Prazosin Plasma Concentration and Blood Pressure Reduction

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SUMMARY Prazosin was administered to 16 patients with essential hypertension in an initial dose of 0.5 mg, after which the blood pressure (BP), pulse, and plasma concentrations of prazosin were measured at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 hours. The dose of prazosin was then increased over 16 to 20 weeks, and similar sequences of measurements were obtained twice. Eleven patients completed the 20-week course. All patients did not respond in a similar way; two distinct patterns of BP and pulse response emerged, although there was no significant difference in the pharmacokinetic parameters, namely, absorption rate constant (K_a), maximum plasma concentration (C_{max}), time to reach the maximum concentration (T_{max}), prazosin plasma half-life (T_{1/2}), elimination rate constant (k_e), prazosin plasma concentration-time curve (AUC), and clearance. Patients in Group 1 had a marked reduction (52/30 mm Hg) of BP after the first dose of prazosin, no pulse increase, and needed a small dose of prazosin to maintain an adequate BP response. Patients in Group 2 had a minimal reduction in BP (14/13 mm Hg) after a first dose, a significant pulse increase, and needed a high dose of prazosin to control their BP. We conclude that this effect might be due to a different drug-receptor interaction, and the BP response and dose could be predicted from the response of the first dose of prazosin. (Hypertension 4: 93-101, 1982)

KEY WORDS • hypertension • treatment • prazosin • pharmacokinetic

PRAZOSIN is an antihypertensive drug with peripheral vasodilating properties through the blockade of postsynaptic alpha-adrenoreceptors. The pharmacological and pharmacokinetic properties of prazosin have been reviewed by Brogden et al. and Jaillon. The correlation or absence of correlation between the plasma concentration and blood pressure (BP) reduction is still the subject of some discussion. Various authors have reported results indicating a good correlation between plasma concentration after a first dose of prazosin and BP reduction. Results after chronic administration of prazosin, however, do not report this correlation.

This study was designed to evaluate the relationship between prazosin plasma concentration and its antihypertensive effect after a first dose and after 16 to 20 weeks of chronic treatment in the same patients. We also investigated the kinetic characteristics of prazosin in patients who presented a significant first-dose response to the drug and in patients who did not have this response.

Methods

Sixteen patients with essential hypertension were admitted to the trial. There were nine men and seven women with a mean age of 48 ± 3 years (± SD). The diagnosis of essential hypertension was defined by an investigation which included a complete blood count (CBC), platelets, systemic multiple analysis (SMA-15), electrocardiogram (ECG), chest x-ray, hypertensive pyelography, and renal arteriography when indicated. They were also seen by a dietician who advised them as to the content of 110 mmoles of sodium per day in the diet, but there was no attempt to control either their adherence to the diet or to measure their urinary electrolytes.

Patients who were previously untreated were given a placebo capsule of "prazosin" for a minimum of 3 weeks.
continued for 1 month in the patients on active treatment, and they received a placebo capsule during this period. At each clinic visit, BP was measured in the supine and standing position. Three readings were obtained in each position, and the average of these three readings was recorded as the BP level for this particular visit. Diastolic BP readings were obtained at the disappearance of the auscultated sound.

Patients were admitted to the trial if their diastolic BP was between 95 and 119 mm Hg for three measurements at 1-week intervals.

On admission to the trial, the patients received a first dose of 0.5 mg of prazosin. The drug was given fasting in the outpatient clinic of the Clinical Research Institute of Montreal. Blood pressure was measured supine and standing, and blood samples for plasma prazosin pharmacokinetic study were obtained at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 hours after the dose of prazosin. The dose of prazosin was then increased on a biweekly basis from 0.5 mg to 1, 2, 4, 5, and 10 mg twice a day, until the BP was reduced below 140/90 mm Hg.

