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Captopril in clinical hypertension

Changes in components of renin-angiotensin system and in body composition in relation to fall in blood pressure with a note on measurement of angiotensin II during converting enzyme inhibition

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SUMMARY The effect of the converting enzyme inhibitor captopril on arterial pressure, the components of the renin-angiotensin-aldosterone system, and body sodium and potassium content was studied in eight hypertensive patients with renal artery stenosis and, in conjunction with diuretics, in seven patients with hypertension unresponsive to previous treatment. Two hours after the first dose, captopril caused significant falls in systolic and diastolic pressures, plasma angiotensin II, and aldosterone, with converse increases in angiotensin I and both active and total renin; the initial fall in diastolic pressure was significantly related to the drop in plasma angiotensin II. The biochemical changes were sustained during prolonged treatment, even when diuretics were added.

One untreated patient with renal artery occlusion had severe secondary aldosterone excess, was sodium and potassium depleted, and severely hyponatraemic and hypokalaemic; captopril restored blood pressure, plasma electrolyte concentrations, and exchangeable sodium and total body potassium to normal. In one man with renal artery stenosis and overall renal impairment captopril led to sodium retention, and blood pressure did not fall until a diuretic was added. In the remaining patients with renal artery stenosis, pretreatment renin, angio tensin II, and aldosterone concentrations were either normal or only modestly raised, and plasma electrolyte concentrations and body content of sodium and potassium were normal. Captopril alone controlled arterial pressure in all, three cases showing a gradual fall of pressure over the first six weeks of treatment; no significant changes in exchangeable sodium or total body potassium were seen.

The group of patients with previously intractable hypertension were all controlled with a combination of captopril and diuretic.

Clinical accounts of the use of captopril (Squibb SQ 14 225), an inhibitor of the enzyme responsible for the conversion of angiotensin I to angiotensin II, have hitherto concentrated largely on the hypotensive action, the suppression of aldosterone, and the relation to pretreatment plasma renin levels.[1–5] There have been few reports of alterations in circulating concentrations of angiotensin I and II during treatment.[6–8] Lowering of plasma angiotensin II concentration is probably a major, though not the only, mechanism of the hypotensive action of captopril.[1] Evaluation of the body content of sodium or potassium before and during captopril treatment is also of interest, because the pressor effect of angiotensin II is directly related to the body content of sodium; moreover, body potassium might be expected to increase and sodium to decrease with captopril treatment, as angiotensin II, and hence aldosterone, falls.

We give here a detailed analysis of measurements of the individual components of the renin-angiotensin aldosterone system, and of sodium and potassium status, in relation to the fall in arterial pressure

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Table 1 *Effect of captopril alone on blood pressure, plasma angiotensin II, and aldosterone, and on plasma and body compositions of potassium and sodium in eight patients with renal artery lesions (mean ±SEM)*

	Before captopril	*Two hours after first dose of captopril*	*After six days on captopril*	*After six weeks on captopril*
Blood pressure (mmHg)	183/115 ±10/5	152/97 ±12/8 ($p < 0.01$)	159/95 ±8/6 ($p < 0.02$)	149/89 ±8/7 ($p < 0.02$)
Plasma angiotensin II (pg/ml)	104·9 ±87·0	20·1 ±13·2 ($p < 0.02$)	22·6 ±15·6 ($p < 0.02$)	13·5 ±7·7 ($p < 0.02$)
Plasma aldosterone (ng/100 ml)	19·6 ±7·8	13·9 ±6·5 ($p < 0.05$)	10·4 ±1·5 (NS)	8·1 ±1·3 (NS)
Total exchangeable sodium (mmol)	2458 ±289	—	—	2493 ±275 (NS)
Total body potassium (mmol)	2920 ±331	—	—	2842 ±355 (NS)
Plasma sodium (mmol/l)	137·6 ±2·0	—	—	137·9 ±1·0 (NS)
Plasma potassium (mmol/l)	3·8 ±0·3	—	—	4·4 ±0·2 ($p < 0.05$)

during oral captopril treatment. Two types of patients were studied; the first group had renal artery stenosis (Table 1), while all of the second group had been resistant to previous antihypertensive treatment (Table 2).

