MAINTENANCE OF THE ANTIHYPERTENSIVE EFFICACY OF CAPTOPRIL DESPITE CONSISTENT REDUCTION IN DAILY DOSAGE

ALBERT MIMRAN & BERNARD JOVER

Department of Medicine, Centre Hospitalier Universitaire, Montpellier, France

1 After a period of 7 ± 1.4 months of good control of hypertension by thrice daily administration of captopril (85 ± 9 mg three times a day), captopril was given twice daily and the total dose was progressively reduced to sometimes very low levels in 12 patients. Twice daily administration of captopril 85 ± 9 mg did not modify blood pressure control.

2 During reduction of captopril dosage to a minimum of 36 ± 4 mg twice a day, the acute effect of the morning dose of captopril (last dose taken at least 12 hours before study) was assessed. Administration of the morning dose induced a decrease in mean arterial pressure from 112 ± 4 mm Hg (104 ± 3 mm Hg during administration of 85 ± 9 mg) three times a day to 106 ± 4 mm Hg, an increase in plasma renin activity, and a decrease in plasma aldosterone concentration.

3 These acute effects of captopril suggest that blood pressure was well controlled in the presence of a non-blocked circulating angiotensin-converting-enzyme activity, thus raising the possibility of alternate mechanisms by which captopril reduces arterial pressure.

4 The daily dosage of captopril needed to control hypertension may be reassessed after a certain period of good blood pressure control with 50 to 100 mg captopril three times a day.

Introduction

The orally active angiotensin-converting enzyme captopril is a very effective antihypertensive agent when given alone or in combination with diuretics (Brunner *et al.*, 1979), though a few cases of sometimes serious adverse effects have been reported. While rashes and other cutaneous side effects are observed within the first four to six weeks of treatment and appear to be dose-related, neutropenia may occur within one to three months (Cooper, personal communication) and proteinuria with or without nephrotic syndrome within three to 15 months of captopril therapy (Vidt *et al.*, 1982). Most haematological and renal adverse reactions (50–80% of cases) were observed with doses of captopril higher than 300 mg/day.

In most studies treatment by captopril has been conducted with a thrice daily administration; however, Waeber *et al.* (1980) have reported that twice daily administration of 200 mg of captopril is associated with a sustained and satisfactory control of blood pressure.

In the present investigation, conducted in patients whose blood pressure had been under good control for several months, we tried to switch from thrice

daily administration of captopril—that is, from 100 mg three times a day to 100 mg twice a day—and then to study the effects of a sometimes drastic reduction in the dose of captopril.

Methods

Twelve patients, nine men and three women, aged 30 to 65 years with sustained hypertension associated with unilateral renovascular abnormalities (two patients) or essential hypertension (10 patients) were included in this study. As shown in Table 1, seven patients were treated with diuretics before the addition of captopril, while the remaining five patients were first given captopril; in two of the latter patients hydrochlorothiazide was also necessary. In all patients the acute effect of the first tablet of captopril was assessed and captopril treatment was conducted as suggested by the manufacturer—that is, the drug was given on a thrice daily basis and the dosage was doubled every one to two weeks to reach a maximum dose of 150 mg three times a day.

After a period of satisfactory control of hyper-

Table 1 Clinical data. The treatment given before captopril was continued in association with captopril

Case no.	Age/Sex	Clinical diagnosis	Ocular fundus	Serum creatinine (mg/100 ml)	Arterial pressure (mm Hg) before captopril	Treatment		Before decrease in dose of captopril Duration (months)	Arterial pressure (mm/Hg)
						Before	Captopril (mg)		
1	49 M	EH	2	1.1	194/123	H 50	100 bid	2	135/98
2	52 M	EH	3	1.2	184/118	F 80	100 tid	13	167/103
3	65 M	EH	2	1.4	191/108	F 80	100 tid	2	166/87
4	51 F	EH	1	0.8	170/110	H 25	50 tid	19	130/86
5	40 M	EH	Normal	1.0	180/112	H 50	100 tid	11	137/88
6	46 M	EH	2	1.8	163/116	F 80	50 tid	5	127/82
7	30 M	EH	4	2.5	188/142	F120-A 100	100 tid	4	106/76
8	59 M	EH	2	1.2	190/104	—	100 tid	12	143/85
9	49 M	EH	1	1.0	155/115	—	150 tid	20	128/87
10	50 F	EH	4	1.5	205/120	—	50 tid*	4	135/88
11	63 F	RVH	2	1.1	196/98	—	50 tid	6	147/73
12	58 M	RVH	2	1.1	197/123	—	100 tid*	10	150/94
mean	51			1.3	185/116		254	9	139/87
± SEM	2.3			0.13	4/3		27	1.8	5/2.4

EH = essential hypertension; RVH = renovascular hypertension; H = hydrochlorothiazide; F = frusemide; A = atenolol.

