TREATMENT OF MODERATE TO SEVERE HYPERTENSIVE PATIENTS WITH AN ORALLY ACTIVE CONVERTING-ENZYME INHIBITOR

E J L Prins, A J M Donker, S J Hoortje, F H H Leenen, G K van der Hem

State University Hospital, Groningen, The Netherlands

Summary

Seventeen hypertensive patients were treated with captopril, an orally active inhibitor of converting-enzyme. All patients showed a fall in blood pressure (BP), although in some patients only after the addition of diuretics. In 2 patients a skin rash developed. One patient developed proteinuria. A renal biopsy revealed membranous glomerulopathy.

Correlations were found between pretreatment plasma renin activity (PRA) and the decrease in BP, and between pretreatment PRA and the decrease in plasma aldosterone concentration (PAC). Filtration fraction (FF) fell, indicating a decrease in renal vascular resistance.

Captopril decreased the sensitivity to exogenous angiotensin I (AI), dependent on the captopril dose used. The sensitivity to exogenous bradykinin increased impressively even on the lowest dose of the drug. These observations suggest extrapulmonary conversion of AI to angiotensin II (AII).

Introduction

Converting-enzyme inhibition (CEI) with D-3-mercapto-2-methylpropanoyl-L-proline (SQ 14, 225; captopril), which is orally active, has been shown to be effective in the treatment of moderate and malignant hypertension [1]. Its hypotensive action is potentiated by sodium restriction and by diuretics [2,3]. As yet it is not clear if the effect of the drug is solely due to decreased levels of AII. The effect may be partially mediated through potentiation of kinins [4]. Furthermore, little is known about the influence of captopril on renal function in man. The purpose of this study was to investigate in hypertensive man the influence of CEI on the effects of exogenously administered AI, AII and bradykinin (BK) and secondly, on glomerular filtration rate (GFR), effective renal plasma flow (ERPF) and FF.
Patients and Methods

Seventeen patients, aged 18–55 years, with mild to severe hypertension participated in the study. Ten patients with mild hypertension were seen in the outpatient clinic. After an initial 8 weeks single blind placebo period with supine diastolic blood pressure (SDBP) varying from 100 to 120mmHg, captopril was titrated during a 4-week period up to a maximal dose of 150mg three times daily according to the BP response. A diuretic was added if the SDBP persisted above 90mmHg.

Seven patients with previously drug-resistant severe hypertension were hospitalised. All previous anti-hypertensive agents were withdrawn for at least 36hr before captopril was initiated. At the maximal dose of captopril, diuretics were added in the non-responders.

Supine BP readings were made with the London School of Hygiene sphygmanometer or with an automatic recorder (type Godart Statham IA). PRA was measured by a radioimmunoassay for AI [5], and plasma aldosterone concentration (PAC) according to a method previously described [6]. Blood samples were drawn after at least 30min recumbency.

Dose-response curves were obtained for exogenously administered AI, AII and bradykinin in the control period without anti-hypertensive treatment, and at each captopril dose (25, 50, 100 and 150mg three times daily, respectively). Sensitivities were defined as the amount of AI, AII or BK necessary to cause a 20mmHg increase in BP with AI and AII or a 10mmHg decrease with BK. The start of the first curve (AI) was approximately 1½hr after the last dose of captopril. Blood pressure had to return to stable levels before the second curve (AII) was started. The third curve (BK) was performed likewise, the whole procedure being completed in 1½ to 2hr. GFR and ERPF were determined in 14 patients, using $^{125}$I iothalamate and $^{131}$I hippuran [7], before captopril was started and at the maximal dose of captopril.

Results

The average mean arterial pressure (MAP) for all patients on single drug therapy decreased from 130mmHg before captopril was initiated, to 114mmHg at the maximal daily dose (Figure 1). Addition of a diuretic was required in 4 patients for adequate BP control.

An increase in PRA during captopril treatment was found in 15 patients. The 2 patients who showed no rise in PRA were amongst the ones with the lowest initial PRA. PAC fell in 13 patients. A moderate rise was noticed in 4, including the 2 patients with low initial PRA in whom no adequate BP control was obtained on captopril alone.

The decrease in MAP ($\Delta$MAP) during CEI for all patients was positively correlated with log PRA ($r = 0.76; p<0.001$). Log PRA also correlated with $\Delta$MAP in the 10 sodium unrestricted patients ($r = 0.63; p<0.05$). The change in PAC was found to be correlated with the initial PRA ($r = -0.66; p<0.01$).

GFR before and during CEI showed minor changes in 10 patients. In 5 out of 6 patients with renovascular hypertension however, a decline in GFR could
Figure 1. The effect of captopril (C) on mean arterial pressure (MAP) in 17 hypertensive patients. In 4 patients an additional diuretic (D) was necessary. The dotted lines represent the changes in blood pressure in patients with a low initial PRA, not increasing after converting-enzyme inhibition alone.

