Synergistic Effect of Captopril with Hydrochlorothiazide for the Treatment of Low-Renin Hypertensive Black Patients

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SUMMARY Diuretics have been particularly successful for treatment of low-renin hypertension (LRH), although they may cause metabolic complications such as hypokalemia and hyperglycemia. Since the efficacy of diuretics is largely limited by reactive angiotensin II production, a combination of a converting enzyme inhibitor with a diuretic should be synergistic, particularly in LRH, where heightened aldosterone production in response to angiotensin II has been noted. Eighteen patients with LRH were treated initially with either captopril alone (450 mg/day) or hydrochlorothiazide (HCTZ) (up to 100 mg/day). Captopril alone only reduced average placebo standing blood pressure from 151/100 to 146/96 mm Hg. Combination of HCTZ with captopril reduced average standing blood pressure to 111/76 mm Hg at 3 months and 116/81 mm Hg at 1 year while allowing reductions in average captopril dosage to 100 mg/day and HCTZ dosage to 40 mg/day and reductions in supplemental potassium administration and in HCTZ-induced hyperglycemia. Captopril monotherapy did not increase urinary excretion of kallikrein, prostaglandin E₂, or 6-keto prostaglandin F₁α, a metabolite of prostacyclin, and did not reduce urinary aldosterone excretion chronically. Thus, a synergism of captopril with HCTZ may be advantageous in certain patients with LRH.

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KEY WORDS • captopril • hydrochlorothiazide • low-renin hypertension • kallikrein • prostaglandins • renin • aldosterone • diabetes

A common etiologic role for the renin-angiotensin system in essential hypertension was postulated after a vasodepressor response was noted in 85% of patients with essential hypertension during converting enzyme inhibition. Curiously, however, captopril, a converting enzyme inhibitor that can be administered by mouth, occasionally causes a blood pressure fall in patients with low-renin hypertension (LRH), suggesting that it has antihypertensive activity other than through blockade of angiotensin II-induced vasoconstriction.

Many patients with LRH exhibit enhanced aldosterone secretion in response to administered angiotensin II, as do patients with primary aldosteronism with bilateral zona glomerulosa hyperplasia, and have thus been postulated to have a mild form of primary aldosteronism. Captopril blockade of angiotensin II formation might diminish aldosterone production in these patients sufficiently to reduce the blood pressure. Diuretics frequently control the blood pressure in patients with LRH. However, the antihypertensive effect of diuretics is limited significantly by stimulation of renin release, which leads to angiotensin II-induced vasoconstriction and aldosterone secretion. Thus, in low-renin patients a combination of captopril with a diuretic might allow effective sodium depletion with minimal interference from angiotensin II-induced vasoconstriction and aldosterone secretion. A synergistic effect of these two agents might reduce metabolic complications such as hypokalemia and hyperglycemia which have been noted with diuretic therapy.

The following study was performed to evaluate the use of captopril with a diuretic for the treatment of LRH. Plasma renin activity (PRA) and levels of urinary aldosterone, kallikrein, prostaglandin E₂ (PGE₂), and 6-keto prostaglandin-F₁α (6-keto PGF₁α), the major metabolite of prostacyclin, were determined to allow better understanding of the mechanism of the hypertensive synergism.

Materials and Methods

Patient Selection

Twenty-nine patients with essential hypertension by usual clinical criteria (normal rapid sequence intrave-
nous pyelogram, urinalysis, plasma potassium, and urinary metanephrine, and lack of physical findings indicative of secondary hypertension) were evaluated for the study. Most low-renin patients were originally identified with the intravenous furosemide test, and suppressed PRA (less than 0.6 ng/ml/hr) after 2 hours of ambulation during the placebo phase confirmed the low-renin categorization. Eleven patients failed to meet study criteria during the initial 4 to 8 week placebo period, primarily because they were not consistently hypertensive with supine diastolic blood pressure of 100 to 120 mm Hg. Eighteen patients (17 women and one man) satisfactorily completed 3 months of the study; 13 patients completed 6 months; 12 patients completed 1 year. All subjects were black and ranged in age from 38 to 66 years.

