The Antihypertensive Effect of Captopril
Evidence for an Influence of Kinins

ALBERT MIMRAN, M.D., REMY TARGHETTA, M.D., AND BERNADETTE LAROCHE, M.D.

SUMMARY The acute effect of the orally-active converting enzyme inhibitor, captopril, was compared to that of saralasin in 13 patients with various forms of hypertension on ad libitum sodium intake. A significant difference between the effects of the two drugs on mean arterial pressure (MAP) was found (−11 ± 3 mm Hg with saralasin, −24 ± 4.5 mm Hg after captopril). This difference was not correlated with control plasma renin activity (PRA). To determine the influence of the endogenous kallikrein-kinin system in the antihypertensive action of captopril, the effect of aprotinin (Apro), an inhibitor of kinin generation, on the MAP level achieved by captopril was assessed in five normal subjects and 15 patients with hypertension on ad libitum sodium intake. In normal subjects, captopril did not alter MAP, nor did Apro have any effect. In six patients with essential hypertension and normal PRA, MAP decreased by 5.5 ± 2 mm Hg following captopril, and Apro did not modify this level. In nine patients with renovascular hypertension (RVH), MAP fell by 22 ± 3 mm Hg after captopril administration, and Apro infusion induced a rise in MAP of 13 ± 1.7 mm Hg. A positive correlation between log control PRA and the effect of aprotinin was obtained (r = 0.63, p < 0.005). Apro had no effect in two patients with RVH who experienced a large drop in MAP during salasin.

These results suggest that endogenous kinins as well as other substances, the generation of which is inhibited by aprotinin, may participate to the antihypertensive effect of captopril in patients with angiotensin-dependent hypertension. The lack of an aprotinin effect on the MAP level achieved during saralasin infusion suggests that the influence of the kallikrein-kinin system is related to the effect of captopril rather than the fall in arterial pressure resulting from angiotensin blockade. (Hypertension 2: 732–737, 1980)

KEY WORDS • converting enzyme inhibition • captopril • saralasin • hypertension • aprotinin

INHIBITORS of the renin-angiotensin system have permitted a rational approach of the role of the system in cardiovascular homeostasis; however, they do not share a single action (i.e., inhibition of angiotensin II). Saralasin, the widely used angiotensin II analog acting at the receptor level, displays partial agonistic activity in some circumstances, while converting enzyme blockers also inhibit kininase II, the major degradation enzyme of circulating kinins, and potentiate the vasodilating effect of kinins.

It has been shown that the nonapeptide SQ 20,881 induces a decrease in arterial pressure in patients with normal renin hypertension, while saralasin is ineffective in such patients. In addition, Williams and Hollenberg found that the decrease in arterial pressure induced by SQ 20,881 was associated with a rise in plasma bradykinin level in patients with normoreninemic essential hypertension, thus suggesting an influence of kinins on the antihypertensive effect of SQ 20,881. Nevertheless, no evidence for a vasodilatating effect of this increase in circulating bradykinin has been provided to date.

The present studies aimed at showing that captopril, the orally active inhibitor of angiotensin-converting enzyme (SQ 14,225, D-3-mercapto-2-methylpropanoyl-L-proline), has a more pronounced antihypertensive effect than saralasin. Moreover, to investigate the potential contribution of the kallikrein-kinin system to the effect of captopril, endogenous generation of kinin was inhibited by aprotinin, a potent inhibitor of human plasma kallikrein and other proteases. The rationale of these studies is that, if kinins participate to the hypotensive effect of captopril, the administration of aprotinin will blunt the vasodepressor response to the agent. In addition, the response to aprotinin was assessed during the infusion of saralasin, a compound devoid of any action on the kallikrein-kinin system.