*Hydrochlorothiazide 50 mg added to captopril regimen.

tension of 1 to 15 months (mean ($\pm$ SEM) 7 ± 1.4 months) the daily dose of captopril was decreased to two-thirds of the previous dosage and given on a twice daily basis; subsequently the dose of captopril was reduced to 50 mg and 25 mg or 12.5 mg twice daily. Each dose was administered for 2 to 6 weeks. At the end of each period patients came to the outpatient clinic, where arterial pressure was recorded in the supine position, before they took the morning dose of captopril—that is, at least 12 hours after the last dose and for 60 to 90 minutes after the morning dose. Blood samples for determining plasma renin activity and plasma aldosterone concentration were drawn before and after captopril administration.

Arterial pressure determinations were obtained using an indirect sphygmomanometer (Arteriosonde, Roche Products). Plasma renin activity was estimated by radioimmunoassay using the CEA-Sorin Kit and plasma aldosterone was measured by radioimmunoassay (Vetter *et al.*, 1973). In supine healthy subjects on ad libitum sodium intake, plasma renin activity and aldosterone concentrations are 0.5 to 2.5 ng/ml/h and 4 to 10 ng/dl respectively.

Results are expressed as means $\pm$ SEM and data were analysed using the Student's *t* test for paired data.

Results

Before the start of captopril treatment arterial pressure was $185/116 \pm 4/3$ mm Hg (mean arterial pressure 139 ± 3 mm Hg), plasma renin activity was 5.3 ± 1.46 ng/ml/h, aldosterone concentration was 19.5 ± 1.8 ng/dl, plasma potassium concentration was 3.8 ± 0.2 mmol/l, serum creatinine was 1.3 ± 0.13 mg/dl and body weight was 77.6 ± 4 kg. Satisfactory control of hypertension (mean arterial pressure 104 ± 3 mm Hg) was obtained with a mean daily dose of captopril of 254 ± 37 mg (85 ± 9 mg three times a day); this was associated with an increase in plasma renin activity to 12.2 ± 3 ng/ml/h and a decrease in aldosterone concentration to 12.4 ± 1.6 ng/dl ($p < 0.01$ for both), while plasma potassium and body weight were unchanged (see Figure 1).

After a period of good control of hypertension of 7 ± 1.4 months, during which severe retinopathy regressed in the three patients with grade III or IV retinopathy, the daily dose of captopril was reduced. When patients were switched to 85 ± 9 mg twice daily, arterial pressure remained under satisfactory control as shown in Figure 1.

A fall in captopril dosage to a minimum of 12.5 to 50 mg twice daily was associated with good therapeutic results in cases 2 and 3 in which the dose had to be increased from 50 mg to 100 mg twice daily because of arterial pressure values of 190/106 mm Hg and 192/113 mm Hg respectively. At a mean dose level of

36 ± 4 mg twice daily and before administration of the morning dose, mean arterial pressure was 112 ± 4 mm Hg ($p < 0.01$ when compared with the level obtained with the maximum dose of captopril). Administration of captopril was associated with a slight fall in mean arterial pressure to 106 ± 4 mm Hg while plasma renin activity increased from 4.6 ± 1.3 (a value similar to the pre-treatment value) to 8.6 ± 3 ng/ml/h ($p < 0.05$) and plasma aldosterone decreased significantly (Figure 1). At the end of the study (after a total duration of captopril administration of 17 ± 1.2 months) plasma potassium and body weight were unaffected and no adverse effects had been observed.

Discussion

Most clinical studies using captopril in hypertensive patients have used doses of 200 to 600 mg/day (Brunner *et al.*, 1979) and the drug has had to be administered three to four times daily because of captopril's rather short half life of less than two hours in subjects with normal renal function (Kripalani *et al.*, 1980). In our investigation we have shown that twice daily administration of captopril was associated with maintenance of a level of arterial pressure similar to that achieved with thrice daily administration of the same dose when this change was made after a period of very good control of hypertension on thrice daily treatment. Waeber *et al.* (1980) also observed that twice daily administration was enough to keep blood pressure under control throughout the day; however, they used a dose of captopril (200 mg twice daily) much higher than ours (mean of 85 mg twice daily) and treatment was started and maintained on a twice daily basis.

The observation that the daily dose of captopril can be consistently reduced from 85 mg three times a day to an average value of 36 mg twice a day—that is, 70% decrease in the total daily dose of captopril—after quite a long period of good blood pressure control (7 ± 1.4 months) is interesting. As with the highest dose, the lowest dose of captopril was associated with the maintenance of blood pressure within acceptable limits throughout the day, for at least 12 hours after the last dose of the drug and was not strikingly affected by oral administration of the morning dose. In addition to a slight effect on arterial pressure, the morning dose of captopril produced an increase in plasma renin activity and a decrease in plasma aldosterone concentration. Although plasma converting-enzyme activity was not measured, as in the study of Waeber *et al.* (1980), it is logical to assume that these acute effects of the morning dose of captopril on arterial pressure and renin and aldosterone secretions are the consequence of the inhibition by the agent of circulating and probably of pulmonary angiotensin-converting-enzyme activity.

