Acute and Chronic Cardiocirculatory Effects of Oral Prazosin in Chronic Refractory Heart Failure

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SUMMARY

The acute hemodynamic effects of oral prazosin were investigated in 7 patients with chronic refractory heart failure. A single dose of 1 to 3 mg prazosin produced a significant increase in cardiac index (+17.6%, $p < 0.01$) associated with substantial decreases in pulmonary arterial diastolic pressure (-31.6%, $p < 0.02$), systemic vascular resistance (-29.7%, $p < 0.01$), and double product (-24.1%, $p < 0.02$). Plasma renin activity was significantly elevated (+42.4%, $p < 0.02$). These effects were found maximum at 2 hours and persisted for 8 hours.

The chronic hemodynamic effects in 5 patients with chronic refractory heart failure were evaluated by administration of 1 to 2 mg prazosin 3 times daily for 8 weeks, and ventricular function was assessed by echocardiography and carotid pulse recording. All the patients showed improvement in the clinical symptoms of heart failure. Peripheral venous pressure decreased slightly (-12.5%). ET/PEP increased (+24.5%) without any significant changes in EF and mVcf. Plasma renin activity also slightly increased (+17.8%).

Thus, prazosin possesses sustained nitroprusside-like actions, and is effective in the management of chronic congestive heart failure refractory to conventional therapy. While, further investigation is necessary to define the effect of prazosin on plasma renin activity.

Additional Indexing Words:

Vasodilator therapy Preload Afterload Plasma renin activity

MANY recent studies have demonstrated the effectiveness of vasodilator therapy^{1),2)} in patients with acute heart failure. The infusion of nitroprusside³⁾ or phentolamine⁴⁾ increases cardiac output and decreases pulmonary venous pressure, also relieves the signs of congestive heart failure.

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However, orally effective drugs in the treatment of chronic refractory heart failure have been demanded.

The nitrates,⁵⁾ which principally cause venodilation, reduce ventricular preload and pulmonary congestion. On the other hand, hydralazine⁶⁾ increases cardiac output by reducing ventricular impedance subsequent to peripheral arterial dilation. Therefore, the combination of nitrates and hydralazine can relieve the symptoms of both pulmonary congestion and low output.⁷⁾ Chronic hydralazine therapy, however, may be associated with sodium retention, the development of drug tolerance, and the induction of systemic lupus erythematosus syndrome.⁸⁾

Prazosin,⁹⁾ a new oral antihypertensive agent, has been reported to have balanced vasodilator effects on the systemic arterial and venous beds.

The purpose of this study, therefore, was designed to evaluate the acute cardiocirculatory effects of orally administered prazosin in patients with congestive heart failure and to determine whether chronic oral prazosin therapy might be useful in the long-term management of chronic refractory heart failure.

PATIENTS AND METHODS

1. Acute cardiocirculatory effects

Acute cardiocirculatory effects were investigated in 7 patients with chronic congestive heart failure, refractory to conventional therapy with digitalis and diuretics (Table IA).

In all patients, right atrial pressure (RA), pulmonary arterial diastolic pressure (PADP) were recorded with a balloon-tipped triple-lumen catheter. Cardiac output (CO) was measured by thermodilution techniques¹⁰⁾ by using ice cold water as the indicator. Arterial blood pressure (AP) was obtained by cuff recordings. The mean arterial pressure ($\overline{AP}$) was estimated from the formula $\overline{AP} = D + (S - D)/3$, where S=peak systolic and D=diastolic pressure. Derived hemodynamic parameters were calculated as followings:

Cardiac index (CI)=CO/body surface area (L/min/m²)

Stroke volume index (SVI)=SV/body surface area (ml/m²)

Stroke work index (SWI)=SVI $\times$ ($\overline{AP}$ - PADP) $\times$ 0.136 (Gm·m/m²)

Systemic vascular resistance (SVR)

=80 ($\overline{AP}$ - $\overline{RA}$ /CO) (dynes·sec·cm⁻⁵)

After obtaining baseline hemodynamics, a single dose of 1 to 3 mg of prazosin was administered orally and hemodynamic measurements were repeated every hour for 8 hours following administration of the agent.

