Interruption of the Renin-Angiotensin System in Hypertensive Patients by Captopril Induces Sustained Reduction in Aldosterone Secretion, Potassium Retention and Natriuresis

STEVEN A. ATLAS, M.D., DAVID B. CASE, M.D., JEAN E. SEALEY, D. SC., JOHN H. LARAGH, M.D., AND DORIS N. MCKINSTRY, PH.D.

SUMMARY The orally active angiotensin converting enzyme inhibitor, captopril, was administered to 23 hypertensive patients maintained for 10 days on a constant sodium and potassium intake. Because the antihypertensive action of the drug might depend in part on a functional reduction in angiotensin II levels, we sought to determine whether continuous blockade of the renin axis might be reflected in induced changes in aldosterone secretion and by consequent changes in sodium and potassium balance.

Blood pressure fell in response to captopril in 22 of the 23 patients studied, reaching a nadir after 7 to 10 days of continued treatment. Captopril promptly produced falls in urinary aldosterone excretion and plasma aldosterone in all patients except one with low plasma renin activity. Moreover, aldosterone secretion remained suppressed in the face of progressive potassium retention and increased plasma potassium, effects that normally increase aldosterone secretion. Concurrently, the drug produced negative sodium balance in most patients, although four patients (three of whom had renal artery stenosis) developed significant sodium retention when blood pressure was reduced.

These effects on aldosterone secretion and potassium balance, as well as the concurrent drug-induced reductions in blood pressure, were greatest in patients with high plasma renin activity and least in the low-renin patients. After 7 days of maintenance treatment, the changes in mean arterial pressure were also directly related to changes in aldosterone excretion ($r = 0.73, p < 0.001$) and inversely related to changes in serum potassium concentration ($r = -0.72, p < 0.001$).

Altogether, the observed effects on aldosterone secretion and potassium balance strongly suggest that inhibition of angiotensin converting enzyme in vivo produces a sustained reduction in biologically active angiotensin II levels. These findings, together with previous evidence that the antihypertensive action of the drug is also related to the pretreatment plasma renin level, make it reasonable to suspect that reductions in blood pressure during captopril treatment result in some large measure from blockade of angiotensin II formation.

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KEY WORDS • renin-angiotensin system • aldosterone • hypertension • angiotensin-converting enzyme inhibition • potassium • sodium • captopril

ALDOSTERONE, the most potent mineralocorticoid secreted by the adrenal cortex, participates in the control of sodium and potassium homeostasis by acting on the distal renal tubule to cause sodium retention and potassium loss. The rate of aldosterone secretion is normally determined by two principal stimuli: plasma angiotensin II and plasma potassium.

An orally active inhibitor of angiotensin converting enzyme has recently been developed that is able to block the pressor response to angiotensin I infusion in normal human subjects, and which has been shown to be an effective antihypertensive agent. However, from these early studies, uncertainty remains as to the contribution of blockade of the renin axis to the antihypertensive action of the drug. Although they noted that high-renin patients responded better as a group, Gavras and co-workers did not find a relationship between the magnitude of the supine blood pressure response and control renin levels. In contrast, Case et al. and Bravo et al. reported significant correlations using ambulatory, seated and supine pressures. While this seeming discrepancy may simply be related
to small sample size, it would seem appropriate to look further for evidence of blockade of endogenous angiotensin II formation and its possible relevance to the blood pressure lowering effect.

To pursue this question, we have examined whether converting enzyme blockade induces the changes in aldosterone secretion and in sodium and potassium balance that would be expected when angiotensin II formation is blocked. Demonstration of sustained changes in these parameters would provide more evidence that captopril induces functional interruption of the renin-angiotensin-aldosterone axis and at the same time might also provide relevant information on the mechanism of antihypertensive action of the drug.