Figure 1 Long-term effect of captopril in patients with hypertension. When captopril dosage was reduced, blood pressure and hormonal values were estimated before (open bars) and after (closed bars) the morning dose of captopril (last dose taken at least 12 hours before measurements).

* $p < 0.05$ when compared to pre-captopril mean value

These findings suggest that arterial pressure may be kept under good control in the presence of a non-blocked angiotensin conversion and they raise the question of alternate mechanisms by which captopril exerts and maintains its antihypertensive effect.

Maintenance of the antihypertensive effect of captopril may be explained in several ways. Firstly, there may be a reduction in sodium balance and extracellular fluid volume, though this is unlikely since no change in body weight occurred during captopril treatment. Secondly, there may be an accumulation of endogenous vasodilating substances such as kinins (as a result of kininase II inhibition by captopril) or prostaglandins. During long-term captopril administration the observation of an increase in arterial pressure associated with infusion of aprotinin was interpreted as an argument for a role

of kinins (Mimran *et al.*, 1980); but it is unlikely that the kininase activity would remain inhibited while angiotensin-converting enzyme activity has resumed. Thirdly, there may be persistence of blockade of tissue angiotensin-converting-enzyme activity (mainly vascular type) despite non-blockade of circulating angiotensin-converting-enzyme activity; Cohen and Kurz (1982) have recently observed that in spontaneous hypertensive rats aortic angiotensin-converting enzyme remains low 24 hours after a single dose of captopril while circulating angiotensin-converting enzyme returned to precaptopril levels and arterial pressure remained below the pretreatment value. Fourthly, a decrease in the ratio of wall thickness to lumen, probably as a consequence of a consistently long period of good control of blood pressure (Falkow *et al.*, 1973), may be associated with

a decrease in vascular responsiveness to vasopressor stimuli. Such a non-specific mechanism is possible since interruption of other antihypertensive drugs after long-term administration may be associated with a long period of blood pressure control (Dustan *et al.*, 1968).

Taken together, these data suggest that twice daily

administration of captopril is advisable and that reduction of dosage may be attempted when hypertension has been well controlled for a certain period of time. Such a therapeutic strategy may help to prevent adverse effects and reduce to some extent the cost of treatment.

References

- BRUNNER, H.R., GAVRAS, H., WAEBER, B., KERSHAW, G.R., TURINI, G.A., VUKOVICH, R.A., McKINSTRY, D.N. & GAVRAS, I. (1979). Oral angiotensin-converting enzyme inhibitor in long-term treatment of hypertensive patients. *Ann. Intern. Med.*, **90**, 19-23.
- COHEN, M.L. & KURZ, K.D. (1982). Angiotensin converting enzyme inhibition in tissues from spontaneously hypertensive rats after treatment with captopril or MK 421. *J. Pharmacol. Exper. Therap.*, **220**, 63-69.
- DUSTAN, H.P., PAGE, I.H., TARAZI, R.C. & FROHLICH, E.D. (1968). Arterial pressure responses to discontinuing antihypertensive drugs. *Circulation*, **37**, 370-379.
- FALKOW, B., HALLBACK, M., LUNDGREN, Y., SIVERTSSON, R. & WEISS, L. (1973). Importance of adaptive changes in vascular design for establishment of primary hypertension, studied in man and spontaneously hypertensive rats. *Circ. Res.*, **32**, Suppl., 1, 2-16.
- KRIPALANI, K.J., McKINSTRY, D.N., SINGHVI, S.M., WILLARD, D.A., VUKOVICH, R.A. MIGDALOF, B.M. (1980). Disposition of captopril in normal subjects. *Clin. Pharmacol. Therap.*, **27**, 636-641.
- MIMRAN, A., TARGHETTA, R. & LAROCHE, B. (1980). The antihypertensive effect of captopril. Evidence for an influence of kinins. *Hypertension*, **2**, 732-737.
- VETTER, W., VETTER, H. & SIEGENTHALER, W. (1973). Radioimmunoassay for aldosterone without chromatography. *Acta Endocrinol.*, **74**, 558-567.
- VIDT, D.G., BRAVO, E.L. & FOUAD, F.M. (1982). Captopril. *N. Engl. J. Med.*, **306**, 214-219.
- WAEBER, B., BRUNNER, H.R., BRUNNER, D.B., CURTET, A., TURINI, G.A. & GAVRAS, H. (1980). Discrepancy between antihypertensive effect and angiotensin converting enzyme inhibition by captopril. *Hypertension*, **2**, 236-242.