Peripheral venous blood was drawn before and 30 min, 1, 3, 6 hours after administration of prazosin to measure plasma renin activity (PRA) and free fatty acid (FFA) by radioimmunoassay and Itaya-Ui method respectively.

2. Chronic cardiocirculatory effects

Chronic cardiocirculatory effects were investigated in 5 ambulatory patients

Table I. Patient Population

	No.	Age Sex	Diagnosis	NYHA	Therapy prior to study	Dose of prazosin
A. Acute effects	1	71 M	IHD	IV	D+F	2 mg
	2	58 F	HHD	III	D+F	1.5 mg
	3	58 F	HHD	III	D+F+MD	2 mg
	4	60 F	MS	III	D+F+S	1.5 mg
	5	77 M	MI	III	D	3 mg
	6	63 F	MSI	III	D+F+S	1 mg
	7	71 M	MSI & AI	III	D+F+S	1.5 mg
B. Chronic effects	1	62 F	MS	IV	D+E+S	1 mg × 3
	2	53 M	MI	III	D+F+S+H	1 mg × 3
	3	67 M	MSI	IV	D+F+S	1 mg × 3
	4	72 M	MSI & AI	IV	D+F+S	2 mg × 3
	5	56 F	CCM	III	D+F+S	1 mg × 3

Abbreviations: NYHA=New York Heart Association functional class; IHD=ischemic heart disease; HHD=hypertensive heart disease; CCM=congestive cardiomyopathy; D=digoxin; F=furosemide; S=spironolactone; MD=methyldopa; H=hydralazine.

with chronic refractory heart failure (Table IB). Five patients were administered 1 to 2 mg prazosin 3 times daily for 2 to 8 weeks.

Ventricular function was assessed by echocardiography¹¹⁾ and carotid pulse recording.¹²⁾ These recordings were performed before and during administration of prazosin. The end-diastolic dimension (Dd) and the end-systolic dimension (Ds) by echocardiography, and ejection time (ET) and preejection period (PEP) by carotid pulse recording were measured. And other parameters were calculated as followings;

$$SV = Dd^3 - Ds^3 \quad (\text{ml})$$

$$EF = SV / Dd^3 \quad (\%)$$

$$mVcf = (Dd - Ds) / Dd \cdot ET \quad (\text{circ./sec})$$

Peripheral venous blood was drawn before and during administration of prazosin, and plasma renin activity and free fatty acid were measured.

RESULTS

1. Acute cardiocirculatory effects (Figs. 1, 2, 3)

While the control heart rate of 68 ± 2.8 (SEM) beats per minute remained unchanged at 71 ± 4.6 beats per minute ($+3.8\%$), the control mean arterial pressure of 96 ± 7.9 mmHg was reduced to 77 ± 4.5 mmHg (-19.9% , $p < 0.01$) after administration of prazosin. The double product of heart rate $\times$ systolic blood pressure, an index of myocardial consumption of oxygen,¹³⁾ decreased from 9755 ± 1158 to 7403 ± 675.2 (-24.1% , $p < 0.02$). Pulmonary arterial diastolic pressure, regarded as representative of left ventricular filling pres-

sure, decreased significantly from 20.9 ± 2.94 mmHg to 14.3 ± 1.82 mmHg (-31.6% , $p < 0.02$). Cardiac index increased from 2.39 ± 0.279 l/min/m² to 2.81 ± 0.248 l/min/m² ($+17.6\%$, $p < 0.01$). Both stroke volume index and stroke work index rose significantly, from 35.5 ± 4.35 ml/beat/m² to 41.7 ± 4.52 ml/beat/m² ($+17.5\%$, $p < 0.05$), and from 37.5 ± 6.25 Gm·m/m² to 41.9 ± 6.38 Gm·m/m² ($+11.7\%$, $p < 0.05$), respectively. Systemic vascular resistance decreased from 2367 ± 309.4 dynes·sec/cm⁵ to 1663 ± 168.0 dynes·sec/cm⁵ (-29.7% , $p < 0.01$) (Fig. 1).

