Acute and chronic haemodynamic effects of prazosin in left ventricular failure*

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SUMMARY We evaluated the acute and chronic effects of prazosin treatment in 11 patients with chronic congestive heart failure, NYHA functional class III and IV. Before treatment mean arterial pressure averaged 100 ± 15 mmHg, left ventricular filling pressure 29 ± 11 mmHg, and systemic vascular resistance 2372 ± 1121 dynes s cm^{-5} . Prazosin administration resulted in haemodynamic improvement in all but one patient with significant lowering of the mean arterial pressure, left ventricular filling pressure, and systemic vascular resistance. Nine patients completed a 10-week course of ambulatory treatment. Five patients remained improved while four developed significant fluid retention; two of these had transient exacerbation of congestive heart failure. This was controlled by increasing diuretic and/or prazosin treatment. After 10 weeks all nine patients had advanced to NYHA functional class II. Repeat haemodynamic measurements disclosed complete haemodynamic tolerance in one patient while three other patients showed partial tolerance with a lower cardiac output (CO) response to prazosin. The nine patients, however, still showed significant lowering of the mean arterial pressure, left ventricular filling pressure, as well as the systemic vascular resistance. Though pharmacodynamic tolerance was noted in four out of nine patients, beneficial clinical and haemodynamic effects could be demonstrated after 10 weeks of prazosin treatment in most patients.

Further evaluation of the long-term effects of prazosin in chronic congestive heart failure is warranted.

The search for an oral vasodilator effective in relieving symptoms in patients with congestive heart failure has led several investigators¹⁻³ to evaluate prazosin. This quinazoline derivative produces alpha-adrenergic blockade, dilating both arteries and veins and providing a balanced reduction in preload and afterload.¹⁻⁴ After initial promising reports in acute and chronic congestive heart failure¹⁻² several investigators have reported tachyphylaxis during acute studies using continuous haemodynamic monitoring.⁵⁻⁶ The relevance of this acute phenomenon to chronic ambulatory treatment is uncertain, since other investigators have reported sustained benefit during chronic ambulatory treatment.²⁻⁷⁻⁸ Drug tolerance during chronic prazosin treatment has been described less frequently.⁹⁻¹⁰ Long-term controlled studies with a large study population will eventually

be needed to resolve these conflicting results. In most reported chronic studies the patients have been evaluated by non-invasive means. The present study was designed to test the effects of prazosin during acute and chronic treatment for congestive heart failure over a 10-week period with sequential invasive haemodynamic measurements.

Subjects and methods

Eleven patients were initially evaluated and nine completed the 10-week study. Their clinical features are listed in Table 1. There were seven men and four women aged 55 to 77 (mean 61 years). All patients had chronic congestive heart failure (mean duration 5.3 years). Each patient entered the study after a period in hospital for decompensated congestive heart failure (NYHA class III or IV) while receiving digitalis and diuretics. The aetiology was atherosclerotic heart disease in seven patients and cardiomyopathy in four.

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Fig. 1 (a) and (b) Haemodynamic response to prazosin in 11 patients after titration. Base, control measurements obtained after an 18 to 24 hour washout period. (A) CI, cardiac index; SVR, systemic vascular resistance. (B) $\overline{AP}$, mean arterial pressure; HR, heart rate; PAW, pulmonary artery wedge pressure. Arrows indicate second dose given to two patients. p values = * < 0.05 , ** < 0.02 , *** < 0.01 , * < 0.005 , ** < 0.002 , *** < 0.001 .

STUDY DESIGN

The study was divided into three phases. An initial inpatient pretreatment evaluation and titration with prazosin (phase I); an outpatient follow-up period lasting nine weeks (phase II); and a re-admission for a final evaluation (phase III).

Phase I

After informed consent the patients had right heart catheterisation and then entered into the study

if their left ventricular filling pressure exceeded 15 mmHg and the cardiac index was less than 2.5 l/min per m².

