EFFECTS OF THE ANGIOTENSIN CONVERTING ENZYME INHIBITOR, CAPTOPRIL, IN ESSENTIAL HYPERTENSION

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- 1 The effects of the orally active angiotensin converting enzyme inhibitor, captopril, were examined in 15 patients with mild or moderate essential hypertension.
- 2 Following initial dosing with captopril 25 mg, there was a significant fall in supine and erect blood pressure at 2 h and lasting for 6 h. There was no significant alteration of heart rate. No reduction was seen in plasma noradrenaline concentration. Maximum inhibition of plasma converting enzyme activity occurred 60 min post-dosing.
- 3 There was a strong positive correlation between blood pressure reduction and converting enzyme inhibition. The magnitude of the blood pressure reduction and converting enzyme inhibition following initial dosing was reflected in subsequent success with captopril monotherapy during a 12 week follow-up period.
- 4 It was also found that patients who did not achieve adequate blood pressure control on captopril in doses of 50 mg three times daily or less still were not controlled on a dose of 150 mg three times daily without the addition of a diuretic.
- 5 The risks of renal and marrow toxicity from captopril may be reduced by administering only low doses with the addition, where necessary, of a thiazide diuretic.

Introduction

Several classes of drugs are now available for the treatment of hypertension. Nevertheless, problems can still occur with currently available agents in a minority of patients because of resistance to treatment even when three or more drugs are employed or because of side-effects and compliance difficulties. A novel method of lowering blood pressure is by interference with the renin-angiotensin-aldosterone system either using the angiotensin antagonist saralasin (Stokes & Edwards, 1976) or by inhibition of converting enzyme, dipeptidyl carboxypeptidase (E.C.3.4.15.1) which is responsible for the conversion of angiotensin I (AI) to the vaso-active octapeptide angiotensin II (AII) (Erdos, 1975; Ondetti, Rubin & Cushman, 1977).

The therapeutic potential of converting enzyme inhibition in hypertension has been enhanced by the availability of an orally active angiotensin converting enzyme inhibitor captopril (Rubin *et al.*, 1978). This drug has been shown to lower blood pressure in animals and in patients with hypertension especially when renovascular in origin (Freeman *et al.*, 1977; Vollmer *et al.*, 1978; Cody *et al.*, 1978; Gavras *et al.*, 1978). It is uncertain, however, whether AII withdrawal (Murthy, Waldron & Goldberg, 1978) brady-

kinin potentiation (Williams & Hollenberg, 1977) or some other mechanism (Tree & Morton, 1980; Conway *et al.*, 1980) is of greatest importance in mediating this effect.

Captopril in clinical use has been associated with reports of potentially serious toxic effects, notably proteinuria (Hoorntje *et al.*, 1980) and agranulocytosis (Staesson *et al.*, 1980; Elijevich & Krakoff, 1980) which may be dose-related. However, determination of the ideal dose and frequency of captopril administration in order to minimise the risk of toxic effects has been hindered by the absence of a convenient reliable assay of captopril in biological fluids. There is animal evidence that plasma converting enzyme activity may be used as an index of captopril concentration (Petty, Reid & Miller, 1980). We have studied the use of captopril in mild and moderate essential hypertension with particular reference to dosage and its value as monotherapy. We measured the effects of the first oral dose of captopril (25 mg) on blood pressure, angiotensin converting enzyme activity, plasma noradrenaline concentration and plasma renin activity in patients with essential hypertension at the beginning of a 12 week study of the efficacy and safety of captopril in these patients.

Methods

The study was conducted in 15 patients, 7 male and 8 female, aged 40–68 years (mean 52.8 years) with mild to moderate (WHO Grade I and II) essential hypertension. The pretreatment blood pressure of the group was $170.8 \pm 22.6/105.8 \pm 10.0$ mmHg (average $\pm$ s.d.). They were on unrestricted sodium intake and had received no antihypertensive medication for at least seven days preceding the study. They were admitted to hospital on the morning of the study having fasted from 22.00 h the previous evening and they rested quietly, supine, for 1 h before the study was commenced.

Captopril (25 mg) was administered orally with 50 ml of water. Blood pressure and heart rate (supine and erect) were measured at 0, 15, 30, 60, 90, 120, 180, 240, 300, 360, 420 and 480 min, using a semi-automatic sphygmomanometer (Bosomat IID, Bosch and Sohn). At the same intervals blood for converting enzyme measurement was drawn into heparinized tubes, the plasma separated and stored at -20°C and measured by a radioenzymatic method (Ventrex Laboratories, Portland, Maine, U.S.A.). Blood was also taken at 0, 120 and 480 min for measurement of plasma renin activity and noradrenaline concentration. Plasma renin activity was measured by the method of Boyd *et al.* (1969) and noradrenaline by a sensitive radioenzymatic method (Henry *et al.*, 1975). Supine measurements were made after 10 min recumbency and erect measurements after 5 min standing.

