Long-term treatment of hypertension in man by an orally
active angiotensin-converting enzyme inhibitor

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Summary

1. Captopril or SQ 14 225, administered orally
twice a day, reduced the blood pressure of hyper-
tensive patients whatever their clinical diagnosis
and even when their plasma renin activity was
'normal' or low.

2. Long-term administration of captopril, either
alone or together with diuretics, provides a power-
ful new tool with which to treat ambulatory hyper-
tensive patients.

3. The renin system may play an important role
in maintaining blood pressure in a majority of
hypertensive patients.

Key words: captopril, hypertension.

Introduction

Whether the renin-angiotensin system participates
actively in maintaining clinical hypertension has
been debated for many years. Accurate measure-
ments of the activity of the renin system, specific
antibodies against angiotensin II and polypeptide
inhibitors of the system (Pals, Masucci, Sipos &
Denning, 1971; Ondetti, Williams, Sabo, Plusec,
Weaver & Kocy, 1971) have been the tools used in
an attempt to elucidate the problem. Although
much new insight has been gained, understanding
of the pathophysiology of hypertensive diseases is
still incomplete. The antihypertensive efficacy of a
new, orally active inhibitor of angiotensin-
converting enzyme, SQ 14 225 or captopril
(Ferguson, Turini, Brunner, Gavras & McKinstry,
1977) suggests that renin may play a key role
(Gavras, Brunner, Turini, Kershaw, Tifft, Cuttelod,

Methods

Twenty-six hypertensive patients, 19 males and 7
females, aged 23 to 65 were included in this study
which was performed simultaneously in the
Departments of Medicine of Lausanne and Boston
University. Diagnostic work-up, in addition to
physical examination and routine laboratory
measurements, included intravenous pyelography
and determinations of plasma renin and converting-
enzyme activity, plasma aldosterone and 24 h
urinary excretion of aldosterone. When appropri-
ate, renal arteriography and/or renal biopsy were
also carried out. All patients were fully informed of
the experimental nature and the potential risks of
this new treatment.

Antihypertensive medication was discontinued
whenever possible 3 weeks before the study and
exceptionally, in cases with severe hypertension, 1
week before administration of captopril. All
patients were hospitalized and maintained on a
constant diet containing 100 mmol of Na and
60–80 mmol of K per day. After an initial placebo
period lasting 3 days, captopril was started and,
after discharge from hospital, this treatment was
continued at 200 mg b.i.d. orally in 22 patients,
who have so far been followed for up to 10 months.

Study procedures, analytical methods and nor-
mal ranges for our laboratories have been
described in detail (Gavras et al., 1978).

Results

Among the 26 patients, nine had essential, eight
renovascular and seven hypertension associated
with chronic renal failure. Plasma creatinine levels
of the latter varied between 1.5 and 7.4 mg/dl (3.5
± 0.8 mg/100 ml, mean ± se). The two remaining
patients were receiving chronic haemodialysis.
Baseline renin levels of the 26 patients were found to be high in eight, 'normal' in 13 and low in five.

Within 4–6 days of SQ 14 225 therapy, blood pressure of the 26 patients decreased from 178/111 ± 5/2 to 146/93 ± 5/2 mmHg ($P < 0.001$). Pulse rate did not change. Blood pressure fell to normal in patients with high plasma renin activity, from 181/113 ± 7/2 to 134/87 ± 5/3 mmHg ($P < 0.001$) but in those with normal renin levels blood pressure also fell from 179/112 ± 9/4 to 151/97 ± 7/3 mmHg ($P < 0.001$). Most surprisingly, however, even patients with low plasma renin exhibited a blood pressure reduction from 171/104 ± 12/3 to 152/97 ± 15/4 mmHg which was even significant ($P < 0.05$) when expressed as change in mean blood pressure. There was a significant correlation between pretreatment plasma renin activity and the captopril-induced blood pressure reduction ($r = 0.58$, $n = 22$, $P < 0.01$).