Patients were excluded from the study if they had a history or evidence of any of the following: hepatic or gastrointestinal diseases, malignant neoplasm, myocardial infarction, angina pectoris, congestive heart failure, serious allergy, recurrent dermatitis, emotional instability, or mental retardation. Patients with pregnancy or possibility of pregnancy during the study were excluded. No other antihypertensive or diuretic agent other than the study medications were taken. The study protocol was approved by the Human Research Committee of the University of Texas Health Science Center at Dallas, and informed written consent with explanation of the study protocol in lay language was obtained in all patients before entry into the study.

Study Design

Placebo Phase

A 4 to 8-week placebo period served to establish baseline values. Each patient was administered 1 placebo tablet three times daily (at least 1 hour before or 2 hours after breakfast and the noonday meal plus a bedtime dose) and seen every 2 weeks. Systolic and diastolic (Korotkoff Phase V) blood pressure readings were determined twice with a standard mercury sphygmomanometer after 10 minutes in both supine and standing positions, and the two values were averaged. Only patients with a supine diastolic blood pressure (SDBP) consistently within ± 5 mm Hg during the last 4 weeks of the placebo phase were continued in the study. Patients who previously had been using antihypertensive agents were required to complete 8 weeks of placebo unless their SDBP rose to 110 mm Hg or more at two consecutive visits. When SDBP was noted to be above 110 mm Hg, a second visit was scheduled within 3 to 7 days. If the elevated pressure was confirmed, the patient began treatment with active medication. Blood pressure and pulse determinations during the last three visits of the placebo phase were averaged (table 1).

Treatment

Treatment was divided into three phases: 4 weeks of open-label treatment with captopril or HCTZ alone; 8 weeks of combination therapy in those patients who had not achieved blood pressure normalization; and an extended phase of combination therapy lasting an additional 9 months. The randomization protocol was designed so that more patients received captopril initially than HCTZ. Patients were seen on a weekly basis for blood pressure determination. The initial captopril dosage was 25 mg three times daily increasing to 50, 100, and 150 mg three times daily at weekly intervals if SDBP had not fallen to less than 90 mm Hg. Each patient had the blood pressure closely monitored for approximately 2 hours following the first dose of captopril and with each increase in dosage.

The initial dose of HCTZ was 25 mg twice daily. If SDBP was less than 90 mm Hg after 2 weeks, the dosage remained the same. However, if the SDBP was not controlled, the dosage was increased to 50 mg twice daily for an additional 2 weeks.

If the SDBP increased during the titration phase by more than 10 mm Hg from that at the end of the placebo phase or exceeded 120 mm Hg, the daily dose of captopril was increased one step more rapidly than usual and a second visit scheduled in 2 to 3 days. If the diastolic blood pressure remained elevated to the same degree, the daily dosage was again increased in stepwise fashion with visits scheduled within 2 to 3 days between each dosage increment. If the SDBP remained above 90 mm Hg after the maximum daily dosage was administered, the patient was entered into the next phase of the study. If the standing systolic blood pressure was below 85 mm Hg, or the patient developed orthostasis, the daily dose was reduced one step. During the next 8 weeks, those patients with elevated SDBP (> 90 mm Hg) had the alternate test drug added to their regimen. Dosage of the second drug was titrated in the same manner as described for the initial 4 weeks of treatment until either SDBP was normalized or the maximum daily dosage had been reached. Those patients who became hypokalemic with HCTZ treatment were administered supplemental potassium chloride to keep the plasma potassium above 3.0 mEq/liter.

An electrocardiogram, chest x-ray, and slit-lamp examination by an ophthalmologist were done at the beginning and end of the study. Complete blood count, PRA, 12-factor automated chemical analysis, and 24-hour urinary sodium, potassium, creatinine, kallikrein, and aldosterone excretion were determined at 2-week intervals during the first 3 months of the study and then at 3-month intervals. Urinary PGE\(_1\) and 6-keto PGF\(_\alpha\) were determined before and at the end of monotherapy with captopril alone. Urinalysis and antinuclear antibody determination were performed at 4-week intervals during the first 3 months and then at 3-month intervals. Plasma renin activity,\(^{10}\) urinary aldosterone,\(^{11}\) urinary prostaglandin E\(_\alpha\),\(^{12}\) and urinary 6-keto prostaglandin F\(_\alpha\) excretions\(^{13}\) were determined by radioimmunoassay. Urinary kallikrein excretion was determined by the method of Margolius et al.\(^{14,15}\) Statistical comparisons were performed with Student's \(t\) test (paired comparisons of placebo vs treatment).