Methods

Patients

Twenty-three patients with documented hypertension were entered into the study of long-term treatment with the angiotensin converting enzyme inhibitor captopril (SQ14,225). Diagnoses were based on complete clinical examination, serum electrolytes, urinary metanephrines, cortisol and aldosterone, renin-sodium profiling, renal artery stenosis, and six had essential hypertension. Of the nine patients with high renin profiles, seven had renovascular hypertension (two bilateral renal artery stenosis and six had essential hypertension of the nine patients with high renin profiles, seven had renovascular hypertension (two bilateral and five unilateral), and the remaining two had essential hypertension. There was no evidence in any of these patients of accelerating or malignant hypertension. All patients had normal renin profiles; of these, two had bilateral renal artery stenosis and six had essential hypertension. Of the nine patients with high renin profiles, seven had renovascular hypertension (two bilateral and five unilateral), and the remaining two had essential hypertension. There was no evidence in any of these patients of accelerating or malignant hypertension.

Design of the Study

After a period of 3 weeks without any medication, the patients were admitted to the Clinical Research Center of the New York Hospital-Cornell Medical Center. Each patient received an 1800 calorie diet containing 60 mEq of potassium and 10 mEq of sodium; to this diet, 90 mEq of sodium was added daily in the form of sodium chloride tablets. The 24-hour excretion of sodium and potassium was measured daily throughout the study, using a standard flame photometer.

All patients were maintained in metabolic balance for at least 5 days before the study, during which time they received placebo four times daily. The rate of urinary aldosterone excretion was measured on each of the 3 days before receiving captopril. On the last day of this control period, blood pressure was measured in the seated position using an Arteriosonde at 2-minute intervals. Blood pressures were analyzed by averaging the values over a 30-minute period after the blood pressure had stabilized. On this day, blood was collected at 12 noon for measurement of plasma renin activity, plasma aldosterone and serum potassium after the patient had been ambulatory for 4 hours.

At 10 a.m. on the next day, each patient received a 10-mg oral dose of captopril (SQ14,225), followed 3 hours later by a 25-mg dose of same drug. This dose was repeated every 6 hours and was doubled on each of the ensuing 2-3 days (dose-ranging period) until a decline in diastolic blood pressure of at least 10 mm Hg was maintained or the maximum allowed dosage (200 mg four times a day) was reached. The maintenance dose ranged from 150 to 800 mg/day and averaged 400, 325 and 450 mg/day for the low-, normal- and high-renin subgroups, respectively. The determination of urinary aldosterone excretion was repeated on alternate days during the treatment period, and the average change in aldosterone excretion was determined by comparing the average of these values with the average of the three pretreatment values. Daily aldosterone excretion was measured in one high-renin subject. Cumulative changes in sodium and potassium balance were calculated by determining the differences between intake and excretion after accounting for insensible losses; the latter were defined as the average difference between intake and excretion for the 5 days before drug administration. Measurements of Arteriosonde blood pressure and of 12 noon plasma renin activity, plasma aldosterone and serum potassium were repeated on Days 3 and 7 of maintenance treatment.

Hormonal Measurements

Plasma renin activity was determined by the method of Sealey and Laragh. Twenty-four hour urinary aldosterone excretion was measured by the excretion of the acid-labile conjugate (aldosterone 18-glucuronide), as previously described. Plasma aldosterone was measured by modification of the method of Bihler et al. with highly specific antiserum kindly provided by Dr. John K. McKenzie. The use of this antiserum eliminates the need for celite chromatography and gives virtually identical results.

Statistical Methods

The data are expressed as means ± standard error. Non-parametric statistical methods were used to detect differences between groups (paired and unpaired Wilcoxon tests). Regression lines were determined by the method of least squares. Significance of the correlation coefficients obtained was confirmed by the Spearman rank correlation, and these latter values are given throughout.

Results

Representative studies of the effects of captopril in two patients with renal artery stenosis and high plasma renin are shown in figure 1. Blood pressure fell immediately following the first dose of captopril but, as previously reported, there was a tendency for blood pressure to stabilize or even rise transiently toward control levels before pursuing a more gradual decline. There were prompt and sustained falls in both urine aldosterone excretion and plasma aldosterone in
Captopril-induced changes in blood pressure, plasma renin activity, plasma and urinary aldosterone and sodium and potassium balance in two patients with renal artery stenosis and high-renin profile. The dashed vertical line indicates the time of administration of the first 10-mg dose. Blood pressures are the daily average of at least five determinations made after the patient had been supine for 5 minutes and standing for 2 minutes. The solid squares in the upper-most panels represent the seated systolic and diastolic pressure at 90 minutes after the first dose. Plasma renin activity, plasma aldosterone and serum potassium were measured at 12 noon after the patient had been ambulatory for 4 hours.