The patients were titrated slowly with increasing doses of prazosin on an eight hour schedule until maximum benefit was felt to be achieved as determined by daily assessment of their symptoms and signs of congestive heart failure. This took an average dose of 5.6 ± 2.2 mg every eight hours, and an average of six days. Prazosin was then withheld

Table 1 Clinical data

Case no.	Age (y)	Race	Sex	Duration CHF (y)	Diagnosis	NYHA class	Treatment
1	65	B	M	8	ASHD*	IV	Digoxin, dyrenium 50 mg, hydrochlorothiazide 25 mg
2	61	B	F	6	Cardiomyopathy**	IV	Digoxin, hydrochlorothiazide 25 mg
3	77	C	F	5	Cardiomyopathy	III	Digoxin, frusemide 120 mg
4	54	B	F	4	ASHD	IV	Digoxin, frusemide 120 mg
5	55	B	M	10	Cardiomyopathy	IV	Digitoxin, frusemide 80 mg
6	62	B	F	4	ASHD	IV	Digoxin, frusemide 200 mg
7	57	B	F	3	ASHD	III	Digitoxin, dyrenium 50 mg, hydrochlorothiazide 25 mg
8	65	C	F	3	ASHD	IV	Digoxin, frusemide 160 mg
9	52	B	M	3	Alcoholic cardiomyopathy	IV	Digoxin, frusemide 80 mg
10	64	B	F	1	ASHD	IV	Digoxin, frusemide 80 mg
11	57	C	M	10	ASHD	III	Digoxin, frusemide 160 mg

ASHD, arteriosclerotic heart disease; B, black; C, Caucasian.

*No response after titration.

**Cerebrovascular accident at 5 weeks, dropped from study.

STATISTICAL ANALYSIS

The data were analysed by analysis of variance except for the hourly measurements shown in Fig. 1 and 2 which were analysed using Student's paired *t* test. The null hypothesis was rejected with $p < 0.05$. Results are expressed as mean $\pm$ SD.

Results

CLINICAL COURSE

The in-hospital titration phase was completed by 11 patients and 10 patients reported an improvement in their symptoms of dyspnoea and/or fatigue. One patient showed no clinical or haemodynamic improvement and was dropped from the study. Of the 10 patients who entered the ambulatory phase, one had a cerebrovascular accident during the fifth week of treatment and was dropped from the study. This patient remained subjectively improved until then. Nine patients completed the 10 weeks of treatment with prazosin. The clinical status of five patients continued to improve with gradual diuresis and weight loss, while four showed significant weight gain associated with clinical evidence of oedema. Of these four patients, three had increasing symptoms of dyspnoea and two had an overt exacerbation of left ventricular failure with reappearance of pulmonary rales. Prazosin was increased in all four patients and diuretics were increased in the

three patients with increased symptoms of dyspnoea or signs of left ventricular failure. All four experienced a favourable response with the increase in drugs. All nine patients had improved to NYHA functional class II at the completion of the study. The mean prazosin dose of the nine patients averaged 5.5 ± 2.4 mg every eight hours before discharge and 6.3 ± 4 mg after 10 weeks of prazosin treatment. Their baseline weight averaged 72.6 ± 17.7 kg (160 ± 39 lb) and was reduced to 61.1 ± 24.5 kg (148 ± 54 lb) after 10 weeks of treatment (NS).

HAEMODYNAMIC STUDIES

The haemodynamic data are presented in Table 2 and Fig. 1 to 3. Table 2 shows the pretreatment, post-titration control measurements after washout and peak response to prazosin during the initial period in hospital (phase I), and the post-washout control measurements and peak response to prazosin after 10 weeks of treatment (phase III). Peak response was defined as the ventricular function curve with the simultaneous highest cardiac index and lowest pulmonary artery wedge.

Pretreatment heart rate averaged 91 ± 14 beats/min, mean arterial pressure 100 ± 15 mmHg, mean pulmonary artery pressure 43 ± 13 , left ventricular filling pressure 29 ± 11 mmHg, and cardiac index 1.76 ± 0.61 l/min per m^2 . The post-titration control haemodynamics after washout were not