A second prazosin pharmacokinetic study was done after the supine BP was lowered to 140/90 mm Hg or when the patient had reached a dose of prazosin of 5.0 mg twice a day. The patients were admitted to the outpatient clinic 12 hours after their last dose of prazosin, where they received their normal fasting dose in the morning. The BP and plasma samples were obtained in a sequence similar to the first kinetic study. A third prazosin pharmacokinetic study was done after 4 months of daily administration of prazosin or, in the case of nonresponders, after 4 weeks of 10 mg twice a day.

Pharmacokinetic Studies

To estimate prazosin kinetic parameters, the following assumptions were made: 1) prazosin kinetics are linear at 0.5 mg dose; 2) prazosin confers upon the body the characteristics of a one compartment open model; 3) prazosin bioavailability is considered to be 0.569. The area under the prazosin plasma concentration-time curve (AUC) was calculated using the trapezoidal rule, from $0$ to $\tau$ (interval period of oral administration), or by extrapolation to infinity, according to the relationship:

$$AUC_{0-\infty} = \int_{0}^{\tau} Cdt + \frac{C_{r}}{kel} \text{ (µg \cdot h/ml).}$$

The apparent elimination rate constant (kel) was determined by linear regression analyses of the terminal phase of the plasma decay concentration values. Prazosin plasma half-life ($T^{\omega}$) was calculated using the equation:

$$T^{\omega} = \frac{0.693}{kel} \text{ (h).}$$

Apparent total body clearance (Cl) and apparent volume of distribution (V) were calculated using model independent equations:

$$Cl = \frac{F.D.}{AUC} (l/h); \quad V = \frac{F.D.}{AUC \times kel} (l).$$

The apparent absorption rate constant (ka) was calculated using the computer program NONLIN (Metzler 1969) once it was demonstrated that the kinetics of prazosin were apparently linear. The predicted mean plasma concentration at steady state of prazosin was calculated, following the 0.5 mg dose, according to the relationship:

$$\text{predicted } c = \frac{AUC_{0-\infty}}{\tau} \text{ (µg/ml).}$$

The calculated average plasma concentration at steady state following the 2.5 and 10 mg doses was estimated according to the relationship:

$$\text{calculated } c = \frac{AUC_{0-\tau}}{\tau} \text{.}$$

To allow comparisons, the calculated $c$ was normalized by the dose. Accumulation of prazosin, following chronic administration, was calculated using the equation:

$$\text{accumulation} = \frac{1}{1 - e^{-kel \times \tau}} \times 100 \%.$$

Correlation coefficients were also calculated between $C_{p}$, $C_{p,max}$, AUC, and supine, standing diastolic blood pressure (BP). These correlation coefficients were calculated for each patient, kinetic study, and dose.

Analytical Method

Prazosin concentrations in plasma were measured by high performance liquid chromatography (HPLC) using fluorescence detection. The method was a modification of the one described by Twomey and Hobbs. Prazosin was extracted twice from plasma with ethyl acetate (HPLC-grade); a 250 x 4.6 mm HPLC column containing ZOR-BAX-CN (Dupont Company, Willmington, Delaware) was used. The mobile phase contained 0.2 M citric acid and methanol in the volume ratio of 40:60. The flow rate through the column was 3.0 ml/min. Recovery of prazosin and of an internal standard from plasma was 82% and 70% respectively. The useful range of the assay was between plasma concentrations of 0.4 and 100 µg/ml. The coefficient of variation for day-to-day determinations varied from 5.9% to 11.1%, depending on the concentration.

Statistics

Results are expressed as means ± standard deviations. Statistical analysis was carried out by regression analysis and by analysis of variance.
Results

Sixteen patients received a first dose of prazosin in the outpatient clinic. Blood pressure and prazosin concentration were measured during this first study. In 13 of these patients, prazosin kinetics were determined a second time (B), and 11 of these underwent a third prazosin kinetic study (C). The average dose of prazosin was $3.4 \pm 2.1$ mg twice a day at the second study, and $6.3 \pm 2.7$ mg twice a day at the third study.

