Prazosin in the treatment of hypertension

M. FERNANDES, I. SANFORD SMITH, A. WEDER, K. E. KIM, ANNE B. GOULD, PATRICIA BUSBY, C. SWARTZ AND G. ONESTI

Department of Medicine of the Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania, U.S.A.

Summary

1. Prazosin decreases blood pressure in normotensive, renal hypertensive and spontaneous hypertensive rats. The effect is greatest in the last-named.
2. In spontaneously hypertensive rats the decrease in pressure is associated with a decrease in heart rate.
3. In hypertensive patients prazosin decreases blood pressure by decreasing total peripheral resistance with minor effects on cardiac output.
4. Prazosin is effective in the long-term therapy of hypertensive patients, alone and in combination with a diuretic. The effect on blood pressure is the same in the supine and standing position.

Key words: hypertension, polythiazide, prazosin, renin, spontaneously hypertensive rats.

Introduction

Prazosin, 2-[4-(2-furoyl)-piperazine-1-yl]-4-amino-6,7-dimethoxyquinazoline hydrochloride, is a peripheral vasodilator with two discernible components of action: (a) direct smooth-muscle relaxation and (b) interference with peripheral sympathetic function, distal to the alpha-adrenergic receptor site (Constantine, McShane, Scriabine & Hess, 1973).

The present report summarizes (1) the effects of prazosin on blood pressure and renin in rats, (2) the acute systemic haemodynamic effects in essential hypertension and (3) the clinical efficacy of prazosin in ambulatory hypertensive patients.

Methods and results

Effect on blood pressure, heart rate and renin in the rat

Intravenous prazosin was administered to three groups of rats: (1) normal Wistar rats, (2) rats with renal hypertension with unilateral renal artery clipping and intact contralateral kidney (Wistar) and (3) spontaneously hypertensive rats (Okamoto-Aoki). An indwelling catheter in the left carotid artery allowed direct recording of blood pressure. Peripheral plasma renin concentration was measured by the method of Gould, Skeggs & Kahn (1966). Studies were conducted in the conscious unrestrained animal.

The results are shown in Table 1. After intravenous prazosin (0.1 mg/100 g) there was a reduction in blood pressure in all groups, more marked in the SH rats. Heart rate increased significantly in the normal rats, showed only a transient increase in renal hypertension and underwent a significant decrease in SH rats. In the normal Wistar rats the decrease in blood pressure was associated with a significant increase in PPRC (430% at 30 min and 470% at 120 min). In the renal hypertensive rats there was also an increase in PPRC, but of less magnitude (79% at 30 min and 114% at 120 min). In contrast, the profound blood pressure reduction in SH rats was not associated with significant change in PPRC.

Correspondence: Dr Gaddo Onesti, Division of Nephrology and Hypertension; Department of Medicine, Hahnemann Medical College and Hospital, 230 North Broad Street, Philadelphia, Pennsylvania 19102, U.S.A.

Abbreviations: SH, spontaneously hypertensive; PPRC, peripheral plasma renin concentration.
Table 1. Acute effect of prazosin (0.1 mg/100 g body weight, intravenously) on blood pressure, heart rate and plasma renin concentration in the conscious rat

