Hemodynamic and Clinical Tachyphylaxis to Prazosin-Mediated Afterload Reduction in Severe Chronic Congestive Heart Failure

MILTON PACKER, M.D., JOSE MELLER, M.D., RICHARD GORLIN, M.D., AND MICHAEL V. HERMAN, M.D.

SUMMARY Sequential doses of 5 mg of oral prazosin hydrochloride were administered to eight patients with severe chronic congestive heart failure refractory to conventional therapy. Initial doses of the drug produced marked increases in cardiac index (+0.87 l/min/m²) associated with substantial decreases in left ventricular filling pressure (−10.7 mm Hg), total systemic vascular resistance (2118 to 1154 dyn-sec-cm⁻⁵), and heart rate (89 to 76 beats/min). However, serial administration of the same dose at 12-24-hour intervals was accompanied by the rapid development of tachyphylaxis, such that the magnitude of hemodynamic effects with second doses was less than 50% of the magnitude of effects seen with first doses (p < 0.01), and third doses produced no overall significant hemodynamic responses. Diuresis with furosemide failed to restore the circulatory effects of prazosin, and the use of 10-mg doses improved cardiovascular performance to only a small extent. Only two of eight patients had sustained hemodynamic responses large enough to justify chronic oral ambulatory therapy. Administration of oral hydralazine caused hemodynamic improvement superior to even high-dose prazosin therapy (p < 0.02).

THE BENEFICIAL HEMODYNAMIC and clinical effects of peripheral vasodilators in patients with severe heart failure are well established, but the search continues for a well-tolerated oral agent which is chronically effective for the therapeutic reduction of preload and afterload. Although nitrates are orally active, their duration of action is short, and they have minimal effects on cardiac output. The use of hydralazine results in marked increases in cardiac output (CO), significant reductions in left ventricular filling pressure (LVFP), and amelioration of clinical symptoms, but is often accompanied by poorly tolerated adverse effects. Therefore, the recent demonstration of balanced preload and afterload reduction with prazosin has stimulated interest in its use in chronic ambulatory therapy. Prazosin exerts a peripheral vasodilator action by producing α-sympathetic blockade; some have proposed an additional direct smooth muscle relaxant effect mediated by increased intracellular levels of cyclic AMP due to drug-induced phosphodiesterase inhibition. Despite extensive experience in antihypertensive therapy, previous work with prazosin in heart failure has involved hemodynamic monitoring of only initial doses of the drug, as a result, the ability of maintenance therapy to produce sustained reduction of preload and afterload has not been demonstrated. As tolerance to the effects of other afterload-reducing agents has been demonstrated in the therapy of hypertension and has also been suspected with prazosin, an examination of the hemodynamic effects of repeated doses of prazosin in patients with severe heart failure seems warranted.

Methods

Patient Population

We evaluated eight patients with severe chronic congestive heart failure refractory to optimal therapy with digitalis and diuretics. All patients had persistent dyspnea at rest or on minimal exertion and developed fatigue and azotemia with progressive increments in diuretic dosage. Clinical information concerning these patients is summarized in table 1. There were seven men and one woman, with a mean age of 64 years (range 56–71 years). The etiology of heart failure was idiopathic cardiomyopathy in five and ischemic cardiomyopathy in three. Diagnosis was confirmed by cardiac catheterization in four patients, all of whom had angiographic ejection fractions less than 35%. All had clinical or angiographic evidence of mitral regurgitation. The duration of heart failure ranged from 7 months to 8 years. All patients were in normal sinus rhythm, and all were receiving therapeutic doses of digoxin and furosemide, the latter in daily doses of 80–800 mg. Two patients were also taking spironolactone. Six patients had been treated with sublingual or oral isosorbide dinitrate without clinical benefit. One patient had responded hemodynamically and clinically to hydralazine therapy, but had discontinued its use due to adverse effects (rash and hemolysis). One patient had previously taken prazosin, but not for the preceding three months.