Blood Pressure

The initial standing BP at the end of the placebo period was $157/102 \pm 15/7$ mm Hg. The BP response to the first dose of prazosin is summarized in figure 1. The standing BP after bedrest and before the initial dose was $155/97 \pm 16/12$ mm Hg, and was reduced to $129/87 \pm 24/16$ mm Hg after 2 hours. There was a gradual increase in BP to $154/95 \pm 36/12$ mm Hg after 8 hours. The pulse in the standing position increased from $83 \pm 8$ beats to $90 \pm 8$ beats/min after 2 hours and $86 \pm 8$ beats/min after 8 hours. The supine pulse was reduced but not significantly from $78 \pm 2$ to $72 \pm 8$ beats/min after 2 hours and $72 \pm 8$ beats/min after 8 hours.

The second study was carried out $11 \pm 4$ weeks after the first study. Thirteen patients were taking an average dose of $3.4 \pm 2.1$ mg of prazosin twice a day. Six patients were receiving a dose of $5.0$ mg twice a day, one patient was receiving $4.0$ mg twice a day, three were receiving $2.0$ mg twice a day, one was receiving $1.0$ mg and two were receiving $0.5$ mg twice a day. The last dose prior to the study was taken at 20 hours on the previous day. The standing BP prior to the morning dose was $152/97 \pm 14/7$ mm Hg. It was reduced to $128/88 \pm 18/14$ mm Hg after 2 hours and increased to $151/95 \pm 21/7$ mm Hg after 8 hours and $151/98 \pm 14/12$ mm Hg at 24 hours (fig. 2). The standing pulse remained constant from $83.5 \pm 7$ beats/min to $84 \pm 11$ beats/min after 2 hours and $83 \pm 11$ beats/min after 8 hours. The supine pulse was reduced from $75 \pm 14$ beats/min to $70 \pm 7$ beats after 2 hours and $71 \pm 7$ beats after 8 hours.

The third study took place $20 \pm 4$ weeks after the first study. Eleven patients were taking an average of $6.3 \pm 2.7$ mg of prazosin twice a day. Five patients were receiving $10$ mg twice a day, three were receiving $5$ mg twice a day, two were receiving $2.0$ mg twice a day, and one was receiving $1.0$ mg twice a day. The BP prior to the morning dose was $145/96 \pm 14/7$ mm Hg.
Hg and was reduced to 126/87 ± 21/10 mm Hg after 2 hours, 151/96 ± 23/7 after 8 hours, and 147/95 ± 17/7 mm Hg after 24 hours (fig. 3). Standing pulse was unchanged from 85 ± 10 beats/min to 86 ± 13 after 2 hours and 86 ± 10 after 8 hours. Supine pulse was not reduced significantly from 75 ± 13 to 71 ± 10 beats/min after 2 hours and 72 ± 9 beats/min after 8 hours.

Further analysis of the results obtained with the 11 subjects who completed the three kinetic studies showed that not all patients did not respond in a similar way and could be subdivided into three groups. In Group 1, there were four patients who had significant hypotension at the 0.5 mg dose. The dose of prazosin they received at the second kinetic study was 1.0 ± 0.7 mg twice a day and at the third kinetic study was 2.5 ± 1.7 mg twice a day. The standing BP of these patients during placebo was 143/100 ± 7/5 mm Hg, and their pressure taken at time 0 after bedrest was 140/94 ± 13/9 mm Hg (fig. 4). They had a significant reduction in their BP of 52/30 mm Hg at 90 to 120 minutes and a gradual increase toward normal between 6 to 8 hours. In the supine position, pulse was not significantly changed from 73 ± 6 to 67 ± 5 beats/min and in the standing position from 81 ± 6 to 80 ± 8 beats/min. Two of these patients felt faint and dizzy but there was no episode of loss of consciousness after the first dose. The second and third studies in these patients were repeated after 8 weeks and after 20 weeks. The maximal reduction in the standing BP after Study B was 23/11 and 20/19 mm Hg after the third kinetic study. The BP always returned toward baseline after 6 to 8 hours (figs. 5 and 6). In the supine position, pulse was significantly reduced (p < 0.001) from 79 ± 2 to 66 ± 2 beats/min in the second kinetic and from 80 ± 1 to 66 ± 4 beats/min during the third kinetic study. In the standing position, pulse was not significantly changed.

