Captopril affects blood pressure equally in renovascular and essential hypertension and in the fluid-depleted anephric state


Department of Internal Medicine I, Erasmus University, Rotterdam, The Netherlands

Summary

1. The haemodynamic effects of 100 mg of captopril in renovascular hypertension (n = 11), essential hypertension (n = 12) and the anephric state (n = 7) were compared. Brachial artery pressure was measured in all patients, and changes in right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure and cardiac output were followed in renovascular and essential hypertension. Nephrectomized patients were studied before and after fluid withdrawal by ultrafiltration.

2. The pretreatment concentration of active renin in plasma was 100 ± 24 μ-units/ml (mean ± SEM) in renovascular hypertension, and 24 ± 4 μ-units/ml in essential hypertension. In nephrectomized patients pretreatment renin was 1.7 ± 0.3 μ-units/ml, and renin was unresponsive to withdrawal of 1.8 ± 0.21 of body fluid.

3. The effects of captopril were maximal after 60–90 min. Mean arterial pressure after 90 min was lowered by 19 ± 4% in renovascular hypertension, by 17 ± 4% in essential hypertension and by 16 ± 3% in fluid-depleted nephrectomized patients. These changes were not significantly different despite the marked differences in renin. Captopril had no effect on arterial pressure in the fluid-replete anephric state.

4. The effects of captopril on cardiac filling pressures and cardiac output in renovascular and essential hypertension were also not different.

5. It is concluded that the antihypertensive action of captopril may be largely independent of circulating renin.

Key words: anephric state, captopril, essential hypertension, haemodynamics, renin, renovascular hypertension.

Introduction

The orally active angiotensin-converting enzyme inhibitor, captopril (SQ 14 225), has now proved to be an effective antihypertensive agent. The drug is thought to act mainly or at least partly through interference with the conversion of angiotensin I into angiotensin II (Case, Atlas, Laragh, Sealey, Sullivan & McKinstry, 1978; Atkinson & Robertson, 1979). It might therefore be expected that captopril would be especially effective in hypertensive patients with high levels of circulating renin.

Several reports, however, suggest that captopril is also effective when plasma renin or angiotensin II are normal or low (Gavras, Brunner, Turini, Kershaw, Tiff, Cuttelod, Gavras, Vukovich & McKinstry, 1978; Atkinson, Brown, Fraser, Leckie, Lever, Morton & Robertson, 1979b; Bravo & Tarazi, 1979; Brunner, Gavras, Waebler, Kershaw, Turini, Vukovich, McKinstry & Gavras, 1979; Johnston, Millar, McGrath & Matthews, 1979; McGregor, Markandu, Roulston & Jones, 1979). Atkinson et al. (1979b), while demonstrating a close correlation between the fall in plasma angiotensin II and the fall in blood pressure after the initial dose of captopril, emphasized that this does not establish cause and effect; factors other than the change in angiotensin II might be involved. In an effort to assess the importance of plasma renin as a determinant of the cardiovascular responses to captopril, we have compared the short-term haemodynamic effects of this drug in renovascular hypertension, essential hypertension and the anephric state.

Patients and methods

Eleven patients (mean age 47 ± SEM 5 years) with renovascular hypertension, who showed angiographic evidence of unilateral renal artery
stenosis, 12 patients (age 50 ± 3 years) with essential hypertension, and seven normotensive subjects (38 ± 4 years) who had undergone bilateral nephrectomy, agreed to participate in the study.

The pretreatment concentration of active renin in plasma was 100 ± 24 μ-units/ml (range 21–290 μ-units/ml) in renovascular hypertension, 24 ± 4 μ-units/ml (range 4–68 μ-units/ml) in essential hypertension and 1.7 ± 0.3 μ-units/ml (range 0.0–3.4 μ-units/ml) in nephrectomized patients. The normal range is 15–35 μ-units/ml (Derkx, Wenting, Man in ‘t Veld, Verhoeven & Schalekamp, 1978).

The patients with renovascular and essential hypertension had a diet containing 100 mmol of sodium/day, and were on placebo for 3 weeks before captopril was given. Studies were performed in the recumbent patient. A catheter was introduced into the brachial artery for measuring arterial pressure and for blood sampling. A Swan–Ganz flow-directed triple-lumen catheter was introduced via an antecubital vein for recording right atrial pressure, pulmonary artery pressure and pulmonary capillary wedge pressure, and for measuring cardiac output by thermodilution. All patients received a 100 mg tablet of captopril.

The nephrectomized subjects underwent dialysis three times a week on a Rhodial-75 single-patient unit with a RP-6 disposable polyacrylonitril membrane kidney. The recirculating dialysate contained 140 mmol of sodium/l. Captopril (100 mg) or placebo was given in a randomized crossover study on two occasions: (1) after fluid withdrawal by ultrafiltration (weight loss 1.8 ± 0.2 kg), 1 h after the patients were disconnected from the kidney, and (2) 2 days after haemodialysis when the patients were fluid-replete. The concentration of active renin in plasma was unresponsive to fluid withdrawal. Blood pressure in these subjects was measured by the London School of Hygiene sphygmomanometer (Rose, Holland & Crowley, 1964), and mean arterial pressure was calculated according to the formula: mean arterial pressure = diastolic pressure + 0.33 × pulse pressure.