Figure 2. The influence of captopril (C) on GFR, ERPF and filtration fraction in 14 hypertensive patients. The dotted lines represent the changes in GFR, ERPF and FF in 6 patients with renovascular hypertension.
Figure 3. The mean sensitivities (± SEM) to exogenously administered angiotensin I (AI), angiotensin II (AII) and bradykinin on different dosages of captopril (C). In panel B these sensitivities are plotted on a logarithmic scale.
be observed (Figure 2). Ten patients showed an increase in ERPF. A moderate decrease could be demonstrated in only one patient. In 12 patients a fall in filtration fraction was observed, most dramatically in the patients with renovascular hypertension.

During increasing dosages of captopril, the sensitivity to exogenous AI diminished gradually, whereas the sensitivity to AII showed a gradual increase. The sensitivity to BK, however, showed a sharp increase at the lowest dosage of captopril and only a moderate increase during further enhancement of CEI (Figure 3).

Captopril was well tolerated, except in 3 patients. Two patients developed a transient rash, 1 hr and 8 days, respectively, after therapy was initiated (total daily dose: 75 and 300 mg, respectively). The rash was accompanied by fever and myalgia in the second patient. In this patient captopril in lower dosage was tolerated well, with good BP control. The third patient developed proteinuria after 6 months (protein excretion 5 g/24 hr). Proteinuria was known not to exist before captopril therapy. Drugs, other than captopril, had not been used. A renal biopsy was performed and revealed an early stage of membranous glomerulopathy with IgG, IgM, IgA and complement distributed along the capillary wall in a finely granular pattern.

Discussion

The present study extends previously published experience with captopril in hypertensive man [1–3, 8–11]. The drug is especially effective in renin-dependent hypertension. In some patients captopril may have to be combined with sodium depletion for optimal BP control [2, 10, 11].

We found a significant relationship between the initial log PRA and the decrease in BP achieved with captopril alone. A similar observation has been made by Case et al. [2]. Furthermore, a significant relationship was established between the initial PRA and the response of PAC to captopril. Captopril alone increased PRA in all but 2 patients. These patients had an extremely low initial PRA and showed a decrease in BP to normal values only after addition of diuretics to the therapeutic regimen.

The effects of captopril on glomerular filtration were different in patients with essential hypertension and in patients with renovascular hypertension, respectively. In both groups FF fell, suggesting a decrease in renal vascular resistance. A decrease in filtration fraction during treatment with converting enzyme inhibitors has also been noticed by Hall et al in dogs [12]. The decrease in renal vascular resistance during treatment with captopril cannot be attributed solely to a decrease in AII concentration, as it was also noticed in the patients with ‘low renin hypertension’, and even in the non-responders who showed no increase in PRA after captopril alone. Therefore, potentiation of kinins at the renal level may be involved in the observed fall in vascular resistance [13]. Since in primary hyperaldosteronism no decrease in BP could be demonstrated during CEI [14], it seems unlikely that inhibition of BK degradation plays an important role in the antihypertensive effect of the drug. In accordance with the latter supposition is the observation of Hultén and Hökfelt [15] who found a (minor) decrease
in arterial kinin concentration following intravenous administration of the converting-enzyme inhibitor SQ 20, 881.

Interestingly, captopril blocked the pressor response to exogenously administered AI to a lesser degree than the BP-decreasing response to exogenously administered bradykinin. As the affinity of pulmonary converting-enzyme (= kininase II) for bradykinin is higher than for AI [16,17], our observation suggests extrapulmonary conversion of AI to AII which seems moreover, more resistant to blockade by SQ 14, 225. Extrapulmonary generation of AII has also been demonstrated by Oparil et al in dogs, using the nonapeptide SQ 20, 881 [18]. Their results suggest generation of AII in the systemic vascular bed without the release of the peptide into the circulation. The systemic vascular bed furthermore contains large amounts of a bradykinin converting-enzyme (kininase I) which is also more resistant to SQ 14, 225 than pulmonary kininase II [19].

Skin rashes with or without fever have been described before [1,2] and appeared to be of minor importance since they are transient and dose-dependent. The observed membranous glomerulopathy in one of our patients, however, makes careful monitoring of patients on this new drug essential.

Acknowledgments

This study was supported by a grant (C 97 V) of the Dutch Kidney Foundation (Nierstichting Nederland). We wish to express our gratitude to Miss AK van Zanten and Miss GE von Dülmen Krumpelmann (renal function studies and PRA determinations), Dr JJ Pratt (Plasma aldosterone determinations) and Miss V van der Heide (secretarial assistance).

References

8 Bravo, EL and Tarazi, RC (1977) Kidney Int., 12, 497
10 Bravo, EL and Tarazi, RC (1979) Hypertension, 1, 39

608
18 Oparil, S, Koerner, T and O’Donohue, JK (1979) Hypertension 1, 13