Physiologic Evaluation of a New Antihypertensive Agent: Prazosin HCl

M. C. Koshy, M.D., Diane Mickley, M.D., Jacques Bourgoignie, M.D., and M. Donald Blafox, M.D.

SUMMARY The mechanism of action of prazosin hydrochloride, a new antihypertensive agent, was studied in 14 patients with essential hypertension. Mean supine blood pressure for the group fell from 148±102/78±50 (SE) mm Hg at baseline to 139±91/54±4 after eight weeks of therapy (P < 0.05). No significant postural hypotension was noted in the patients who responded to therapy. Glomerular filtration rate (endogenous creatinine or inulin clearance) and effective renal plasma flow (PAH clearance) remained unchanged during therapy as did supine and stimulated peripheral plasma renin activity. Cardiac output did not change significantly although plasma volume increased in ten out of 12 patients in whom it was measured (P < 0.025).

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PRAZOSIN HYDROCHLORIDE* is a new type of antihypertensive agent (fig. 1) which effectively lowers the blood pressure in hypertensive subjects. It is relatively free of serious side effects. Although it has been studied extensively in animal models, there are few physiologic studies reported in humans. The mechanism of action of prazosin is not fully understood. It does not appear to be related chemically or pharmacologically to any of the antihypertensive agents in general clinical use. Animal data suggest that its antihypertensive action is associated with peripheral vasodilation. The present study was designed to evaluate some physiologic parameters of importance in the therapy of moderate essential hypertension with prazosin HCl.

Methods

Fourteen patients with essential hypertension were studied on an outpatient basis. Criteria for participation in the study included sustained diastolic blood pressure between 90 and 130 mm Hg in patients who had received no antihypertensive therapy in the last four weeks. Diabetes, coronary heart disease, cerebrovascular disease or renal insufficiency were criteria for exclusion from the study. Renal and renovascular causes of hypertension were ruled out with triple isotope renal studies using 125I orthoiodohippurate and by rapid sequence intravenous urography. Pheochromocytoma was excluded with urinary VMA. All patients were offered par-

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*Prazosin hydrochloride — Minipress, C. P. 122991 (Pfizer).

From the Albert Einstein College of Medicine of Yeshiva University, Bronx, New York.

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PRAZOSIN HYDROCHLORIDE

\[1-(4-Amino-6,7-Dimethoxy-2-Quinazolinyl)
-4-(2-Furoyl) Piperazine Monohydrochloride\]

Figure 1. Prazosin is a quinazoline derivative with in vitro \(\alpha\) blocking and phosphodiesterase inhibiting properties. The quinazolines are a group of drugs with antihypertensive properties which are distinct from other currently available antihypertensive agents. Their mode of action appears to be direct vasodilation.

Participation in the study on a voluntary basis and gave formal written consent after detailed explanation of the aims and objectives of the investigators.

Baseline blood pressure was determined in the supine and standing positions from the average value of readings on at least three separate visits prior to initiation of therapy. Serum electrolytes, liver function tests, serum creatinine and blood urea nitrogen were measured before initiation of therapy and at repeated intervals of two to four weeks during the study. In addition plasma volume was determined in 12 patients using \(^{131}\text{I}\) human serum albumin. Ten of these same patients also had resting cardiac output calculated by isotope dilution. Glomerular filtration rate was estimated from endogenous creatinine clearance in ten subjects and by continuous infusion of insulin in six patients. Para-aminohippurate clearance was also determined in these six patients. Peripheral plasma renin activity was measured by radioimmunoassay with the patients on a regular home diet. The blood samples for measurement of renin activity were obtained between 10 A.M. and 12 noon after the patients had rested three hours in the supine position and again after they had been upright for ninety minutes. Sodium excretion estimated from a 24-hour urine sample completed the morning of the renin study was used as an index of sodium intake.

