Br. J. clin. Pharmac. (1982), **14**, 121S–126S

LONG-TERM EFFICACY OF ANGIOTENSIN-CONVERTING-ENZYME INHIBITION WITH CAPTOPRIL IN MILD-TO-MODERATE ESSENTIAL HYPERTENSION

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1 Thirty-one patients with mild-to-moderate essential hypertension were treated with captopril for 30 months.

2 Captopril effectively lowered raised blood pressure in hypertensive patients with high, low, and normal renin concentrations. There was no significant change in heart rates. Captopril alone normalised blood pressure (diastolic pressure below 95 mm Hg) in 11 patients. In the other patients the addition of hydrochlorothiazide produced a further hypotensive effect. Blood pressure control could be maintained without any signs of tachyphylaxis.

3 Plasma concentrations of aldosterone and angiotensin II were significantly lower after 30 months of therapy than pretreatment values whether captopril was associated with diuretics or not. No relevant symptomatic or biochemical adverse reactions were observed.

4 These data establish the long-term potential of captopril for outpatient therapy in mild-to-moderate forms of essential hypertension.

Introduction

Angiotensin-converting inhibition with captopril has been shown to be effective in reducing blood pressure in patients with essential as well as renal hypertension (Case *et al.*, 1978; Gavras *et al.*, 1978; Overlack *et al.*, 1980). The hypotensive action of captopril is due totally to a decrease in total peripheral vascular resistance with no significant changes in cardiac output and heart rate (Cody *et al.*, 1978). Captopril is not a direct vasodilator, has no direct effects on sympathetic nerve function, and does not interfere with receptor activation of any agonist tested. This may explain the absence of any relevant symptomatic side effects. Although these characteristics make captopril (and perhaps its successors) the most exciting drug which has been seen for many years in antihypertensive treatment, some serious haematological and renal side effects have been reported. These include proteinuria (Hoorntje *et al.*, 1979; Prins *et al*, 1979) and neutropenia (Amann *et al.*, 1980; Staessen *et al.*, 1980). Because of these adverse reactions, captopril has been reserved for otherwise refractory hypertension. Nevertheless, the incidence of side effects is extremely low—for example 0.06% for neutropenia. More important, neutropenia developed almost entirely in patients with severe treatment-resistant hypertension who had some degree of renal impairment, or in patients with connective tissue disease who received other drugs known to be capable of producing neutropenia. In patients with mild-to-moderate essential hypertension without other serious underlying disease or drug treatment these side effects are uncommon and practically absent (Rubin & Antonaccio 1980). Thus, captopril may be safe and suitable for treatment of mild forms of essential hypertension.

In the present study we evaluated for up to 30 months the effect of captopril either alone or in combination with hydrochlorothiazide on blood pressure and on circulating levels of renin, angiotensin II, angiotensin-converting enzyme, and aldosterone in patients with mild to moderate hypertension. All patients were carefully watched for symptomatic, haematological, and biochemical side effects.

Methods

A total of 112 patients with essential hypertension were initially enrolled in this study. We report here only the data on 31 patients in whom repeated analysis of haemodynamic and biochemical variables were possible up to 30 months. Except for three patients who had mild proteinuria before treatment, all subjects had normal renal function test results and a

0306–5251/82/100121–06 $01.00

supine diastolic pressure of at least 100 mm Hg but less than 115 mm Hg.

After four weeks of placebo treatment 31 patients with untreated essential hypertension (mean age 46.4 years, 21 men and 10 women) were given increasing doses (25–150 mg three times a day) of captopril for four weeks. Patients who showed no satisfactory pressure response (diastolic blood pressure below 95 mm Hg) with the maximum dose of captopril after four weeks were given a combination of captopril plus hydrochlorothiazide 25 mg twice a day.

All patients underwent a complete physical examination, chest radiography, electrocardiography, and renal function tests. Each patient was seen weekly in our hypertension clinic for the first 12 weeks, then every three to four weeks for the next 40 weeks and then every three months until now.

Arterial blood pressure was measured by using a mercury sphygmomanometer (13 cm cuff), and the readings were taken in the supine and standing positions. Venous blood samples were obtained after one hour's rest in the supine position for determination of plasma renin activity (Haber *et al.*, 1969) and plasma concentrations of aldosterone (Vetter *et al.*, 1973), angiotensin II (Spech *et al.*, 1976), and angiotensin-converting-enzyme activity (Cushman & Cheung, 1971).

In seven patients measurements of cardiac output were obtained before captopril, and at 90 minutes and 14 months after starting treatment. Cardiac output was measured by thermal dilution technique as described (Heck *et al.*, 1980). Cardiac index (l/min/m^2), mean arterial pressure (mm Hg), and total peripheral resistance (dyne/s/cm^{-5}) were calculated by standard methods. Results are expressed as mean ± SEM.