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Materials and Methods

Subjects

This investigation was carried out in five normal volunteers 18 to 30 years of age and 23 patients with hypertension ranging in age from 16 to 68 years. All patients with hypertension underwent physical examinations, routine laboratory measurements, and a diagnostic evaluation including renal arteriography when necessary. Eight patients had hypertension associated with severe renal artery stenosis (one bilateral), three had unilateral renal artery thrombosis, and one had thrombosis of the left inferior polar artery. Hypertension was associated with unilateral pyelonephritis in one patient and bilateral nephropathy with terminal chronic renal failure in two patients. Essential hypertension was found in eight patients.

Antihypertensive medications were discontinued at least 2 weeks prior to studies in all cases with the exception of two patients with severe hypertension. All patients were maintained on ad libitum sodium intake and were fully informed of the experimental procedure.

Protocols

Studies were carried out with the subjects in the supine position and after an overnight bed rest. Four separate protocols were followed, as described below.

1. Comparison Between the Effects of Acute Administration of Saralasin and Captopril

This study was undertaken in 13 patients with hypertension: seven had renovascular disease, one unilateral pyelonephritis, and two terminal chronic renal failure, and three essential hypertension. Studies were carried out in the morning, with patients in the recumbent position after an overnight bed rest. When arterial pressure was stable, saralasin (l-sarcosine-8-alanine-angiotensin II, Eaton laboratories, Norwich, New York) was administered intravenously at a dose of 2.5 μg/kg/min for 30 minutes. If arterial pressure fell, an additional dose of 5 μg/kg/min was infused for 30 minutes to obtain a maximal effect. Afterward, and following the return of arterial pressure to control (at least 1 hour later), patients were given one 50 mg tablet of captopril (Squibb and Sons, Princeton, New Jersey). The effect of captopril was assessed during a 2-hour period, which had been shown to be sufficient to produce a maximal effect.

Blood samples for the determination of plasma renin activity (PRA) were obtained before captopril and before and at the end of the saralasin study.

2. Influence of Aprotinin Infusion on the Effect of Acute Administration of Captopril

This investigation was conducted on five healthy volunteers and 15 patients with hypertension (nine with renovascular hypertension, and six with essential hypertension). Among patients with renovascular hypertension, five had already undergone the first study. After 60 to 80 minutes had elapsed following administration of one 50 mg tablet of captopril, an intravenous infusion of aprotinin (Specia Laboratories, France) was started. A total dose of 500,000 KIU (kallikrein inhibitor units) of aprotinin was administered within approximately 60 minutes. In previous studies, it has been shown that the effect of captopril is maximal and constant during the second hour following acute oral administration.

Blood samples for the determination PRA were obtained before captopril and before and at the end of aprotinin infusion.

3. Influence of Aprotinin on Saralasin-Induced Hypotensive Response

In two patients with renovascular hypertension, an infusion of saralasin was given as previously described. When the maximum decrease in arterial pressure was achieved, the administration of aprotinin was superimposed.

4. Effect of Aprotinin During Chronic Captopril Treatment

In two patients with renal artery stenosis, we studied the effect of aprotinin infusion on the antihypertensive action of the first 50 mg/tablet of captopril (as previously described) and during chronic treatment by the converting enzyme inhibitor. In one patient, treatment consisted of 100 mg of captopril three times a day (tid), and in another it consisted of captopril (150 mg tid) and hydrochlorothiazide (25 mg bid). In both patients, hypertension was fully controlled at the time of the second aprotinin infusion study.

Analytical Methods

Arterial pressure was determined with a semiautomatic device (Elag Kohn). Three consecutive measurements were obtained every 5 minutes. Each arterial pressure value represents the average of nine determinations. The PRA was estimated by radioimmunoaasay of angiotensin I generated during incubation at pH 5.5 in the presence of endogenous substrate (CEA, Sorin Kit). Values are expressed as mean ± standard error of the mean (SEM). Statistical significance was assessed by the Student's t test for paired data, where appropriate.