Group 2 included only two patients. Their initial standing BP on placebo was 166/96 mm Hg. The maximal reduction in BP after the 0.5 mg dose was 25/17 mm Hg, and the two patients needed a dose of 5 mg of prazosin to maintain adequate BP control. At that dose, the maximal reduction in BP was 40/12 mm Hg after more than 16 weeks.

Group 3 included five patients. Their initial standing BP on placebo was 159/109 ± 12/7 mm Hg and their BP in the clinic after bedrest was 155/107 ± 5/3 mm Hg. The average maximum reduction in standing BP after the first dose of 0.5 mg of prazosin was 14/13.
mm Hg (fig. 7). Pulse was unchanged in the supine position but was significantly increased ($p < 0.05$) in the standing position from 82 ± 4 to 100 ± 9 beats/min. The maximal reduction in the standing BP position 12 weeks later was 47/23 mm Hg at a dose of 5.4 ± 0.8 mg twice a day, and the maximal reduction 15 weeks later was 50/19 mm Hg at a dose of 10 mg twice a day (figs. 8 and 9). Pulse was significantly reduced ($p < 0.05$) in the supine position, but was unchanged in the standing position.

Relationship Between Plasma Concentration and Blood Pressure

There was a significant correlation between BP reduction (systolic, diastolic, supine, and standing) after the 0.5 mg dose of prazosin and the plasma concentration of the drug ($p < 0.05$). However, there was no correlation between the BP reduction and plasma concentration after the results for all patients at all doses were pooled.

When the analysis was done separately for the three sub-groups, there was a significant correlation ($p < 0.001$) $r = 0.30$ and 0.24 for systolic, supine, and standing; and $r = 0.61$ and 0.51 for diastolic, supine, and standing, $n = 164$) between plasma concentration and all BPs of the patients in Group 3, which were the patients with the minimal response at 0.5 mg and who needed the dose of 10 mg of prazosin twice a day, indicating a dose-response curve. On the other hand, there was no correlation between plasma concentration and all BPs of the patients in Group 1, which were the patients with the marked response at the 0.5 mg dose of prazosin (figs. 10 and 11), indicating the absence of a positive dose-response curve in these patients.

Pharmacokinetic Studies

Prazosin pharmacokinetic parameters for patients in Group 1 who had a marked response at the dose of 0.5 mg of prazosin were compared to prazosin disposition parameters estimated in patients of Group 3 (tables 1 and 2). There was no difference in the kinetic parameters estimated. The maximum plasma concentration ($C_{\text{max}}$) corrected for the dose was identical. The time to reach the maximal concentration ($T_{\text{max}}$) was not significantly different in both groups, but there was an increase as the dose increased. There was a significant difference in the $T_{\text{max}}$ between doses
FIGURE 7. Blood pressure response in a patient (n = 5) of Group 3 who had a minimal response to a first dose of prazosin 0.5 mg in clinic.

FIGURE 8. Blood pressure response in patients (n = 5) of Group 3 at kinetic study B, mean dose, 5.4 ± 0.8 mg.

FIGURE 9. Blood pressure response in patients (n = 5) of Group 3 at kinetic study C; mean dose, 10 mg.
FIGURE 10. Plasma concentration of prazosin in patients of Group 1 at the three kinetic studies.