All patients were studied during a period of relative clinical stability. Bed rest was maintained, and patients were fed 2-gram sodium diets. Nitrates, an-
tiarrhythmics, diuretics, and potassium-sparing diuretics were discontinued for at least 5 days before study.

**Hemodynamic Measurements**

After we obtained written, informed consent from all patients, we performed right heart catheterization using a triple lumen flow-directed balloon-tipped catheter (Kimray Medical Associates, Oklahoma City) through which measurements of right atrial, pulmonary arterial, and pulmonary capillary wedge pressures were made. Arterial cannulae (Angiocath, Deseret Pharmaceuticals) were inserted percutaneously or by cutdown into the radial or brachial artery in all patients. Measurements were made using Bentley Trantec #800 pressure transducers with zero reference level at the midaxillary line with the patient supine; all pressures were recorded in this position on a Hewlett Packard multichannel modular display (Hewlett Packard, Inc, Sanborn Division, Waltham, Massachusetts). LVFP was measured as pulmonary capillary wedge pressure or as pulmonary arterial diastolic pressure after its identity with wedge pressure was established. CO was determined by thermodilution using the same catheter connected to a bedside CO computer (Columbus Instruments, Columbus, Ohio) using room temperature injectate (23-25°C) as 10-ml boluses of 5% dextrose in water; injection was made reproducibly with the assistance of a manually triggered injector (Columbus Instruments), and the determinations were performed in triplicate. Heart rates (HR) were determined from a continuously recorded ECG.

**Administration of Drugs**

We designed a protocol to compare first doses of prazosin with subsequent doses administered at 12-24-hour intervals under identical control hemodynamic conditions. After digoxin and furosemide had been withheld for 24 hours, baseline determinations of the following hemodynamic variables were made for at least 3 hours to ensure stability of the control hemodynamic state: mean systemic arterial pressure (MAP), heart rate, left ventricular filling pressure, mean pulmonary artery pressure (MPAP), mean right atrial pressure (MRAP) and cardiac output. Each patient then received 5 mg of prazosin hydrochloride (as Minipress capsules, Pfizer Laboratories) administered orally; the mean dose normalized for body weight was 86 μg/kg (range 47-106 μg/kg). We chose a dose of 5 mg because of its equivalence to 100 mg of hydralazine in the treatment of hypertension; this dose of hydralazine had previously been very effective in the therapy of heart failure.

Second, third, and fourth doses of prazosin were then administered at 12-24-hour intervals under similar hemodynamic monitoring as follows. A second dose of 5 mg of prazosin was administered when the hemodynamic variables returned to control values after the first dose of the drug. After its peak effects were observed, digoxin (0.125-0.25 mg) and furosemide (100-200 mg) were administered intravenously (4-6 hours after the second dose); in this way, digoxin and furosemide therapy was maintained but spaced at intervals that permitted independent evaluation of the effects of prazosin. Only one dose of daily maintenance digoxin and furosemide therapy was omitted during the trial. A third dose of 5 mg of prazosin was given 12-18 hours after administration of digoxin and furosemide. If the third dose produced minimal hemodynamic effects, a 10-mg dose of prazosin was administered 12 hours later; if this dose produced significant hemodynamic responses, patients received a second 10-mg dose of the drug. If prazosin had no persistent effects, a 100-mg dose of hydralazine hydrochloride (Apresoline tablets, Ciba Pharmaceutical Company) was given and its hemodynamic effects were observed before we discontinued invasive monitoring. Special care was taken to ensure similarity of all control hemodynamic states before...
the administration of either prazosin or hydralazine. As with the first dose, the stability of each control state was confirmed for 3 hours before each drug trial. With the administration of each dose, all hemodynamic variables were determined every 30 minutes for 4 hours and then hourly until control values were achieved.

For each patient, maintenance therapy with prazosin started with doses that varied according to the results of the drug trials. During and after discontinuing hemodynamic monitoring, doses were progressively increased in an effort to produce sustained clinical responses. Clinical symptoms were carefully recorded in each case. If prazosin failed to produce sustained clinical improvement, therapy with hydralazine 300 mg daily (100 mg every 8 hours) was begun, and clinical responses observed in a similar fashion.