The face of increases in plasma renin activity. These changes were associated with a decline in potassium excretion and an increase in serum potassium concentration. Transient natriuresis occurred in one patient (A), while the other (B) developed significant sodium retention.

The cumulative effects of captopril on potassium and sodium balance in the three renin subgroups are shown in figure 2. Twenty of the 23 patients gradually developed positive potassium balance. One patient in each subgroup had slight kaliuresis (less than 50 mEq cumulative loss over 8 days). Cumulative potassium balance was greatest (p < 0.05) in the high-renin subgroup (94 ± 22 mEq after 8 days, range 60–175 mEq) and least in the low-renin patients (25 ± 13 mEq). Potassium retention was associated with significant increases in serum (K⁺) in the high-renin and normal-renin subgroups.

On average, net negative sodium balance occurred in all three groups (fig. 2). Sodium losses were similar in the normal- and high-renin patients but were less (although not statistically significant) in the low-renin patients. However, changes in sodium balance were more variable than those in potassium balance, since four patients (including the one shown in fig. 1B) developed considerable sodium retention during the course of the study. One normal-renin subject retained 90 mEq over 8 days. Even more striking sodium retention (149 ± 24 mEq) was observed in three of the high-renin patients who had renal artery stenosis. The remaining four patients with high-renin profiles and renal artery stenosis lost between 40 and 220 mEq, while the two patients with high-renin essential hypertension lost 180 and 320 mEq, respectively. Within the high-renin group, there was no significant difference in the blood pressure response between those who retained sodium (−23.7 ± 7.1% fall in mean pressure after 7 days maintenance treatment) and those with net negative sodium balance (−24.1 ± 10.5% fall).

Sustained falls in urine aldosterone excretion were observed in all but one patient who had low plasma renin activity. For the group as a whole, aldosterone excretion fell from 12.8 ± 1.2 to 5.6 ± 0.6 µg/day (p < 0.001) after 2 days of captopril, and remained low after 3 and 7 days of maintenance therapy (6.3 ± 0.5 and 6.4 ± 0.7 µg/day, respectively). Significant suppression of aldosterone excretion was maintained in each of the renin subgroups (table 1). Although there was a tendency for urine aldosterone excretion to in-
increase slightly following the second day of treatment (table 1), this was not statistically significant.

As shown in figure 3, the average degree of suppression of urinary aldosterone during the entire treatment period was greatest in the high-renin patients (−61 ± 4%) and least (p < 0.001) in the low-renin group (−25 ± 6%). The normal-renin patients had an intermediate degree of aldosterone suppression (−44 ± 5%) which differed significantly from that observed in the low- (p < 0.05) or high- (p < 0.03) renin groups. Parallel changes (r = 0.71, p < 0.001) were observed in 12 noon levels of plasma aldosterone (fig. 3). For the patients as a whole, changes in sodium balance did not correlate with changes in aldosterone, but there was a

Table 1. Urine Aldosterone Excretion and Blood Pressure (mean ± SE) in the Three Renin Subgroups Before and During Treatment with Captopril

<table>
<thead>
<tr>
<th>Renin subgroup</th>
<th>Urine aldosterone (µg/24 hrs)</th>
<th>Blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>Control</td>
<td>9.4  ± 1.7</td>
<td>10.8  ± 1.0</td>
</tr>
<tr>
<td>Captopril*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose-ranging</td>
<td>6.7  ± 1.4</td>
<td>5.0  ± 1.1</td>
</tr>
<tr>
<td>(Day 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td>7.7  ± 1.4</td>
<td>5.4  ± 0.7</td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 days</td>
<td>7.2  ± 2.2</td>
<td>6.1  ± 0.7</td>
</tr>
</tbody>
</table>

*On the second day of treatment, during the dose-ranging period, all patients received 50 mg four times a day. The maintenance treatment period began between the second and fourth day of the study (see Methods).
significant relationship between cumulative potassium balance and the average fall in urinary aldosterone excretion ($r = 0.55, p < 0.01$).

