LONG-TERM EXPERIENCE OF CAPTOPRIL IN THE TREATMENT OF PRIMARY (ESSENTIAL) HYPERTENSION

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- 1 Forty-one patients with primary (essential) hypertension were treated with captopril alone or in combination with hydrochlorothiazide for 12–36 months.
- 2 During an initial dose-titration period mean blood pressure fell from 174/111 mm Hg to 134/88 mm Hg supine and from 170/116 mm Hg to 126/93 mm Hg standing after 3 months' treatment.
- 3 During long-term treatment with unchanged or reduced doses of captopril or hydrochlorothiazide, or both, blood pressure remained substantially reduced. Mean supine blood pressure at 24 months was 136/90 mm Hg and at 36 months 138/90 mm Hg.
- 4 In 12 patients with clearly defined low renin (essential) hypertension initial blood pressure reduction was less than in patients with normal renin hypertension after 1 month's treatment (162/102 mm Hg v 143/92 mm Hg). After 24 months of treatment, however, the treatment results were similar in the two groups.
- 5 Except for one case of reversible proteinuria no serious side effects were seen during treatment periods of up to three years.
- 6 Captopril alone or in combination with hydrochlorothiazide seems to be an effective and safe drug in the long-term treatment of primary hypertension.

Introduction

There is increasing clinical experience of the orally active converting-enzyme inhibitor captopril in the treatment of both primary (essential) and secondary hypertension. Most studies have reported results after acute and short-term treatment periods. There are some studies in which treatment has been continued for over one year (Brunner *et al.*, 1979; Carlier *et al.*, 1981; Case *et al.*, 1982). The safety, efficacy, and tolerance of a new drug must also be re-evaluated after treatment for several years.

We have followed a reasonably large group of patients with primary hypertension treated with captopril alone or in combination with hydrochlorothiazide for over one year, in some patients for over three years. We report our overall long-term clinical experience with this regimen and the effects of captopril on some biochemical values.

Methods

Our study was conducted in 41 patients with primary hypertension (Table 1). Initially, patients were

Table 1 Patients studied

Number	41
Men	21
Women	20
Mean age (years)	48 (32–61)
WHO stage I	32
WHO stage II	9
Fundoscopic changes:	
Grade 0	13
Grade I	22
Grade III	6
Mean blood pressure at entry (mm Hg)	
Supine	174/111
Standing	170/116
Number previously untreated	22

evaluated clinically and several haematological and biochemical tests were performed as reported (Karlberg *et al.*, 1981). Secondary hypertension was excluded and all renin values were measured in all patients after frusemide provocation as described elsewhere (Karlberg & Tolagen, 1977; Tolagen & Karlberg, 1978).

Patients were seen twice a week for the first three months, monthly for 12 months, and then at least every third month. Blood pressure measurements were performed by specially trained nurses after 10 minutes' supine rest and after standing for 2 minutes.

Diastolic blood pressure was measured at Korotkoff phase 5. All blood pressure measurements were performed at the same time of the day (8–11 am) about two to four hours after drug intake. Treatment was started with captopril 25 mg in increasing doses according to a dose titration schedule as described elsewhere (Karlberg *et al.*, 1981). The maximum dose used was 450 mg a day. Hydrochlorothiazide 25–100 mg a day was added for patients not achieving adequate blood pressure control (supine diastolic blood pressure 90 mm Hg).

During long-term follow-up, physical examination and biochemical monitoring were performed and possible side effects were elicited and evaluated.

All protocols were approved by the local ethical committees. Each patient gave informed consent. Statistical evaluation was performed by standard methods including Student's *t* test for paired data. Results are given as means $\pm$ SD unless otherwise stated.

Results

The number of treated patients and effects of captopril on blood pressure and heart rate at 12, 24, and 36 months are shown in Figures 1–3. The average dose of captopril and the number of patients on concomitant hydrochlorothiazide treatment are shown in Table 2. In some patients the dose of captopril could be reduced and changed to a twice-daily regimen without loss of blood pressure control.

The effects of treatment in patients with low-renin hypertension ($n = 12$) and in those with normal-renin hypertension ($n = 23$) over one to 24 months are shown in Figure 4.

Renal and liver function and haematological values were normal throughout the study, except in one patient who developed proteinuria (see below). Other effects of captopril on biochemical values are shown in Table 3.

Side effects probably related to captopril and their time of appearance during the long-term treatment are shown in Table 4. The patient who developed proteinuria showed no other signs of impaired renal function: the results of intravenous pyelography were normal, and the proteinuria slowly subsided despite prolonged treatment with a reduced dose of captopril.

Figure 1 Effects of captopril alone or combined with hydrochlorothiazide on blood pressure and heart rate in 41 patients at 3 and 12 months of treatment. □ supine blood pressure, ▨ standing blood pressure. All blood pressure reductions $p < 0.001$ compared with entry blood pressure.

Figure 2 Effects of captopril alone or combined with hydrochlorothiazide on blood pressure and heart rate in 38 patients at 12 and 24 months of treatment. □ supine blood pressure, ▨ standing blood pressure.