Data Analysis

MAP and MPAP were measured electronically. Hemodynamic parameters were calculated as follows:

- cardiac index (CI) = CO/body surface area (l/min/m²)
- total systemic vascular resistance (TSVR) = 80(MAP - MRAP)/CO (dyn-sec-cm⁻⁴)
- pulmonary vascular resistance (PVR) = 80(MPAP - LVFP)/CO (dyn-sec-cm⁻⁴)

Statistical analysis was performed using the t test for paired data. The hemodynamic responses to first doses of prazosin at peak effect (1–2.5 hours after administration) were compared with the peak effects of second, third, and fourth doses of the drug administered under similar control hemodynamic states.

Results

Hemodynamic changes with sequential doses of prazosin are summarized in tables 2, 3A, 3B, 3C, and 3D, and figures 1–4.

First Dose Prazosin

Administration of the initial 5-mg dose of prazosin produced a marked improvement in cardiac performance. In the eight patients studied, the CI increased from 1.68 to 2.55 l/min/m² (±0.87 ± 0.08) and right and left ventricular filling pressures dropped substantially (12.4 to 4.9 mm Hg, -7.5 ± 0.8 and 25.3 to 14.6 mm Hg, -10.7 ± 0.8, respectively). There was a marked drop in MAP (83.0 to 64.1 mm Hg, -18.9 ± 2.7) and MPAP (40.1 to 28.4 mm Hg, -11.7 ± 1.5). TSVR was reduced 45% (2118 to 1154 dyn-sec-cm⁻⁴) and PVR declined 41% (461 to 271 dyn-sec-cm⁻⁴). HR slowed from 89 to 76 beats/min (–13 ± 1). All changes were significant (p < 0.001).

The onset of action of first doses of prazosin was observed at 30–90 minutes. Peak CO occurred at 60–120 minutes, but maximal decreases in LVFP and MAP were usually delayed until 90–150 minutes after.
oral administration. The response to initial doses was prolonged; hemodynamic variables remained near peak effect for 6–10 hours, and then gradually returned to control values over the next 12–30 hours (mean 18 ± 2 hours).

Sequential Prazosin Doses

Despite very similar control hemodynamic states, a second dose of 5 mg of prazosin produced hemodynamic changes of lesser magnitude than the initial dose. With the second dose, CI rose only 0.41 ± .11 l/min/m² from control values (p < 0.01), LVFP fell only slightly (−4.7 ± 1.2 mm Hg, p < 0.01), MAP decreased moderately (−6.6 ± 1.7 mm Hg, p < 0.01), MPAP declined only 4.4 ± 1.4 mm Hg (p < 0.05), and MRAP fell slightly (−2.7 ± 0.9 mm Hg, p < 0.05). HR did not change significantly, and TSVR and PVR declined only 22% and 16%, respectively. The magnitude of the hemodynamic changes with second doses of prazosin were less than 50% of the magnitude of changes seen with first doses and differed significantly from changes with first doses (p < 0.01 for all hemodynamic variables). In no patient did the second dose of prazosin provoke the same degree of response as the first dose; in fact, a second dose of prazosin produced no observable hemodynamic effects in two patients in whom first doses had elicited changes that were typical for the entire group (tables 3A, 3B, 3C, and 3D).

To determine if an increase in plasma volume due to the withholding of digitalis and diuretic therapy for 24–48 hours could play a role in the observed tachyphylaxis, third doses of prazosin were evaluated

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**Table 3A. Individual Changes in Cardiac Index with Sequential Doses of Prazosin and Hydralazine**

<table>
<thead>
<tr>
<th>Patient</th>
<th>1st 5-mg dose prazosin</th>
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<th>3rd 5-mg dose prazosin</th>
<th>1st 10-mg dose prazosin</th>
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Mean 1.68 2.55* 1.68 2.09† 1.79 1.98 1.76 2.15‡ 1.82 2.98*

± SEM 0.13 0.14 0.13 0.12 0.15 0.17 0.18 0.28 0.18 0.21

Data are expressed as l/min/m². Control values refer to the mean of three hourly baseline determinations before drug administration. Drug values reflect peak effect observed at 1–2.5 hours. Expressions of statistical significance as follows: * = p < 0.001, † = p < 0.01, and ‡ = p < 0.05.

