Hemodynamic and Antihypertensive Effects of Captopril, an Orally Active Angiotensin Converting Enzyme Inhibitor

JAY M. SULLIVAN, M.D., BURT A. GINSBURG, M.D., THOMAS E. RATTS, M.D., JAMES G. JOHNSON, M.D., BEN R. BARTON, B.S., DAVID H. KRAUS, M.D., DORIS N. MCKINSTRY, PH.D., AND E. ERIC MUIRHEAD, M.D.

SUMMARY Captopril inhibits angiotensin II formation and bradykinin degradation in vivo. Eleven patients with essential hypertension (EH) and four patients with renovascular hypertension (RVH) were treated with captopril for periods ranging from 3 days to 12 months. All patients had a diastolic blood pressure (DBP) over 95 mm Hg after receiving a placebo for 3 days. Captopril given in ascending doses (10-1000 mg/day) caused normalization of blood pressure in all but three patients, one with severe RVH whose pressure fell 11%, one patient with severe EH, whose pressure fell 27%, and one with EH whose blood pressure fell 8.5%. The average control DBP in patients with EH was 113.7 ± 5.5 (SE) mm Hg and fell to 89.9 ± 3.6 mm Hg (p < 0.001), while DBP in patients with RVH fell from 110.7 ± 7.6 mm Hg to 94.5 ± 8.2 (p < 0.005). All patients were studied in balance on a 100 mEq sodium (Na) diet. Plasma renin activity (PRA) versus 24-hour urinary Na excretion increased sevenfold during therapy while converting enzyme activity fell by about one half. The magnitude of the blood pressure response was not related to control PRA. Cardiac output was estimated by echocardiography during placebo administration and during maintenance therapy with captopril. A significant change was not observed. Total peripheral resistance fell an average of 18.9% (p < 0.05) in 11 of the 13 patients in whom the measurement could be made. It is concluded that captopril effectively lowers blood pressure in patients with EH or RVH by reducing total peripheral resistance.

KEY WORDS • hemodynamics • angiotensin • hypertension • captopril • renin • converting enzyme inhibitor • vascular resistance

A PARENTERAL angiotensin converting enzyme inhibitor, teprotide,1,2 and an angiotensin receptor blocking agent, saralasin3,4 have been used to study the role of angiotensin II in the initiation and maintenance of blood pressure elevation in various disease states. Recently, an orally active angiotensin converting enzyme inhibitor, captopril, has been developed5 and found to lower blood pressure in small groups of patients with either renovascular or essential hypertension.5 As the antihypertensive effect did not appear to be related to the baseline plasma renin activity, the mechanism of the blood pressure lowering effect was not clear. Thus, additional studies are needed to uncover information that will contribute to understanding the undoubtedly complex mechanism of action of these important therapeutic agents. The present study concerns the hemodynamic effects of captopril in hypertensive human subjects and the relationship of these effects to hormonal and metabolic changes.

Methods

The protocol for this investigation was approved by the Patient Participation Committee of the University of Tennessee Center for the Health Sciences. Fifteen patients agreed to participate in the study. Six were male, nine were female, nine were black and six were white. Their ages ranged from 20 to 62 years. Eleven had essential hypertension and four had renovascular hypertension.

Diuretic agents were stopped at least 2 weeks before admission to the hospital and other antihypertensive agents at least 3 days before admission. None of the patients had received recent treatment with reserpine or guanethidine. At the time of admission, the patients underwent a complete physical examination and routine urinalysis, as well as hematological and
Hemodynamic Effects

Captopril resulted in a gradual fall in blood pressure over a dose ranging period of 2 to 8 days. The decrement in pressure seen on the first day of therapy was absent on the second day in eight of the 15 cases. Subsequently, the diastolic blood pressure of the 15 patients fell an average of 19%, from 112.9 ± 16.9 mm Hg on the third day of placebo treatment, to 91.2 ± 3.2 mm Hg before discharge from the hospital. The reduction was statistically significant (p < 0.001). The average diastolic blood pressure of the 11 patients with essential hypertension fell from 113.7 ± 5.5 mm Hg to 89.9 ± 3.6 mm Hg (p < 0.001) while that of the four patients with renovascular hypertension fell from 110.8 ± 7.6 mm Hg to 94.6 ± 8.2 mm Hg (p < 0.005). Diastolic blood pressure failed to fall below 95 mm Hg in three of the patients; one patient had severe renovascular hypertension and experienced an 11% reduction of diastolic pressure, while reductions of 27% and 8.5% (the former received concomitant diuretic therapy) were seen in two patients with severe essential hypertension whose diastolic pressures were 156 and 118 mm Hg, respectively, before treatment. The diastolic pressure of the other 13 patients was reduced to levels of 93 mm Hg or less, only one of whom received diuretics.