A brief account of this work was presented to the International Society of Hypertension, Göteborg, 1979.[9]

Methods

Fourteen patients were investigated. Plasma concentrations of active (normal range 10 to 50 uU/ml) and total (normal 60 to 200 uU/ml) renin, angiotensin II (5 to 33 pmol/l; 5 to 35 pg/ml), and aldosterone (< 499 pmol/l; < 18 ng/dl), and blood concentrations of angiotensin I (8 to 73 pmol/l; 10 to 90 pg/ml) were measured in peripheral venous blood by methods described previously.[8]

CORRECTION FOR ANGIOTENSIN I CROSS-REACTION

The angiotensin II antiserum used in these studies has a low cross-reaction (less than 1·0%) with angiotensin I; therefore under normal circumstances this does not cause technical difficulty with angiotensin II assay. When converting enzyme is inhibited, however, high concentrations of renin and hence angiotensin I build up in the circulation, while plasma angiotensin II falls to very low levels; moreover, further generation of angiotensin I can occur during the processing of plasma extracts. Thus, falsely high values for plasma angiotensin II can be obtained with immunoassay unless technical precautions are taken, particularly in patients with raised endogenous renin levels. In earlier studies, this was corrected by prior chromatography[10]; in the present work, a simpler method was used as follows. Increasing quantities of exogenous angiotensin I (ileu 5; Schwarz/Mann) (from 1·2 to 7·2 ng) were added to a pooled plasma extract and the apparent increase in angiotensin II was measured by radioimmunoassay. The results are plotted in Fig. 1 and show a linear relation between the amount of angiotensin I added and the apparent increase in angiotensin II. Subsequently, in all plasma samples after extraction, both angiotensin I and angiotensin II were estimated. Using Fig. 1, the appropriate correction factor was calculated, taking into account the cross-reaction caused by angiotensin I. This was then applied in determining the circulating angiotensin II concentration.

Table 2 *Effect of captopril and diuretics in a group of seven patients with severe treatment-resistant hypertension (mean ±SEM)*

	Before captopril	*On captopril alone*	*On captopril plus diuretics (3 to 26 days)*	*On captopril plus diuretics (3 months)*
Blood pressure (mmHg)	215/116 ±11/8	199/114 ±15/8 (NS)	153/93 ±10/6 ($p < 0.05$)	140/90 ±8/2 ($p < 0.05$)
Plasma angiotensin II (pg/ml)	39·8 ±15·9	11·9 ±2·7 ($p < 0.05$)	7·3 ±2·4 ($p < 0.05$)	—
Plasma aldosterone (ng/100 ml)	13·0 ±2·6	7·9 ±1·4 (NS)	10·4 ±1·4 (NS)	—

Patients

All patients took a constant diet which was the same for each subject on each admission to the metabolic ward; sodium and potassium content varied between individuals from 85 to 155 and 44 to 90 mmol per day, respectively.

Eight patients (Table 1) had renal ischaemia. It is our practice to take the findings at ureteric catheterisation as the most reliable criteria of unilateral renal ischaemia, the essential features being reduced urine flow, creatinine, and para-aminohippurate (PAH) clearances and urinary sodium concentration, with increased urinary creatinine and PAH concentrations, on the affected side. Increased ipsilateral renal vein renin and angiotensin II concentrations are often corroborative, but less specific features.[11–14] Seven patients had the typical radiological and ureteric catheterisation findings of unilateral renal artery stenosis, together with appropriate lateralising features on renal vein sampling for renin and angiotensin.[13 14]

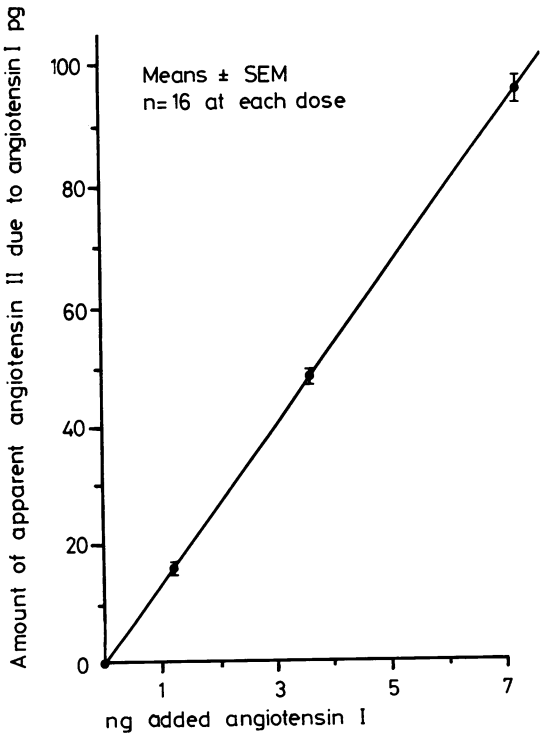

Fig. 1 *Apparent increase in angiotensin II caused by the cross-reaction of the antiserum with increasing amounts of angiotensin I added to a pooled plasma extract. Each point is the mean ±SEM of 16 separate estimates at each dose of added exogenous angiotensin I.*

One patient, previously in the malignant phase, was presumed to have consequent and predominantly unilateral intrarenal arterial lesions, having normal renal arteriograms, but evidence of unilateral renal ischaemia on both renal vein sampling and ureteric catheterisation. None of the patients with renal ischaemia had received any treatment other than bethanidine for four weeks before study; bethanidine was stopped 12 or more hours before the initial dose of captopril.

