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CAPTOPRIL TREATMENT: INTER-DOSE VARIATIONS IN RENIN, ANGIOTENSINS I AND II, ALDOSTERONE AND BLOOD PRESSURE

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1 The ability of captopril, 150 mg three times daily by mouth, to effect sustained reduction in plasma angiotensin II, with converse increases in circulating angiotensin I, and in active, inactive and total renin concentrations, has been assessed.

2 During prolonged treatment with captopril alone, and 12 h after the last dose of the drug, plasma angiotensin II remained approximately one-sixth of basal concentrations, while angiotensin I and renin concentrations were proportionately increased. However, further increases in angiotensin I, and in active, inactive and total renin concentrations, were seen 2 and 6 h after the morning dose of 150 mg captopril.

3 Inter-dose variations in plasma aldosterone and blood pressure were not closely related to concurrent variations in the renin-angiotensin system.

4 Arguments are presented for relying on measurements of plasma renin and angiotensin concentrations rather than of renin activity or aldosterone in assessing the effectiveness of converting enzyme inhibition.

Introduction

Captopril, an orally-active inhibitor of angiotensin I-converting enzyme, has proved effective in the treatment of several forms of hypertension, and may be useful also in cardiac failure (Atkinson & Robertson, 1979). Estimates of the duration of effectiveness of each dose in reducing plasma angiotensin II have been based on assays of plasma converting enzyme activity, plasma renin activity and plasma aldosterone concentration, which for a variety of reasons may not always be either reliable or relevant. An alternative, more direct, approach is to measure inter-dose variations in the concentrations of angiotensin II, angiotensin I and renin in the circulation.

The present paper examines variations in the circulating concentrations of active and total renin, angiotensin I and angiotensin II, at 2, 6 and 12 h after an oral dose of 150 mg captopril, during long-term treatment with captopril alone, 150 mg three times daily. Concurrent measurements of plasma aldosterone and arterial pressure are also presented. The main aim of this study was to assess the effectiveness of this dose schedule in achieving sustained lowering of plasma angiotensin II.

Methods

Plasma angiotensin II (normal range 5–35 pg/ml) and blood angiotensin I (10–90 pg/g) were estimated respectively by the methods of Düsterdieck & McElwee (1971) and Waite (1973) with minor modifications (Morton *et al.*, 1976). Cross-reaction of angiotensin I with the angiotensin II antibody during converting enzyme inhibition was corrected for as described by Atkinson *et al.* (1980). Plasma active and total renin concentrations were measured by an antibody trapping technique (Millar *et al.*, 1978, 1980), the normal ranges being respectively 10–50 and 60–200 μU/ml. Inactive renin concentration was obtained by subtracting active from total (Millar *et al.*, 1978). Plasma aldosterone was assayed as described by Fraser *et al.* (1973) (normal < 18 ng/100 ml). Blood pressures were measured using a random zero sphygmomanometer (Hawksley) so as to minimise observer bias.

Eight patients (four males) aged 16 to 54 years were studied. Seven had radiological evidence of unilateral renal artery stenosis and one aortic coarctation. Overall renal function was normal in seven, whose plasma creatinine concentrations were consistently

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below 120 μmol/l. Modest impairment of renal function was present in one man (plasma creatinine 140–160 μmol/l). Peripheral venous blood samples were drawn before treatment, after overnight recumbency and fasting, at 10.00 h ('basal sample'). After 5 to 6 weeks of treatment with captopril alone, 150 mg three times daily by mouth, again after overnight recumbency and fasting, a blood sample was taken at 10.00 h, 12 h after the last dose of captopril ('12 h sample'). Captopril 150 mg was given, the patient remained recumbent and fasting, and a further blood sample was drawn at 12.00 h ('2 h sample'). The patient then ate a light breakfast. Another blood sample was drawn at 16.00 h ('6 h sample'), the patient having been recumbent again from 15.00 h. Plasma potassium was estimated on the 'basal' and '12 h' samples.

