Captopril in hypertension with renal artery stenosis and in intractable hypertension; acute and chronic changes in circulating concentrations of renin, angiotensins I and II and aldosterone, and in body composition

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Summary
1. The converting-enzyme inhibitor captopril has been given in doses up to 450 mg daily to hypertensive patients with renal artery stenosis and to patients resistant to other therapy.
2. Captopril alone was effective in controlling hypertension in renal artery stenosis, irrespective of whether pretreatment plasma angiotensin II was raised or normal, except in one man with overall renal impairment.
3. In one woman with the hyponatraemic hypertensive syndrome secondary to renal artery thrombosis, captopril restored depleted exchangeable sodium and potassium to normal. In the other cases of renal artery stenosis with normal renal function, exchangeable sodium and total body potassium were not significantly altered, and there were no marked changes in plasma sodium and potassium.
4. The combination of captopril with a diuretic controlled blood pressure long-term in every case of previously resistant hypertension.
5. Within 2 h, captopril induced highly significant falls in arterial pressure, in plasma angiotensin II and aldosterone, with converse increases in plasma active and total renin and blood angiotensin I.
6. The initial fall in plasma angiotensin II was closely related to the concomitant fall in diastolic pressure.
7. The pattern of change in circulating renin, angiotensins I and II and aldosterone was maintained during long-term therapy, whether or not a diuretic was added. There was no tendency for plasma angiotensin II to increase despite sustained elevation of active renin and angiotensin I.

Key words: angiotensin, captopril, renal artery stenosis, renin.

Abbreviations: K_e, Na_e, exchangeable potassium, sodium; TBK, total body potassium.

Introduction
In the early accounts of the use of captopril (SQ 14 225), an inhibitor of the enzyme responsible for the conversion of angiotensin I into angiotensin II, there has been little attention paid to changes in circulating concentrations of angiotensins I and II during therapy (Case, Atlas, Laragh, Sealey, Sullivan & McKinstry, 1978; Cody, Tarazi, Bravo & Fouad, 1978; Gavras, Brunner, Turini, Kershaw, Tiff, Cuttelod, Gavras, Vukovich & McKinstry, 1978). The present study reports a detailed analysis of changes in circulating concentrations of active and total renin, angiotensins I and II and aldosterone, and in sodium and potassium status, during oral captopril treatment, in hypertensive subjects with renal artery stenosis and in patients unresponsive to previous therapy.

Methods
Plasma concentrations of active (normal range 10–50 μ-units/ml) and total (normal 60–200 μ-units/ml) renin (Millar, Leckie, Semple, Morton,
Sonkodi & Robertson, 1978), angiotensin II (5–35 pg/ml) (Morton, Semple, Waite, Brown, Lever & Robertson, 1976) and aldosterone (less than 18 ng/100 ml) (Fraser, Guest & Young, 1973), and blood concentrations of angiotensin I (10–90 pg/ml) (Morton et al., 1976), were measured in peripheral venous blood.

Because high concentrations of angiotensin I may accumulate in plasma (and hence in plasma extracts) during captopril administration, cross-reaction of angiotensin I with antibodies to angiotensin II may give falsely high values for plasma angiotensin II (Morton, Casals-Stenzel, Lever, Millar, Riegger & Tree, 1979). This was corrected for in the earlier studies reported here by chromatography as previously described (Morton et al., 1979). In later studies, angiotensin I concentrations were separately measured in plasma extracts, and interference with the plasma angiotensin II assay was determined from a graph constructed by adding known concentrations of angiotensin I to a plasma pool and assaying for angiotensin II; the appropriate correction was then applied.

Blood samples were taken after overnight recumbency and fasting at 09.30 and 10.00 hours, before the initial dose of captopril, and 30 min, 2 h and 6 h subsequently, the patients remaining fasting and recumbent until the 2 h sample had been taken. Patients were again recumbent for 1 h before the 6 h sample. The initial dose of oral captopril was 25 mg (ten cases) or 6.25 mg (three patients). A maximum dose of 450 mg daily was employed long-term. The values given for the various components of the renin-angiotensin-aldosterone system during prolonged therapy are, in the patients with renal artery stenosis, the means obtained in samples taken at 10.00, 12.00 and 16.00 h, 150 mg of captopril having been given at 22.00 hours on the previous evening, and again immediately after the 10.00 hours sample. In the patients with drug-resistant hypertension the values are those obtained at 10.00 hours, 12 h after the previous dose of captopril and diuretic.

