

A review of the long-term effects of prazosin and hydralazine in chronic congestive heart failure

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In the last two years, six studies using prazosin in doses of 3-32 mg/day for two and 16 months have shown a persistent but variable benefit in 50-80% of those who initially responded favorably. However, serious side-effects occurred in up to 40% and, in many cases, tolerance developed. Mortality was 25-38% in 3-6 months, 50% by one year.

In five studies using hydralazine (sometimes combined with long acting nitrates), 150 patients observed from six up to 29 months showed sustained benefit in 26 to 59%, while in many cases hemodynamic values returned to pretreatment values. Again side-effects were considerable, with worsening of angina, fluid retention, gastrointestinal symptomatology and, rarely, lupus erythematoses. Mortality was 28-41% in 10-12 months, higher in non-responders than in responders.

Although exercise capacity increased in responders, no data are available today to prove that these vasodilators allow heart failure patients to live longer. Prudence is indicated in patients with congestive heart failure due to coronary artery disease. Furthermore, tolerance development, which only may be surmountable if discontinuation for a few weeks or switching to another drug is possible, is a serious problem limiting chronic vasodilator application.

Heart failure is a state of abnormal cardiovascular regulation in which the afterload mismatch is of major importance⁽¹⁾, fundamental compensatory changes having led to an increase in peripheral vascular resistance and an increase in heart size. Early treatment by vasodilators would therefore delay, or might even prevent heart failure: arterial dilatation would lead to a better unloading of the ventricle during systole, providing an increased muscle shortening⁽¹⁾; venous dilatation together with increased ventricular emptying would favor a decrease in end-diastolic heart size⁽²⁾. This attractive hypothesis has been tested in congestive heart failure and found to be true in several acute studies⁽³⁻⁵⁾.

For vasodilators to be effective in chronic heart failure, the beneficial acute hemodynamic actions of these agents should be maintained in long-term treatment. An increase in exercise capacity or the same exercise with more favorable hemodynamic parameters is an important long-term goal. Optimally

one would like naturally to see reduced morbidity and mortality. Finally, these goals should be achieved without major adverse side-effects.

This presentation reviews the results of treatment with prazosin and hydralazine administered for several months to patients in chronic heart failure. Prazosin is mainly a postsynaptic alpha-adrenergic blocker⁽⁶⁾. It increases cardiac output and stroke volume significantly during exercise and to a lesser degree at rest, alpha-adrenergic blockade being more evident during exercise⁽⁷⁾.

Recently, four studies have been reported using prazosin in doses of 3-32 mg/day for 6-16 months and involving 68 patients⁽⁸⁻¹¹⁾; in two further studies treatment was only assessed for 2-3 months⁽¹²⁻¹³⁾. All patients were in heart failure and treated continuously with digitalis and diuretics. Table I gives details about the observed beneficial and side-effects in these studies and their mortality.

Depending on the underlying degree of heart failure and the level of sympathetic tone, the results of the initial therapy may vary considerably. The

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Table 1 Recent long-term prazosin studies in patients with chronic congestive heart failure

	Months	n	Dosage (mg/day)	Beneficial effects	Side-effects	Mortality at		
						2-3 months	6 months	12 months
Rouleau <i>et al.</i> ⁽⁸⁾	15.9	34	3-21	If spironolactone added good long-term effects	Spironolactone prevents attenuation			50%
Awan <i>et al.</i> ⁽⁹⁾	12	16	8-32	NYHA 4 → 2.5, persistent symptomatic benefit	Delayed tolerance in 30%	Not mentioned		
Kuck <i>et al.</i> ⁽¹⁰⁾	6	10	15-20	SVR during exercise and PAP at rest and exercise $P < 0.05$	Hypotension in 40% tendency to fluid retention	Not mentioned		
Bertel <i>et al.</i> ⁽¹¹⁾	6	8	3-20	CI and SVI at rest $P < 0.05$ exercise tolerance improved	Orthostatic dizziness in 8%			25%
Feldman <i>et al.</i> ⁽¹²⁾	3	13	5		In 30% deterioration	38%		
Colucci <i>et al.</i> ⁽¹³⁾	2	10	16-24	NYHA 3.7 → 2.3, exercise duration and EF $P < 0.01$	Increased diuretics necessary	Praz. 0%		Pbo. 17%
Randomized double-blind								