Blood pressure was measured at weekly intervals during baseline and at least bi-weekly thereafter. Therapy was initiated with a single oral dose of 0.5 to 1 mg of prazosin in tablet form. Subsequent doses were administered in capsule form and ranged from 2 mg b.i.d. to a maximum daily dose of 5 mg q.i.d. Prazosin was administered in increasing dosage aiming at blood pressure control or a maximum dosage of 20 mg/day, whichever came first. The cardiac output, plasma volume, and renal function studies described above were repeated after eight weeks of therapy at which time either adequate blood pressure control had been achieved or a maximum tolerable amount of drug had been given. Data were analyzed by paired \(t\)-test for statistical significance.

Results

Fourteen of 20 patients completed at least eight weeks of prazosin therapy while six patients had to be removed from the study for the reasons given below. Two were asked to withdraw because of poor compliance, two because of rapid acceleration of blood pressure necessitating emergency intervention with noninvestigational drugs, and two because of initial reactions to the drug. Therefore only two patients failed to complete the study because of problems related to prazosin. Of these, one manifested an unusual reaction after an initial test dose of 1.0 mg which was characterized by tachycardia at 130–140 beats/min, nausea, diarrhea, abdominal cramps, fluttering movements of the eyelids and superior rotation of the eyes for a period of 15–20 min without any hypotension. When another test dose was given to this person no untoward reaction occurred. However, palpitation and tachycardia persisted and she was removed from the study. The second patient had a rapid orthostatic drop in blood pressure from 148/96 mm Hg (supine) to 51/36 mm Hg standing which lasted about 15 min following a 2.0 mg test dose. Because of this hypotensive reaction she was withdrawn from the study. The 14 patients who remained under therapy for the duration of the investigation are listed in table 1. They ranged in age from 25 to 50 years with a mean age of 36.0 ± 8 (SD). Four subjects were white, ten black (nine males, five females). Ten of the 14 patients experienced a reduction in systemic blood pressure (table 1). The mean systolic and diastolic blood pressure averaged 148/102 ± 3/2 before therapy and 139/91 ± 5/4 after eight weeks of therapy (table 2). As shown in table 1, there appeared to be no significant postural effect of treatment on blood pressure. The mean systolic and diastolic supine and standing blood pressures were not significantly different at any time during the course of therapy.

The mean creatinine clearance rose from 108 ± 5.4 (se) ml/min to 127 ± 6.9 ml/min after therapy (NS); insulin clearance was 144.0 ± 9.1 ml/min at baseline and 144.7 ± 19.5 ml/min after therapy and PAH clearance was 621.2 ± 100.0 ml/min before and 606 ± 117.5 ml/min after therapy (fig. 2). The mean plasma volume was 2812 ± 147 (se) ml before treatment and 3201 ± 115 after 8 weeks of treatment (\(P < 0.025\)).

Cardiac output averaged 6564 ± 413 (se) ml/min before therapy and 7029 ± 512 ml/min after therapy (NS). Peripheral resistance calculated from the cardiac output and mean blood pressure at the time of this determination fell from 1621 ± 97 dynes/sec/cm\(^4\) to 1441 ± 112 dynes/sec/cm\(^4\) after therapy (NS). The mean blood pressure at the time of cardiac output \(\frac{\text{systolic + diastolic}}{2}\) was 131 ± 4 (se) before therapy and 122 ± 6 (\(P < 0.01\)) after therapy.

Although the fall in peripheral resistance was not statistically significant, the results were compatible with a vasodilator effect of the drug when the patients were grouped according to degree of blood pressure response. Five subjects had a fall in mean blood pressure of 10 mm Hg or more and five had a smaller change in blood pressure, none at all, or a slight increase at the time of cardiac output determination. Peripheral resistance in "responders" fell 432 ± 178 dynes/sec/cm\(^4\) (se) (\(P < 0.025\)), while in the "nonresponders" there was a nonsignificant increase (mean: 71 ± 114 dynes/sec/cm\(^4\)). The changes in cardiac output were 1160 ± 705 ml/min in the responders and (-) 240 ± 717 ml/min in the nonresponders. Neither change was significant. Plasma volume in responders was
TABLE 1. Clinical Data and Effects of Prazosin Therapy