Plasma angiotensin-converting enzyme activity was markedly reduced by captopril from 76 ± 6 to 14 ± 3 nmol min$^{-1}$ ml$^{-1}$ ($P < 0.001$). Simultaneously plasma renin activity increased from 7.4 ± 2 to 28 ± 5 ng h$^{-1}$ ml$^{-1}$ ($P < 0.001$) whereas plasma aldosterone fell from 18.4 ± 3 to 8 ± 1 ng/100 ml ($P < 0.001$).

In order to normalize blood pressure of all patients treated with captopril, a diuretic had to be added in 10. Thus, spironolactone or chlorthalidone (50–100 mg/day) was given to five patients with essential hypertension and frusemide (40–250 mg/day) to five patients with chronic renal failure.

The duration of the follow-up of the 26 patients varied considerably. Therefore, only the results of 12 patients who received captopril for at least 5 months are presented (Fig. 1). Blood pressure of these 12 patients fell from 176/110 ± 7/4 to 144/91 ± 7/3 mmHg within 4 to 6 days. After discharge, 5 of the patients required additional diuretic therapy to normalize their blood pressure which at the end of 5 months still remained at 133/89 ± 6/2 mmHg.

Captopril was well tolerated by all 26 patients, although two developed a rash.

**Discussion**

Angiotensin-converting enzyme inhibition by long-term oral administration of SQ 14 225 or captopril reduced blood pressure of all hypertensive patients included in the study, whatever their clinical diagnosis. To normalize blood pressure, 5 patients with essential and 5 with renal hypertension needed additional diuretics. Therapy was generally well tolerated. Further, at least when associated with diuretics, captopril seemed more effective in lowering blood pressure than $\beta$-adrenoreceptor-blocking agents (H. R. Brunner, H. Gavras, B. Waeber, G. A. Turini, D. N. McKinstry, R. A. Vukovich & I. Gavras, unpublished work). Accordingly, captopril appears to provide a powerful new tool with which to treat clinical hypertension.

This efficacy of captopril suggests an important role for the renin system in blood pressure maintenance in hypertensive patients. However, the observation that captopril lowered blood pressure even in the presence of 'normal' or low renin levels does not exclude another hypotensive, renin-independent mechanism of the drug. Converting enzyme being identical with kininase II (Erdős, 1975), bradykinin accumulation has been proposed as an alternative mode of action of captopril (Williams & Hollenberg, 1977). However, there exists so far no definite evidence of a bradykinin-mediated hypotensive effect of SQ 14 225. On the other hand it is conceivable that even low renin levels can contribute to blood pressure maintenance via an increase in arteriolar receptor sensitivity to angiotensin II (Brunner, Chang, Wallach, Sealey & Laragh, 1972).

Blocking the generation of angiotensin II not only reduces the direct effect of the renin–angiotensin system on arteriolar smooth muscle but also its trophic action on aldosterone secretion. Reduced aldosterone levels probably provide the basis for a unique feature of captopril: unlike any other antihypertensive drug with the exception of diuretics, SQ 14 225 tends to increase urinary sodium excretion despite the simultaneous marked
blood pressure drop (H. R. Brunner, H. Gavras, B. Waeb, G. R. Kershaw, G. A. Turini, R. A. Vukovich, D. N. McKinstry & I. Gavras, unpublished work). This may not only explain why captopril alone is so effective in lowering blood pressure, but also why patients treated with captopril might respond better to diuretics, their natriuretic effect being unopposed by the action of a compensatory rise in aldosterone levels (H. R. Brunner, B. Waeb, J. P. Wauters, G. A. Turini, D. N. McKinstry & H. Gavras, unpublished work). Simultaneously, more complete blockade of the compensatory increase in angiotensin II levels in response to diuretic therapy may also account for the greater efficacy of captopril in lowering blood pressure as compared with β-adrenoreceptor-blocking agents.

Taken together, clinical experience gained so far suggests that captopril is a new powerful agent which lowers blood pressure in patients with most forms of hypertension whatever their baseline renin levels. Therapy is well tolerated with neither orthostatic hypotension nor tachycardia. Moreover, the present study suggests that the renin–angiotensin system may play a role in the maintenance of hypertension which is much more important than has previously been recognized.

References