These hemodynamic effects on mean arterial pressure, double product and pulmonary arterial diastolic pressure, appeared in 30 min and became maximum at 2 hours and persisted for 8 hours following administration of prazosin. The effects on cardiac index and systemic vascular resistance appeared in 30 min and persisted for 3 hours (Fig. 2).

Plasma renin activity rose from 3.14 ± 1.109 ng/ml/hr to 4.47 ± 1.118 ng/

Fig. 1. Maximum effects of a single oral dose of prazosin (P) compared with control values (C). Open circles indicate average values $\pm$ SEM. Mean percent change and statistical level are marked in the parentheses. HR=heart rate; $\overline{AP}$ =mean arterial pressure; DP=double product; PADP=pulmonary arterial diastolic pressure; CI=cardiac index; SVI=stroke volume index; SWI=stroke work index; SVR=systemic vascular resistance.

Fig. 2. Sequential effects of a single oral dose of prazosin in 7 patients with chronic congestive heart failure. Average values $\pm$ SEM are shown for the 8 hour period of hemodynamic evaluation. HR=heart rate; $\overline{AP}$ =mean arterial pressure; DP=double product; PADP=pulmonary arterial diastolic pressure; CI=cardiac index; SVR=systemic vascular resistance.

ml/hr (+42.4%, $p < 0.02$). Free fatty acid decreased from 0.46 ± 0.132 mEq/L to 0.20 ± 0.043 mEq/L (-56.5% , n.s.) (Fig. 3).

2. Chronic cardiocirculatory effects (Figs. 4, 5)

Heart rate decreased from 93 ± 7.2 beats/min to 80 ± 6.6 beats/min (-14.0%), and mean arterial pressure decreased slightly from 87 ± 4.7 mmHg to 81 ± 2.7 mmHg (-6.9%). The double product decreased from 11417 ± 1218.6 to 9518 ± 737.7 (-16.7%). Peripheral venous pressure decreased slightly from 16 ± 2.4 cmH₂O to 14 ± 1.3 cmH₂O (-12.5%). ET/PEP increased from 2.45 ± 0.504 to 3.05 ± 0.962 ($+24.5\%$), while ejection fraction (EF) and mean rate of left ventricular circumferential fiber shortening (mVcf) were not significantly changed from $44 \pm 7.2\%$ to $43 \pm 6.2\%$ (-2.3%), and from 0.64 ± 0.118 circ./sec to 0.63 ± 0.097 circ./sec (-1.6%), respectively (Fig. 4). Plasma renin activity rose slightly from 4.5 ± 1.12 ng/ml/hr to 5.3 ± 1.56 ng/ml/hr ($+17.8\%$). Free fatty acid rose, too, from 0.28 ± 0.39 mEq/L

Fig. 3. Effects of a single dose of prazosin (P) on plasma renin activity (PRA) and free fatty acid (FFA). Open circles indicate average values $\pm$ SEM. Mean percent change and statistical level are marked in the parentheses.

Fig. 4. Maximum effects of long-term prazosin therapy (P) compared with control (C). Open circles indicate average values $\pm$ SEM. Mean percent change is marked in the parentheses. All of these changes are not significant. HR=heart rate; AP=mean arterial pressure; DP=double product; PVP=peripheral venous pressure; ET/PEP=ratio of ejection time over pre-ejection period; EF=ejection fraction; mVcf=mean rate of left ventricular circumferential fiber shortening.

Fig. 5. The effects of long-term prazosin therapy (P) on plasma renin activity (PRA) and free fatty acid (FFA). Open circles indicate average values $\pm$ SEM. Mean percent change is marked in the parentheses.

