Acute and Chronic Treatment of Severe and Malignant Hypertension with the Oral Angiotensin-converting Enzyme Inhibitor Captopril

DAVID B. CASE, M.D., STEVEN A. ATLAS, M.D., PATRICIA A. SULLIVAN, R.N., and JOHN H. LARAGH, M.D.

SUMMARY Ten patients with severe and 10 with accelerated or malignant hypertension were treated with the angiotensin-converting enzyme inhibitor captopril. Captopril acutely reduced blood pressure in all patients except two who had suppressed plasma renin activity. Four patients with encephalopathy showed immediate improvement after the first dose. Two patients could be withdrawn from nitroprusside infusion upon administration of captopril. Nineteen of 20 patients have remained on captopril for 12–32 months. Blood pressure is controlled in 18 and improved in two. Eleven required addition of diuretic and one addition of clonidine. The maximal antihypertensive effect of captopril with or without diuretics was evident after 3 months of continuous therapy and was associated with elevated plasma renin levels, normal aldosterone excretion and preservation of renal function. Captopril was well-tolerated, but produced occasional rash, loss of taste and proteinuria. We conclude that captopril, alone or in combination with other drugs, is effective in both the acute and long-term management of severe and malignant hypertension.

EFFECTIVE TREATMENT of patients with severe and accelerated forms of hypertension is a complex therapeutic challenge. Patients are often treated initially with potent parenteral vasodilators such as diazoxide or sodium nitroprusside and are then switched to oral therapy, usually with several drugs. Malignant and severe hypertension are frequently associated with hyperactivity of the renin-angiotensin-aldosterone axis. As a result, drugs that block or inhibit the renin system, such as propranolol, the non-apeptidase angiotensin-converting enzyme inhibitor teprotide (SQ 20881), and the angiotensin antagonist saralasin, have been shown to lower blood pressure in these forms of hypertension. Captopril (Capoten, SQ14225) is an orally active inhibitor of angiotensin-converting enzyme, the peptidase that converts the inactive decapeptide angiotensin I to the vasopressor aldosterone-stimulating octapeptide angiotensin II. The present study was designed to determine the clinical effectiveness of captopril in severe and malignant hypertension. In addition to its renin-blocking action, the drug has a rapid onset of action, with an antihypertensive effect that begins 15 minutes after the first dose. It is available as an oral preparation suitable for long-term therapy.

Materials and Methods

Patient Selection

Ten patients with severe hypertension (diastolic pressure greater than 120 mm Hg) and 10 with accelerating or malignant hypertension (grade III or IV neuroretinopathy) were selected for study. Each patient gave written consent to the use of captopril after a protocol approved by the Human Rights in Research Committee of The New York Hospital–Cornell Medical Center. Clinical characteristics of these patients are listed in Table I. The patients were 10–67 years old. Eleven of the patients had underlying renovascular hypertension, seven with bilateral renal artery stenosis and four with unilateral lesions. One patient had systemic lupus erythematosus and seven patients had essential hypertension; in one patient (no. 4), no diagnosis was established. At the time captopril was started, six of the patients were receiving other medications: All six were on propranolol; two were also on clonidine and two others were being given i.v. sodium nitroprusside. The 14 other patients were not taking any drugs.

Four patients with malignant hypertension had a course complicated by mild-to-moderate encephalopathy, and one patient had a type III dissecting aortic aneurysm. None of the subjects had acute congestive cardiac failure, stroke or advanced renal insufficiency.

Study Design

Each patient underwent a complete history, physical examination and routine blood chemistry analysis. Blood pressure was taken at 2-minute intervals by Arteriosonde in 18 patients; in the remaining two, direct intraarterial pressure was monitored. After a stable baseline during which blood pressure was recorded in the head-up position, a single dose of captopril, 10–50 mg orally, was given. Blood pressure recordings were continued for 90 minutes after the first dose.

