treatment and 4 to 5 days during treatment
revealed no significant change in any of those
values (fig. 3).

**Partial Responders**

A partial response was defined as a decrease in DBP
of at least 10 mm Hg without going below 90 mm Hg.
Six patients with normal renal function had a partial
response to captopril alone. The BP in these patients
was 179 ± 11/107 ± 5 mm Hg before treatment and
155 ± 5/96 ± 2 mm Hg (p < 0.05) with the highest
dose of captopril (440 ± 75 mg daily). None of these
patients received a diuretic.

Three of the six partial responders had renovascular
hypertension; one of these has exhibited marked BP
reduction on maintenance doses of captopril for 6
months and has required fewer antihypertensive
medications. Another patient, a 64-year-old white
woman with renovascular hypertension and a baseline
PRA of 42.1 ng/ml/hr, developed a myocardial in-
farction after four doses of 25 mg of captopril given

![Figure 3. Daily weights and 24-hour urinary excretion of sodium, potassium, and creatinine before and after captopril therapy (mean ± 1 se).](http://hyper.ahajournals.org/figs/10508/0/HF0300746F003L1.jpg)
over a 12-hour period. That patient is reported in detail elsewhere.

The third patient with renovascular hypertension developed a rash (without fever) on a daily dose of 600 mg of captopril. Because of poor compliance, no attempt was made to continue treatment on a lower dose of captopril.

The fourth partial responder had primary aldosteronism due to idiopathic adrenal hyperplasia. Two partial responders had essential hypertension (one normal PRA; one low PRA). One of those developed nausea and vomiting on a daily dose of 200 mg of captopril, which led to discontinuation of the drug.

Nonresponder

One patient with low renin essential hypertension failed to respond to maximal doses of captopril and exhibited a rise in BP during the 3-day treatment period (MAP increased from 128 to 138 mm Hg). The PRA fell slightly, from 2.7 to 1.5 ng/ml/hr at the maximal dose of captopril, and PAC fell simultaneously from 22.2 to 15.6 ng/dl.

Hormonal and BP responses in the 22 patients who achieved a normal BP with captopril were analyzed using the method of least squares linear regression. A significant relationship was demonstrated between the increase in PRA and the decrease in MAP on the effective dose of captopril \( r = 0.53; p < 0.05 \), but no correlation was observed between the increase in PRA and the reduction in MAP on the initial dose of captopril. A relationship was seen between the decrease in PAC and the decrease in MAP with the initial dose of captopril \( r = 0.62; p < 0.05 \), but that relationship was not present with the effective dose of captopril.

Neither the control PRA nor PAC predicted BP responses. However, at the effective dose of captopril, both the increase in PRA and decrease in PAC were directly proportional to the control PRA (increase, \( r = 0.76; p < 0.01 \); decrease, \( r = 0.81; p < 0.01 \)).

The age of the patient correlated with the BP reduction at the effective dose \( r = 0.52; p < 0.001 \), but not after the initial dose of captopril. Age did not correlate with baseline PRA, PAC, or BP. Moreover, there was no relationship between duration of hypertension prior to entering the study and BP, PRA, or PAC responses nor to the baseline BP, PRA, or PAC.

Chronic Administration of Captopril

After discharge from the hospital, 19 patients were maintained on captopril; one, a partial responder, has already been discussed. In the remaining 18 patients (fig. 4) the BP has remained controlled up to 18 months (up to 24 months in two patients not shown). At the time of discharge from the Clinical Research Center, the mean daily dose of captopril was 225 ± 37 mg. Three patients (17%) were on maximal therapeutic regimen (captopril 400 mg daily and a diuretic) at the time of discharge. One patient has remained normotensive for 12 months. The remaining two patients have exhibited mild DBP elevations (from 90 to 100 mm Hg) at 15 and 20 months. Five patients (44%) have required addition of a diuretic (three in the first 4 weeks and two by the fifth month of outpatient management). Five patients (28%) have required a captopril dose increase only, without addi-
tion of a diuretic (two within the first 4 weeks and the remaining in Months 3, 6, and 19). Five patients (28%) have required no adjustment of their therapy. Three of these patients have been normotensive for 3, 13, and 18 months respectively, and the remaining two have exhibited mild BP elevation after 4 and 18 months of maintenance therapy.

