Low dose captopril in the treatment of severe refractory hypertension associated with renal failure

G. M. BELL
M.R.C.P.

A. DOIG
F.R.C.P. (Ed.)

M. L. WATSON
M.R.C.P.

A. L. MUIR
F.R.C.P. (Ed.)

R. J. WINNEY
F.R.C.P. (Ed.)

Department of Medicine and Medical Renal Unit, The Royal Infirmary, Edinburgh EH3 9YW

Summary

Six patients with severe refractory hypertension and chronic renal failure were treated with a low dose of captopril (mean daily dose 75 mg) in combination with dietary sodium restriction, frusemide and either metoprolol, labetalol or prazosin. Sustained control of blood pressure was achieved in all six patients. Adverse effects noted were severe hyperkalaemia (2 patients), skin rashes (2 patients) and taste disturbance (1 patient).

Introduction

The angiotensin-I converting inhibitor, captopril, has been used to control severe hypertension in doses of up to 450 mg daily (Brunner *et al.*, 1978; Brunner *et al.*, 1979). A number of adverse effects have been reported with the drug (Atkinson *et al.*, 1980) and in view of its renal excretion (Kripalani *et al.*, 1980) a reduced dosage regime has been recommended for patients with renal impairment.

We report six patients with severe refractory hypertension and chronic renal failure whose blood pressure has been effectively controlled by the use of a low dose of captopril (mean daily dose 75 mg) in combination with other antihypertensive agents.

Patients and methods

Details of the patients and their underlying renal disease are given in Table 1. All patients suffered from severe refractory hypertension complicated recently by grade III hypertensive retinopathy and impaired renal function. None of the patients had adequately controlled blood pressure while in hospital on treatment with a combination of various different drugs in the maximum tolerated dosage or at the expense of intolerable adverse effects, and dietary sodium restriction (100 mmol/day in all

patients except patient 4 who was receiving 50 mmol/day).

All patients gave informed consent before entering the study.

Blood pressure (mean of 2 values) was recorded by an experienced observer after 10 min in the supine position and again after 2 min standing. Readings were obtained by an ordinary clinical sphygmomanometer using phase IV as the diastolic phase. Previous drug therapy was discontinued 24 hr before captopril was introduced. Blood samples for measurement of plasma renin activity (PRA) were obtained after overnight fasting and recumbency immediately before captopril therapy. Captopril was started in a dose of 12.5 mg orally and gradually increased to the maximum daily dose which was dependent on the patient's renal function. Brunner *et al.* (1979) noted satisfactory blood pressure control using a twice daily captopril regime. Captopril in this present study was given orally in a divided daily dose at 08.00 and 18.00 hours. This was 50 mg a day in patients 1, 3 and 4 (plasma creatinine greater than 350 $\mu\text{mol/litre}$) and 100 mg a day in patients 2, 5 and 6 (plasma creatinine 200-350 $\mu\text{mol/litre}$). Patients were discharged from hospital when their blood pressure was stable at an acceptable level.

The dramatic, but short-lived, fall in blood pressure in all six patients following the first dose of captopril (12.5 mg) showed no relation to the PRA. The hypotensive response to subsequent doses was smaller and after three days therapy with captopril in the maximum dosage, frusemide 40 mg oral b.d. was added. However, at 7 days labetalol or metoprolol was added to an unchanged dose of captopril to improve blood pressure control in 5 of the patients. Prazosin was added in patient 4, beta-adrenoceptor blockers being contraindicated due to severe bronchial asthma.

Wilcoxon's Rank Sum Test was used throughout.

TABLE 1. Patient details

Patient	Age/Sex	Diagnosis	Plasma renin activity [ng/ml/hr]	Previous drugs* and daily dose [mg]	Present drugs and daily dose [mg]
1	48/M	Essential hypertension	16.8	FR(80) LAB(1200) HYD(200) PR(16)	CAP(50) LAB(600) FR(80)
2	64/M	Chronic glomerulonephritis	1.6	PR(12) DEB(60) FR(80) LAB(800)	CAP(100) LAB(600) FR(80)
3	32/M	Chronic glomerulonephritis	6.1	MET(200) HYD(200) PR(8) FR(80)	CAP(50) MET(100) FR(120)
4	49/F	Essential hypertension	15.1	METH(2000) HYD(200) DEB(40)	CAP(50) PR(6) FR(80)
5	38/F	Chronic pyelonephritis	6.3	FR(80) MET(800) HYD(200)	CAP(100) MET(800) FR(80)
6	52/M	Essential hypertension	2.3	FR(160) MET(400) HYD(200)	CAP(100) MET(400) FR(160)

*FR = frusemide;
HYD = hydralazine;

METH = methyldopa;
CAP = captopril;

LAB = labetalol;
DEB = debrisoquine;

PR = prazosin;
MET = metoprolol.