The dose of captopril was gradually increased over the next 3–5 days to 300–600 mg/day except in two patients who initially received 800 mg/day and one patient who was given 225 mg/day. During this period, all other drugs were withdrawn except for
propranolol in one patient with a dissecting aneurysm and in another with angina. Patients who had ambulatory diastolic pressure greater than 105 mm Hg after 1 week of captopril therapy received a diuretic: chlorthalidone, 25–50 mg/day, in six patients and furosemide, 40–80 mg/day, in two. Drug dosages were reduced during outpatient follow-up to determine the lowest dose required for blood pressure control.

At each follow-up visit, plasma renin activity, urinary aldosterone, 24-hour urine protein, blood urea nitrogen, serum creatinine and other routine chemistries of confirmation were measured.

Statistical Methods

Mean values have been expressed, with the standard error of the mean as the index of dispersion. Statistical significance was determined using the t test for paired data; confirmation was obtained using Wilcoxon's rank-sum test for small samples. Correlations were made using Spearman's correlation coefficient.

Results

Response to the First Dose

The blood pressure responses to the first oral doses of captopril in 18 of the 20 patients who were not receiving i.v. sodium nitroprusside are shown in figure 1. Diastolic pressure fell in all but two patients, who had suppressed levels of plasma renin activity (0.16 and 0.38 ng AI/ml/hour). After 90 minutes, mean diastolic blood pressure in 18 patients had declined from 132 ± 4 mm Hg to 107 ± 4 mm Hg (p < 0.001). Heart rate did not change significantly (from 74 ± 6 to 79 ± 9 beats/min). In the two patients already receiving sodium nitroprusside to maintain diastolic blood pressure at about 100 mm Hg, nitroprusside was gradually withdrawn during the 30-minute period after the first oral dose of captopril.

For the group as a whole, the logarithm of the pretreatment plasma renin activity and the percent reduction in diastolic pressure correlated well (r = 0.82, p < 0.001).

Within one-half hour of the initial dose, all four patients with encephalopathy had relief from headache and a clearing of nausea, mental confusion and decreased visual acuity. These benefits were maintained even though blood pressure sometimes rose transiently during the first week of therapy.

Responses after 1 Week

In 19 of the patients, diastolic blood pressure levels after one week of captopril therapy (fig. 1) were comparable to those after the first dose (mean 107 ± 4 mm Hg vs 108 ± 14 mm Hg). In one patient, diastolic pressure returned to control levels after 1 week on captopril alone; but he had been receiving furosemide up until the administration of the first dose, so his initial response was greatly exaggerated (fig. 1).

Long-term Effects

In 13 patients whose diastolic pressure remained above 105 mm Hg, a diuretic was added after 1 week of captopril therapy, resulting in a further fall in diastolic pressure (from 114.0 ± 4.0 mm Hg to 96 ± 6 mm Hg). The long-term pressure responses of these patients were comparable to those of the seven patients who were adequately controlled with captopril alone (fig. 2). The antihypertensive effect was maximal by the third month of therapy and stable thereafter. After 1 year, the mean diastolic pressure was 93 ± 3 mm Hg for patients treated with captopril alone and 96 ± 4 mm Hg for those treated with captopril plus a diuretic.

Neuroretinopathy cleared in all patients during the initial months of therapy. After 12 months treatment, there was no fundoscopic evidence of accelerated hypertension in any of the 10 patients who had presented initially with retinal hemorrhages or exudates.

The effects of treatment on renal function are shown in figure 3. Pretreatment serum creatinine was 1.4 ± 0.12 mg/dl and blood urea nitrogen was 15 ± 2 mg/dl in the group of patients who responded to captopril alone and were 1.6 ± 1.9 mg/dl and 22 ± 5 mg/dl, respectively, for the group of patients who required addition of a diuretic after 7 days of captopril. These values remained unchanged during the first week of captopril treatment. The addition of diuretic to captopril led to a modest rise in blood urea nitrogen (range of 30–35 mg/dl) after 3 and 6 months of therapy, which returned to baseline after 12 months. Patients treated with captopril alone had a slight but significant rise in blood urea nitrogen (15 ± 2 to 20 ± 2 mg/dl, p < 0.02), but not in serum creatinine, during the 12-month treatment period.