Statistical analysis was performed using paired and unpaired Student's *t* test and correlation coefficients were calculated by the methods of least squares.

Results

Figure 1 shows the acute effect of the first oral dose of 25 mg of captopril on supine blood pressure and on heart rate obtained in 22 of the 31 patients. The enzyme inhibitor induced a prompt and striking fall in both systolic and diastolic pressure within 40 to 120 minutes after its administration. There were no significant changes in heart rate. When the patients were classified according to their plasma renin activity it became evident that four patients had raised supine renin concentrations—that is, higher than 5 ng angiotensin I/ml/3 h. In these patients the acute blood pressure drop was more pronounced than in the other patients with normal or low-normal renin levels.

Figure 2 shows the responses of plasma converting-enzyme activity and of plasma concentrations of

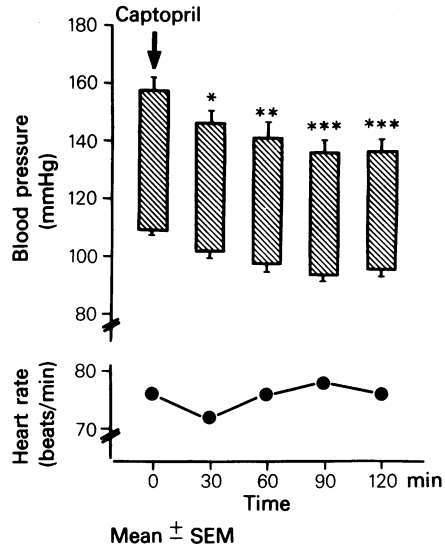

Figure 1 Effect of a single oral dose of captopril (25 mg) on systolic and diastolic blood pressures and on heart rate in 22 patients. *$p<0.05$; **$p<0.01$; ***$p<0.001$.

angiotensin II and of aldosterone to the first single dose of captopril. All three values showed the expected declines after administration of captopril. The decrease in plasma aldosterone was already evident 60 minutes after administration of the drug. Plasma renin activity rose significantly within the first 60 minutes.

When the patients were put on to long-term treatment with captopril systolic and diastolic blood pressures fell progressively over the four weeks of the titration period without any postural effect (Figure 3). Again, no changes in heart rate occurred. As can be seen, the maximum blood pressure response to captopril was usually achieved after one week of treatment with the relatively low dose of 75 mg/day. Increasing the dose up to 450 mg captopril a day had only a small additional pressure lowering effect.

At the end of the four week titration period blood pressure had returned to normal in 11 of the 31 patients (diastolic blood pressure below 95 mm Hg; Figure 4). In the other patients the addition of hydrochlorothiazide 50 mg a day produced a further hypotensive effect and blood pressures were controlled in the range of 140/90 mm Hg or less. No tolerance to the pressure-lowering effect of the drug developed during the 30 months of observation whether captopril was given alone or in combination with the diuretic. The initial high doses of captopril were reduced between the eighth and sixteenth week after the start of treatment to lower doses ranging from 75 to 150 mg/day. In patients who were treated with

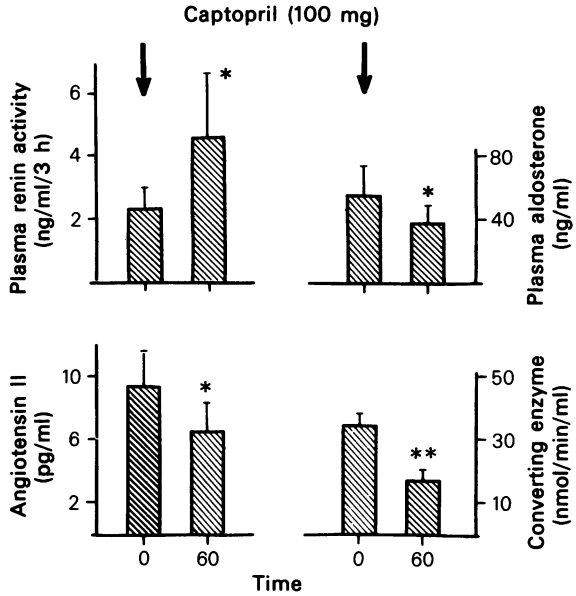

Figure 2 Effect of a single oral dose of captopril (25 mg) on converting enzyme, plasma renin activity, and on plasma concentrations of aldosterone and angiotensin II. Mean ± SEM, $*p<0.05$; $**p<0.01$.

