The effect of oral prazosin on blood pressure and plasma concentrations of renin and angiotensin II in man

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Summary
1. We studied the effect of oral prazosin on blood pressure, plasma active renin and angiotensin II in 16 recumbent hypertensive patients between 09.00 and 12.00 hours.
2. In untreated patients there were no significant changes in blood pressure, plasma active renin or angiotensin II during the 3 h period.
3. After an initial dose of prazosin (2 mg) there was a significant fall in recumbent blood pressure with progressive increases in plasma active renin and angiotensin II concentrations.
4. After 3-4 weeks' treatment with oral prazosin only, recumbent blood pressure at 09.00 hours, 15 h after the last dose of prazosin, was significantly lower than before treatment, but plasma active renin and angiotensin II were not significantly different from untreated values.
5. After the usual morning dose of prazosin, blood pressure did not change, but there were significant rises in plasma active renin and angiotensin II, less marked than after the first dose of prazosin.
6. Prazosin therefore stimulates the renin-angiotensin system acutely, both after the initial dose and during long-term therapy; however, no effect on renin and angiotensin II is apparent 15 h after the last dose of prazosin.

Key words: angiotensin II, prazosin, renin.

Introduction
A drug which could control blood pressure without altering plasma renin would be of considerable use in facilitating the evaluation of hypertensive patients. Prazosin is a postsynaptic α-adrenoceptor blocker which has been reported variously not to influence plasma renin [1, 2] or to cause a decrease [3-6]. However, a recent study showed that oral prazosin increased plasma renin activity in upright but not in recumbent normal volunteers [7]. No definite conclusions can be drawn from these latter results because upright posture itself stimulates renin release [8, 9].

The present study was undertaken to investigate whether prazosin affects plasma renin in recumbency.

Methods

Patients
Sixteen untreated hypertensive patients aged 29–58 years (mean 43·2 years) were studied. All had normal serum sodium and potassium, and normal plasma active renin, angiotensin II and aldosterone concentrations. Renal function and excretion urography were normal in 15; the remaining patient had renal impairment (serum urea 13·5 mmol/l, creatinine 266 μmol/l) and his renal arteriogram showed unilateral branch renal artery stenosis.

Protocol
During each part of the experiment patients took a diet with a fixed known and normal content of sodium and potassium, the same on each occasion for each patient. Patients were weighed on the day before each study. All studies began at 08.45 hours after overnight recumbency and fasting, both of which were maintained until the experiment ended at 12.00 hours.

At 08.45, 09.00 and at hourly intervals thereafter to 12.00 hours, blood pressure was
recorded with a mercury sphygmomanometer, and blood was withdrawn for measurement of serum urea and electrolytes, packed cell volume, plasma active renin [10] (normal range 10–50 μ-units/l), angiotensin II [11] (normal range 5–35 pmol/l) and prazosin [11a].

The procedure was carried out on three separate occasions:

**Part I. Untreated patients.**

**Part II.** Two days after part I, patients were given prazosin (2 mg orally) immediately after the blood sample taken at 09.00 hours.

**Part III.** Patients were re-admitted to hospital after 3–7 (mean 4.3) weeks’ treatment with prazosin alone in doses from 2 to 10 mg twice daily (mean daily dose 9.6 mg). Immediately after the blood sample at 09.00 hours and 15 h after the previous dose, the normal morning dose of prazosin was given.

**Statistical methods**

Data were analysed by repeated measures analysis of variance and by paired t-tests (with log transformation where appropriate).

**Results**

Four patients were withdrawn from the study after completing part I only because blood pressure had settled in the ward to normal levels.

A further three patients were withdrawn after part II, two because unsatisfactory blood pressure control required the addition of other drugs and one because of the development of angina.

**Part I: untreated patients**

There were no significant changes in blood pressure (mean systolic 162.4 ± SEM 9.5 mmHg at 09.00 hours, 159.8 ± 7.5 mmHg at 12.00 hours; mean diastolic 102.8 ± 4.2 mmHg at 09.00 hours, 101.0 ± 4.6 mmHg at 12.00 hours) or in plasma concentrations of active renin (mean 26.1 ± SEM 6.2 μ-units at 09.00 hours, 33.1 ± 8.3 μ-units/ml at 12.00 hours) and angiotensin II (mean 17.2 ± 5.0 pmol/l at 09.00 hours, 17.0 ± 4.5 pmol/l at 12.00 hours) (Fig 1a).