A further six patients (Table 2) had severe hypertension unresponsive to a combination of diuretic and beta-adrenoceptor blocker together with either a vasodilator or a post-synaptic alpha-adrenoceptor blocking agent. All were on this combination immediately before captopril treatment. One patient in the renal artery stenosis series was added to this group as his blood pressure before captopril had been unresponsive to treatment.

Blood samples were taken, after overnight recumbency and fasting, at 0930 hours and 1000 hours. The initial dose of captopril (25 mg in 10 cases, 6·25 mg in three cases) was then given and further samples were taken after two hours and six hours, respectively. The patients remained recumbent throughout and fasted until the two hour sample had been taken. The maximum captopril dosage used long term was 450 mg per day. In the patients with renal artery stenosis, the values given for the various components of the renin-angiotensin-aldosterone system during prolonged treatment are the means obtained in samples taken at 1000, 1200, and 1600 hours, 150 mg captopril having been given at 2200 hours on the previous evening, and again immediately after the 1000 hours sample. In the patients with drug-resistant hypertension the values are those obtained at 1000 hours, 12 hours after the previous dose of captopril and diuretic.

Exchangeable sodium (NaE),[15] exchangeable potassium (KE),[15] and total body potassium (TBK)[16] were measured by isotope dilution; in one man total body sodium (TBNa)[17] was measured by activation analysis. The relation between NaE and plasma angiotensin II in patients before and during treatment was expressed in comparison with data previously obtained in normotensive subjects.[18 19]

Throughout the study blood pressures were taken after at least 10 minutes rest. A routine clinical sphygmomanometer was used; phase V was taken as diastolic. Mean blood pressure was taken as diastolic plus one-third of pulse pressure.

Non-parametric statistical tests (Wilcoxon signed rank and Spearman rank correlation) were used as the data were not distributed normally.

Results

PATIENTS WITH RENAL ARTERY STENOSIS (Table 1)

One patient has been reported in detail elsewhere.[8] This woman had unilateral renal artery occlusion and developed classical features of the hyponatraemic hypertensive syndrome.[8 20–22] She was initially severely sodium and potassium depleted, with hyponatraemia and hypokalaemia and raised plasma concentrations of renin, angiotensin II, and aldosterone. Plasma angiotensin II fell steeply after the initial dose of captopril. Because the maintenance of arterial pressure is heavily dependent on plasma angiotensin II in sodium depletion, the initial fall of blood pressure was pronounced. With continued captopril treatment, sodium was steadily retained, the cumulative balance increasing by 598 mmol over eight days. In the same period 226 mmol potassium were retained and the plasma sodium and potassium concentrations reverted to normal. Blood pressure stabilised at a higher level as the electrolyte abnormalities were corrected and became similar to that seen after subsequent unilateral nephrectomy.

One patient with renal artery stenosis had impaired overall renal function (creatinine clearance 30 ml/min). On captopril alone TBNa rose by 157 mmol over two weeks and blood pressure remained high (190/120 mmHg) despite the drop in plasma angiotensin II. Blood pressure fell to 130/90 mmHg, and remained well controlled under outpatient conditions, when 80 mg frusemide daily was added.

The remaining patients in this group had good overall renal function, normal or only modestly raised plasma concentrations of renin, angiotensin II, and aldosterone, normal plasma electrolytes and body sodium and potassium. Captopril induced an initial modest fall in arterial pressure in parallel with the fall in plasma angiotensin II; a further distinct reduction in blood pressure was seen over six weeks with continued treatment in three patients. In this whole group, throughout the period of observation on captopril, plasma angiotensin II and aldosterone remained suppressed, while active and total renin, and angiotensin I, were raised. Plasma sodium was unchanged, while mean plasma potassium rose marginally; frank hyperkalaemia was not encountered in any case. There was no appreciable change in mean NaE or TBK.