There was also a gradation in the response of blood pressure among the three renin subgroups. Mean arterial pressure fell by more than 5% in all but one patient, who had a low-renin profile. The response was generally maximal following 8 to 10 days of continuous treatment (i.e., 6–7 days of maintenance dosage), and was greatest in the high-renin group and least in the low-renin group (table 1, fig. 3). Moreover, for all patients considered together (but not within each subgroup), the percentage of fall in mean arterial pressure after 7 days of maintenance treatment was directly related to the percentage of fall in urine aldosterone ($r = 0.73, n = 23, p < 0.001$) and was inversely related to the percentage of change in serum potassium concentration ($r = -0.72, n = 23, p < 0.001$). There was no relationship between the changes in blood pressure and the changes in sodium balance, either for the patients as a whole or within the renin subgroups.

Discussion

In the present study we have demonstrated that maintained inhibition of angiotensin converting enzyme with captopril in hypertensive patients produces on the average a 50% reduction in aldosterone secretion, together with potassium retention that is related in degree to the fall in aldosterone. These findings confirm and illustrate the important role of angiotensin in maintaining aldosterone secretion in hypertensive subjects. They also emphasize the importance of aldosterone in maintaining potassium balance and demonstrate that reductions in aldosterone can usually lead to natriuresis, even in the face of concurrently induced falls in arterial pressure.

Early reports on this orally active converting enzyme inhibitor indicate that it is a potent antihypertensive agent in a major fraction of patients tested. Despite the potential for this drug to inhibit conversion of angiotensin I to angiotensin II, Gavras and his colleagues were unable to relate its antihypertensive action to the baseline renin activity, suggesting that additional factors may mediate the antihypertensive effect. Since angiotensin converting enzyme is one of at least two peptidases that inactivates bradykinin, kinin accumulation could also play a role in the drug's action. There are no reports that captopril increases bradykinin in humans, but one group has reported increases in plasma bradykinin during acute infusion of teprotide (SQ20,881), the nonapeptide converting enzyme inhibitor. Although the magnitude of the increments in plasma bradykinin did not correlate with the depressor
response, a more recent study by the same group showed that responders to teprotide have both the greatest increments in bradykinin and the greatest decrements in angiotensin II, and that angiotensin II had to be infused at a rate that maintained the plasma level above control in order to restore blood pressure to the pretreatment level. On the other hand, other workers have not been able to document any increases in plasma bradykinin with teprotide, and still others have found much lower baseline values for plasma bradykinin, suggesting a serious methodological problem. Thus, the role of kinin accumulation in mediating the antihypertensive effect of converting enzyme blockade is still unresolved.

Although a potentiating effect of bradykinin on the antihypertensive effect of captopril is not ruled out, our studies were carried out to determine to what extent, if any, the antihypertensive effect of captopril might be related to concurrent sustained changes in the renin-angiotensin-aldosterone system. Because of the inherent inaccuracy in measuring subnormal angiotensin II levels, we sought more reliable evidence of captopril-induced interruption of the renin axis by examining the effect of the drug on a major biological action of angiotensin II, namely, stimulation of aldosterone biosynthesis. Since bradykinin has no reported effect on aldosterone secretion, demonstration of a fall in aldosterone secretion during converting enzyme inhibition would be supportive evidence that plasma angiotensin II has remained decreased.

We have shown in this report that administration of captopril to hypertensive patients produces sustained reductions in both plasma aldosterone and urine aldosterone excretion over a 10-day period and at the same time causes marked potassium retention that is directly related to the fall in aldosterone. The parallel changes in both plasma and urine aldosterone suggest that captopril reduces secretion of aldosterone by the adrenal cortex. Moreover, the reductions in aldosterone were sustained in the face of substantial potassium accumulation, an effect which might, ceteris paribus, be expected to increase aldosterone secretion. These findings, therefore, provide strong evidence that the drug induces a sustained decrease in biologically effective plasma angiotensin II.