CI (l/min per m ²)					SVI (ml/m ²)					SWI (g m/beat per m ²)					SVR (dynes s cm ⁻⁵)							
I			III			I			III			I			III			I			III	
P	C	PZ	C	PZ		P	C	PZ	C	PZ		P	C	PZ	C	PZ		P	C	PZ	C	PZ
2.30	1.75	1.80				19	17	18				12	15	14				1438	2193	2043		
1.30	1.33	1.68				17	12	16				—	14	19				—	5551	4368		
1.93	2.17	3.08	2.99	3.13		25	26	44	33	39		27	28	50	37	43		2182	1880	1251	1584	1370
1.42	1.43	1.63	1.71	2.24		14	14	18	17	25		21	16	19	19	28		3060	2878	2196	2336	1531
0.82	1.81	2.34	1.46	1.55		8	18	23	16	17		8	18	23	18	20		5163	2319	1829	2956	2848
2.27	2.20	2.66	2.12	2.54		24	24	27	24	28		23	23	26	22	29		1910	1863	1538	1882	1555
1.15	2.25	2.73	2.68	2.40		18	25	34	33	29		18	24	35	30	29		2921	1864	1571	1379	1398
2.80	2.62	4.17	2.08	2.79		24	29	43	34	44		22	32	50	36	45		1541	1634	979	1699	1166
2.19	1.62	2.74	1.47	2.14		21	16	27	18	27		19	15	25	16	23		1623	2424	1402	2335	1560
1.97	2.35	3.09	2.62	2.41		25	25	32	41	43		27	28	32	51	48		2000	1863	1249	1558	1468
1.28	1.60	1.81	1.69	1.79		13	17	22	20	21		11	18	17	19	16		1888	2300	1371	1951	1493
1.77	1.92	2.52	2.09	2.33		19	20	28	26	30		19	21	28	28	31		2373	2434	1800	1964	1599
0.61	0.42	0.78	0.56	0.48		6	6	10	9	10		7	6	12	12	11		1121	1092	925	499	484
<0.001			NS			<0.001			<0.05			<0.01			NS			<0.001			<0.01	
↑			↑			↑			↑			↑			↑			↑			↑	
									***						***						**	

significantly different from the pretreatment measurements. After we administered prazosin a significant haemodynamic improvement was noted in all but one patient. This patient received a second dose of 2 mg after two hours without benefit and was dropped from the study. The peak effect of prazosin usually occurred between one and two hours after administration and was significant for mean arterial pressure ($p < 0.02$), pulmonary artery wedge pressure ($p < 0.02$), right atrial pressure ($p < 0.02$), cardiac index ($p < 0.001$), stroke volume index ($p < 0.001$), stroke work index ($p < 0.01$), and systemic vascular resistance ($p < 0.001$).

Fig. 1 shows the hourly changes in heart rate, mean arterial pressure, pulmonary artery wedge pressure, cardiac index, and systemic vascular resistance after titration with prazosin. The significant lowering of the mean arterial pressure, pulmonary artery wedge pressure, and systemic vascular resistance, and the increase in cardiac index was sustained during the four hour study period.

After 10 weeks of treatment with prazosin, and after another 18 to 24 hour washout period, there

was a significant lowering of the heart rate ($p < 0.05$), pulmonary artery wedge pressure ($p < 0.005$), right atrial pressure ($p < 0.05$), stroke volume index ($p < 0.05$), stroke work index ($p < 0.005$), and systemic vascular resistance ($p < 0.02$) when compared with the pretreatment baseline (Fig. 2, Table 2). One patient failed to respond to prazosin; but the group as a whole showed a significant reduction in mean arterial pressure ($p < 0.02$), mean pulmonary artery pressure ($p < 0.05$), pulmonary artery wedge pressure ($p < 0.02$), stroke volume index ($p < 0.05$), and systemic vascular resistance ($p < 0.01$) when compared with the washout control measurements. The reduction in mean arterial pressure and pulmonary artery wedge pressure was sustained and remained significant during the four hours it was measured (Fig. 2, panel b). The cardiac index, however, failed to increase. The reason for this becomes clear when one compared the ventricular function curves in Fig. 2. During phase I, the control pulmonary artery wedge pressure was raised in all patients and after administration of prazosin all but one patient increased their cardiac index significantly as they

Fig. 2 Haemodynamic response in nine patients who completed 10 weeks of prazosin treatment. Control measurements are compared with pretreatment baseline. Abbreviations and symbols as in Fig. 1.