Figure 3 Effects of captopril alone or combined with hydrochlorothiazide on blood pressure and heart rate in 16 patients at 12, 24, and 36 months of treatment. □ supine blood pressure, ▨ standing blood pressure.

Table 2 Number of patients and doses of captopril and hydrochlorothiazide during treatment for 3, 12, 24, and 36 months.

Months	3	12	24	36
Total number of patients	41	41	38	16
Mean dose of captopril (range)	307 (75-450)	269 (75-450)	239 (50-450)	246 (100-450)
Number of patients on concomitant hydrochlorothiazide	21	23	21	7
Mean dose of hydrochlorothiazide (range)	56 (25-100)	53 (25-100)	51 (25-100)	43 (25-75)

Table 3 Biochemical data before and during treatment with captopril alone or in combination with hydrochlorothiazide

	Pretreatment	R _x last visit
Serum potassium (mmol/l)		
Captopril	4.0 ± 0.4	4.2 ± 0.4*
Captopril and hydrochlorothiazide	4.0 ± 0.3	3.9 ± 0.3
Serum glucose (mmol/l)		
Captopril	4.6 ± 0.5	5.1 ± 0.5**
Captopril and hydrochlorothiazide	5.2 ± 1.1	5.5 ± 1.0**
Serum uric acid (μmol/l)		
Captopril	276 ± 58	300 ± 70*
Captopril and hydrochlorothiazide	318 ± 56	381 ± 78***

No significant changes in any group for: white cell count, serum cholesterol, or serum triglycerides

* $p < 0.05$; ** $p < 0.005$; *** $p < 0.001$

Table 4 Side effects during long-term treatment with captopril ($n = 41$)

		Occurred at (month = m)
Tiredness	3	1 m, 4 m, 7 m
Cold hands and/or feet	3	5 m, 3-13 m, 7-13 m
Rash	1	2 m
Ageusia	1	1 m
Proteinuria	1	5 m

Discussion

Numerous studies have shown the antihypertensive efficacy and tolerability of captopril during short-term treatment for up to three months in both primary and secondary hypertension. Experiences with captopril during long-term treatment—that is, for over a year in patients with various forms of hypertension—have been reported (Brunner *et al.*, 1979;

Figure 4 The effects on supine blood pressure and doses of captopril and hydrochlorothiazide in patients with low-renin hypertension (▨, $n = 12$) and normal renin hypertension (□, $n = 23$), during 24 months of treatment.

Carlier *et al.*, 1981; Case *et al.*, 1982; Havelka *et al.*, 1982). We studied a homogenous population of patients with primary hypertension. The initial treatment results in some of these patients have been reported previously (Karlberg *et al.*, 1981). Our long-term treatment results show comparable and sustained reduction of blood pressure for treatment times up to three years despite a slight reduction in the total daily dose of captopril. In about half of the patients addition of hydrochlorothiazide (see Table 2) was performed to achieve adequate blood pressure control. These results indicate that there is no development of resistance or tolerance to long-term treatment with captopril, contrary to what has been reported by Tarazi *et al.* (1981).

In our previous study (Karlberg *et al.*, 1981) we found that patients with low-renin hypertension initially responded less well to captopril alone, although more prolonged treatment resulted in good blood pressure control in many patients with low-renin hypertension. We have confirmed this in the present study, although this group of patients needed a higher dose of captopril and also the addition of higher doses of hydrochlorothiazide to reach adequate blood pressure control. Thus, there seems to be a dissociation between the acute antihypertensive effect of captopril and the long-term effect, the acute response probably being more dependent on the inhibition of circulating angiotensin II.

Long-term monitoring of various biochemical tests did not show any toxic or unexpected effects. There were no consistent effects on lipid metabolism, and the small increase in fasting blood glucose and serum uric acid concentrations is hardly clinically important.

The addition of hydrochlorothiazide caused the well-known increase in serum uric acid concentration. A combination of captopril and hydrochlorothiazide did not lower serum potassium values, possibly because of the captopril effect on aldosterone secretion.

There were few side effects of captopril during long-term treatment and most patients tolerated the treatment very well. In contrast to conventional anti-hypertensive therapy, patients taking captopril often report a sense of well being. Captopril has some potential and serious side effects such as proteinuria and blood dyscrasias (Lancet, 1980). It seems, however, that these develop within the first months of therapy and are related to the use of high doses. We observed one case of proteinuria without other signs of renal impairment. The proteinuria subsided despite continued treatment with a reduced dose of captopril for more than two years. Thus, we do not believe that captopril will induce chronic toxic effects on renal function. We did not observe any haematological changes throughout this long-term study.

We conclude that captopril alone or in combination with a diuretic is a safe and well-tolerated anti-hypertensive drug in patients with moderately severe primary hypertension, resulting in a very effective blood pressure control during long-term treatment. The dose of captopril can be reduced over time without any loss of blood pressure control. There may be other mechanisms responsible for the chronic anti-hypertensive action of captopril than the immediate ones, especially in patients with low-renin hypertension.

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