Fig. 6. Symptomatic evaluation of the efficacy of long-term prazosin therapy.

to 0.31 ± 0.144 mEq/L (+10.7%) (Fig. 5). All of these changes were not statistically significant.

3. Chronic Effects on symptoms (Fig. 6)

Symptomatic evaluation and physical examination were performed before and during prazosin therapy. Prior to the treatment, 4 of the 5 patients had predominant symptoms of pulmonary congestion (wheezing and dyspnea), and 3 had severe symptoms of low output (fatigue and shortness of breath). During treatment, these symptoms were greatly diminished in all patients and the improvement was maintained through the follow-up period. Three patients in functional class IV were well enough to be in class III, and 2 patients in class III were well enough to be in class II, respectively, after prazosin therapy (Fig. 6). One patient complained of anorexia at 2 weeks after therapy.

DISCUSSION

Prazosin is reported to have peripheral vascular relaxing effects by a combination of post-synaptic alpha blockade and direct action.¹⁴⁾ The agent also relieves congestive heart failure by reducing left ventricular filling pressure, and ventricular impedance with augmentation of cardiac output.¹⁵⁾

The first purpose of our study was to investigate the acute cardiocirculatory effects of a single dose of prazosin.

The present results indicate that a sustained reduction in pulmonary arterial pressure accompanied with a significant increase in cardiac output can be achieved. In conclusion, oral prazosin alone possesses both systemic arteriolar and venodilator effects similar to short-acting nitroprusside.¹⁶⁾

These hemodynamic effects appeared within 30 min and were maximum at 2 hours, being still maintained at 8 hours following a single oral dose of the drug.

Although there was a decline in systemic blood pressure, heart rate showed no change. These changes of blood pressure and heart rate caused the decline in the double product, and could improve the myocardial oxygen supply-demand relation. The mechanism of the lack of increase in heart rate in these patients is not clear, but, attenuation of augmented sympathetic nervous system activity, by improvement of congestive heart failure, seemed to be one of the most possible mechanisms. This assumption may be supported by the fact that free fatty acid, which is increased by catecholamine,¹⁷⁾ was decreased by prazosin.

As prazosin exerts a rapid and prolonged hemodynamic effects, this agent was expected to be beneficial in the long-term vasodilator therapy. And the second purpose of this study was to determine the efficacy of the long-term oral prazosin therapy in patients with chronic refractory heart failure.

The present investigation demonstrated that oral prazosin chronically improved heart failure symptoms indicated by lessened fatigue and dyspnea during the long-term ambulant therapy. And this effect was supported by the findings that peripheral venous pressure declined and ET/PEP by carotid pulse recording increased during the administration of the agent.

In patients with mitral stenosis, the reduction of afterload¹⁸⁾ and preload may not increase cardiac output, but aggravate heart failure. The other report¹⁹⁾ indicated that nitroglycerin alleviated pulmonary vascular congestion without a change in cardiac index in patients with mitral stenosis.

In our study, a beneficial effect was observed in 1 patient with mitral stenosis (Case No. 4); pulmonary arterial diastolic pressure fell from 20 to

18 mmHg, but cardiac index increased from 1.81 to 2.15 l/min/m² after a single dose of prazosin. This beneficial effect in a patient with mitral stenosis may be produced in some cases when pulmonary vascular resistance is pathologically, but reversibly, elevated.¹⁹⁾

Several observers^{20), 21)} have noted that plasma renin activity is not significantly increased with prazosin in hypertensive patients, when compared with the other vasodilator drugs such as hydralazine. On the contrary, our data indicated the increase of plasma renin activity in congestive heart failure by prazosin therapy. Further investigation is necessary to define the effect of prazosin on plasma renin activity in patients with congestive heart failure.

Thus, prazosin possesses sustained nitroprusside-like balanced dilator actions on the systemic arterial and venous systems, and is effective in the ambulatory management of chronic refractory heart failure.

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