During therapy with captopril, mean peripheral resistance in the 13 patients from whom technically adequate echocardiograms could be obtained fell an average of 18.9%, from 1883 ± 159 to 1523 ± 123 dynes • sec • cm⁻⁵ (p < 0.05; table 1). Cardiac index was 3.14 ± 0.24 liter/min/m² before and 2.93 ± 0.24 liter/min/m² during treatment. The change was not statistically significant, nor was the slight fall in heart rate from 79 ± 3 before to 76 ± 2 beats/min during therapy. Stroke volume was 70.3 ± 3.36 ml before therapy and 67.2 ± 3.0 ml afterward. The change was not statistically significant. The average body weight of the 15 patients fell from 80.3 ± 5.67 kg to 78.8 ± 2.99 kg (p < 0.025). The plasma volume of 12 patients was measured after 3 days of placebo and during inpatient maintenance therapy with captopril. The average plasma volume was 43.7 ± 3.5 ml/kg before and 45.8 ± 4.8 ml/kg during treatment. The individual changes were not consistent and the differences were not statistically significant.

Endocrine and Metabolic Effects

Serum converting enzyme activity was measured in the last nine patients admitted to the study before and during maintenance therapy. Enzyme activity fell
HEMODYNAMIC EFFECTS OF CONVERTING ENZYME BLOCKADE/Sullivan et al. 399

Table 1. Hemodynamic Effects of Captopril

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Placebo</th>
<th>Captopril</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BP (mm Hg)</td>
<td>SV (ml)</td>
</tr>
<tr>
<td>1*</td>
<td>122</td>
<td>68</td>
</tr>
<tr>
<td>2†</td>
<td>133</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>148</td>
<td>83</td>
</tr>
<tr>
<td>4†</td>
<td>124</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>118</td>
<td>67</td>
</tr>
<tr>
<td>6</td>
<td>96</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>115</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>178</td>
<td>74</td>
</tr>
<tr>
<td>9</td>
<td>110</td>
<td>58</td>
</tr>
<tr>
<td>10</td>
<td>126</td>
<td>53</td>
</tr>
<tr>
<td>11*</td>
<td>118</td>
<td>47</td>
</tr>
<tr>
<td>12</td>
<td>154</td>
<td>67</td>
</tr>
<tr>
<td>13</td>
<td>104</td>
<td>74.6</td>
</tr>
<tr>
<td>Mean</td>
<td>126.6</td>
<td>70.31</td>
</tr>
<tr>
<td>SE</td>
<td>0.16</td>
<td>3.36</td>
</tr>
</tbody>
</table>

Probability: NS < 0.001 < 0.05

% change from control: 22.8 4.4 3.2 6.7 18.9

*Patients with renovascular hypertension.
†Plasma renin activity less than 2 ng/ml/hr before and after captopril.
‡Duration of captopril administration at time of hemodynamic study.

Abbreviations: BP = mean blood pressure; SV = stroke volume; HR = heart rate; CI = cardiac index; TPR = total peripheral resistance.

significantly from 30.3 ± 1.4 units to 12.6 ± 2.2 units (p < 0.001). However, converting enzyme activity remained detectable in the serum of all treated patients. The level of post-treatment activity was not correlated with the antihypertensive effect.

Plasma renin activity rose sevenfold by the time a maintenance dose of captopril had been established; rising from 5.4 ± 1.1 ng/ml/hr before to 37.5 ± 8.4 ng/ml/hr during therapy (p < 0.005). Initial PRA was measured after each patient had received a 100 mEq Na, 60 mEq K diet for 3 days. No relationship was found between baseline PRA and the percent fall in diastolic blood pressure after the first dose of captopril, after 7 days of therapy or at the time of maximum antihypertensive response (fig. 1). Similarly, no significant correlation was found between PRA and the change in TPR (r = 0.215) or the change in cardiac output (r = 0.261).

Plasma cortisol was 15.5 ± 1.6 µg/dl before and 18.9 ± 1.7 µg/dl during treatment (NS). Serum potassium rose from 3.86 ± 0.09 to 4.34 ± 0.12 mEq/liter (p < 0.005). Serum sodium did not change significantly, the average during the placebo period was 140.4 ± 0.61 mEq/liter and 139 ± 0.66 mEq/liter during treatment. Complete blood cell counts, urinalysis, electrocardiograms, serum creatinine, liver and thyroid function tests did not change during therapy.

A transient maculopapular skin rash and a low-grade fever occurred in two patients, after 6 and 78 days of therapy with 1000 mg and 600 mg daily, respectively. No changes were noted on clinical blood and urine studies and the rash disappeared on cessation of captopril therapy. No attempt was made to restart therapy for the first patient. The second patient was able to resume therapy with captopril at a lower dose level (50 mg daily) with adequate control of blood pressure and without a recurrence of the rash. The average daily maintenance dose was 430 mg.