Patients were thereafter discharged from hospital taking captopril 25 mg three times daily and were followed up at weekly intervals for 12 weeks. On each occasion blood pressure, supine and erect, was recorded as before. Specific enquiry was made for side-effects, blood taken for routine haematological and biochemical measurements and urine collected for the detection of proteinuria. If blood pressure control were inadequate ($> 140/90$ mmHg supine or erect) the dose of captopril was increased stepwise to 50, 100 and 150 mg three times daily with the ultimate addition of hydrochlorothiazide, 25 mg twice daily.

All patients gave informed, witnessed consent to take part in the study, which had received the approval of the local research and ethical committee.

Statistical evaluation of results was by the Wilcoxon matched-pairs signed-ranks test.

Results

For the group as a whole there was a marked reduction in mean arterial pressure (MAP) maximal at 120 min in both supine and erect postures ($P < 0.01$). MAP (supine) fell from 121.8 ± 3.5 (mean $\pm$ s.d.) mmHg to 102.7 ± 4.0 mmHg, and MAP (erect) from

125.0 ± 3.1 mmHg to 99.9 ± 5.4 mmHg (Figure 1). Blood pressure thereafter returned towards the pre-treatment value and did not differ from it significantly by 360 min. A different response was observed in those subjects whose blood pressure was subsequently controlled on captopril alone from that seen in those who required the addition of a diuretic. In the first group mean arterial pressure fell by 23 mmHg (mean) following initial dosing but in the second group mean arterial pressure fell by only 12 mmHg. The response to initial dosing and subsequent course in these two groups is shown in more detail in the Table. As can be seen, a marked initial response to captopril was associated with the early establishment of adequate control of blood pressure by captopril given alone in dose of 50 mg three times a day or less. On the other hand, the group who had a less dramatic response to initial captopril dosing showed no significant improvement in blood pressure control despite receiving captopril in a dose of 150 mg three times a day. The addition of a thiazide, however, resulted in satisfactory control in most of these patients.

Figure 1 Mean arterial pressure, supine and heart rate, supine, following a single 25 mg oral dose of captopril (mean $\pm$ s.e. mean results). The fall in mean arterial pressure was significant ($P < 0.01$) but there was no significant change in heart rate.

Angiotensin converting enzyme activity fell significantly by 45 min following captopril ($P < 0.01$) and maximum inhibition, 45% of the initial value, was achieved at 60 min, somewhat in advance of maximum blood pressure reduction (Figure 2). Angiotensin converting enzyme activity returned to normal by 240 min. In the group subsequently unresponsive to captopril alone mean and angiotensin converting enzyme inhibition was only 31%. A strong positive correlation was found between blood pressure reduction and percentage angiotensin converting enzyme inhibition (Figure 3) ($r = 0.93$, $P < 0.001$).

No reflex tachycardia was noted in response to the fall in blood pressure, indeed heart rate tended to fall

Table 1 Blood pressures (supine) of patients controlled on captopril monotherapy or captopril plus hydrochlorothiazide, showing response to initial captopril dosing and control achieved over the following 12 weeks (mean $\pm$ s.d. results).

Time	Captopril 25 or 50 mg three times daily		Captopril 150 mg three times daily and hydrochlorothiazide 25 mg twice daily	
	Systolic (mmHg)	Diastolic (mmHg)	Systolic (mmHg)	Diastolic (mmHg)
Pre-treatment	180.6 $\pm$ 25.1	105.9 $\pm$ 8.5	160.9 $\pm$ 20.1	105.7 $\pm$ 11.4
2-h after initial dosing (25 mg)	137.9 $\pm$ 22.9	79.1 $\pm$ 11.9	146.9 $\pm$ 24.8	89.6 $\pm$ 20.9
Week 2	152.3 $\pm$ 20.0	88.7 $\pm$ 2.4	160.1 $\pm$ 25.0	102.0 $\pm$ 11.7
Week 4	145.0 $\pm$ 15.8	85.0 $\pm$ 3.3	167.3 $\pm$ 18.7	99.7 $\pm$ 9.8
Hydrochlorothiazide added				
Week 6	141.8 $\pm$ 13.4	84.7 $\pm$ 6.9	143.0 $\pm$ 24.3	86.0 $\pm$ 11.1
Week 12	140.2 $\pm$ 17.7	81.3 $\pm$ 14.1	136.5 $\pm$ 25.4	84.8 $\pm$ 8.4

Figure 2 Inhibition of converting enzyme activity following captopril (25 mg) administration (mean $\pm$ s.e. mean).

Figure 3 Correlation of inhibition of converting enzyme activity with change in mean arterial pressure (supine) over 8 h ($r = 0.93$, $P < 0.01$). Mean arterial pressure fall (erect) v % inhibition of angiotensin converting enzyme, $r = 0.9$, $P < 0.001$.

slightly. The fall was maximum at 120 min but this change was not statistically significant. Plasma renin activity rose from $0.9 \text{ ng ml}^{-1} \text{ h}^{-1}$ (mean) before treatment to $1.5 \text{ ng ml}^{-1} \text{ h}^{-1}$ at 120 min and returned to $0.9 \text{ ng ml}^{-1} \text{ h}^{-1}$ by 480 min. These changes did not achieve statistical significance. Supine plasma noradrenaline concentration rose from 3.9 nmol/l initially to 4.4 nmol/l at 120 min. Erect measurements rose from 4.8 nmol/l to 6.6 nmol/l . These changes were not statistically significant.