<table>
<thead>
<tr>
<th></th>
<th>Control values</th>
<th>30 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal Wistar rats (n = 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>97 ± 6</td>
<td>82 ± 5*</td>
<td>88 ± 8 N.S.</td>
</tr>
<tr>
<td>HR</td>
<td>350 ± 12</td>
<td>430 ± 11</td>
<td>400 ± 10 N.S.</td>
</tr>
<tr>
<td>PRC</td>
<td>1.0 ± 0.4</td>
<td>5.3 ± 3.0***</td>
<td>5.7 ± 3.8*</td>
</tr>
<tr>
<td>Renal hypertension (Wistar) rats (n = 9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>140 ± 7</td>
<td>80 ± 5**</td>
<td>98 ± 6**</td>
</tr>
<tr>
<td>HR</td>
<td>348 ± 12</td>
<td>368 ± 17</td>
<td>350 ± 14 N.S.</td>
</tr>
<tr>
<td>PRC</td>
<td>1.4 ± 0.6</td>
<td>2.53 ± 0.7**</td>
<td>3.0 ± 1.7**</td>
</tr>
<tr>
<td>SH rats (n = 11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>132 ± 11</td>
<td>66 ± 6***</td>
<td>98 ± 8**</td>
</tr>
<tr>
<td>HR</td>
<td>445 ± 10</td>
<td>340 ± 9**</td>
<td>410 ± 12 N.S.</td>
</tr>
<tr>
<td>PRC</td>
<td>0.7 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td>1.2 ± 0.3 N.S.</td>
</tr>
</tbody>
</table>

Acute systemic haemodynamic effects

These studies were conducted in four patients with essential hypertension. Intra-arterial pressure was recorded through an indwelling catheter in the brachial artery. Cardiac output was determined by the dye-dilution technique with Indocyanine Green. Acute administration of intravenous prazosin resulted in a decrease in blood pressure. The average mean arterial pressure decreased from 133 mmHg to 113 mmHg. Total peripheral vascular resistance decreased from 1763 to 1396 dynes s⁻¹ cm⁻⁵. Cardiac output was 6.16 l/min before prazosin and 6.48 l/min after prazosin. Average heart rate was 81 beats/min before prazosin and 88 beats/min after prazosin. These studies were conducted in the supine position. Passive head-up tilting of these patients caused no significant postural hypotension.

Prazosin versus alpha-methyldopa

A comparison of the anti-hypertensive efficacy of prazosin and alpha-methyldopa was performed in a double-blind study of fifty-three ambulatory essential hypertension patients. After from 2 to 8 weeks' administration of placebo, the patients were randomly allocated prazosin or alpha-methyldopa capsules for a further 12 weeks. All patients were seen every 2 weeks. Daily dosages of 3 mg, 6 mg, 10 mg, 15 mg and 20 mg of prazosin were compared with dosages of alpha-methyldopa of 750 mg, 1000 mg, 1500 mg and 2000 mg respectively. With each drug, the dosage was increased until a standing pressure of 140/90 mmHg was obtained or the maximum dose reached. The evaluation was conducted on mean arterial pressure, calculated as the diastolic pressure plus one-third of the pulse pressure.

In the group treated with alpha-methyldopa the average control supine mean arterial pressure was 137 ± 12.7 mmHg; at the end of the treatment it was 115 ± 17.8 mmHg (16% decrease, P < 0.0005). In the prazosin-treated group, the average control mean arterial pressure was 137 ± 16.4 mmHg; at the end of therapy it was 121 ± 20.4 mmHg (12% decrease, P < 0.0001).

When the blood pressure was measured in the standing position, the control average mean arterial pressure was 137 ± 12.7 mmHg in the alpha-methyldopa-treated group; after therapy it was 109 ± 14.7 mmHg (20% decrease, P < 0.0005). In the prazosin-treated group the average control mean arterial pressure was 137 ± 16.4 mmHg; at the end of therapy it was 120 ± 15.6 mmHg (12% decrease, P < 0.0005).

Long-term effect of prazosin alone, and in combination with polythiazide in ambulatory patients

Forty-eight ambulatory patients with essential hypertension received prazosin, 6–20 mg/day, for 4–6 months. Prazosin was given after a period of 4–10 weeks' administration of placebo. All patients
Prazosin in the treatment of hypertension

183s

returned at 2 week intervals. Dosage was increased until a standing pressure of 140/90 mmHg was attained, or maximum dose reached.

In the supine position, the average diastolic pressure at the end of the placebo period was 116±12.3 mmHg. At the end of the prazosin therapy the average diastolic pressure was 104±13.6 mmHg (10% decrease, P<0.0005).