**Part II: initial effects of prazosin**

After the initial oral dose of prazosin (2 mg) there was a significant fall in mean blood pressure (systolic 158.2 ± 6.2 mmHg at 09.00 hours to 141.7 ± 6.3 mmHg at 12.00 hours, *P* < 0.001; diastolic 105.0 ± 2.4 mmHg at 09.00 hours to 85.2 ± 5.0 mmHg at 12.00 hours, *P* < 0.001) (Fig. 1b). During this time plasma active renin rose from a mean of 28.2 ± SEM 4.8 μ-units/ml to 55.6 ± 7.4 μ-units/ml (*P* < 0.001) and angiotensin II from 17.0 ± 2.7 pmol/l to 30.0 ± 5.1 pmol/l (*P* < 0.001) (Fig. 1b). Increases in

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**Fig. 1.** Changes in blood pressure and plasma active renin and angiotensin II concentrations in (a) untreated patients, (b) patients given prazosin (2 mg orally) at 09.00 hours and (c) patients given a morning dose of prazosin after 3–7 weeks’ treatment with prazosin only. Statistical comparisons are between values at 09.00 and 12.00 hours. N.S., Not significant.
Part 111: long-term effects of prazosin

Blood pressure was significantly reduced after chronic therapy with prazosin alone, although our experimental design did not exclude the so-called 'placebo effect' [21] in addition to that of prazosin. However, basal measurements of plasma active renin and angiotensin II at 09.00 hours (15 h after the previous dose of prazosin) were not different from those in untreated patients, a result which is consistent with previous reports [1, 3].

We found no change in blood pressure in the 3 h after the morning dose of prazosin, although there were again consistent, albeit less-marked increases in both plasma active renin and angiotensin II concentrations respectively of 42% and 37% within 3 h. Stimulation of renal arterial baroreceptors cannot be invoked as contributory at this stage. However, an increase in catecholamines, either within the circulation or at the juxtaglomerular presynaptic nerve endings [22], could be partly responsible. Elimination by prazosin of the inhibitory effect of α-adrenoceptors could also again contribute.

We conclude therefore that oral prazosin stimulates the renin–angiotensin system in recumbent subjects. This effect was seen consistently with independent assays of two different components, active renin and angiotensin II. Stimulation was more marked after the initial dose of prazosin, when recumbent blood pressure fell, but was also seen during long-term treatment with prazosin alone. Nevertheless, as the stimulant effect was not apparent 15 h after the last dose of prazosin, the drug may be useful in the assessment of hypertensive patients permitting an evaluation of the renin–angiotensin system. This aspect is being examined further.

Discussion

In untreated recumbent hypertensive patients the absence of change in blood pressure, active renin and angiotensin II concentrations between 09.00 and 12.00 hours is in agreement with several previous reports [12–14]. Gordon et al. [15] found a slight fall in plasma renin activity during the late morning in normal subjects on a low sodium diet.

After an initial dose of 2 mg of prazosin, blood pressure did not change significantly (mean systolic 143.0 ± 4.9 mmHg, mean diastolic 89.2 ± 3.6 mmHg at 12.00 hours). However, there were again consistent progressive increases in both plasma active renin (39.1 ± 7.8 μ-units/l) and angiotensin II (21.7 ± 3.5 pmol/l, P < 0.001) concentrations by 12.00 hours, although these changes were less marked than after the initial dose of prazosin. There were no significant changes in serum electrolytes and packed cell volume or in weight or in heart rate in any part of the study.

We found no change in blood pressure, active renin rose progressively by 97% and angiotensin II by 77% within 3 h. These results are therefore at variance with several previous reports [2, 4, 7]. The rises in renin and angiotensin II after an initial dose of prazosin probably result from several stimuli. Systolic and diastolic blood pressure fell by some 20 mmHg and such changes could directly cause release of renin from the juxtaglomerular cells [9]. Plasma noradrenaline increases in normal supine volunteers given 5 mg of prazosin orally [7]. This could also increase renin secretion [16, 17]. Thirdly, adrenergic stimulation inhibits renin secretion [18–20]; thus α-adrenoceptor blockade by prazosin might be expected to enhance renin release. Serum electrolytes may influence renin [9] but did not change during this study.

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References


Studies on the clinical pharmacology of prazosin. I: Cardiovascular catecholamine and endocrine changes following a single dose. British Journal of Clinical Pharmacology, 10, 23–32.