The magnitude of blood pressure reduction and converting enzyme inhibition following initial captopril dosing was the only detected difference between the group subsequently controlled on captopril monotherapy and those who required the addition of a thiazide. The non-responders, indeed, appear to have the lower pretreatment blood pressure but wide inter-individual variation meant that the two groups did not differ significantly in this respect. There were three males, five females in the group responding, four males, three females in the group not responding. There was no significant difference in age or in pretreatment plasma renin activity. There was no obvious difference in previous patterns of antihypertensive medication. One of the responders had previously received a thiazide whilst three of those failing to respond had done so.

A number of side-effects was noted which in three cases meant that therapy had to be withdrawn. A maculopapular rash was noted once and a widespread severe urticarial reaction once. Intractable vomiting in one patient and severe myalgia of sudden onset in another resulted in withdrawal of captopril. No leucopenia was noted nor was there any proteinuria. One patient was withdrawn from the study when his blood pressure did not fall on the highest captopril dose (150 mg three times a day) even with the addition of hydrochlorothiazide. The remainder of patients tolerated the drug well.

Discussion

Captopril (25 mg) given orally will produce a significant blood pressure reduction in patients with mild or moderate essential hypertension with normal plasma renin activity and not only in those with high renin or renovascular hypertension. The response lasts for about 6 h. This is not necessarily a surprising finding. There is no doubt that the renin-angiotensin-aldosterone system has a role in maintaining blood pressure both in normotensive subjects and in patients with hypertension. Interference with that system, therefore, might be expected to result in a lowering of blood pressure irrespective of the aetiology of the hypertension. Accompanying the fall in blood pressure was a significant inhibition of angiotensin converting enzyme activity in plasma, and there was a strong positive correlation between these two. However, maximum angiotensin converting enzyme inhibition slightly preceded the maximum hypotensive effect. The strong correlation does support the concept that the hypotensive efficacy of captopril is mediated by converting enzyme inhibition. On the other hand the lack of synchrony may provide further evidence that it is converting enzyme inhibition other than in the plasma, for example in the vessel wall, (Swales, Tange & Thurston, 1975) which is responsible for the hypotensive effect. As captopril inhibition of converting enzyme activity is not stable even at -20°C the actual level of inhibition was probably underestimated in the present study (Roulston, MacGregor & Bird, 1980). However, as all samples from each individual were processed together the relative changes are a reflection of captopril induced inhibition.

The finding of an apparent relationship between both hypotensive effect and angiotensin converting enzyme inhibition following initial captopril dosing and subsequent satisfactory control on captopril monotherapy may, if confirmed in larger numbers, be of therapeutic importance. Furthermore, the observation that in patients in whom optimal blood pressure control was not achieved at lower doses of captopril (50 mg three times daily or less) the addition

of a diuretic was always required suggests that there may be little benefit in using high doses of captopril alone in essential hypertension. Restriction of the captopril dose to 150 mg daily or less with the addition, if necessary, of a diuretic may, therefore, control hypertension in many patients. Clinical experience indicates that although the side-effects of captopril are not strictly dose related they occur most often in patients on highest doses or with pre-existing renal impairment. The possibility of using low dose captopril plus a diuretic clearly merits further investigation.

The absence of reflex tachycardia during hypotension has also been observed in volunteer studies (Campbell, Reid & Shepherd, 1980) and in congestive cardiac failure (Turini *et al.*, 1979) although a small increase in patients with severe hypertension was noted by Brunner *et al.* (1979). This does suggest that captopril is not acting solely by reducing the arteriolar vasopressor effect of AII. On the other hand, such a response has been observed with sodium nitroprusside where both arteriolar resistance and venous capacitance are affected (Cody *et al.*, 1978). The vasodilator profile of captopril is not yet sufficiently clarified to confirm this explanation for the absence of tachycardia. It may be that captopril exerts some effect on sympathetic tone or adrenoceptor sensitivity. Such an effect could be mediated through modification of presynaptic facilitatory effects of AII. However, the absence of a fall (indeed, there was a slight rise) in plasma noradrenaline concentration in this study does not support this explanation.

In conclusion, the converting enzyme inhibitor, captopril, produces an initial blood pressure reduction in patients with essential hypertension. The results suggest that the hypotensive effect of captopril is mediated through angiotensin converting enzyme inhibition. Initial response may be a guide to subsequent success with captopril monotherapy and it seems possible that the early addition of a diuretic may allow control to be achieved at low doses of captopril with reduction in the risk of toxic side-effects.

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