Fig. 3 Ventricular function curve showing peak changes in cardiac index and pulmonary artery wedge pressure after prazosin administration. Top panel shows the initial response in 11 patients. Bottom panel shows the response of the nine patients who completed 10 weeks of prazosin treatment. Heavy arrow and closed circles indicate mean response for the group. Dashed vertical lines show limit of normal pulmonary artery wedge pressure. For explanations see text.

lowered their pulmonary artery wedge pressure. During phase III control pulmonary artery wedge pressure was normal in two patients (8 and 12 mmHg) and their cardiac index dropped after administration of prazosin, probably because their pulmonary artery wedge pressure was reduced to suboptimal levels. Among the seven patients with a raised pulmonary artery wedge pressure, one failed to respond and showed total drug tolerance. Another patient had a significant lowering of the mean arterial pressure and pulmonary artery wedge pressure but his cardiac index did not increase. Five patients increased their cardiac index significantly though in two patients the increase was less than during phase I.

Discussion

Prazosin treatment improved symptoms of dyspnoea and fatigue in 10 of 11 patients to whom it was administered during in-hospital titration. The clinical course of these patients differed during ambulatory treatment. In five patients, the clinical improvement was sustained and associated with gradual diuresis. Fluid retention was a significant problem in four patients, in two of whom there was

transient exacerbation of left ventricular failure. This problem occurred early and required an increase in diuretic and/or prazosin treatment. After 10 weeks of prazosin treatment, however, all patients were symptomatically improved and had advanced to NYHA functional class II.

We were able to show a significant haemodynamic improvement in 10 out of 11 patients after initial administration and titration of prazosin treatment and this improvement was still evident in eight of nine patients who completed the 10 weeks of ambulatory prazosin treatment. Several investigators have recently reported pharmacodynamic tachyphylaxis to prazosin during short-term administration under haemodynamic monitoring,^{5,6} but others have failed to confirm this observation.¹¹ This phenomenon is poorly understood and it may be manifest at rest but not during exercise.¹²

Our procedure for invasive haemodynamic assessment followed an 18 to 24 hour washout period. It is possible that the mechanisms causing tachyphylaxis reversed during this interval and responsiveness to prazosin was restored when re-administered. All but one of our patients, however, reported clinical improvement at the start of the washout and haemodynamic studies. In three patients the improvement could have been related in part to the increase in diuretic treatment; this would not explain, however, the improvement in the other seven. Furthermore, we noted that after the final washout period there was a significant reduction in the control heart rate, pulmonary artery wedge pressure, right atrial pressure, stroke volume index, stroke work index, and systemic vascular resistance when compared with the pretreatment baseline. These results suggest a persistent effect of prazosin treatment after the drug had cleared from the plasma. Prazosin as well as hydralazine and minoxidil have been shown to remain in the blood vessel walls for longer periods.¹³ An alteration of the many feedback loops or endogenous chemicals, hormones, and neurotransmitters involved in the homeostasis of congestive heart failure during chronic prazosin treatment may be an additional or alternative explanation.

During the final administration of prazosin one patient failed to respond and three others showed a blunting of the cardiac index response. Blunting of haemodynamic responses has been previously reported during chronic prazosin treatment^{10,11} and less frequently with hydralazine.¹⁴ Significant haemodynamic improvement was shown, however, in most of our patients after 10 weeks. If one were to accept the studies that show acute haemodynamic tachyphylaxis as the predictors of chronic effectiveness of prazosin treatment, one would not expect to

see the beneficial responses observed in our patients or those patients reported in other long term studies.^{7,8} We, therefore, must question the clinical relevance of acute haemodynamic tachyphylaxis in predicting the effectiveness of chronic prazosin treatment for congestive heart failure. It has been shown that the acute haemodynamic changes produced by reserpine and propranolol during treatment for hypertension may be quite different from those that occur during chronic administration.¹³ For example, the cardiac output decreases during the initiation of treatment with reserpine but returns to control levels during chronic treatment. Propranolol increases the systemic vascular resistance acutely but lowers it during chronic treatment. This suggests that long term effects of vasodilator therapy cannot always be predicted with acute drug testing and are best examined with long term studies.

Conclusions

Our study indicates that in spite of the development of tolerance, significant haemodynamic benefits from prazosin can be shown in many patients for several weeks. Our results can only be considered preliminary as the number of patients was small, the study uncontrolled, and the follow-up extended to only 10 weeks. The differences in patient population and study design and the small number reported by others, usually in uncontrolled studies, make it difficult to reach definitive conclusions. We believe that the haemodynamic effectiveness of prazosin in congestive heart failure should be examined in a larger study population with double blind controlled studies to assess conclusively its value in the long term treatment of chronic congestive heart failure.

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