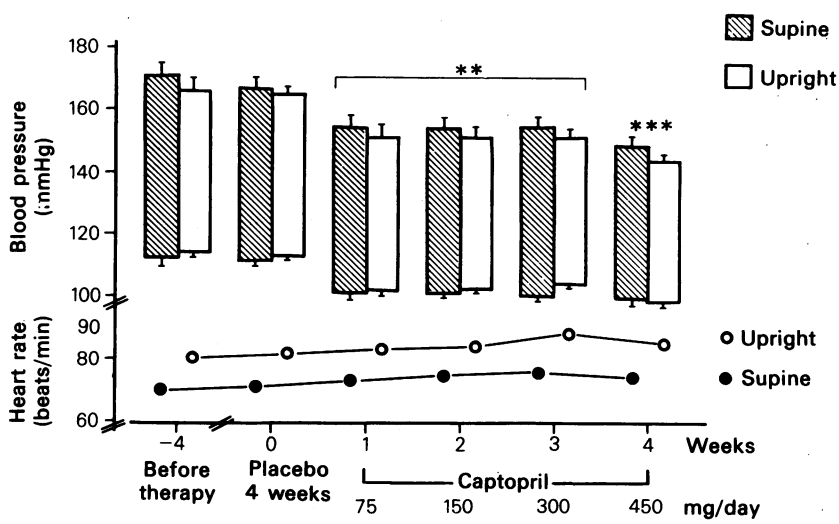

Figure 3 Blood pressure and heart rate responses to four weeks' treatment (titration period) with captopril in the supine and standing position. Mean ± SEM $**p < 0.01$; $***p < 0.001$.

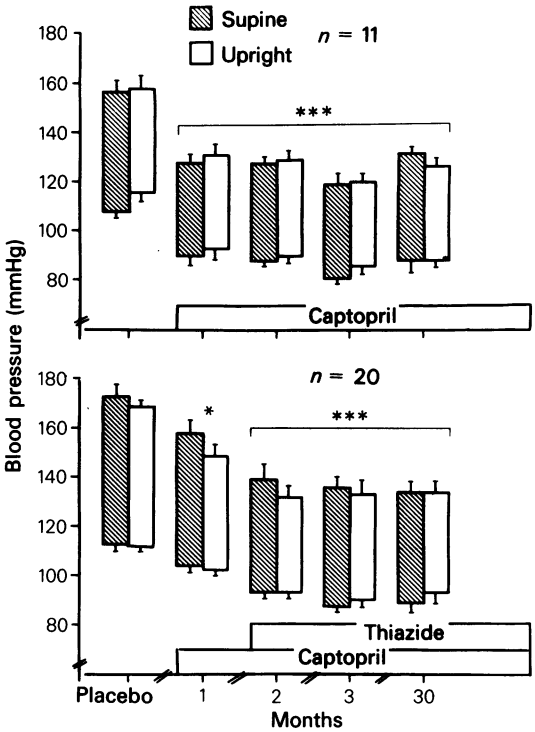

Figure 4 Long-term effect of captopril alone (upper part) and of captopril in combination with hydrochlorothiazide on systolic and diastolic blood pressures in the supine and standing position. Mean ± SEM. $*p<0.05$; $***p<0.001$.

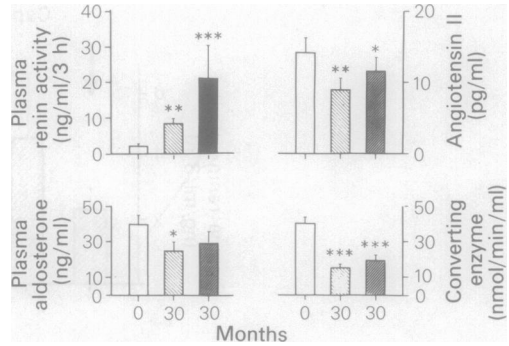

Figure 5 Changes in hormonal values after long-term treatment with captopril alone or in combination with hydrochlorothiazide. □ Control; ▨ Captopril; ■ Captopril and hydrochlorothiazide. Mean ± SEM. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

captopril alone the mean final dose was 110 mg/day and in the captopril plus diuretic group the mean dose was 92 mg/day. Usually a twice-daily schedule was followed.

In six patients whose blood pressures were controlled at 130/80 mm Hg or less with captopril alone, the drug was abruptly withdrawn for one week between the sixth and tenth month of treatment. Blood pressures recorded either by the patients at home or in the clinic increased gradually to hypertensive values within one and five days after the withdrawal of captopril without the occurrence of symptoms; most noticeably, no 'rebound' increase in blood pressure was seen.