Figure 5 compares PRA in 12 patients prior to receiving captopril with values obtained after 1 hour, and 2 and 6 months of therapy. A one-way analysis of variance revealed a progressive increase in PRA ($p < 0.05$) from $10.3 \pm 3$ to $16.9 \pm 4$, $34.3 \pm 11$, and $54.0 \pm 15 \text{ ng/ml/hr}$ respectively. Seven of these 12 patients had received a diuretic by Month 1. The PRA in those seven patients increased from $8.6 \pm 2$ to $13.1 \pm 3$, $14.1 \pm 16$, and $63.0 \pm 22 \text{ ng/ml/hr}$ over the same time period ($p < 0.05$). The five patients in this group who did not require a diuretic showed a significant increase at 1 hour from $12.6 \pm 7$ to $22.1 \pm 10 \text{ ng/ml/hr}$ ($p < 0.05$). The PRA in these five patients at 1 and 6 months was $26.4 \pm 15$ and $41.4 \pm 22 \text{ ng/ml/hr}$. Those latter changes were not statistically significant at the $p < 0.05$ level.

**Discussion**

Inhibition of angiotensin converting enzyme by captopril significantly reduced BP in 98% of 29 consecutively treated hypertensive patients. The BP was normalized in 76% of the patients, although 27% of the patients required a diuretic during the initial treatment period. Those patients who became normotensive on captopril alone did so rapidly, all within 6 days and most within 3 days, whereas those who required a diuretic took up to 13 days to achieve a similar response. No difference in magnitude or rate of BP reduction was observed when patients were grouped according to clinical classification or renin subtype. However, patients with high baseline PRA appeared to respond to a lower dose of captopril, which may reflect a difference in the mechanisms responsible for the lowering of BP.

Eighteen patients have been treated chronically with captopril, and all have remained well controlled from 3 to 18 months. However, all except five patients have required an increase in medication (most by Week 4 but some as late as Month 19 of therapy). Patients with high PRA responded for a longer period of time to the lower doses of captopril.

The severity of the hypertension in outpatients ranged from mild to severe, but BP was well controlled in only three patients on conventional medication prior to entering this study. The number of antihypertensive medications per patient was reduced substantially and could probably be reduced further by the substitution of a twice daily regimen.

Untoward effects of captopril were minimal in two patients, and all effects were seen within the first 2 weeks of treatment. The skin rash in one patient (daily dose of 600 mg) resolved within 1 week of discontinuation of captopril, and no skin rash has been observed on daily doses of 400 mg of captopril up to 18 months of treatment. One patient with no previous history of coronary artery disease developed myocardial ischemia after a moderate but rapid reduction of BP. Myocardial ischemia has not been reported with captopril but has been observed in elderly patients after discontinuation of propranolol. Rapid hypotension has been reported in one patient with severe diuretic-induced hypovolemia and sympathetic blockade with guanethidine, and we have described one patient with volume depletion from hemodialysis who developed severe hypotension after a single 10 mg dose of captopril. Thus, we advocate caution in initiating therapy with converting enzyme inhibitors in patients with hypovolemia, particularly those on sympatholytic agents or in elderly patients with vascular disease. Supplementation of captopril with diuretics may be necessary and appears without danger. No orthostatic hypotension was seen in the group of patients receiving both captopril and a diuretic.

