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LONG-TERM CAPTOPRIL TREATMENT IN MODERATE TO SEVERE HYPERTENSION

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1 The long-term effects of the oral angiotensin-converting enzyme inhibitor captopril with the addition of a diuretic (chlorthalidone) were examined in 16 patients with moderate or grave hypertension. Of these, 14 had essential hypertension and two renovascular hypertension.

2 Blood pressure fell sharply in all patients and this antihypertensive effect was maintained during 2, 4, 6, 12, and 24-month follow-up periods. The efficacy of treatment was not predicted by basal values of plasma renin activity.

3 Urinary excretion of sodium and potassium increased, but the increases were never such as to modify significantly sodium and potassium serum concentration.

4 The long-term treatment was generally well tolerated.

Introduction

The therapeutic effect of the oral angiotensin-converting-enzyme inhibitor captopril in both renovascular and essential hypertension is well known. The drug has also been used successfully in patients who have proved resistent to multiple antihypertensive drug treatment. Captopril is, however, still quite new, so that less is known about its efficacy and tolerance in long-term treatment. The present report describes the long-term effects of angiotensin-converting-enzyme inhibition in patients with hypertension of various types.

A thiazide diuretic was added to captopril so that we could use the minimum effective dose and so reduce the risk of serious side effects, which may be dose-related. (Hoorntje *et al.*, 1980; Staesson *et al.*, 1980; Elijovich & Krakoff, 1980).

Methods

The study was conducted in 16 patients (12 men and four women) aged 38–70 (mean 52.1), of whom two had renovascular hypertension and the rest essential hypertension. The hypertension was moderate or grave (WHO grade II and III). All the patients were followed up for at least six months, 11 were followed up for a year and eight for two years.

The patients were initially admitted to hospital, where the necessary tests were carried out to establish the type of hypertension and treatment with captopril was begun. The daily sodium intake was 110 mmol. After a month's treatment the patients were discharged from hospital with a dose of captopril of 25–50 mg 3 times a day with the addition of chlorthalidone (100 mg every other day). The patients were advised to continue the same diet. They were followed up at monthly intervals. On each occasion arterial blood pressure and heart rate, supine and erect, were recorded along with haematological and biochemical measurements, including tests for proteinuria. We also made specific inquiries about side effects.

Before treatment and after two, four, six, and 24 months on captopril plasma volume was measured (by a radioiodinated human serum albumin method (RISA^{125}-kit)), plasma renin activity supine and after two hours' standing (by radioimmunoassay (Haber *et al.*, 1969)), and plasma aldosterone (by radioimmunoassay) (Vetter *et al.*, 1973).

All the patients gave informed consent to take part in the study, which had received the approval of the competent authorities. Statistical analysis of the data was performed using the *t* test for paired observations.

Results

The reduction of arterial blood pressure remained constant in all 16 patients. The average basal values were 202 ± 27.3/116.2 ± 14.3 mm Hg (mean arterial pressure (MAP) 144.7 ± 17.2 mm Hg); after two months 154 ± 23.7/87.1 ± 25.4 mm Hg (MAP 113.5 ± 13.8 mm Hg) ($p < 0.0005$); after four months 150.3 ± 16.7/84.5 ± 22.9 mm Hg (MAP 109.8 ± 8.1 mm Hg)

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($p < 0.0005$) and after six months 151 ± 14.5/91.9 ± 5.3 mm Hg (MAP 111.8 ± 6.9 mm Hg) ($p < 0.0005$) (Figure 1). In the 11 patients examined for a year pressure levels were then 157.4 ± 14.5/94.7 ± 10.2 mm Hg (MAP 115.5 ± 10.8 mm Hg) ($p < 0.0005$) compared with pretreatment values of 206.8 ± 31.1/118.3 ± 15.7 mm Hg (MAP 147.7 ± 19.3 mm Hg) (Figure 2). At two years mean blood pressure in eight patients was 160.1 ± 18.5/95.1 ± 11.1 mm Hg (MAP 116.7 ± 12.5 mm Hg) ($p < 0.0025$) compared with pretreatment values of 207.2 ± 31.1/121.4 ± 16.3 mm Hg (MAP 149.9 ± 20.2 mm Hg) (Figure 2).

The heart rate increased slowly only in the first period of treatment (two months), increasing from average values of 73 ± 9.9 beats/min to values of 81.5 ± 6.9 beats/min ($p < 0.025$). Successively pretreatment values returned. Basal mean plasma renin activity when supine was 0.8 ng/ml/h and when standing 1.9 ng/ml/h; at two months in supine it was 2.8 ng/ml/h ($p < 0.01$) and upright 5.8 ng/ml/h ($p < 0.005$). In six patients studied at six months it was 4.9 ng/ml/h supine (basal value: 1.1 ng/ml/h; $p < 0.025$) and 9.7 ng/ml/h upright (basal value: 2.2 ng/ml/h; $p < 0.025$). In the five cases studied at two years plasma renin activity values were 4.6 ng/ml/h supine (basal value: 0.7 ng/ml/h; $p < 0.05$) and 6.1 ng/ml/h upright (basal value: 1.0 ng/ml/h; $p < 0.1$).

Basal plasma aldosterone average values were 92.5 pg/ml supine and 202.6 pg/ml upright; at two months and posture 90.6 pg/ml supine; 184.6 pg/ml upright. In six patients studied at six months mean values were 54.5 pg/ml supine (basal value: 72.4 pg/ml) and 99.8 pg/ml upright (basal value: 167.8 pg/ml ($p < 0.05$)).