Among all patients, plasma renin activity rose from a mean of 15 ± 3 AI/ml/hour to 40 ± 6 ng AI/ml/hour (p < 0.001) after 3 months of therapy and remained in that range throughout the study (fig. 4). Urinary aldosterone excretion remained in the normal range (less than 25 μg/day) despite adjunctive diuretic therapy in 13 of these patients. Control rates of urinary aldosterone excretion were not determined in most patients because treatment was initiated before such a specimen could be obtained.

Sixteen of the 20 patients in this study have been maintained on captopril therapy for 20–35 months (table 2). One patient was withdrawn from captopril at the time of corrective renal artery surgery. Patient 20 was withdrawn from captopril after 2 years of controlled blood pressure and has remained normotensive for at least 3 months without treatment. Three patients developed proteinuria; in two (patients 1 and 5), proteinuria receded spontaneously on the same dose of captopril. Only patient 2 required discontinuation of therapy because of the development of nephrotic syndrome associated with a decline in renal function. Since stopping captopril, renal function and urinary protein excretion in this patient have returned to pretreatment levels.

In addition to diuretics, β-adrenergic blocking agents were used in four patients for management of angina, dissecting aneurysm or arrhythmias. In one patient, addition of clonidine produced further improvement in blood pressure control.
Side Effects of Captopril

Two patients had transient rashes lasting less than 1 week during the initiation of therapy and one had loss of taste lasting for 1 month. These side effects cleared spontaneously without alteration of captopril dosage. Three patients developed proteinuria, but this was transient in two patients, regressing spontaneously despite continued therapy. One patient required withdrawal of the drug.

Discussion

This study demonstrates the success of the orally active angiotensin-converting enzyme inhibitor captopril in both the initial treatment and the long-term maintenance therapy of patients with severe, accelerated or malignant hypertension. A drug that blocks the renin system is ideal for patients with severe and malignant hypertension, because such patients frequently have elevated plasma renin activity.1-4 The use of captopril, other converting-enzyme inhibitors, and new, potent vasodilators such as minoxidil should virtually eliminate the need to recommend bilateral nephrectomy for severe, drug-resistant hypertension.15

Acute Therapeutic Response to Captopril

The onset of action of captopril was within 15 minutes of the first oral dose, reaching a maximal effect within 30–90 minutes. Because of this rapid onset of action, captopril is suitable for initial treatment of severe hypertension. While blood pressure falls promptly after the first dose of captopril, the decline is not as precipitous as that which occurs frequently with diazoxide. There is recent evidence of the risks of abrupt hypotension, including irreversible blindness.15,16 In addition, captopril does not induce significant reflex tachycardia, in contrast to the direct-acting vasodilators diazoxide, hydralazine and minoxidil,17 thereby averting potential tachyarrhythmias and angina. Captopril, however, like other angiotensin antagonists, can produce hypotension in sodium-depleted patients.16,18

Because of the rapid onset of captopril, we could wean two patients from i.v. sodium nitroprusside as captopril was administered. The rationale for this procedure is that direct vasodilators such as hydralazine19 and nitroprusside20 stimulate renin release and, thus, the possible additive effect of these agents with captopril could lead to hypotension.

### TABLE 1. Pretreatment Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th>Grade of hypertension</th>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Blood pressure (mm Hg)</th>
<th>Pretreatment PRA (ng AI/ml/hr)</th>
<th>Blood urea nitrogen (mg/dl)</th>
<th>Serum creatinine (mg/dl)</th>
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<td>180/120</td>
<td>13</td>
<td>10</td>
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<tr>
<td></td>
<td>2</td>
<td>67</td>
<td>M</td>
<td>RV-1</td>
<td>230/130</td>
<td>11</td>
<td>16</td>
<td>3.1</td>
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<td>3</td>
<td>29</td>
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<td>EH</td>
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<td>56</td>
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<td>5</td>
<td>52</td>
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<td>RV-2</td>
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<td>16</td>
<td>1.3</td>
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<td>6</td>
<td>50</td>
<td>M</td>
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<td>25</td>
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<td>M</td>
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<td>1.5</td>
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<td>15 ± 2</td>
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<td>M</td>
<td>RV-2, AA</td>
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<td>14</td>
<td>0.8</td>
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<td>22</td>
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<td>59</td>
<td>M</td>
<td>RV-1</td>
<td>190/124</td>
<td>21</td>
<td>13</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>19</td>
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<td>28</td>
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<td>1.2</td>
</tr>
<tr>
<td><strong>Mean ± SEM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>260 ± 14/132 ± 7</td>
<td>18.6 ± 4.5†</td>
<td>24 ± 6</td>
<td>1.6 ± 0.2</td>
</tr>
</tbody>
</table>