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**Table 3B. Individual Changes in Left Ventricular Filling Pressure with Sequential Doses of Prazosin and Hydralazine**

<table>
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<th>1st 5-mg dose prazosin</th>
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Mean 25.3 14.6* 24.6 19.9† 22.5 20.5 25.4 20.6‡ 24.2 17.8*

± SEM 1.1 1.0 1.2 1.2 0.9 1.6 0.8 1.7 1.9 1.7

Data are expressed in mm Hg. Control values refer to the mean of three hourly baseline determinations before drug administration. Drug values reflect peak effect observed at 1–2.5 hours. Expressions of statistical significance as follows: * = p < 0.001, † = p < 0.01, and ‡ = p < 0.05.
Table 3C. Individual Changes in Mean Systemic Atrial Pressure with Sequential Doses of Prazosin and Hydralazine

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<td>64.1*</td>
<td>81.6</td>
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*SEM 4.1 3.3 3.6 3.7 3.3 3.7 3.5 5.6 3.3 5.1

Data are expressed in mm Hg. Control values refer to the mean of three hourly baseline determinations before drug administration. Drug values reflect peak effect observed at 1–2.5 hours. Expressions of statistical significance as follows: * = p < 0.001, † = p < 0.01, and ‡ = p < 0.05.

After intravenous administration of digoxin (0.125–0.25 mg) and furosemide (100–200 mg), these doses were being selected according to renal function and previous clinical responses. The diuresis that followed resulted in a weight loss of 1.9 ± 0.4 lbs. Hemodynamic variables returned toward control values 12–18 hours later (MAP, LVFP, and MRAP were necessarily somewhat lower). At this time, third 5-mg doses of the drug produced only small and insignificant overall responses (table 2), and six patients manifested no discernible effects. Administration of 10-mg doses in five of these six patients produced significant hemodynamic effects in only three (tables 3A–3D); with second 10-mg doses of prazosin in two patients, the same attenuation of effect was observed. Overall, the hemodynamic changes with first 10-mg doses were significantly different from control, but were small. All six patients continued on prazosin therapy for 3–42 days (mean 16 ± 6 days), with progressive increments in dosage up to 45 mg daily (mean 31 ± 5 mg) in an effort to produce sustained clinical responses. Although all six patients spontaneously remarked on relief of fatigue and dyspnea with first doses of prazosin, maintenance therapy produced little amelioration of symptoms, and each increment in dosage produced only transient clinical improvement. Of these six patients, five were subsequently treated with oral hydralazine. Their hemodynamic responses to single doses of 100 mg of the drug determined just before invasive monitoring was stopped are summarized in tables 2, 3A–3D, and figures 1–4. Although many hemodynamic variables changed similarly, the increases in CI and the reduction in TSVR with 100 mg of hydralazine were superior.
to that achieved by therapy with 10-mg doses of prazosin ($p < 0.02$). When we began maintenance hydralazine therapy (300 mg daily), we observed sustained clinical improvement in all five patients.

Only two patients (MS and AM) demonstrated sustained hemodynamic effects with prazosin. Although second 5-mg doses produced less response than first doses, there was little further tolerance after third and fourth doses. CI increased 52% and 43%, and LVFP decreased 6 and 7 mm Hg, respectively. These effects could be sustained with prazosin at 8–12-hour intervals. These two patients did not differ significantly from the six patients who did not manifest sustained responses to prazosin with regard to the etiology of heart failure, control hemodynamic state, or underlying pathophysiology. When discharged, both patients had improved, and the improvement was sustained after 2–4 months of ambulatory therapy.