Arterial pressure was recorded immediately before each blood sampling, the point of disappearance of sounds being taken as diastolic.

Statistical comparisons were made using the Wilcoxon matched pairs signed rank test.

Results

The pattern of biochemical response was consistent in this series, and the conclusions were unaffected whether or not the patient with mild renal impairment was included. Therefore the overall results are presented.

During long-term captopril, plasma angiotensin II concentration was still markedly reduced, in comparison with measurements made before treatment, in the samples taken at 10.00 h, 12 h after the last 150 mg dose (Figure 1). Concurrently, components of the renin-angiotensin system proximal to the induced enzymic blockade, namely angiotensin I, and active, total and inactive renin, were all present in the peripheral circulation in greatly increased concentrations.

Nevertheless, more complete suppression of converting enzyme activity was apparent after the morning dose of 150 mg captopril. In comparison with measurements made on the samples drawn at 10.00 h, further significant increases in angiotensin I, and in active and total renin concentrations, were evident 6 h later (Figure 1). The concurrent fall in angiotensin II was not significant however.

Mean plasma aldosterone at 10.00 h was not lower than before treatment, but had fallen significantly 2 h later (Figure 1).

One of the patients with renal artery stenosis had negligible reduction of arterial pressure during long-term captopril treatment; the patient with coarctation was similarly unresponsive. In the entire series, during long-term captopril treatment, mean systolic, but not diastolic pressure, was significantly reduced

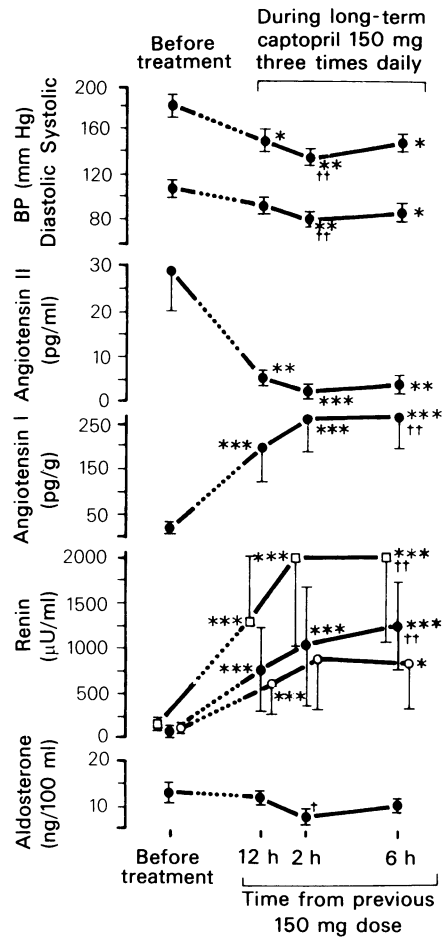

Figure 1 Measurements (mean ± s.e. mean) of arterial pressure, plasma angiotensin II, blood angiotensin I, plasma active (●), total (□), and inactive (○) renin, and plasma aldosterone concentrations before, and at 5–6 weeks treatment with captopril alone. Significant differences from pre-treatment values indicated thus: $^{*}P < 0.05$, $^{**}P < 0.02$, $^{***}P < 0.01$. Significant differences from '12 h' values indicated thus: $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.02$.

at 10.00 h, in comparison with pre-treatment values, while both systolic and diastolic were lowered 2 h and 6 h after the morning dose (Figure 1).

Plasma potassium was slightly higher at 10.00 h during long-term captopril (4.50 ± 0.12 mmol/l) than before treatment (4.13 ± 0.17 mmol/l) (mean ± s.e. mean, $P < 0.05$).

Discussion

In the present study the continued effectiveness of captopril between doses had been demonstrated by the ability of the drug to sustain reduced plasma concentrations of angiotensin II.