Results

At follow-up two values of erect and supine blood pressure were obtained immediately before the 08.00 hr captopril dose and again at 12.00, 16.00 and 17.55 hr. The mean of these 8 supine values was recorded as the respective follow-up blood pressure. The most recent in-patient blood pressures on previous therapy before the start of captopril treatment (Table 2) were compared with those obtained after one month, 3 months and 6 months on the captopril combination. There was a significant reduction in both systolic ($P < 0.01$) and diastolic ($P < 0.01$) pressure without evidence of a postural fall in pressure. There was no suggestion of loss of blood pressure control during each 24 hr period.

Plasma creatinine increased in all patients during the 3 months before captopril on previous therapy but remained unchanged during the 6 months treatment with captopril (Table 2). Mean ($\pm$ s.d.) plasma creatinine at three months and one week before captopril and 1, 3 and 6 months after captopril was respectively 372 ± 240 μ mol/litre, 493 ± 262 μ mol/litre, 514 ± 266 μ mol/litre, 523 ± 267 μ mol/litre and 529 ± 252 μ mol/litre.

All patients showed an increase in plasma potassium by the end of the second month of therapy (mean increase 1.2 mmol/litre). Severe hyperkalaemia (plasma potassium greater than 6 mmol/litre) occurred in two patients both during the second month of treatment. This initially required oral calcium resonium but latterly has been controlled on dietary potassium restriction alone. Within patient analysis showed no relationship between plasma creatinine and plasma potassium levels.

A transient, itchy maculopapular rash developed in two patients. This responded to calamine lotion in one case, but in the other an antihistamine was required. One patient complained of a marked disturbance of taste during the third month of therapy. There were no changes in the white cell count, platelet count and 24 hr urinary protein loss in all patients during the 6-month treatment period.

After this 6-month study period we attempted to reduce the captopril dosage in two patients both with a plasma creatinine greater than 350 μ mol/litre from a divided daily dose of 50 mg of captopril firstly to 25 mg on alternate days and then to 25 mg once a day. This resulted in a temporary loss of blood pressure control in both patients at both the single and alternate day dosage which came under satisfactory control on returning to the original 25 mg twice a day regime.

Discussion

Captopril in a daily dose of 450 mg in combination with frusemide has proved to be effective therapy for severe refractory hypertension (Brunner *et al.*, 1979; Atkinson *et al.*, 1980). Although the renin-angiotensin system is effectively inhibited by a single dose of less than 25 mg of captopril, the hypotensive effect is short-lived (Swartz *et al.*, 1980), as captopril is thought to be cleared from the circulation within 6 hr (Kripalani *et al.*, 1980). The high renal clearance (70%) of the drug suggests that accumulation is liable to occur in patients with renal failure and in view of the adverse effects associated with captopril (Atkinson *et al.*, 1980) a reduced dosage regime has been recommended for use in such patients.

This study demonstrates that in patients with renal failure significantly improved blood pressure control can be achieved when a low dose of captopril is combined with other therapy which may either increase the dependency of the blood pressure on the renin-angiotensin system, e.g. sodium restriction and diuretics (Oelkers *et al.*, 1974) or act via other antihypertensive mechanisms. Until a plasma captopril assay becomes available and the therapeutic levels of captopril are clearly defined, this captopril regime provides effective blood pressure control in patients with renal failure and severe hypertension which has previously failed to respond to a wide range of other antihypertensive drugs. The possible accumulation effect of captopril in these patients makes it difficult to estimate the antihypertensive action of the beta-adrenoceptor blocking drugs used in this study. However, considering the previous refractory hypertension of these patients while receiving large doses of beta-blocking drugs we suggest that the improved blood pressure control was mainly the result of low dose captopril in conjunction with frusemide and dietary sodium restriction.

Captopril can cause a number of severe adverse effects. White *et al.* (1980) noted that in patients with renal impairment receiving 450 mg of captopril a day severe hyperkalaemia exceeding 6 mmol/litre occurred in 3 patients. Our data indicate that hyperkalaemia remains a particular problem in patients with chronic renal failure despite using low dose captopril. However, the blood dyscrasias (Gavras *et al.*, 1981; El Matri *et al.*, 1981) and nephropathy (Hoorntje *et al.*, 1980) previously reported after standard dose captopril therapy have not, to date, developed in any of our patients.

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TABLE 2. Blood pressure (BP) (mmHg) and plasma creatinine ($\mu\text{mol/litre}$) before and after captopril treatment

Patient no.	3 months pre-captopril		1 week pre-captopril	
	Plasma creatinine	Out-patient BP	Plasma creatinine	In-patient BP
1	520	230/150	675	200/130
2	260	180/120	320	170/115
3	800	160/110	830	200/110
4	208	220/140	670	205/145
5	211	220/120	230	202/112
6	235	160/120	235	190/140

Patient no.	1 month post-captopril		3 months post-captopril		6 months post-captopril	
	Plasma creatinine	Out-patient BP	Plasma creatinine	Out-patient BP	Plasma creatinine	Out-patient BP
1	680	130/90	700	150/90	650	130/85
2	360	150/90	430	140/90	505	140/92
3	814	180/100	847	160/100	851	150/100
4	757	190/110	714	178/102	697	142/90
5	220	160/90	210	170/100	237	160/90
6	254	136/98	241	170/106	236	136/90