Hormonal changes with long-term converting-enzyme inhibition by captopril in essential hypertension

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Summary

1. Captopril was shown to be as effective as hydrochlorothiazide in lowering the blood pressure in patients with moderately severe essential hypertension.
2. With the combination of captopril and hydrochlorothiazide satisfactory control of blood pressure was maintained over 8 months.
3. Inhibition of angiotensin converting enzyme by captopril in man was associated with falls in plasma angiotensin II and urinary aldosterone and rises in angiotensin I and plasma renin.
4. No change in venous concentrations of bradykinin could be demonstrated during therapy.
5. Captopril attenuated the hyperaldosteronism and hypokalaemia associated with diuretic therapy.

Key words: aldosterone, angiotensin, bradykinin, captopril, converting-enzyme inhibition, essential hypertension, renin.

Materials and methods

Seventeen patients (nine male, eight female) with essential hypertension aged 28–68 years whose lying diastolic blood pressures were between 100 and 120 mmHg after 2 weeks of placebo therapy were studied. All were placed on a diet with 100 mmol of sodium/day. Eleven patients were treated with captopril (25–150 mg three times daily) for 4 weeks, after which hydrochlorothiazide (25–50 mg twice daily) was added (group 1). Six additional patients were treated for 4 weeks with hydrochlorothiazide, followed by therapy with hydrochlorothiazide and captopril (group 2). Patients were reviewed at weekly intervals for 4 weeks and thereafter at fortnightly intervals. At each visit lying and standing systolic and diastolic blood pressures were measured. Blood samples for hormone estimations were drawn after 15 min recumbency.

endogenous concentrations of renin (Gavras, Brunner, Turini, Kershaw, Tifft, Cuttelod, Gavras, Vukovich & McKinstry, 1978) but its effect on the peptide substrates of angiotensin converting enzyme (angiotensin I and bradykinin), as well as angiotensin II, have not been studied in man. It has also been shown in short-term studies to reduce blood pressure in patients with essential as well as renovascular hypertension (Gavras et al., 1978; Case, Atlas, Laragh, Sealey, Sullivan & McKinstry, 1978). The aim of this study was to examine the long-term effectiveness of captopril given alone or in combination with a diuretic in the treatment of essential hypertension. The effects of captopril on the renin–angiotensin–aldosterone system and circulating bradykinin concentrations have also been studied.

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Plasma renin concentration was measured by the method of Johnston, Mendelsohn & Doyle (1972) and plasma angiotensin II by the method of Boyd, Landon & Peart (1967). Blood angiotensin I and bradykinin were measured by specific radioimmunoassay after extraction of blood with ethanol by the method of Mashford & Roberts (1972). Urinary aldosterone was measured by radioimmunoassay ( Diagnostic Products). All values are expressed as the mean ± 1 SEM and the differences between groups were tested by the paired and unpaired Student’s t-test. Correlation coefficients were calculated by the method of least squares.

Results

The results are depicted in Fig. 1. Treatment with captopril for 4 weeks progressively lowered systolic and diastolic blood pressure from 186 ± 7/117 ± 2 mmHg to 164 ± 7/105 ± 3 mmHg (group 1). In the six patients treated with hydrochlorothiazide there was a more prompt fall in blood pressure, but the pressures recorded after 4 weeks of therapy were very similar to those of group 1. Captopril and hydrochlorothiazide had additive effects on blood pressure and similar pressures were achieved in both groups after 8 weeks (group 1, 143 ± 6/91 ± 4; group 2, 140 ± 7/87 ± 5 mmHg).

Blood angiotensin I concentrations were not significantly altered by either captopril or hydrochlorothiazide, but the combination of both drugs led to a significant and sustained elevation of blood angiotensin I from control values of 29 ± 6 pg/ml to 49 ± 11 pg/ml after 8 weeks’ therapy (paired t-test, t = 2.92, P < 0.005, v = 16). Plasma angiotensin II increased from 10 ± 4 pg/ml to 30 ± 14 pg/ml when hydrochlorothiazide was given. This was associated with a rise in urinary aldosterone excretion and a marked fall in plasma potassium (Fig. 1). The addition of captopril resulted in a fall in plasma angiotensin II to 6.1 ± 1.4 pg/ml and a reversal of both the hyperaldosteronism and the hypokalaemia. Captopril administered alone produced significant falls in plasma angiotensin II from 16 ± 3 pg/ml to 5 ± 1 pg/ml (t = 4.25, P < 0.0025, v = 10). It also reduced aldosterone secretion and minimized the fall in plasma potassium concentration when hydrochlorothiazide therapy was added.