Several alternative approaches have been employed, although all of these have disadvantages. One widely used method has been to assay plasma converting enzyme activity using a tripeptide substrate. However, if plasma is stored frozen before such assay, erroneous results may be obtained (Roulston *et al.*, 1980; Boomsma *et al.*, 1981). Waeber *et al.* (1980), administering captopril 200 mg twice daily for 9 weeks to hypertensive patients, found, when renal function was normal, that plasma converting enzyme activity had returned to control values 14 h after the last dose of the drug. By contrast, in patients with chronic renal failure, plasma converting enzyme activity remained partially suppressed at this time interval. Noting that hypertension remained under control in both groups of patients despite these variations, they speculated that converting enzyme activity might be suppressed in sites other than plasma (Brunner *et al.*, 1981). However, if these assays were performed on stored samples, the inhibition of *in vivo* plasma converting enzyme would be underestimated.

Another approach is to assess the increase in plasma renin activity during converting enzyme inhibition, this being taken as an indication of the rise in renin concentration, which in turn reflects the fall in plasma angiotensin II. However, plasma renin activity measurements depend on the concentrations of both renin and renin-substrate in the sample. Rasmussen *et al.* (1981) have shown that during captopril therapy, plasma renin-substrate decreases markedly, perhaps in part because of consumption of substrate by the increased plasma renin concentration, and also because of loss of the stimulant effect of angiotensin II on renin-substrate release (Khayyal *et al.*, 1973). Therefore plasma renin activity measurements will underestimate the rise of renin concentration and thus the fall in plasma angiotensin II, with captopril administration.

Some workers have recommended employing aldosterone measurement as a guide to plasma angiotensin II concentration (Atlas *et al.*, 1979; Waeber *et al.*, 1980). However, angiotensin II is only one of several stimuli to aldosterone secretion (Fraser *et al.*, 1979). In the present study plasma potassium rose significantly during captopril treatment. While this increased potassium is almost certainly the result of a fall in mean plasma aldosterone, the rise of potassium will limit the fall in aldosterone secretion resulting from reduced formation of angiotensin II (Atlas *et al.*, 1979) and thus will alter the relationship between angiotensin II and aldosterone. Moreover, Maslowski *et al.* (1981) have noted a rise in both plasma and urinary cortisol on withdrawing captopril treatment and have raised the question of an inhibitory effect of captopril on corticotrophin secretion. These various observations warn against over-reliance on aldosterone measurements as a guide to angiotensin II suppression during captopril treatment.

The relationship between plasma angiotensin II concentration and arterial pressure is complex. Angiotensin II has a direct vasoconstrictor and thus immediate pressor action, and also a second, slower pressor effect, which can be demonstrated by the continuous infusion of angiotensin II at low dose (Dickinson & Lawrence, 1963; Brown *et al.*, 1981). Hypertension induced by the infusion of angiotensin II at low dose in the dog takes over 24 h to subside when the infusion is stopped (Bean *et al.*, 1979).

When captopril is given to hypertensive man, there is an immediate fall in arterial pressure which is directly proportional to the immediate fall in plasma angiotensin II (Atkinson *et al.*, 1980, 1982). With continued dosage a slower additional fall in pressure may be seen over days or weeks, which is not related to the long-term decrement of angiotensin II (Atkinson *et al.*, 1982). It is possible that the slow component of the fall in blood pressure with captopril represents antagonism of the slow pressor action of angiotensin II. These varying tempi of the pressor action of angiotensin II and of the depressor effects of captopril perhaps help explain the absence of a close association between converting enzyme inhibition and blood pressure reduction (Boomsma *et al.*, 1981). It should also be borne in mind that a fall in the concentration of angiotensin II in plasma may not always parallel a reduction of angiotensin II generation at other sites.

The present studies have been limited to one dose range of captopril, 150 mg three times daily. While suppression of plasma angiotensin II to one-sixth of basal values has been seen 12 h after this dose, smaller doses could well have a less marked and less prolonged action.

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