TABLE 1. Pharmacokinetic Absorption Parameters

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>$k_a$ (h$^{-1}$)</th>
<th>$C_{p_{max}}$ (ng/ml)$^*$</th>
<th>$T_{max}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n = 4)</td>
<td></td>
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<td></td>
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<tr>
<td>0.5</td>
<td>0.3817 ± 0.0287</td>
<td>5.41 ± 1.75</td>
<td>1 ± 0.58</td>
</tr>
<tr>
<td>1-2</td>
<td>6.36 ± 1.99</td>
<td>2.50 ± 0.58</td>
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</tr>
<tr>
<td>Group 3 (n = 5)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>0.5</td>
<td>0.3943 ± 0.1121</td>
<td>4.85 ± 2.86</td>
<td>1.90 ± 1.24</td>
</tr>
<tr>
<td>5-7</td>
<td>5.40 ± 1.61</td>
<td>2.10 ± 1.14</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>4.56 ± 2.63</td>
<td>2.50 ± 1.08</td>
<td></td>
</tr>
</tbody>
</table>

*Results are corrected for the dose.
$\bar{k}_a$ = absorption rate constant; $C_{p_{max}}$ = maximum plasma concentration; $T_{max}$ = time to reach maximum concentration.

TABLE 2. Prazosin Disposition Parameters

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>$T_{1/2}$ (h)</th>
<th>$kel$ (h$^{-1}$)</th>
<th>AUC (ng/h/ml)$^*$</th>
<th>Cl (ml/min)$^+$</th>
<th>Accumulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n = 4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>2.84 ± 1.08</td>
<td>0.2852 ± 0.0700</td>
<td>20.28 ± 2.85</td>
<td>414.3</td>
<td>1.24</td>
</tr>
<tr>
<td>1-2</td>
<td>3.35 ± 0.84</td>
<td>0.2226 ± 0.0688</td>
<td>25.51 ± 9.58</td>
<td>59</td>
<td>0.27</td>
</tr>
<tr>
<td>Group 3 (n = 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>2.57 ± 1.17</td>
<td>0.3185 ± 0.1355</td>
<td>21.76 ± 11.66</td>
<td>534.2</td>
<td>1.11 (0.5-10 mg)</td>
</tr>
<tr>
<td>5-7</td>
<td>2.91 ± 0.79</td>
<td>0.2524 ± 0.0669</td>
<td>26.49 ± 13.28</td>
<td>559.3</td>
<td>0.27</td>
</tr>
<tr>
<td>10</td>
<td>3.24 ± 0.99</td>
<td>0.2325 ± 0.0723</td>
<td>22.00 ± 9.27</td>
<td>52</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*Results are corrected for the dose.
$T_{1/2}$ = prazosin plasma half life; $kel$ = elimination rate constant; AUC = prazosin plasma concentration-time curve; Cl = clearance.
for patients in Group 1, but no difference in Group 3 or between both groups. The absorption rate constant (ka) was identical in both groups.

There were no changes in kel between both groups although there was a tendency toward a decrease in kel as the dose increased, also in both groups. At steady state, there was a mild accumulation of the drug when the observed plasma concentration was compared to the predicted plasma concentration estimated with the 0.5 mg dose.

**Side Effects and Withdrawals**

Of the 16 patients admitted to the trial, five did not complete the three studies: two asked to be withdrawn, one because of a hypotensive episode (Case 7) and the other because of headaches (Case 13); one was admitted to the hospital because of uncontrolled hypertension; and two did not present themselves on one study day.

The side effects reported by the patients during the study are summarized in table 3. There were three episodes when the patients felt faint after the first dose. Only one patient had a syncopal episode during the study, and it was after his third dose at night when he stood up.

**Discussion**

Previous studies by different authors as reviewed by Brogden et al. have reported that prazosin is readily absorbed, although there were considerable variations in the absorption parameters between individuals. The mean half-life was calculated to vary between 2.5 and 4 hours. Constantine et al. observed initially that there was no correlation between plasma prazosin levels and BP reductions, while Graham et al. reported that the peak plasma concentration coincided with the maximal hypotensive effect only in the first day of administration. Wood et al. reported that the BP-lowering effect of the drug was not closely related to the plasma concentration of the drug, but a study done by Bateman et al. observed a good correlation between plasma concentration and the fall in BP after an intravenous dose of 1 mg of prazosin. They also calculated that, when compared to a prazosin tablet of 1 mg, the bioavailability of prazosin appeared to be an average of 56.9%. They explained the bioavailability by a first pass metabolism or by an impaired absorption. In their opinion, the first dose hypotension appeared to be the dose related after intravenous prazosin and that if the same relationship applied after oral dosing marked postural hypotension would be expected at plasma concentration exceeding 30 μg/ml.