**Abbreviations:** EH = essential hypertension; RV-1 = unilateral renovascular hypertension; RV-2 = bilateral renovascular hypertension; SLE = systemic lupus erythematosus; AA = dissecting aortic aneurysm; UNK = unknown.

*On propranolol.

†During nitroprusside infusion.

‡p < 0.05 compared with patients with severe hypertension.
Diastolic blood pressure (mmHg)

**Figure 1.** Effect of captopril on the seated diastolic blood pressure of 18 patients with severe or malignant hypertension, measured 90 minutes after the first dose of captopril and after 1 week of continued treatment. Blood pressure fell in all but two patients. The two patients who were receiving i.v. sodium nitroprusside were not included.

Administration of captopril resulted in the prompt clearing of encephalopathy in four patients. The clinical response was similar to that described in patients who developed acute encephalopathy after withdrawal of saralasin and were treated by prompt reinstitution of the angiotensin antagonist. The prompt reversal of this neurologic state can be, as with other drugs that acutely lower blood pressure, attributed in large part to the reduction in arterial pressure. However, these observations do not exclude the possibility of a direct role for angiotensin in the pathogenesis of hypertensive encephalopathy by inducing diffuse vasoconstriction of the cerebrovascular bed as well as raising pressure. The encephalopathic symptoms did not recur again, even when blood pressure rose transiently toward control levels during the first week of continued therapy. This transient escape of blood pressure has occurred frequently in patients who have had large depressor responses to the first dose of captopril. The mechanism for this escape is not understood, but it may not be due to inadequate blockade of the renin system. The maximal degree of blockade of angiotensin II formation that can be achieved by this converting-enzyme inhibitor, as reflected by the suppression of aldosterone excretion, occurs within 1 day of treatment and is sustained at that level.

**The Diagnostic Value of Acute Captopril Therapy**

The therapeutic response to captopril can provide diagnostic information about the magnitude of the renin-angiotensin contribution to the hypertension. Captopril can be used in the same manner as the i.v. converting-enzyme inhibitor teprotide because the acute depressor response is closely correlated with the pretreatment level of plasma renin activity. In this study, large acute diagnostic depressor responses to captopril corresponded to elevated renin levels and good pressure control with captopril as primary agent. However, two patients with low renin levels in whom the continued use of captopril alone was inadequate had poor initial responses.

In this study and in other studies of hypertension, the measured level of plasma renin activity corresponded with the long-term response to captopril. However, some other investigators have not found such a relationship, even though the first-dose response correlated well with the plasma renin activity. This discrepancy may have several causes. Inspection of these studies reveals a wider range of drug dosages, variable sodium intakes, different methods for measuring plasma renin activity, and the use of other drugs, including diuretics. Initial therapy with captopril could also induce changes in the underlying hypertensive mechanism so that blood pressure becomes progressively more or less angiotensin-dependent. Detailed metabolic studies of Atlas and others 1981.
Antihypertensive Treatment with Captopril

A single dose of a converting-enzyme inhibitor has also been used in screening for renovascular hypertension, because both teprotide and captopril induce diagnostically large increases in plasma renin activity in renovascular hypertension.\textsuperscript{31, 32} This test, however, produces false-positive results in patients with accelerated hypertension.\textsuperscript{32}