PATIENTS WITH INTRACTABLE HYPERTENSION (Table 2)

Captopril alone did not significantly reduce arterial pressure compared with the previous regimens, though mean plasma angiotensin II fell significantly. When either hydrochlorothiazide (50 mg twice daily) or frusemide (from 40 to 1500 mg/day) was given in addition to captopril, arterial pressure was clearly lower. During continued treatment with combined diuretic and captopril, blood pressure continued well controlled and plasma angiotensin II remained suppressed. Plasma aldosterone was not significantly altered by adding diuretic to captopril. Treatment has now continued for up to 15 months in this group with no loss of control.

RESUME OF BIOCHEMICAL CHANGES IN RELATION TO FALLS IN ARTERIAL PRESSURE

Two hours after the initial dose of captopril, there were highly significant falls in systolic and diastolic pressure, plasma angiotensin II, and aldosterone concentrations, and increases in the plasma concentrations of active and total renin and blood concentrations of angiotensin I (Table 3). There was a highly significant correlation between the fall in plasma angiotensin II and fall in diastolic blood pressure ($r_s = 0{\cdot}71$; $p < 0{\cdot}01$; Fig. 2) and, less closely, between the fall in plasma angiotensin II and mean blood pressure ($r_s = 0{\cdot}48$; $p < 0{\cdot}05$).

Seven patients in the series were studied after at least six weeks of treatment with captopril 450 mg/day; five were on captopril alone and two were receiving diuretics also (Table 4). While plasma concentrations of active renin, total renin, and blood levels of angiotensin I continued to be significantly raised, plasma angiotensin II remained suppressed, as did plasma aldosterone.

SIDE EFFECTS

One patient with renal artery occlusion and sodium depletion became hypotensive after the initial dose

Table 3 *Effect at two hours of the initial dose of captopril on blood pressure and circulating concentrations of active renin, total renin, angiotensin I, angiotensin II, and aldosterone in 14 hypertensive patients (mean ± SEM)*

	Before captopril	*Two hours after captopril*
Blood pressure (mmHg)	195/118 ±10/5	166/100 ±10/6 ($p < 0{\cdot}01$)
Plasma active renin (uU/ml)	202·9 ±95·2	449·1 ±120·1 ($p < 0{\cdot}01$)
Plasma total renin (uU/ml)	448·4 ±217·8	695·7 ±201·9 ($p < 0{\cdot}01$)
Plasma angiotensin I (pg/ml)	98·3 ±61·9	257·0 ±93·7 ($p < 0{\cdot}01$)
Plasma angiotensin II (pg/ml)	78·6 ±49·6	23·1 ±11·5 ($p < 0{\cdot}01$)
Plasma aldosterone (ng/100 ml)	17·3 ±4·6	11·5 ±3·8 ($p < 0{\cdot}01$)

of 25 mg. Our recommendations in these circumstances have been reported previously.[1 8] In addition, the controlled intravenous infusion of angiotensin II (Hypertensin, Ciba) might usefully be considered as a means of preventing hypotension and regulating arterial pressure accurately if captopril is given to a sodium-depleted patient (as may be necessary for example, if earlier diuretic treatment has been employed for cardiac failure). Sodium can then be more safely replaced as the blood pressure is lowered, and with continued captopril treatment angiotensin II administration becomes unnecessary.[23]

Two patients developed symptomatic sinus tachycardia (up to 160 beats/min) on standing, one while on captopril alone and one after hydrochlorothiazide was added.

Two patients had disturbance of taste which in both instances resolved over a period of four weeks with continued treatment.

Serum urea and creatinine tended to rise when frusemide was added, particularly in patients with renal impairment; these should therefore be monitored closely.

Discussion

We have previously reported that during treatment with converting enzyme inhibitors high concentrations of angiotensin I may accumulate in plasma to such an extent that cross-reaction of angiotensin I with antibodies to angiotensin II may give falsely high values for plasma angiotensin II.[1 8–10 17 23 24] In the light of this we have developed a method of estimating the extent of the interference so that the data can be more accurately interpreted.

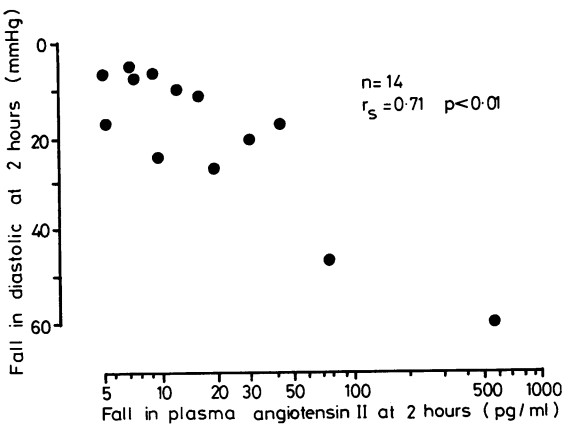

Fig. 2 *Relation between falls in diastolic pressure and angiotensin II two hours after initial dose of captopril. Not plotted, but included in the calculation, are data from one patient who had no change in angiotensin II and a fall of 8 mmHg in diastolic pressure.*