Mean basal plasma volume values were 19.9 ± 3.3 ml/cm height; after two months 17.4 ± 2.1 ml/cm ($p < 0.01$), and after six months 19.8 ± 2.7 ml/cm (basal value: 21 ± 2.9 ml/cm).

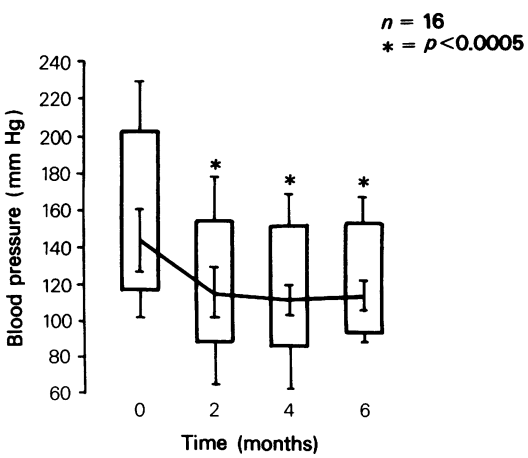

Figure 1 Changes in systolic, diastolic, and mean arterial blood pressure in 16 patients after 2, 4, and 6 months of treatment with captopril (75–150 mg daily) and chlorthalidone (100 mg every other day). Results are means ± SEM.

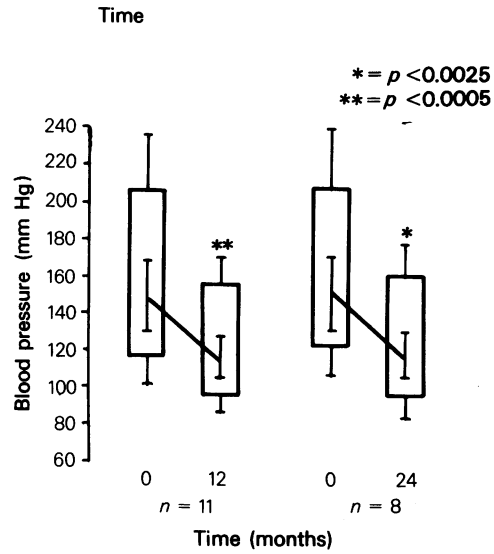

Figure 2 Changes in systolic, diastolic, and mean arterial blood pressure in 11 patients after 12 months and in eight patients after 24 months of treatment with captopril (75–150 mg daily) and chlorthalidone (100 mg every other day). Results are ± SEM.

During treatment there was a significant ($p < 0.05$) increase in urinary sodium (30%) and potassium (40%). No significant changes occurred in sodium and potassium serum concentration. Most patients tolerated the drug well. None of the patients developed any physical signs or biochemical abnormalities in haematological, hepatic, renal, or vascular function. The side effects observed were: Loss of taste in two patients, in one of whom it had an onset at the beginning of treatment, was initially moderate and lasted for six months, and in the other patient it appeared later and was mild. Gastric pain was present in two patients, appeared late in both, and was mild. In one of these cases it lasted two months. Constipation was also present in two patients but only at the start of treatment, and it was mild. The side effects were never serious enough to necessitate withdrawal of the drug.

Discussion

Angiotensin-converting-enzyme inhibition by long-term oral administration of captopril reduced blood pressure of all the hypertensive patients included in the study, whatever their clinical diagnosis. In fact, in none of the patients did arterial blood pressure return

to pathological levels. The treatment was generally well tolerated. The combination with a diuretic not only made captopril more effective in patients who at first showed no response to it (Brunner *et al.*, 1978; Brunner *et al.*, 1979; Johnston *et al.*, 1979; Aguglia *et al.*, 1981; Campbell *et al.*, 1982) but the diuretic also permitted a lower dose of the drug itself. Such a reduction probably reduces its side effects. In fact only a few patients had any side effects and these were minor. We never found proteinuria or agranulocytosis.

The combination with a diuretic might also have modified the changes in electrolyte balance which occur with captopril, which increases sodium urinary excretion (Brunner *et al.*, 1979; Santucci *et al.*, in press). The increase in sodium and potassium urinary excretion we observed was never great enough to alter significantly sodium and potassium serum concentrations. The combination of the two drugs also avoided the hyperkalaemia induced by captopril on its own (Johnston *et al.*, 1979; Santucci *et al.*, in press).

As regards the renin–angiotensin–aldosterone system, we observed that the efficacy of long-term treatment was not predicted by basal plasma renin activities (Aguglia *et al.*, 1981). The changes produced by the long-term inhibition of the converting enzyme are influenced by additional diuretic therapy. In fact we observed a more pronounced increase in plasma renin activity and a smaller reduction in plasma aldosterone in patients treated with captopril only (Johnston *et al.*, 1979; Aguglia *et al.*, 1981). Plasma volume, which at first fell significantly, tended to return to pretreatment levels when treatment continued.

In conclusion, long-term treatment with the oral converting-enzyme-inhibitor captopril permanently reduces arterial blood pressure in patients with hypertension of various origins and grades. The drug is very well tolerated, and it is possible that its combination with a diuretic, which permits the use of smaller doses of captopril, will minimise the risk of side effects. From such a combination we can also balance the effects of individual drugs on fluid electrolyte exchange.

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