In the absence of changes in arterial pressure, blockade of the renin system should result in natriuresis due to reduced aldosterone secretion and reduced renal vasoconstriction. However, the natriuresis induced by captopril was less consistently related to the pretreatment renin level or to the degree of aldosterone suppression than was potassium retention. In fact, four of the 23 patients actually exhibited sodium retention. This fact is not surprising if one considers that reduction in arterial pressure (by most antihypertensive agents except diuretics or β-blockers) generally causes sodium retention, probably through increased proximal sodium reabsorption and a reduced glomerular filtration rate. It also probably explains why the high-renin patients, who had the largest falls in pressure, did not have, on the average, a greater net natriuresis than the normal-renin group. Similarly, one would expect that the low-renin patients, who had the smallest blood pressure response, would have the least stimulus for sodium retention. The fact that the sodium losses were least in this group therefore suggests that the drug-induced natriuresis is related in some manner to blockade of the renin system. Furthermore, the occurrence of potassium retention in the face of negative sodium balance (fig. 2) suggests that a considerable portion of the sodium loss occurs in the distal tubule at the aldosterone-directed site of Na⁺-K⁺ exchange.

Although the complexity of changes in renal sodium handling during antihypertensive therapy have made it impossible to define quantitative relationships, it seems likely that the changes in sodium excretion can be accounted for by the observed reductions in aldosterone secretion and in arterial pressure. However, other intrarenal effects on sodium excretion are not excluded by this study. Thus, converting enzyme blockade also has the potential to reduce intrarenal angiotensin II formation and possibly increase renal kinin levels. These effects, by reducing intrarenal vasoconstriction or by promoting vasodilatation, might work to enhance sodium excretion, but they are unlikely to induce potassium retention.

The present findings have implications for both the mechanism of action and the safety of captopril in the treatment of hypertension. We have shown that the magnitude of depressor responses is related to the degree of aldosterone suppression and to the magnitude of increases in serum potassium. This suggests that the action of the drug to lower blood pressure is related significantly to a functional interruption of the renin-angiotensin-aldosterone axis. The correlation between induced falls in blood pressure and in aldosterone may be indirect and may merely reflect the degree to which arterial angiotensin II has been reduced. However, suppression of aldosterone could also play a role in the drug-induced falls in blood pressure via induced natriuresis, even though we have thus far been unable to demonstrate this unequivocally. Whether or not this proves to be the case, the natriuretic effect at least suggests that tolerance to captopril may not develop as readily as it does with many other antihypertensive agents.

We have previously shown that, at the doses used, captopril does not completely block the effects of angiotensin II formation and aldosterone continues to respond to changes in posture in parallel with changes in renin. Since hyperkalemia has not occurred to date in any of the patients treated chronically with the drug, it appears that both plasma potassium and any residual angiotensin II continue to interact homeostatically to govern aldosterone secretion during long-

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*It is, of course, possible that aldosterone would have decreased even further with time had the patients not retained potassium. The stimulatory effect of potassium accumulation on aldosterone secretion might also explain why the relationship between the degree of aldosterone suppression and the amount of potassium retained was not even stronger.
term blockade of the renin axis. Therefore, variations in potassium intake would not be expected to have an adverse effect during chronic treatment, with the important possible exception of patients with renal parenchymal disease and impaired capacity for potassium excretion. However, it is clear that long-term reductions in blood pressure have been maintained with captopril and thus have not been overcome by any compensatory influences. This suggests that the antecedent levels of angiotensin II in a large fraction of hypertensive patients may be inappropriate for blood pressure homeostasis.

In conclusion, the phenomena described in this study define coincident changes in the renin-angiotensin-aldosterone axis that are associated with sustained reduction in blood pressure during treatment with captopril. While it remains for future research to determine and quantify to what extent the induced falls in plasma angiotensin II and aldosterone secretion contribute directly to the antihypertensive effect, the circumstantial evidence described herein make it a likely possibility that this blockade of the renin axis is a major factor in the action of the drug.

References


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S A Atlas, D B Case, J E Sealey, J H Laragh and D N McKinstry

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