CI = cardiac index; EF = ejection fraction; NYHA = New York Heart Association classification; PAP = mean pulmonary artery pressure; Pbo. = placebo; Praz. = prazosin; SVI = stroke volume index, SVR = systemic vascular resistance.

response to long-term therapy with prazosin depends even more on the underlying cause and severity of heart failure. Only in a subset of patients did a sustained beneficial effect persist, mainly during exercise. The phenomenon of tolerance was observed in most studies. The addition of spironolactone or an increase of other diuretics may prevent attenuation.

Hydralazine has potent direct arteriolar dilator

effect. In five recent studies using hydralazine (mostly in doses up to 400 mg/day) a total of 150 patients were observed for six to 29 months⁽¹⁴⁻¹⁸⁾. About 20% were considered early non-responders and about the same percentage stopped therapy because of side-effects. The main positive effects, as well as the considerable adverse effects and the mortality of these studies are summarized in Table 2. In these

Table 2 Recent long-term hydralazine and nitrate studies in patient with chronic congestive failure

	Months	n	Dosage (mg/day)	Beneficial effects	Side-effects	Mortality at		
						6 months	12 months	18 months
Morand <i>et al.</i> ⁽¹⁴⁾ (H)	29	37	200-400	CI increased initially 80%*, later less difference	Nausea, headaches, only first month, 13% antinuclear antibodies	32%	41%	> in IHD
Massie <i>et al.</i> ⁽¹⁵⁾ (H+N)	13	56	< 400	59% improvement by NYHA-classes in 6 months	Gastro-intestinal 32%, headache 14%, 18% stopped therapy, 5% systemic lupus erythematoses	22%	37%	63%
Walsh <i>et al.</i> ⁽¹⁶⁾ (H+N)	10	34		50% of patients maintained on therapy have sustained benefit	21% early non-responders, 24% stop because side-effects			0% R 87% NR
Packer <i>et al.</i> ⁽¹⁷⁾ (H)	8.6	11	Up to 900					Not mentioned
Mathey <i>et al.</i> ⁽¹⁸⁾ (H)	6	12	100-300	6 months: CI + 59%*, renal plasma flow + 35%*				Not mentioned

CI = cardiac index; IHD = ischemic heart disease; NR = non-responders, NYHA = New York Heart Association; R = responders; H = hydralazine; N = nitrates.

* $P < 0.05$.

studies, too, the pronounced initial hemodynamic effect was attenuated in most patients with time and benefit was sustained in only about half of those patients maintained on therapy.

A tendency toward higher mortality is reported in patients with heart failure due to coronary heart disease^(14,15). The effect on the coronary circulation has to be considered. Reduced diastolic aortic pressure means a generally reduced coronary perfusion pressure. Therefore the flow through fixed coronary stenoses decreases. A coronary steal phenomenon can take place, leading to lactate production⁽¹⁹⁾.

Discussion

Even with vasodilators which have differing molecular mechanisms and effects on regional flow, the main problem in long-term use is an attenuation of the desired effect in a high percentage of patients⁽²⁰⁾. It is at the present not clear which subsets of patients receive the greatest profit from a given vasodilator. In severe heart failure with markedly increased plasma levels of norepinephrine, but not necessarily always increased renin-angiotensin, the application of prazosin has been thought to be most favorable. But a reduction of sympathetic activity could be counteracted by the release of preformed norepinephrine with no net effect on plasma norepinephrine levels⁽²¹⁾. Furthermore the changes in receptor sensitivity as documented, e.g. by the blunted baroreceptor reflex in heart failure, may be more important than the plasma level of a hormone.

Also since the sympathetic nervous system and the renin-angiotensin system may be activated independently in congestive heart failure, it is understandable that inhibition of one system may not give the desired response because of compensation by the other⁽²²⁾. This reason may explain the fact that the reaction to both prazosin and hydralazine in chronic congestive failure varies, and that the chronic effects are less evident than the acute.

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