**Discussion**

Initial doses of orally administered prazosin produced marked increases in CI and substantial reductions in MRAP and LVFP, yet serial doses of the drug at the same and even higher levels were accompanied, in most patients, by the rapid development of tolerance and complete loss of drug action. Clinically, initial doses resulted in a marked amelioration of dyspnea and fatigue which lasted 12–24 hours, but repeated doses did not prevent the recurrence of dyspnea, as hemodynamic variables returned toward control values. Administration of digoxin and furosemide failed to restore the circulatory effects of prazosin, and the use of higher doses of prazosin improved cardiovascular performance minimally and the drug's effect failed totally upon repeated administration. Only two of eight patients had sustained hemodynamic effects of sufficient magnitude to justify chronic oral ambulatory therapy.

Similarly impressive hemodynamic changes with first doses of prazosin have been previously reported. The improvements in CI, LVFP, and MRAP that we observed agree substantially with
FIGURE 3. A) and B) Changes in mean systemic arterial pressure and total systemic vascular resistance with sequential doses of prazosin and hydralazine. As with other variables, rapid tachyphylaxis with serial prazosin doses is observed. (The values before the third dose of prazosin are determined after the administration of diuretics and are necessarily somewhat lower.) See figure 1 for explanation of symbols.

those seen by other investigators. Compared with these studies, however, our patients experienced a significant reduction in HR. The explanation for this difference is unclear, but may be related to the larger doses of the drug we administered. Previous investigators used 2-7 mg of prazosin with the mean dose normalized for a body weight of 46 µg/kg. We administered a fixed dose of 5 mg to each patient, so that doses normalized for body weight were approximately twice as great (86 µg/kg). Prazosin has a negative chronotropic effect — as previously suggested, since peripheral dilatation is not accompanied by the expected reflex tachycardia and can block hydralazine-induced tachycardia. We feel that this is mediated by the enhancement of cholinergic myocardial stimuli by increased levels of cyclic GMP at cholinergic receptor sites in the myocardium. The chronotropic response to sympathetic stimulation in dogs is unchanged at low doses of prazosin, but hydrolysis of cyclic GMP is more efficiently inhibited at higher concentrations of the drug, potentially comparable to those used in our study. This negative chronotropic effect is attenuated after repeated doses of prazosin and disappears with maintenance therapy.

In contrast to our experience, Awan et al.23 reported sustained clinical improvement with the use of maintenance prazosin therapy in doses of 8-28 mg daily in nine patients with severe heart failure due to ischemic heart disease. However, they evaluated the improvement of ventricular function only by echocardiography and exercise testing. Unfortunately, echocardiography is of limited value in the evaluation of left ventricular function in ischemic heart disease. Moreover, one must cautiously interpret improvements in exercise tolerance by exercise testing, since significant improvement has been observed with placebo therapy,27 emphasizing the need for a double-blind interpretation of data. More importantly, invasive studies were performed for only first doses of prazosin and for only 6 hours, and thus the reported clinical improvement in dyspnea and fatigue after 2-4 months of therapy has no invasive hemodynamic substantiation. In contrast, using invasive monitoring, we found only two patients in whom prazosin had sustained hemodynamic effects after 3-4 days of therapy. In most of our patients we observed only minimal hemodynamic and clinical effects, even with high doses of prazosin (10 mg per dose) administered as maintenance therapy.

An exaggerated response to first doses of prazosin with subsequent marked attenuation of effect after repeated doses is well-known in the treatment of hypertension. Manifested as a syndrome of marked postural hypotension, this "first dose phenomenon" was initially considered to be an idiosyncratic reaction or due to poor renal clearance. Further experience has shown that the effect could be precipitated in all patients, especially if first doses were larger than 1 mg or if the patients were
physically stressed\textsuperscript{20, 26} or sodium-depleted.\textsuperscript{16} The severe postural hypotension was maximal at 1–2 hours and persisted for 8–10 hours.\textsuperscript{28, 30, 36} These effects disappeared despite continued therapy, and a repeat challenge with the same dose 2 days later had little demonstrable effect.\textsuperscript{22, 36} Our invasively derived data establish a hemodynamic counterpart to this first dose phenomenon in the therapy of heart failure.