Exchangeable sodium (Na\textsubscript{e}), exchangeable potassium (K\textsubscript{e}) and total body potassium (TBK) were measured by isotope dilution (Davies & Robertson, 1973; Boddy, King, Tothill & Strong, 1971); in one man, total body sodium was measured by activation analysis (Boddy, Brown, Davies, Elliot, Harvey, Haywood, Holloway, Lever, Robertson & Williams, 1978).

Blood pressures were measured with a clinical sphygmomanometer, after at least 10 min rest, phase V being taken as diastolic. Because of the wide scatter of results, statistical calculations were performed with non-parametric methods.

Patients

All patients were taking a fixed diet of known and normal sodium and potassium content. Seven patients (two males; age range 16–55 years) had renal ischaemia; five had typical radiological and ureteric catheterization findings of unilateral renal artery stenosis (Brown, Owen, Peart, Robertson & Sutton, 1960), together with appropriate lateralizing features on renal vein sampling for renin and angiotensin (Millar et al., 1978; Semple, Cumming & Millar, 1979). One patient had bilateral renal artery stenosis arteriographically, and one, 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 renal vein sampling and ureteric catheterization. No patient in this group had received any therapy except bethanidine for 4 weeks before the study.

Six further patients (three males; age range 31–62 years) had severe hypertension unresponsive to a combination of diuretic, \(\beta\)-adrenoreceptor blocker and vasodilator drugs given in optimal dosage. All were receiving this combination immediately before starting captopril.

Results

Patients with renal ischaemia

Three contrasting cases of renal artery stenosis are summarized to emphasize several diverse aspects of captopril therapy.

(i) A 52 year old woman with severe hypertension (250/135 mmHg) had a unilateral renal artery occlusion, plasma sodium of 123 mmol/l, plasma potassium 2.0 mmol/l, sodium and potassium depletion (Na\textsubscript{e} 74\%, K\textsubscript{e} 78\%, of expected normal; Davies, Schalekamp, Beevers, Brown, Briggs, Lever, Medina, Morton, Robertson & Tree, 1973), thirst and polyuria. Peripheral plasma concentrations of active renin (900 \(\mu\)units/ml), angiotensin II (615 pg/ml) and aldosterone (77 ng/100 ml) were grossly elevated. Captopril (25 mg) led to a steep fall in plasma angiotensin II to 29 pg/ml within 30 min, and arterial pressure fell to 92/62 mmHg. Subse-
quently all features of the syndrome were corrected by continued administration of the drug over 8 days; unilateral nephrectomy was then curative.

(ii) A 23 year old woman had severe hypertension (200/120 mmHg) and unilateral renal artery stenosis. Peripheral plasma concentrations of electrolytes, angiotensin II and aldosterone were normal. Captopril (25 mg) reduced plasma angiotensin II from 16 to 4 pg/ml and arterial pressure from 162/118 to 148/106 mmHg at 2 h. Continuous therapy with captopril (450 mg/day) for 8 weeks maintained arterial pressure at 120–130/80–90 mmHg. Six months after renal artery resection arterial pressure was normal on no treatment.

(iii) A 55 year old man presented with hypertension resistant to treatment with various combinations of drugs. He had a left renal artery stenosis; function of the right kidney (p-aminohippuric acid clearance 116 ml/min, creatinine clearance 30 ml/min), was also impaired. After 14 days of captopril alone (450 mg/day), blood pressure remained at 187/119 mmHg. Six days after the addition of frusemide (40 mg twice daily) this had fallen to 123/83 mmHg, and remained at 140/90 mmHg 3 months later on the same combination.

Resume of results in patients with renal artery stenosis. Mean blood pressures (±SEM) for the 2 days before treatment, and on the morning immediately before the first dose, were respectively 197/112 ± 8/6, 200/112 ± 10/6 and 187/116 ± 11/5 mmHg. Respective readings at 2 h, 6 days and 6 weeks (except in the two patients where captopril alone was discontinued earlier and the last available readings were taken) were: 157/99 ± 13/9 (P < 0.05), 157/93 ± 10/7 (P < 0.05) and 154/92 ± 7/7 mmHg (P < 0.05).