There was no reliable method of predicting BP response of any individual patient on captopril. However, patients with higher baseline BP appeared to require a diuretic earlier than those with relatively lower BP. Although plasma angiotensin II concentration was not measured, the rise in PRA and concomitant fall in PAC strongly imply a simultaneous reduction of angiotensin II levels. The increase in PRA after blockade of angiotensin converting enzyme may result from the release of a negative feedback inhibition by angiotensin II. In the presence of an intact sympathetic nervous system, reduction of BP as a result of a variety of mechanisms would be expected to cause stimulation of PRA through baroreceptor mechanisms. The baroreceptor mechanisms were intact in these patients, as demonstrated by the ability of upright posture to stimulate HR. However, no increase in HR was observed with captopril alone, suggesting a minor contribution of the sympathetic nervous system to the observed rise in PRA.
Although the PRA progressively increased during the dosing period while BP remained normal or continued to fall, the PAC did not continue to decrease; in fact, PAC exhibited a slight increase after the initial dose of captopril. Angiotensin II is a potent stimulus to adrenal aldosterone production; a decrease in plasma angiotensin II concentration may have accounted for the initial fall in aldosterone. The close correlation between the initial degree of PAC and BP reduction, and the lack of correlation later with the effective dose of captopril may reflect the emergence of compensatory mechanisms that stimulated adrenal aldosterone production. There was no difference in plasma cortisol, potassium, or sodium concentrations, or urinary sodium excretion before and after treatment. Thus, it is unlikely that ACTH or potassium excess or hyponatremia contributed to the aldosterone stimulation. Vascular angiotensin receptor avidity, defined as the amount of angiotensin II antibody required to block BP responses to exogenous angiotensin II, has increased in response to maneuvers known to lower endogenous angiotensin II concentration such as sodium loading or ganglionic blockade. The increase in PAC in the face of continued BP reduction may indicate increased adrenal receptor avidity for angiotensin II, or perhaps enhancement of angiotensin II or III production related to the persistent rise in PRA.

The requirement for increased antihypertensive medications in many of the patients after weeks or months of effective BP control with captopril may also reflect increased vascular receptor avidity for angiotensin II. On the other hand, plasma angiotensin II concentrations may have increased chronically as PRA increased, and overcome the blockade of converting enzyme. Bing and Poulsen have reported an increase in BP following acute administration of captopril in anesthetized rats, which may be related to the difference in the dose requirement for blockade of the intrarenal converting enzyme and that for inhibition of systemic angiotensin converting enzyme.

Angiotensin converting enzyme inhibition has been shown to retard bradykinin degradation. Bradykinin, a potent vasodilator, has been reported to release prostaglandins from the kidney and blood vessels, and in higher doses has stimulated catecholamine release from the adrenal medulla. Enhancement of the hypotensive effect of bradykinin has been reported in conscious rabbits by the administration of captopril. Thus, either bradykinin or prostaglandins of renal or vascular origin may contribute to the BP reduction seen in patients treated with captopril.

An unexpected finding was the direct relationship between BP reduction and increasing age. Decreased PRA has been reported with increasing age in normal subjects and in hypertensive patients. No such relationship was observed in the present group, perhaps because of the relatively narrow range of ages. One would expect decreased vascular compliance in more elderly patients. A decrease in vascular distensibility might lead to a greater change in pressure per unit volume within the arterial tree. Thus, for a given alteration of vascular resistance or cardiac output, a larger BP change would result in the presence of less compliant vessels. If that mechanism were operative here, however, one would expect to find a correlation between duration of hypertension and BP reduction. The absence of that finding in our patients may reflect the degree and duration of prior control on conventional medications.

Although the mechanism of BP reduction by angiotensin converting enzyme inhibition remains to be elucidated, captopril has been an effective, well-tolerated agent for the chronic treatment of hypertension of various etiologies. From 30% to 50% of patients required a diuretic for optimal BP control. All untoward effects were seen within 2 weeks of initiation of treatment. One might expect greater BP sensitivity to captopril in patients who are elderly or have very high PRA. Patients with severe hypovolemia or sympathetic blockade and underlying vascular disease require careful cardiovascular monitoring during initiation of therapy.

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