Graham et al. reported that after 4 days of treatment, the first dose phenomenon had subsided despite much higher plasma concentration. The antihypertensive effect is reported to persist longer (10 hours) than the expected short plasma half-life; tissue distribution studies indicate that prazosin is widely distributed and concentrated in vascular tissues, a possible explanation for the longer antihypertensive effect. Similar BP-lowering effects have been reported by Lowenthal et al., although they were much less evident after daily prazosin dosing.

Our results indicate that BP is reduced consistently by prazosin but to various degrees in different individuals. In the 16 patients studied, there is a significant correlation between plasma concentration of prazosin after a first dose of 0.5 mg of prazosin and the BP reduction, but this correlation disappears if the data from all the patients at all kinetic studies are pooled and analyzed.

However, the patients can be subdivided into groups according to their response to the first dose and the needed dose to maintain adequate BP control. Four patients (Group 1) had a marked reduction in standing BP while five patients (Group 3) had a minimal reduction in BP to the first dose. There was no difference in the plasma concentration of prazosin in the two groups and no difference either in the absorption constant, maximum plasma concentration (Cmax), and time to maximum plasma concentration (Tmax). Group 1 patients needed a smaller dose to obtain adequate BP reduction. Group 3 patients needed a much higher dose (10 mg) to obtain the adequate BP response, and there was a more gradual reduction of BP without a first dose effect. Group 3 patients demonstrated a significant correlation between plasma concentration and BP reductions. Pharmacokinetic parameters were not significantly different in both groups. There was a tendency toward a reduction in the elimination constant but this reduction was not significant.

The pulse changes are interesting. Patients with the marked reduction in the standing BP (Group 1) did not have any significant increase in pulse rates while the patients in Group 3 with minimal reduction in BP...
at the first dose had a significant increase in pulse rate (table 3). These results would indicate either a stronger compensatory baroreceptor mechanism in Group 3 patients, which would prevent the BP reduction, or different postsynaptic $\alpha_2$-receptor sensitivity. At very low doses, prazosin may have an effect on presynaptic $\alpha_2$-adrenoceptors or have direct peripheral vasodilating properties in some patients. Langer et al. have argued that there is considerable evidence against a direct vasodilating property of prazosin, and that it is a highly selective postsynaptic $\alpha_2$-adrenoceptor blocking agent. The presence of tachycardia in this small group of patients in the standing position would argue either for some effect on presynaptic $\alpha_2$-adrenoceptors in these patients or for a direct vasodilating property.

Despite the small number of patients, these results suggest that all patients do not respond in a similar manner to prazosin. Since the pharmacokinetic parameters are unchanged, within a group and between groups, this might suggest that the differences in BP levels are due to a different drug-receptor interaction. The results would also indicate that the responders to a low dose of prazosin would maintain the BP control while the patients who are slow responders need a bigger dose but they do eventually respond in a significant manner. This could also be detected by the upright pulse after the first dose. The first dose effect is not related only to plasma concentration of the drug and on the other hand a very high plasma concentration (> 80 $\mu$g/ml) does not appear to be associated with a severe hypotension, as suggested by Bateman et al.

In this trial, prazosin was given twice daily. The time course of the drug's action, however, was shorter, with a duration of action of 6 to 8 hours. Prazosin was given alone without a diuretic, which may have contributed to increasing the duration of action. When used alone, a more frequent dosing would seem to be indicated.

In summary, the results of our trial indicate that the variability in BP response to prazosin is not related to the pharmacokinetic parameters of the drug. A difference in drug-receptor interaction could be the main factor in the variability. A practical consequence of this study appears to be that the response to prazosin can be predicted on the basis of the response to the first dose of prazosin.

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