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Race</th>
<th>Case/yr/</th>
<th>Position</th>
<th>Lowest on prazosin</th>
<th>At 8 Weeks</th>
<th>Maximum dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Supine</td>
<td>Erect</td>
<td>Supine</td>
<td>Erect</td>
</tr>
<tr>
<td>1/30/W/M</td>
<td>139</td>
<td>132</td>
<td>138</td>
<td>139</td>
<td>135</td>
<td>141</td>
<td>5 mg qid</td>
<td>3 mg tid</td>
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<tr>
<td>2/30/W/M</td>
<td>145</td>
<td>126</td>
<td>111</td>
<td>107</td>
<td>111</td>
<td>107</td>
<td>2 mg tid</td>
<td>2 mg tid</td>
</tr>
<tr>
<td>3/42/W/M</td>
<td>148</td>
<td>138</td>
<td>149</td>
<td>146</td>
<td>150</td>
<td>145</td>
<td>5 mg qid</td>
<td>5 mg qid</td>
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<tr>
<td>4/26/W/M</td>
<td>100</td>
<td>108</td>
<td>86</td>
<td>76</td>
<td>86</td>
<td>90</td>
<td>5 mg qid</td>
<td>5 mg qid</td>
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<tr>
<td>5/35/N/F</td>
<td>148</td>
<td>141</td>
<td>136</td>
<td>121</td>
<td>141</td>
<td>118</td>
<td>5 mg qid</td>
<td>5 mg qid</td>
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<tr>
<td>6/50/N/M</td>
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<td>148</td>
<td>130</td>
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<td>130</td>
<td>113</td>
<td>2 mg tid</td>
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<tr>
<td>7/40/N/F</td>
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<td>97</td>
<td>97</td>
<td>97</td>
<td>97</td>
<td>97</td>
<td>2 mg tid</td>
<td>2 mg tid</td>
</tr>
<tr>
<td>8/35/N/M</td>
<td>146</td>
<td>148</td>
<td>142</td>
<td>144</td>
<td>142</td>
<td>144</td>
<td>2 mg qid</td>
<td>2 mg qid</td>
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<tr>
<td>9/27/N/F</td>
<td>97</td>
<td>97</td>
<td>97</td>
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<td>97</td>
<td>97</td>
<td>2 mg six</td>
<td>2 mg six</td>
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<tr>
<td>10/25/N/F</td>
<td>122</td>
<td>123</td>
<td>101</td>
<td>104</td>
<td>130</td>
<td>110</td>
<td>2 mg tid</td>
<td>2 mg tid</td>
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<tr>
<td>11/39/N/M</td>
<td>150</td>
<td>138</td>
<td>115</td>
<td>105</td>
<td>130</td>
<td>118</td>
<td>2 mg bid</td>
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</tr>
<tr>
<td>12/37/N/F</td>
<td>100</td>
<td>115</td>
<td>75</td>
<td>88</td>
<td>95</td>
<td>88</td>
<td>5 mg tid</td>
<td>5 mg tid</td>
</tr>
<tr>
<td>13/48/N/M</td>
<td>152</td>
<td>150</td>
<td>135</td>
<td>130</td>
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<td>140</td>
<td>2 mg tid</td>
<td>None</td>
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<tr>
<td>14/41/N/M</td>
<td>175</td>
<td>188</td>
<td>170</td>
<td>170</td>
<td>190</td>
<td>170</td>
<td>5 mg qid</td>
<td>5 mg qid</td>
</tr>
</tbody>
</table>

2931 ± 292 ml before therapy and 3202 ± 96 after therapy (NS) while in nonresponders it was 2807 ± 235 before therapy and 3237 ± 112 after therapy (P < 0.025). The mean pulse rate for the entire group was 81 ± 4 beats/min supine and 85 ± 3 erect before therapy. After therapy these means were 85 ± 4 (NS) supine and 94 ± 6 erect (P < 0.025). When the changes in pulse rates of responders and nonresponders were compared separately with their respective baseline pulse rates, both the supine and standing