Plasma renin increased from 0.97 ± 0.12 ng of ANG I h⁻¹ ml⁻¹ on placebo treatment to com-

![Fig. 1. Effects of captopril (left panels) and hydrochlorothiazide (right panels) given alone and in combination, on blood pressure, hormone and electrolyte concentrations in essential hypertension. P, Placebo; HCTZ, hydrochlorothiazide; PRC, plasma renin concentration.](image-url)
Hormonal changes with captopril

The rise in renin was accentuated when both drugs were given together and was sustained throughout the period of observation (3.86 ± 0.74 ng of ANG I h⁻¹ ml⁻¹ after 8 weeks on combined therapy: t = 3.515, P < 0.002, v = 16).

Blood bradykinin concentrations on placebo therapy were very similar in the two groups. The values did not change during either captopril or diuretic therapy and remained the same after 8 weeks' combined therapy. Mean values were 0.99 ± 0.09 ng/ml on placebo and 0.96 ± 0.06 ng/ml after 8 weeks' combined therapy.

No correlation was found between the initial plasma renin activities and the hypotensive response to captopril. However, the fall in blood pressure was significantly related to both the rise in plasma renin (r = 0.86, P < 0.001, v = 18) and also the fall in plasma angiotensin II on captopril (r = 0.41, P < 0.01, v = 44).

The 17 patients have now been treated for a mean period of 8.4 ± 0.3 months with combined therapy. Satisfactory control of blood pressure has been maintained (142 ± 4/87 ± 2 mmHg) as well as significant inhibition of the circulating renin–angiotensin system, with the plasma angiotensin II remaining low (4 ± 3 pg/ml) and the plasma renin and blood angiotensin I remaining elevated (4.39 ± 0.85 ng of ANG I h⁻¹ ml⁻¹ and 78 ± 12 pg/ml respectively). Blood bradykinin concentrations remained unchanged (0.94 ng/ml).

Discussion

Captopril produced falls in blood pressure which were similar to those during hydrochlorothiazide treatment in 17 patients with moderately severe essential hypertension. The combination of captopril and the diuretic was well tolerated and proved to have additive hypotensive effects. Very satisfactory control of blood pressure was achieved in all patients on this combined therapy.

Changes in plasma values for renin, angiotensin II and urinary aldosterone excretion during captopril therapy are evidence of angiotensin converting-enzyme inhibition in vitro in man within the therapeutic dose range. Although angiotensin I concentrations did not rise with captopril alone, they did increase significantly during combined therapy.

The secondary hyperaldosteronism induced by diuretic therapy was significantly attenuated by captopril. An important advantage, clinically, of the combination is that it may obviate the need for potassium supplementation during diuretic therapy.

No change in blood bradykinin concentrations could be demonstrated after captopril. This suggests that the hypotensive effect of captopril is not contributed to by increased amounts of circulating bradykinin. It does not, however, exclude effects on bradykinin metabolism at a local level. There are a number of possibilities which may explain the lack of effect on bradykinin degradation as compared with angiotensin I conversion. Bradykinin has a higher affinity for converting enzyme than has angiotensin I (Dorer, Kahn, Lentz, Levine & Skeggs, 1974). Thus in situations of incomplete competitive inhibition of converting enzyme, bradykinin would be expected to be the preferential substrate. Bradykinin production rates may also fall proportionally during the inhibition. Furthermore, angiotensin converting enzyme is only one of several pathways for the metabolism and clearance of bradykinin (Erdős & Yang, 1970).

Plasma renin values were markedly elevated on captopril and combined therapy. This may have resulted from the removal of the negative feedback of angiotensin II on renal renin release (Vander & Geelhoed, 1965). Alternatively, the rise in plasma renin may have resulted from stimulation of the baroreceptor mechanisms of renin release as a consequence of the fall in arterial pressure (Skinner, McCubbin & Page, 1964; Rocchini & Barger, 1979). The close correlation between the changes in plasma renin and blood pressure and the direct relationship between the fall in angiotensin II and blood pressure suggest that the hypotensive response was related to inhibition of angiotensin converting enzyme. However, in normal sodium-replete man, captopril does not cause any change in blood pressure despite comparable falls in plasma angiotensin II and rises in plasma renin (Millar & Johnston, 1979).

The mechanism of the hypotensive action of captopril cannot be elucidated from these studies. However, the drug does inhibit converting enzyme in vivo for long periods and also lowers the blood pressure in patients with essential hypertension. It is possible that the hypotensive effect is mediated by changes in local concentrations of bradykinin and angiotensin in the kidneys or blood vessels.

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References