Results

1. Comparison Between the Acute Effects of Saralasin and Captopril

In all patients, the maximum change in arterial pressure was achieved with 2.5 μg/kg/min of saralasin. In addition, the effect of captopril was significant within 20 minutes after oral administration, reached a maximum by 60 minutes, and remained constant during the following hour.
The results of this study are summarized in table 1. The change in mean arterial pressure (MAP) produced by captopril (range, +1 to −33 mm Hg) was markedly higher (p < 0.001) than that achieved by saralasin infusion (range, +9 to −33 mm Hg). PRA increased with both inhibitors; however, the change in PRA induced by captopril was significantly higher than that produced by saralasin (p < 0.05). There was no correlation between control PRA (range, 1.5 to 173.2 ng/ml/hr) or its logarithm and the difference between the effects of saralasin and captopril on MAP (correlation coefficients of 0.36 and 0.25 respectively).

2. Influence of Aprotinin Infusion on the Arterial Pressure Level Achieved After Acute Administration of Captopril

Results are summarized in figure 1. In normal subjects, captopril had no effect on MAP, and aprotinin did not alter the MAP level achieved by captopril. PRA was 1.68 ± 0.27 before and 8.9 ± 4 ng/ml/hr (p < 0.05) after captopril; at the end of aprotinin infusion, PRA was unchanged (7.4 ± 4 ng/ml/hr) compared to post-captopril mean value.

In patients with essential hypertension, captopril produced a decrease in MAP of 5.5 ± 2 mm Hg (p < 0.05) and a nonsignificant increase in PRA from 1.58 ± 0.5 to 2.74 ± 1 ng/ml/hr. Aprotinin infusion was associated with no significant change in MAP and PRA (2.15 ± 0.8 ng/ml/hr) compared to the captopril phase.

In the group of patients with renovascular hypertension, MAP decreased by 22 ± 3 mm Hg after administration of captopril; infusion of aprotinin produced an increase in MAP of 13 ± 1.7 mm Hg (p < 0.001). However, the MAP level achieved at the end of the infusion was still significantly lower than the pre-captopril mean value (p < 0.001). The change in MAP induced by aprotinin was progressive since,

<table>
<thead>
<tr>
<th>Effect</th>
<th>MAP (mm Hg)</th>
<th>HR (b/min)</th>
<th>PRA (ng/ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>133 ± 4</td>
<td>82 ± 4</td>
<td>15 ± 5.4</td>
</tr>
<tr>
<td>Saralasin</td>
<td>123 ± 4.7</td>
<td>80 ± 4</td>
<td>27.8 ± 8.8</td>
</tr>
<tr>
<td>Absolute change</td>
<td>−11 ± 3</td>
<td>−2 ± 1</td>
<td>12.6 ± 6.4</td>
</tr>
<tr>
<td>Control</td>
<td>134 ± 4</td>
<td>78 ± 4</td>
<td>15.1 ± 5.4</td>
</tr>
<tr>
<td>Captopril</td>
<td>111 ± 5.5</td>
<td>76 ± 3</td>
<td>39.6 ± 13.3</td>
</tr>
<tr>
<td>Absolute change</td>
<td>−24 ± 4.5*</td>
<td>−2 ± 1 NS</td>
<td>24.5 ± 10.8*</td>
</tr>
</tbody>
</table>

*p < 0.05 and NS = nonsignificant compared to the effect of saralasin.

![Figure 1](http://hyper.ahajournals.org/Downloadfile/10.1161/01.HYP.5.6.734)
compared to the level achieved after captopril, MAP increased by 5.7 ± 1.4 at 20 minutes, 7.3 ± 1.5 at 40 minutes, and 13 ± 1.7 mm Hg at 60 minutes after the beginning of the infusion. PRA was 13.9 ± 2.4 before and 49.8 ± 9.2 ng/ml/hr (p < 0.005) after captopril; at the end of aprotinin, PRA decreased slightly but not significantly to 39.5 ± 7.6 ng/ml/hr. There was a positive correlation between the logarithm of pre-captopril PRA and the change in MAP produced by aprotinin (r = 0.63, p < 0.005).