TABLE 2. Mean Systolic and Diastolic Blood Pressure (N = 14) (mm Hg)

<table>
<thead>
<tr>
<th>Position</th>
<th>Baseline</th>
<th>Lowest</th>
<th>Eight Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>148 ± 3</td>
<td>130 ± 5</td>
<td>139 ± 5</td>
</tr>
<tr>
<td>Erect</td>
<td>102 ± 2</td>
<td>86 ± 3</td>
<td>91 ± 4</td>
</tr>
</tbody>
</table>

All values compared to baseline.

**P < 0.05
***P < 0.0025
****P < 0.0005
*****P < 0.00005

FIGURE 2. Effects of prazosin on renal function. Prazosin has no significant effects on glomerular filtration rate or effective renal plasma flow.
increase for the nonresponders were significant \((P < 0.001, P < 0.025)\) while there was no significant change in the responders.

Peripheral plasma renin activity did not change significantly after treatment (fig. 3). The supine value was 23 \(\text{ng/100 ml/hr} \pm 5.6 \text{ (SE)}\) before therapy and 17.8 \(\text{ng} \pm 5.2\) after therapy. Stimulated renins were 96 \(\pm 34.7\) and 91 \(\pm 32.4\) before and after therapy. No trend was noted when the patients were grouped according to blood pressure response or baseline renin. Urinary sodium excretion averaged 140 mEq/24 hrs \(\pm 16\) before therapy and 182 \(\pm 18\) after. In all patient studies there was no significant change in the hemogram, serum electrolytes, SGOT, LDH, alkaline phosphatase, bilirubin, blood sugar, or serum uric acid between the pre and post treatment period.

**Discussion**

The present study supports the previously reported effectiveness of prazosin in lowering high blood pressure. It appears, however, that the antihypertensive properties of prazosin are more prominent early after therapy is initiated than after eight weeks of treatment (table 1). Among the 14 patients who completed this study, nine experienced a prompt decrease in systolic and diastolic blood pressure of 10 mm Hg or more soon after treatment was begun. By contrast eight weeks of therapy the blood pressure was decreased to a similar extent in only five of the 14 patients.

The mean decrease in blood pressure was about 20 mm Hg for both systolic and diastolic pressure at the time of greatest effectiveness of the drug. After eight weeks of therapy, however, blood pressures remained significantly lowered but the mean decrease was only about 10 mm Hg (table 2).

Fluid retention, a side effect of therapy with most antihypertensive drugs occurs with prazosin as well. Although clinically overt fluid retention did not occur in any of our patients, the results of the plasma volume determination are of considerable interest. Plasma volume did not change significantly in patients who responded to prazosin while it increased significantly in patients in whom prazosin was relatively ineffective in lowering the high blood pressure. The observation of an increased plasma volume in non-responders suggests that this may have negated the antihypertensive effect of prazosin. The rationale of initiating antihypertensive therapy combined with a diuretic to prevent subsequent volume expansion appears to be applicable to the use of prazosin as it is to most other antihypertensive agents.

Onesti has reported that intravenous prazosin lowers mean blood pressure and peripheral resistance with a concomitant small increase in cardiac output and heart rate. These observations and the results of the present study support its probable direct action as a peripheral vasodilator.

As previously noted, unlike hydralazine, the hypotensive effect of prazosin is not consistently accompanied by a significant compensatory tachycardia. Some of the patients did complain of palpitations on increasing doses but the increase in pulse rate for the group, although statistically significant in the erect position, was modest. Nonresponders showed a much greater increase in pulse rate than responders. This appears to distinguish it in its action from phenoxbenzamine, an \(\alpha\) adrenergic blocker. Phenoxbenzamine enhances the positive inotropic and chronotropic cardiac response to sympathetic stimulation. This difference in action from a true \(\alpha\) adrenergic blocker although unexplained may account for the more potent antihypertensive effectiveness of prazosin.