Figure 5 shows the changes in hormone levels after 30 months of treatment. Captopril given alone was associated with a significant fall in serum activity of angiotensin-converting-enzyme as well as in plasma concentrations of angiotensin II and of aldosterone. After the addition of hydrochlorothiazide there were definite rises in plasma renin activity, as well as in plasma angiotensin II and aldosterone concentrations. The increase in angiotensin II suggests that either the rise in angiotensin I had completely overcome the inhibition of angiotensin-converting-enzyme by captopril at this dose or that an alternative pathway for angiotensin II formation had been used. Mean concentrations of angiotensin II and aldosterone with the combined captopril-diuretic regimen were still significantly lower when compared with pretreatment values. The decrease in blood pressure observed with long-term captopril treatment in the 31 patients did not correlate with either basal pretreatment plasma renin concentrations or the rise in renin activity. In seven patients who were treated with captopril alone cardiac output was measured before, 90 minutes and 14 months after starting treatment. Cardiac output did not change with captopril treatment, indicating that the fall in mean arterial pressure was due totally to a decrease in total peripheral vascular resistance. The haemodynamic changes were sustained over the 14 months of observation (Figure 6).

No relevant adverse reactions occurred during the 30-month treatment period. All patients appreciated the treatment and indeed felt well on it. In three patients a transient (two to three days) rash occurred after 12 days of therapy, and in one other a transient disturbance of taste after 36 days. Decreasing the daily captopril dose to 75 mg resulted in the disappearance of both reactions within 48 h. None of the patients developed any signs of biochemical or physical irregularities suggesting any abnormalities in haematological, hepatic, renovascular, or autoimmune functions. In particular, there were no changes in complete blood cell counts and urine values. The three patients who had proteinuria before starting treatment with captopril showed no substantial increase in urinary protein for the 30 months of

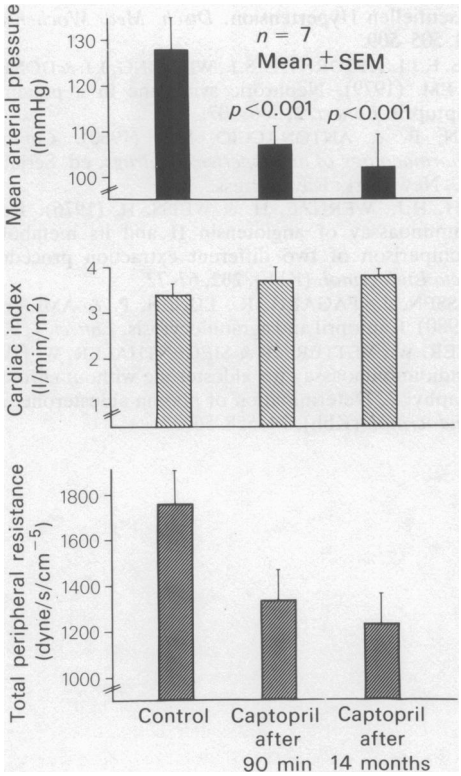

Figure 6 Acute and long-term effect of captopril on mean blood pressure, cardiac output, and peripheral vascular resistance.

treatment. There were small but insignificant decreases both in serum cholesterol and triglyceride concentrations. No significant change in serum potassium concentrations occurred.

Discussion

The present data provide evidence that angiotensin-converting-enzyme inhibition with captopril induces prompt and efficient long-term blood pressure reduction in patients with mild-to-moderate essential hypertension. The decrease in blood pressure was associated with a fall in plasma angiotensin II and aldosterone concentrations and occurred without any postural effect. In one-third of these patients blood pressure returned to normal with captopril alone. In the others the antihypertensive potential of the drug was considerably enhanced when hydrochlorothiazide was added, this combination being capable of correcting hypertension in all of the patients.

It appears that treatment-resistant hypertensive patients should not have their dose of captopril increased because the dose-response curve to captopril is flat; rather, the dose of the diuretic should be increased, since blood pressure, when converting-enzyme is inhibited, is dependent on sodium balance. Possibly treatment with diuretics can exert its effect to the full only under cover of converting-enzyme inhibition, whereas a massive counterregulation via activation of the renin system would otherwise reduce the hypotensive effect of the diuretic.

The fall in mean arterial pressure with captopril was due to a decrease in total peripheral vascular resistance. Similar results have been obtained by others (Cody *et al.*, 1978). No tolerance to the pressure-lowering effect of captopril developed during the 30 months of therapy, whether captopril was associated with hydrochlorothiazide or not. No rebound increase in blood pressure was noted in those six patients in whom captopril was withdrawn for one week. The final dose of captopril used ranged from 75 to 150 mg a day usually given on a twice-daily schedule. No symptomatic side effects and no abnormalities in haematological, hepatic, renovascular, autoimmune function, or urinary values were observed.

We therefore conclude that the antihypertensive effectiveness as well as the absence of tolerance and of any relevant side effects establish the long-term potential of captopril for outpatient therapy in mild-to-moderate forms of essential hypertension. With captopril it appears that for the first time ever a patient can feel as well on treatment for high blood pressure as he does off it.

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