Discussion

Our studies show that the usual hemodynamic effect of converting enzyme blockade in hypertensive subjects was a significant reduction of TPR, a fall in both systolic and diastolic blood pressure and no change in cardiac index. This response was seen in 11 of the 13 patients from whom we were able to obtain satisfactory echocardiograms, in patients with either essential
or renovascular hypertension, as well as in patients whose pretreatment PRA was low, normal or high. The fall in peripheral resistance parallels our findings in the spontaneously hypertensive rat. It is also in accord with the acute fall in TPR observed after teprotide was administrated parenterally to patients with congestive heart failure and co-workers. An atypical response, a fall in cardiac index and an increased peripheral resistance was found in Patient 1, who had renovascular hypertension and Patient 4, who had essential hypertension associated with low PRA (table 1). The latter patient was studied on two separate occasions during therapy, 3 days apart, and each time showed a lower cardiac index and a higher systemic resistance. The reason for this atypical response was not apparent. The echocardiographic studies were of good quality and the difference did not appear to be methodological. The heart rate did not suggest that the patients were unduly anxious during the first study, which might have accounted for a relatively high cardiac output at that time, and which might have fallen during subsequent studies as the patients became accustomed to their surroundings. Patient 1 was a white female and Patient 4 was a black male, thus race and sex did not account for the difference. As the patients represented opposite extremes of the spectrum of PRA, we could not account for the difference on this basis. However, blood levels of other vasoactive substances were not measured.

The interrelationships among baseline PRA relative to sodium intake and the antihypertensive response of the 15 patients were analyzed. No correlations were found between PRA activity during the placebo period and the maximum fall in blood pressure after the first dose of captopril, nor after 7 days of captopril administration. No correlation was found between baseline PRA and the maximum observed fall in blood pressure.

Thus, our data do not support the concept that the degree of acute antihypertensive response to oral captopril is determined by the patients' pretreatment PRA and suggest that the antihypertensive effect of captopril may not depend entirely upon suppression of plasma angiotensin II levels. Recent advances in our understanding of the interrelationships among the renin-angiotensin system, the kallikrein-kinin system, the autonomic nervous system and prostaglandin metabolism lead to the speculation that the mechanism of action of captopril is remarkably complex. It is known that converting enzyme and kininase II, the enzyme responsible for the catabolism of bradykinin are the same, thus converting enzyme blockade is followed by elevation of plasma bradykinin levels. As bradykinin functions primarily as a local hormone and is a vasodilator, accumulation of bradykinin in vascular smooth muscle may add to the effects of reduced plasma angiotensin II levels. Additionally, accumulation of bradykinin via activation of phospholipase A₂ results in release of arachidonic acid and enhanced synthesis of prostaglandins. In vascular smooth muscle, the major compound formed in response to arachidonic acid release in prostaglandin E₁, a vasodilator which could contribute to the antihypertensive response. Activation of the arachidonic acid cascade also results in the formation of prostaglandin D₂ in blood vessel walls, which causes impaired norepinephrine release at the nerve endings. Thus, the administration of captopril should be followed by activation of a number of factors which act to lower blood pressure and the relative contributions of these factors requires further research to establish their importance.

Our results are similar to those reported by Gavras and co-workers in that we have found captopril to be a well tolerated, potent antihypertensive agent in the majority of patients studied, regardless of pretreatment PRA. We have also found that two of our 15 patients developed a skin rash of unknown origin which resolved without permanent ill effects on discontinuation. Unlike Gavras et al., we found that the diastolic blood pressure of three of our patients (20%) remained above 95 mm Hg, on the maximum allowable dose of captopril, and remains above 95 mm Hg in the one patient still under observation despite concomitant diuretic therapy. The untreated blood pressure of the latter three patients, one with...
HEMODYNAMIC EFFECTS OF CONVERTING ENZYME BLOCKADE/Sullivan et al. 401

renovascular and two with essential hypertension, were among the highest of the group, and the post-treatment levels of converting enzyme activity among the lowest of the group. Thus, the reasons for their incomplete antihypertensive response, other than the severity of their hypertension, were not apparent.

We conclude that captopril is an effective antihypertensive agent for many patients with essential or renovascular hypertension. The hemodynamic mechanism of action appears to be a reduction of total peripheral resistance. The compound appears to be well tolerated for periods up to 1 year but the long-term effects, and the significance of the reversible skin rash, remain to be established.

References

Hemodynamic and antihypertensive effects of captopril, an orally active angiotensin converting enzyme inhibitor.


Hypertension. 1979;1:397-401
doi: 10.1161/01.HYP.1.4.397

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1979 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/1/4/397

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/