Effective renal plasma flow and glomerular filtration rate are not affected by prazosin. Urinalysis remains normal during therapy. It appears, therefore, that prazosin does not have any adverse effect on renal function in patients with mild to moderate hypertension. This observation supports its potential value in patients with compromised renal function.

A great deal of attention has been devoted recently to the role of renin in the choice of antihypertensive agents. Most drugs have been characterized as either causing an elevation or a depression of renin activity. The most closely related drugs to prazosin, hydralazine and minoxidil, are reported to increase renin activity. Oral prazosin has no significant effect on renin.

Several of our patients complained of transient symptoms of mild dizziness on starting the drug; thereafter improvement was usually noted. The incidence of acute hypotension appears to be quite variable. We have not encountered any problems recently using an initial dose of 0.5 mg in tablet form. A recent letter to the editors of Lancet reports a case similar to the two noted here and also recommends a reduced initial dose.

No patient reported any decrease of libido or failure of ejaculation. In the 14 patients followed for a full eight weeks or more the drug was very well tolerated.

The present detailed analysis of the physiological effect of prazosin, a new antihypertensive agent, suggests that it acts primarily as a peripheral dilator. Taken together with
previous clinical studies, our experience indicates that it is a useful agent and its effectiveness might be enhanced by the simultaneous use of a diuretic. Under the conditions of this study in which a diuretic was not used, no adverse effect on renal function and no change in peripheral renin activity was noted.

References

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The Effect of Jejunoileal Bypass on the Pharmacokinetics of Digoxin in Man

FRANK I. MARCUS, M.D., EDWARD J. QUINN, M.D., HERSCHELLA HORTON, R.N., SHANNON JACOBS, R.N., SUSAN PIPPIN, M.S., MARVIN STAFFORD, M.S., and CHARLES ZUKOSKI, M.D.

SUMMARY Seven subjects who underwent jejunoileal bypass surgery for massive obesity participated in a study to examine the relative bioavailability of digoxin before and one to two months after surgery. They were given a loading dose of 1 mg digoxin in divided oral doses followed by oral maintenance doses of 0.5 mg daily. There were no significant differences in the area under the serum concentration time curve, steady state serum levels or 24 hour steady state excretion of digoxin before and after surgery. We conclude that the bioavailability of digoxin from the Lanoxin tablets employed is not impaired in these patients, although urinary d-xylene and 24 hour fecal fat excretion indicated moderate to severe malabsorption after surgery.

THE EFFECT OF MALABSORPTION STATES on the absorption of digoxin continues to be a controversial subject. Hall et al. found no impairment of digoxin absorption when it was administered as tritiated digoxin in patients with malabsorption states caused by bacterial overgrowth, small bowel disease, pancreatic insufficiency or rapid intestinal transit time. Beermann et al. also found minimal, if any, malabsorption when tritiated digoxin in solution was given orally to five patients with partial gastrectomy, one patient with vagotomy and plastic reconstruction of the pylorus, and one with jejunal colostomy. In contrast, Heizer and co-workers found diminished absorption of digoxin from tablets in eleven patients with various causes for malabsorption including sprue, radiation enteritis, partial resection of the small intestine, pancreatic insufficiency and hypermotility due to excessive laxative ingestion. Their data suggested a positive correlation between digoxin levels and d-xylene absorption. The mean steady state serum digoxin level for the nine patients with other causes of malabsorption was significantly less than that of the control group. The two patients with pancreatic insufficiency had serum digoxin levels that were not different from the controls.

Jejunoileal bypass, performed for morbid obesity, provided us with an opportunity to study the bioavailability of digoxin in the same patients before and after a well defined malabsorption state.

From the Departments of Medicine and Surgery, University of Arizona College of Medicine, Tucson, Arizona.

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Address for reprints: Frank I. Marcus, M.D., Department of Internal Medicine, Arizona Medical Center, The University of Arizona, Tucson, Arizona 85724.

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M C Koshy, D Mickley, J Bourgiogne and M D Blaufox

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