At the same intervals, plasma angiotensin II fell from 215/91/16 to 154/90 < 0.05); 115/93 ± 10/6 mmHg (P < 0.05). When either hydrochlorothiazide (50 mg twice daily) or frusemide (from 40 to 1500 mg/day) was added to captopril, arterial pressure was clearly lowered, being 153/93 ± 10/6 mmHg (P < 0.05) from 3 to 26 days later, with optimal diuretic dosage. With continued treatment for 3 months, blood pressure remained well-controlled (140/90 ± 8/2 mmHg; P < 0.05) and plasma angiotensin II suppressed (7.3 ± 2.4 pg/ml).

Plasma aldosterone did not increase with the addition of a diuretic to captopril (mean values 13.0 ± 2.6 ng/100 ml before treatment; 7.9 ± 1.4 ng/100 ml on captopril alone; 10.4 ± 1.4 ng/100 ml on combination therapy). Treatment has now continued up to 9 months in this group with no loss of control.

Resume of changes 2 h and 6 weeks after initial dose of captopril

Changes at 2 h. Fig. 1 summarizes the response at 2 h to the initial dose of captopril (25 mg in 10 patients, 6.25 mg in three). There were highly significant falls in systolic and diastolic pressures, plasma angiotensin II and plasma aldosterone, and increases in the plasma concentrations of active and total renin and blood concentration of angiotensin I. There was a highly significant correlation between the fall in plasma angiotensin II and the fall in diastolic pressure (r = 0.73; P < 0.01) and, less closely, between the fall in plasma angiotensin II and mean blood pressure (r = 0.49; P < 0.05).

Changes at 6 weeks. Seven patients have been studied after at least 6 weeks of treatment with captopril (450 mg/day); five were on captopril alone and two were also receiving diuretics. While plasma concentrations of active renin (794.3 ± 22.0 vs
FIG. 1. Blood pressure, plasma active and total renin, angiotensin II and aldosterone and blood angiotensin I (mean ± SEM) before and 2 h after the initial dose of captopril in 13 patients.

pre-captopril mean of 74.6 ± 13.8 μ-units/ml; P < 0.05), total renin (1008.0 ± 260.3 vs 153.0 ± 21.8 μ-units/ml; P < 0.05) and blood concentrations of angiotensin I (193.7 ± 37.1 vs 12.3 ± 14.2 pg/ml; P < 0.05) continued elevated, plasma angiotensin II remained suppressed (5.0 ± 0.8 vs 19.9 ± 3.6 pg/ml; P < 0.05).

Side-effects

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 others had a temporary disturbance of taste. Particularly in patients with renal impairment serum urea and creatinine tended to rise when frusemide was added, and this should therefore be monitored closely.

Discussion

In normal subjects and in hypertensive patients, peripheral plasma concentrations of angiotensin II are within a range in which small changes are capable of affecting arterial pressure (Chinn & Dusterdieck, 1972; Oelkers, Dusterdieck & Morton, 1972; Oelkers, Brown, Fraser, Lever, Morton & Robertson, 1974). The demonstration of a close correlation between the fall in plasma angiotensin II and the fall in diastolic pressure after the initial dose of captopril is consistent with, but does not establish, that this is simple cause and effect; factors other than the change in angiotensin II might be involved.

We have previously presented evidence for an enhanced long-term pressor action of angiotensin II in renal hypertension, although the mechanism has not been precisely defined (Beevers, Brown, Cuesta, Davies, Fraser, Lebel, Lever, Morton, Oelkers, Robertson, Schalekamp & Tree, 1975; Brown, Cuesta, Davies, Lever, Morton, Padfield, Robertson, Trust, Bianchi & Schalekamp, 1976; Bean, Brown, Casals-Stenzel, Fraser, Lever, Millar, Morton, Petch, Riegger, Robertson & Tree, 1979; Brown, Casals-Stenzel, Cumming, Davies, Fraser, Lever, Morton, Semple, Tree & Robertson, 1979; Swales, 1979). The evidence obtained herein does not suggest that overall sodium retention participates, because no fall in Na\textsubscript{a} was seen when blood pressure was controlled with captopril in renal artery stenosis.

The close interdependence of sodium status and angiotensin II in blood pressure maintenance is emphasized again in this study. Sodium retention was observed in the patient with renal artery stenosis resistant to captopril; pressure fell promptly when frusemide was added. In the hyponatraemic sodium-depleted woman, pressure fell steeply when captopril was given. Moreover, the combination of captopril with a natriuretic drug successfully controlled arterial pressure in every patient previously resistant to treatment.

Significant side-effects were seen, although they were not so severe as to require treatment to be stopped. In view of these adverse reactions, however, captopril should be used with caution, particularly in moderate hypertension.
References