Results

Placebo diastolic blood pressures were matched closely in both groups (table 1). During the initial 4
weeks of treatment, there was little fall in blood pressure with captopril alone, and no patient achieved a SDBP less than 90 mm Hg. No patient had a rise in SDBP of over 6 mm Hg. In contrast, HCTZ alone produced an average 14 mm Hg fall in SDBP and a fall of SDBP to < 90 mm Hg in four of seven patients. The addition of HCTZ to captopril normalized the blood pressure in all patients treated with captopril alone and allowed a reduction in the average daily captopril dosage from 450 mg to 102.3 mg and of HCTZ from 78.6 to 50 mg after 8 weeks of combination therapy. At the end of 1 year of treatment, these average daily dosages had been reduced to 100 mg captopril and 39.6 mg HCTZ while the blood pressure remained under excellent control. A synergistic therapeutic response was particularly dramatic in some patients in that normotension was achieved with as little as 25 mg captopril twice daily, and 12.5 mg HCTZ daily.

In addition to the favorable lowering effects on blood pressure, other therapeutic benefits were noted. Five of seven patients treated initially with HCTZ alone and three of 11 patients in which HCTZ was added to captopril became hypokalemic and were administered supplemental KCl at an initial dosage of 40 mEq/day. The average daily potassium supplementation given was reduced from 28.6 mEq with HCTZ alone, to 9.1 mEq with captopril plus HCTZ. In spite of this reduced dosage, the average plasma potassium rose, and all patients had plasma potassium of 3.4 mEq/liter or greater at 1 year. Average fasting blood sugar (FBS), which rose significantly (p < 0.05) with HCTZ alone, returned to normal with combination captopril-HCTZ therapy. Two patients with mildly elevated baseline FBS exhibited a rise in the FBS with HCTZ but then a fall in the FBS after addition of captopril allowed a reduction in the dosage of HCTZ. One patient had an average FBS of 140.2 mg/dl (n = 4) during placebo and captopril alone, 155.8 mg/dl (n = 5) with combination captopril and HCTZ (25–50 mg/day), and 120 mg/dl (n = 7) after reduction of HCTZ to 12.5 mg/day. A second patient had an increase in average FBS from 125 mg/dl (placebo, n = 2) to 174.5 mg/dl (n = 2) with 100 mg HCTZ/day.
which fell to 148 mg/dl (n = 1) after addition of captopril and reduction of HCTZ to 50 mg/day. Blood pressure normalization was maintained in both patients with combination captopril-HCTZ therapy. The blood sugar changes did not appear to be related to changes in body weight. There was a significant (p < 0.05) rise in FBS with initial HCTZ treatment accompanied by a slight fall in body weight. Three patients with blood pressure control with initial HCTZ treatment were dropped from the study. The 15 patients treated with combination captopril-HCTZ therapy had placebo FBS of 108 ± 5 mg/dl and placebo weight of 169 ± 7 lbs. Although there was a slight fall in weight during the initial 3 months of combination captopril-HCTZ therapy, the blood sugar in this group remained about the same, and it fell somewhat during the last 9 months of the study with a slight gain in body weight. Furthermore, the FBS changes during HCTZ therapy in two patients with initial fasting hyperglycemia could not be explained by weight changes.

Serum calcium, creatinine, and uric acid remained essentially unchanged from those levels found with HCTZ alone (table 1). Interestingly, PRA increased only slightly, although significantly (p < 0.01), during treatment with captopril alone but increased dramatically in all patients after addition of HCTZ to captopril (table 1). Urinary aldosterone and kallikrein excretion did not change significantly with captopril administration. Urinary PGE\(_1\) excretion decreased significantly (p < 0.05) during captopril treatment, whereas 6-keto PGF\(_\alpha\) excretion did not.