The effects of captopril were maximal after 60–90 min. Data before and 90 min after captopril were analysed by paired t-test statistics.

**Results**

**Arterial pressure.** Mean arterial pressure fell from 141 ± 6 to 114 ± 6 mmHg in renovascular hypertension, from 136 ± 6 to 114 ± 7 mmHg in essential hypertension and from 90 ± 7 to 75 ± 6 mmHg in the fluid-depleted nephrectomized patients. These changes were significant (P < 0.001). Placebo in the fluid-depleted anephric state, and captopril in the fluid-replete anephric state, had no effect on arterial pressure.

**Heart rate and cardiac index.** In all groups of patients heart rate did not change significantly. Cardiac index in renovascular hypertension was 3.5 ± 0.1 l/min before captopril and 3.4 ± 0.2 l/min after the drug. The difference was not statistically significant. Cardiac index in essential hypertension was 2.9 ± 0.1 l/min both before and after captopril.

**Cardiac filling pressures and pulmonary artery pressure.** Right atrial pressure fell from 2.6 ± 0.9 to 1.6 ± 0.9 mmHg (P < 0.05) in renovascular hypertension, and from 0.7 ± 0.8 to −0.8 ± 0.9 mmHg (P < 0.01) in essential hypertension. Pulmonary artery pressure decreased from 16 ± 2 to 13 ± 2 mmHg in renovascular hypertension (P < 0.01), and from 12 ± 1 to 10 ± 1 mmHg (P < 0.01) in essential hypertension.
Renin and the response to captopril

Pulmonary capillary wedge pressure fell from 7.5 ± 1.1 to 5.2 ± 1.2 mmHg (P < 0.005) in renovascular hypertension and from 4.4 ± 0.9 to 1.0 ± 1.0 mmHg (P < 0.001) in essential hypertension.

Plasma renin. Active renin in plasma rose both in renovascular and essential hypertension, to 890 ± 110 and 116 ± 24 μ-units/ml respectively. Renin did not change after captopril in the nephrectomized patients.

In Fig. 1 the percentage changes in mean arterial pressure 90 min after captopril as well as the pretreatment plasma levels of active renin are compared in the three groups of patients. It is clear that the effect of captopril on blood pressure was unrelated to pretreatment renin values.

Discussion

In the light of our present knowledge on captopril's mode of action, one would expect its effect on blood pressure to be proportional to the pretreatment level of plasma renin. Such a correlation has indeed been found by some authors (Case et al., 1978; Brunner et al., 1979; McGregor et al., 1979) but not by others (Gavras et al., 1978; Bravo et al., 1979; Johnston et al., 1979). The correlation, if it was found, was rather weak or depended on inclusion of data obtained in patients with high plasma renin on low sodium diet or diuretics. In the present study the antihypertensive effect of captopril was similar in renovascular and essential hypertension despite the marked difference in pretreatment plasma renin.

Our haemodynamic studies confirm that captopril acts as a combined arterial and venous dilator (Cody, Tarazi, Bravo & Fouad, 1978; Tarazi, Fouad, Ceimo & Bravo, 1979; Turini, Brunner, Gribic, Waerber & Gavras, 1979), which in contrast to other vasodilators, does not lead to reflex tachycardia. Again, the effects of captopril on systemic and pulmonary haemodynamics were not different in our groups with renovascular and essential hypertension despite the difference in renin.

Diuretic treatment is known to enhance captopril's antihypertensive effect (Case et al., 1978; Brunner et al., 1979; Johnston et al., 1979), and in severe sodium depletion serious hypertensive responses have been observed (Case et al., 1978; Atkinson, Brown, Davies, Fraser, Leckie, Lever, Morton & Robertson, 1979a). This is often used as an argument in favour of the concept that captopril acts through inhibition of renin-mediated angiotensin II formation, because plasma renin is markedly increased by sodium and fluid depletion. It is, however, by no means certain that the increase in renin is the cause of the augmented blood pressure response to captopril. Actually, we found that captopril was capable of lowering blood pressure in anephric subjects only when they were fluid-depleted, whereas plasma renin after fluid depletion was as low as in the fluid-replete state. Blood pressure in the fluid-depleted anephric subjects was lowered by 16% 90 min after captopril, and this is comparable with the effects we observed in renovascular and essential hypertension (Fig. 1).

These findings suggest that the antihypertensive action of captopril is largely independent of circulating renin.

Acknowledgment

This work was supported by a grant from the Dutch Kidney Foundation (Nierstichting Nederland).

References


Atkinson, A.B., Brown, J.J., Fraser, R., Leckie, B., Lever, A.F., Morton, J.J. & Robertson, J.J.S. (1979b) Captopril in hypertension with renal artery stenosis and in intractable hypertension; acute and chronic changes in circulating concentrations of renin, angiotensin I and II and aldosterone, and in body composition. Clinical Science, 57 (Suppl. 5), 139s-143s.