Table 4 *Long-term effects of captopril in circulating concentrations of active renin, total renin, angiotensin I, angiotensin II, and aldosterone in seven patients, all of whom had been on drugs for at least six weeks (mean ±SEM)*

	Before captopril	*After captopril*
Plasma active renin (uU/ml)	74·6 ±13·8	794·3 ±22·0 ($p < 0·05$)
Plasma total renin (uU/ml)	153·0 ±21·8	1008·0 ±260·3 ($p < 0·05$)
Plasma angiotensin I (pg/ml)	12·3 ±14·2	193·7 ±37·1 ($p < 0·05$)
Plasma angiotensin II (pg/ml)	19·9 ±3·6	4·8 ±0·8 ($p < 0·05$)
Plasma aldosterone (ng/100 ml)	14·0 ±2·7	8·7 ±1·3 ($p < 0·05$)

We have seen that prolonged treatment with oral captopril leads to clear and sustained falls in plasma angiotensin II and aldosterone, despite distinct increases in circulating active renin and angiotensin I concentrations. A similar pattern of changes was seen by Johnston and colleagues[7] when captopril was given to patients with essential hypertension, except that in their study captopril given alone did not cause an increase in blood angiotensin I. A significant correlation was seen in the present series between the initial fall in plasma angiotensin II and the concurrent drop in arterial pressure. Several lines of evidence indicate, however, that components additional to the reduction of plasma angiotensin II are involved in the hypotensive action of captopril. Experimental studies in this department on dogs showed that changes in plasma angiotensin II alone were insufficient to account for the acute changes in blood pressure.[25] Moreover, captopril has been found to lower blood pressure both in anephric rats and man.[26 27]

In addition to the initial fall in blood pressure, in three patients with renal artery stenosis in the present series (Table 1), a further reduction in pressure was seen during prolonged treatment. A similar slow fall in pressure has been noted in other series,[3] and is also a feature of prolonged administration of saralasin or converting enzyme inhibitors to rats with one-clip, two kidney renal hypertension.[28 29] This late effect is compatible with, but does not establish, antagonism of a slow pressor action of angiotensin II[1]; on present evidence it could equally represent some other component of captopril action.

There is a close interdependence between sodium status and angiotensin II in blood pressure maintenance[24] and therefore an important determinant of the pressor effect of a given plasma concentration

of angiotensin II is NaE (or TBNa). In previous studies, hypertension in patients with chronic renal failure or the malignant phase was shown to be associated with a disproprotionate increase in plasma angiotensin II in relation to NaE.[18 19] Blood pressure came down when this disproportion was corrected by lowering either plasma angiotensin II or NaE. In the present series a similar disproportion was seen, despite a low NaE, in one patient with the hyponatraemic hypertensive syndrome; the angiotensin II:NaE relation was corrected, and blood pressure fell, with captopril.[8] In another patient, with renal impairment, sodium retention developed on captopril, and, despite the fall in plasma angiotensin II, blood pressure remained high until a natriuretic agent was added.

In the remaining patients with renal artery stenosis, the relation between angiotensin II and NaE was normal before treatment, which lowered angiotensin II and blood pressure without detectably changing NaE. Brunner and colleagues[4] reported a fall in blood pressure on giving captopril to hypertensive patients with chronic renal failure, and interpreted this as confirming earlier descriptions[18 19] of a disproportionate rise of angiotensin II in relation to NaE in these circumstances. While this may be so, neither angiotensin II nor NaE was measured in their study.[4] As seen here, a similar outcome could be the result of a fall in plasma angiotensin II without a change in NaE, in circumstances where the initial relation between the two measurements was normal.

It is to be expected that the addition of natriuretic treatment to captopril should be powerfully antihypertensive.[1] Sodium is lost from the body and the compensatory increases in plasma angiotensin II and aldosterone are prevented. Though failures have been reported with this combination,[1] it was consistently effective in the present series, despite several patients having been resistant to previous drugs in various combinations and in optimal dose. Contrary to earlier reports,[1] however, we did find tachycardia, especially on orthostasis, to be troublesome, and several patients developed increases in plasma creatinine, when captopril was given with a diuretic.[1] Careful clinical and biochemical surveillance is therefore necessary in these circumstances.

Although captopril is undoubtedly effective,[1 23] side effects are not negligible, and a final evaluation of its role in the treatment of hypertension remains for the future.

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