In five patients with renovascular hypertension, comparison between the effects of acute administration of saralasin and captopril and study of the influence of aprotinin infusion on the effect of captopril were undertaken. In these patients (fig. 2) the effect of captopril on MAP (−25 ± 5 mm Hg) was more pronounced than that of saralasin (−15.6 ± 3 mm Hg, p < 0.01). When captopril was administered on a second occasion, MAP fell from 139 ± 5 to 115 ± 5 mm Hg (decrease of 24 ± 4 mm Hg) within 1 hour and rose to 129 ± 5 mm Hg (p < 0.005 compared to the level achieved after captopril and p < 0.02 when compared to control MAP) during aprotinin infusion. These studies showed that the effect of captopril was reproducible and that the effect of saralasin on MAP (−15.6 ± 3.4 mm Hg) was not significantly different from that obtained at the end of aprotinin infusion (−10 ± 2.6 mm Hg compared to control MAP).

3. Effect of Aprotinin on Saralasin-Induced Arterial Pressure Fall

In two patients with renovascular hypertension, saralasin induced a maximum fall in MAP of 33 and 48 mm Hg, and aprotinin infusion had no effect on the arterial pressure level achieved by the angiotensin II antagonist.

4. Effect of Aprotinin During Chronic Captopril Treatment

In one patient, administration of the first 50 mg tablet of captopril induced a decrease in MAP from 131 to 97 mm Hg, and aprotinin infusion produced a rise in MAP to 110 mm Hg. After 1 month of chronic treatment by captopril, MAP was 103 mm Hg before and 132 mm Hg at the end of aprotinin infusion (fig. 3).

In the other patient, MAP fell from 147 to 122 mm Hg after the first captopril dose and rose to 134 mm Hg during aprotinin. To achieve full control of hypertension, hydrochlorothiazide was associated with captopril, and MAP was 100 mm Hg before and 106 mm Hg at the end of aprotinin infusion. This study thus showed that aprotinin infusion caused a rise in MAP after both acute and chronic administration of captopril.

In all patients, the infusion of aprotinin was well tolerated; however, in a 65-year-old woman with renovascular hypertension, prurigo occurred near to the end of aprotinin infusion.

Discussion

In the present investigation it was demonstrated that, in patients with various forms of hypertension maintained on unrestricted sodium intake, acute angiotensin-converting enzyme inhibition by captopril has a more marked effect on arterial pressure than saralasin. In addition, infusion of aprotinin, a known inhibitor of kallikrein and other proteases (i.e., trypsin, chymotrypsin, and plasmin) produced a significant increase in the arterial pressure level achieved after acute captopril administration, only in those patients whose arterial pressure fell substantially after converting enzyme inhibition.

The finding that captopril induced a larger depressor response than saralasin is in agreement with
others² using the nonapeptide converting enzyme inhibitor SQ 20,881 in hypertensive patients on ad libitum sodium intake. There are at least two possible explanations for these observations: the intrinsic angiotensin-like activity of saralasin is responsible for an underestimation of the role of the renin-angiotensin system in the regulation of arterial pressure and/or inhibition of converting enzyme and thus kininase II¹ is associated with an accumulation of kinins. Saralasin displays an agonistic action on vascular receptors mainly in states associated with depressed renin levels¹, ², ⁶, ¹³ and has been shown to produce a simultaneous and transient rise in arterial pressure and plasma noradrenaline concentration following initiation of infusion at a dose of 10 µg/kg/min.¹⁸ It is, however, likely that these properties of saralasin are minimized in patients with high renin levels and when saralasin infusion is started at a low dose and increased progressively until a maximal effect is obtained. In support of this possibility, it was recently shown that saralasin and SQ 20,881 induced a similar depressor response in patients with high renin renovascular hypertension while SQ 20,881 was more effective than saralasin in normal-renin patients.¹⁴ Although this observation was not confirmed in the present studies (fig. 2), a difference between the mechanism(s) of action of SQ 20,881 and captopril, which are two structurally different agents, cannot be excluded.