The mechanism of rapid tachyphylaxis to prazosin is unknown. Induction of hepatic enzymes with enhanced metabolic degradation of the drug has been proposed,\textsuperscript{30} but plasma levels of prazosin are much higher after 2 days of therapy than with initial doses.\textsuperscript{28, 36} Others have suggested that an expansion of plasma volume may be responsible for the tolerance,\textsuperscript{20} but diuresis with high doses of furosemide failed to restore hemodynamic responsiveness in our patients. A more plausible mechanism for tachyphylaxis may be the rapid development of tolerance to any chronically established \(\alpha\)-sympathetic blockade.\textsuperscript{29, 33} Although early work supported the idea of a direct smooth muscle vasodilator effect mediated by phosphodiesterase inhibition,\textsuperscript{28} more recent studies have indicated that all drug action may be completely explained by sympathetic blockade,\textsuperscript{13, 14, 16, 37, 38} specifically of the postsynaptic \(\alpha\)-sympathetic receptor,\textsuperscript{18} since pretreatment with \(\alpha\)-sympathetic blockers can totally abolish the effects of prazosin.\textsuperscript{19-20} As rapid tolerance to drug-induced \(\alpha\)-sympathetic blockade is well-known,\textsuperscript{18, 38} the marked attenuation of prazosin’s effect after first doses probably represents a similar phenomenon. Further work is needed to determine how long it takes to recover responsiveness to prazosin and other \(\alpha\)-blockers so that subsequent doses of the drug can produce hemodynamic effects similar to first doses.

The effectiveness of prazosin maintenance therapy in antihypertensive treatment programs is controversial. Initial, enthusiastic reports have mostly been from uncontrolled studies\textsuperscript{54, 60} or from studies of prazosin in combination with other agents.\textsuperscript{21, 36, 41-43} Some controlled studies have indicated that prazosin has little overall hypotensive action, while others have suggested that chronic ambulatory use does result in sustained antihypertensive effects, although the decrease in blood pressure is relatively small.\textsuperscript{43, 44} Rather large doses are required,\textsuperscript{46} and only a minority of patients manifest a sustained therapeutic effect.\textsuperscript{46, 47} Additional work is necessary to determine if doses of prazosin even higher than those we have used will result in a higher percentage of patients who manifest a sustained response to prazosin in the therapy of either hypertension or heart failure. However, the lack of any additional effect with higher doses has been suggested in animal\textsuperscript{14, 16} and clinical studies.\textsuperscript{44, 46, 48, 49} Furthermore, the safety of chronic, large doses of prazosin must be tested.

We believe that hydralazine remains the most consistently effective agent for acute and chronic therapeutic afterload reduction in congestive heart failure. Sustained clinical improvement does occur,\textsuperscript{5, 60} and hemodynamic monitoring for 6 weeks and longer has revealed no evidence of tachyphylaxis.\textsuperscript{50, 51} The five patients in our study who were treated with hydralazine after exhibiting total tolerance to prazosin had overall hemodynamic responses similar to those reported by us and others,\textsuperscript{22, 32} and superior even to those induced by high doses of prazosin. The major limitation of hydralazine therapy in our experience remains a high frequency of adverse effects (intractable headaches and precipitation of ischemic events)\textsuperscript{52} which unfortunately restricts its therapeutic use in a significant number of patients.

Our study underscores the need for sustained invasive hemodynamic monitoring to confirm the improvement in left ventricular performance during administration of vasodilator agents before we make conclusions about therapeutic effectiveness or a commitment to chronic therapy. We found that the use of oral prazosin for combined preload and afterload reduction in the therapy of patients with severe congestive heart failure is associated with the rapid development of tachyphylaxis and loss of clinical effectiveness after several days of therapy, despite impressive initial responses to the drug. This tolerance precludes the use of prazosin for chronic ambulatory vasodilator therapy except in the few patients who manifest sustained beneficial hemodynamic effects.

Acknowledgments

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