Long-term Response to Captopril

The patients treated in this study with captopril for as long as 3 years have remained controlled. However, they were treated at a relatively early and uncomplicated stage: Renal function was relatively intact and none had pulmonary edema, intracerebral hemorrhage, or myocardial infarction. Captopril alone controlled pressure in seven of these 20 patients, while 13 required a diuretic. The addition of diuretics to captopril resulted in improved blood pressure control, as noted previously.\textsuperscript{10, 33, 34} Clonidine and captopril were used in one patient. The possible supplementary antihypertensive effect of \( \beta \)-blocker therapy in four patients could not be evaluated since their use was dictated by other indications (arrhythmia, angina and dissecting aneurysm). Empirical multidrug therapies have been used to control severe hypertension.\textsuperscript{35-40} Therefore, a converting-enzyme inhibitor alone or with diuretic or one other drug may be a simpler and less costly regimen than those used presently.

Although specific mild drug toxicity occurred in several patients in the form of rash, altered taste and proteinuria, there were no complaints of diminished mental acuity, dry mouth, postural hypotension, altered sexual function, abnormal hair growth or gastrointestinal distress. Three of 20 patients developed proteinuria while on captopril, and in one of them the drug was discontinued because of nephrotic syndrome with deterioration of renal function. The nephrotoxicity of captopril has been described.\textsuperscript{41, 42} Proteinuria has occurred in less than 3\% of all patients treated\textsuperscript{43} and has been associated with biopsy evidence of membranous glomerulopathy.\textsuperscript{40, 41} However, the proteinuria regressed even when the drug was continued in the same or lower dosage.\textsuperscript{41}

Serum creatinine remained unchanged both acutely and after 12 months of captopril treatment, whether or not diuretic therapy was added. Blood urea nitrogen rose, however, in those patients treated with diuretics, reaching a peak after 6 months and then gradually decreasing toward baseline. Preservation of renal function despite large reductions in arterial pressure suggests that captopril may produce renal vasodilation. This is in keeping with the finding that angiotensin antagonists reverse the renal vasoconstricting action of angiotensin.\textsuperscript{43}

Plasma renin activity rose during captopril therapy, as demonstrated previously.\textsuperscript{10, 33, 34} This is probably related to stimulation of baroreflex mechanisms by the reduction of pressure, and to interruption of the negative feedback of angiotensin II on renin release. In

**Figure 3.** Effect of captopril treatment on blood urea nitrogen and serum creatinine. A slight rise in blood urea nitrogen, but not serum creatinine, occurred in the patients treated with captopril plus diuretics. The standard error for serum creatinine in patients treated with captopril was so small that it is obscured in the symbol for the mean value.

**Figure 4.** Effects of captopril on plasma renin activity and urine aldosterone excretion. Plasma renin activity rose on captopril, although urine aldosterone excretion was normal during treatment despite concomitant diuretic therapy in 13 of these 20 patients.
some patients, renin levels have been reported to decline over time, but they did not decline significantly in our patients.

Suppression of aldosterone excretion during captopril therapy is associated with potassium retention and, in most patients, a mild natriuresis during the first week of therapy. In these patients, aldosterone excretion remained normal despite marked increases in renin activity and, in over half of the patients, the addition of diuretics. Because of the acute nature of their illness, most of the patients did not have the rate of aldosterone excretion measured before captopril therapy, which is markedly raised in malignant hypertension. These findings indicate that the converting-enzyme inhibitor prevented hyperaldosteronism secondary to hyperreninemia. Reactive rises in plasma renin activity and aldosterone excretion have been associated with reduced antihypertensive effectiveness of thiazide diuretics.

In summary, the oral converting-enzyme inhibitor captopril was an effective antihypertensive treatment for patients with severe, accelerated, and malignant hypertension. Captopril has a rapid onset of action, so it is suitable for initial therapy in patients who require urgent blood pressure reduction. The magnitude of the initial antihypertensive response was closely related to the pretreatment plasma renin activity. Immediate reversal of encephalopathic signs was observed in the acute treatment period. Continued captopril therapy alone or with other agents resulted in satisfactory long-term blood pressure control. Renal function was well-preserved on captopril, and hyperaldosteronism secondary to concomitant diuretic therapy was blocked. Because of its relative potency and safety, oral converting-enzyme inhibitors should be considered for patients with severe and malignant hypertension for oral long-term and acute therapy.

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