Inhibitors of an angiotensin-converting enzyme which also inhibit kininase II, the major but not sole¹, ⁶ degradation enzyme of circulating kinins, may induce an accumulation of kinins, exerting their vasodepressor activity directly or through stimulation of prostaglandin synthesis. Although determination of changes in plasma bradykinin concentration after acute administration of SQ 20,881 have yielded variable and somewhat conflicting results in normal subjects⁷, ¹² and in patients with hypertension⁷, ¹⁶, ¹⁹ the question remains as to whether the increase in plasma kinins¹⁸ has a significant vasodepressor effect or is related to the decrease in arterial pressure produced by inhibition of angiotensin II generation. It is interesting to note that no study of the effect of saralasin-induced fall in arterial pressure on plasma kinin concentration has ever been published.

In the present investigation, the influence of endogenous kinins on the antihypertensive effect of captopril was approached through assessment of the effect of the inhibition of kinin generation by aprotinin on the arterial pressure level achieved by captopril. In patients who experienced a consistent fall in arterial pressure following captopril administration, aprotinin, which otherwise did not affect resting arterial pressure in two patients with high renin renovascular hypertension, induced a progressive and significant increase in arterial pressure. Aprotinin was ineffective in normal subjects and in patients with essential hypertension, both groups having similar mean values of pre-captopril PRA. Since the plasma level of bradykinin is directly related to PRA,¹⁸, ²⁰ it is reasonable to assume that in patients with high PRA theresponse of kinins to captopril is accentuated, and thus kinins have a significant role in the vasodepressor response to the converting enzyme inhibition.

The results obtained during infusion of aprotinin should be interpreted with caution since aprotinin inhibits several endogenous enzymes with proteolytic and esterolytic activity including the kinin-releasing effect of all known kallikreins in man.¹⁰ It seems adequate to propose that some vasodilating polypeptides including kinins, the generation of which is blocked by aprotinin, participate to the antihypertensive effect of captopril. In a recent report, Swartz et al.¹⁴ brought some indirect evidence suggesting that the effect of SQ 20,881 is not only mediated by blockade of angiotensin II generation. Administering graded doses of angiotensin II during converting-enzyme blockade until arterial pressure returned to control levels, they observed that the plasma angiotensin II level associated with return of blood pressure to control was significantly higher than the pre-SQ 20,881 plasma angiotensin II concentration. The observation of a lack of effect of aprotinin during saralasin-induced fall in arterial pressure suggests that the arterial pressure change produced by aprotinin in captopril-treated patients was related to converting enzyme inhibition rather than the decrease in arterial pressure.

In two patients with renovascular hypertension, aprotinin induced an increase in arterial pressure after both acute and chronic captopril treatment (fig. 3). Although the number of patients is very low, this suggests that factors resulting from the action of endogenous proteases may contribute to the therapeutic efficacy of captopril together with changes in aldosterone secretion, renal hemodynamics, and sodium handling.⁶, ¹¹, ²¹

The results of the present investigation suggest that, among other systems, the endogenous kallikrein-kinin system may play a role in the antihypertensive effect of captopril in patients with renin-dependent hypertension. It is unlikely, however, that this mechanism of action was operative in the captopril-induced decrease in supine arterial pressure together with the severe orthostatic hypotension that occurred only after substantial extracellular volume contraction associated with no change in circulating renin level in an anephric female patient.²² If this observation, which was not reported with SQ 20,881,⁴ is confirmed by others, a possible interference of this new and potent antihypertensive agent with other systems, mainly, the sympathetic nervous system, remains to be clarified.

References
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