In the standing position, the average diastolic blood pressure at the end of the placebo period was 117±11.3 mmHg. At the end of the prazosin-treatment period, the average diastolic pressure was 101±14 mmHg (11% decrease, P<0.005). Heart rate did not change significantly in the supine position. In the standing position, heart rate increased from a control value of 86±8.2 beats/min to 94±11.7 beats/min (9% increase, P<0.0005).

Twenty-eight of the eighty-eight patients, who did not achieve a standing blood pressure of 140/90 mmHg or less on maximum dosages (20 mg/day) of prazosin alone, were treated with the combination prazosin–polythiazide. Polythiazide was administered at the dosage of 1 mg twice a day. Prazosin alone was continued for 3–8 months.

In the supine position, the average diastolic blood pressure of these twenty-eight patients at the end of the placebo period was 118±13.2 mmHg. At the end of the period of therapy with prazosin alone, the average diastolic pressure was 109±11.3 mmHg (81% decrease, P<0.005). At the end of the period of combination therapy, the average diastolic pressure was 92±8.3 mmHg (22% decrease, P<0.0005). Heart rate did not change significantly during the period with prazosin alone. During the period of combination therapy, heart rate increased from a placebo control of 80±7 beats/min to 84±8 beats/min (5% increase, P<0.0005).

In the standing position, the average diastolic blood pressure at the end of the placebo period was 120±12 mmHg. At the end of the period of therapy with prazosin alone the diastolic pressure was 106±11.3 mmHg (11% decrease, P<0.005). At the end of the period of combination therapy the average diastolic pressure was 91±8.2 mmHg (24% decrease, P<0.0005). Heart rate did not change significantly during the period of prazosin alone. At the end of the combination therapy, heart rate increased from 87±8.5 beats/min to 102±9.9 beats/min (17% increase, P<0.0005).

Side effects were: headaches (8%) and palpitations (15%). Laboratory studies, including urine testing, blood count, serum SGOT, SGPT, and lactate dehydrogenase activities, serum creatinine and bilirubin revealed no abnormality.

Discussion

Prazosin lowered blood pressure in the three rat models, more so in SH rats. Heart rate increased in normotensive rats, but decreased in SH rats. With pressure reduction, PPRC increased in normotensive rats, but remained unchanged in SH rats. Different responses in heart rate and renin suggest a different adrenergic tone in SH rats. We speculate that in SH rats, an anti-adrenergic component of prazosin action becomes more prominent. The presently known peripheral actions of the drug cannot explain the above cardiac effects (Constantine, McShane, Scriabine & Hess, 1973). Renin hyporesponsiveness to different stimuli in SH rats has been reported (Forman & Mulrow, 1974).

Acute haemodynamic effects of prazosin in essential hypertension included decrease in pressure, decrease in total peripheral resistance and minor changes in cardiac output. The long-term haemodynamic effects are similar (Lund-Johansen, 1975). At the arbitrary doses employed, prazosin and alpha-methyldopa exhibited similar anti-hypertensive efficacy on the supine pressure. Standing pressure, however, was lower with alpha-methyldopa.

In the long-term study, prazosin produced significant blood pressure reduction and was very well tolerated by the patients. The combination prazosin–polythiazide was very effective when prazosin alone had produced only a modest blood pressure reduction. The anti-hypertensive effects of prazosin were similar in the supine and standing position. A modest but significant increase in heart rate was seen with the combination.

Acknowledgments

The studies were conducted during the tenure by M.F. as Pfizer Research Fellow. I.S.S. was supported by National Institutes of Health grant HE-5878-04. Miss Janice Levy performed the renin determinations. The authors wish to acknowledge with thanks the invaluable technical assistance of Mr Jose Maldonado and Mr Luis Maldonado. Prazosin was generously supplied by Dr Allan Borger, Dr Mary Ghaly and Dr Norman Pitts from Pfizer Laboratories, Groton, Connecticut.
References