**Discussion**

The antihypertensive mechanism of converting enzyme inhibitors such as captopril is not completely understood. Some investigators feel that the antihypertensive effect can be almost completely explained by its blockade of angiotensin II production, thereby blunting vasoconstriction and aldosterone secretion with its attendant sodium retention. Other antihypertensive mechanisms that have been proposed include: pre- and postjunctional inhibition of vascular sympathetic function by blockade of vascular angiotensin II production,\(^{16}\) increase in plasma kinin levels and/or renal kinin production,\(^{15-19}\) and increases in the production of vasodepressor prostaglandins.\(^{19-22}\) Our finding of a slight hypertensive effect of high-dose captopril monotherapy in LPH patients is compatible with the antihypertensive effects of captopril other than through antagonism of angiotensin II-mediated vasoconstriction. However, since this therapeutic response was only slight, we conclude that the major therapeutic effect is upon blockade of angiotensin II production.

In general, plasma aldosterone concentration or urinary aldosterone excretion has been noted to fall with chronic captopril therapy.\(^{2,3,20,24-28}\) However, most of these studies have been done in normal and high-renin patients, in whom aldosterone secretion might be expected to be more dependent on angiotensin. With more chronic therapy, aldosterone secretion may return toward normal,\(^{24-27}\) particularly when the frequency of captopril administration is decreased so that serum converting-enzyme concentration returns to normal\(^{28}\) or during upright posture.\(^{29}\) In one study\(^{26}\) in which a low dosage of captopril (25 mg three times daily) was used in a small number of low-renin patients, plasma aldosterone concentration was not suppressed by chronic captopril treatment. Although we noted only a slight decrease in urinary aldosterone excretion with chronic captopril monotherapy, we cannot conclude that LRH is not caused by excess production of aldosterone mediated through enhanced adrenal sensitivity to angiotensin. The failure of urinary aldosterone excretion to fall with chronic captopril monotherapy is compatible with the thesis that aldosterone secretion is not regulated in a major way by angiotensin in low-renin patients. However, other investigators have noted that, even though plasma angiotensin II concentration falls acutely with initiation of captopril, this decrease may\(^{27,29,30}\) or may not\(^{30}\) remain after chronic therapy. The chronic restoration of plasma angiotensin II concentration to previous levels has been attributed to an increased PRA which overcomes converting enzyme blockade. However, the persistent elevation in PRA does suggest that angiotensin II levels remain inappropriately low and are never fully restored. We noted only slight rises in PRA (0.2 to 0.6 mg/ml/hr) in these low-renin patients with chronic captopril monotherapy. This does not seem to be enough of a change to restore plasma angiotensin II concentration to pretreatment levels, though we cannot be certain of this since plasma angiotensin II concentrations were not measured. However, we, as others,\(^{26,28}\) favor the idea that factors other than angiotensin II play a major role in regulating aldosterone secretion in the sodium-replete, captopril-treated, LRH patient.

Though captopril monotherapy did not decrease aldosterone secretion, the synergistic effect of captopril with HCTZ may be explained by blockade of angiotensin II-mediated vasoconstriction and aldosterone secretion. In patients on combination therapy, PRA increased markedly to 12.9 ng/ml/hr while aldosterone excretion was unchanged, providing the strongest evidence that chronic blockade of angiotensin II production was achieved. Our data did not favor the possibility that stimulation of renal PGE\(_2\) and prostacyclin production is a major chronic antihypertensive mechanism of captopril, since we noted no increase in urinary PGE\(_2\) and 6-keto PGF\(_\alpha\) excretion with captopril therapy. However, we cannot exclude the possibility that captopril stimulates vascular prostaglandin production to lower the blood pressure without leading to an increase in renal prostaglandin production. However, this would seem unlikely as a predominant antihypertensive mechanism in view of the minimal blood pressure changes during captopril monotherapy. Similarly, we did not find that captopril stimulated renal kallikrein excretion. Although some data favor a role for kinins in the mechanism of action of captopril,\(^{17-20}\) some investigators have noted no change\(^{29,30}\) in circulating kinin levels during captopril therapy. Thus, captopril blockade of angiotensin II formation appears to
be a major mechanism for the synergism of captopril with HCTZ, although we cannot rule out the possibility of other mechanisms.

A number of complications associated with diuretic therapy may be related to the dosage of diuretic used. We noted a decreased requirement for potassium supplementation and improvement in thiazide-induced hyperglycemia after addition of captopril allowed reduction in the dosage of HCTZ. Additional evaluation of the use of converting enzyme inhibitors with diuretics in diabetic patients for treatment of their renal sodium retention has been warranted. Thus, the synergism of converting enzyme inhibitors with diuretics may ameliorate diuretic complications while allowing excellent blood pressure control.

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