CLINICAL AND HAEMODYNAMIC RESPONSES TO CAPTOPRIL AND HYDRAZINE IN CHRONIC CONGESTIVE HEART FAILURE: THE IMPORTANCE OF PRELOAD REDUCTION

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Although many vasodilators are effective in the treatment of severe congestive heart failure, there have been few comparative studies of these drugs. We compared the acute haemodynamic effects of captopril and hydralazine in 11 patients with congestive cardiac failure unresponsive to diuretics and digitalis. Both drugs increased resting cardiac index, although this effect appeared more pronounced for hydralazine (33% v 25%). Captopril reduced pulmonary capillary wedge pressure (–8 mm Hg, p < 0.01) which decreased only slightly on hydralazine.

Long-term treatment was then started on the dose found effective during acute administration. Each drug was given for eight weeks. Exercise tolerance improved with both drugs, the increase during the hydralazine phase correlating with the increase in cardiac index at rest (r = 0.75; p < 0.05). Clinical improvement appeared more definite on captopril than on hydralazine, however. This improvement was maintained during the captopril phase only in those patients who had a greater than 25% reduction in pulmonary capillary wedge pressure in the acute study.

Introduction

Although many vasodilators exert acute haemodynamic and long-term clinical benefits in severe congestive heart failure (Franciosa, 1982; Chatterjee et al., 1978), the relative effectiveness of these drugs is not known as there have been few comparative studies among drugs. Moreover, such studies have concentrated on differences in acute haemodynamic responses (Franciosa et al., 1977; Packer et al., 1979; Pierpont et al., 1978; Vrobel & Cohn, 1980; Massie et al., 1981), despite the poor relationship between acute changes and long-term clinical response (Feldman et al., 1981; Fitchett et al., 1979; Franciosa & Cohn, 1980; Levine et al., 1980; Walsh & Greenberg, 1979). In addition, clinical improvement occurs irrespective of the pattern of acute haemodynamic change at rest (Franciosa, 1982; Chatterjee et al., 1978) or during exercise (Massie et al., 1981). Thus it is not known whether there are differences in response to vasodilator drugs during long-term treatment of severe congestive heart failure or whether comparison of acute haemodynamic effects would predict these differences.

We compared the acute and long-term responses to captopril, an angiotensin-converting enzyme inhibitor, and hydralazine in the same group of patients. When assessed in separate studies these drugs have different acute haemodynamic effects (Faxon et al., 1981; Franciosa et al., 1977) and both clinical and haemodynamic improvement occur during long-term therapy (Ader et al., 1980; Chatterjee et al., 1976) with tolerance occurring infrequently (Packer et al., 1982).

Methods

Patients The study population consisted of 11 patients who were in severe congestive heart failure despite treatment with digitalis and maximally tolerated diuretics in that increasing diuretic doses were ineffective or led to a deterioration in renal function (Table 1). The duration of heart failure ranged from three months to five years. Four patients had clinical evidence of some degree of mitral incompetence. Informed consent was obtained from all patients and the protocol was approved by the hospitals’ ethics committees.

Acute haemodynamic study The study was performed during a period of relative clinical stability after baseline measurements of chest radiograph, symptom-limited exercise tolerance, and left ventri-
cicular ejection fraction. Vasodilators, if any, were discontinued seven days before the study, and digoxin and diuretic therapy was maintained unchanged. The two drugs were compared on successive days. On the first day captopril was given in doses of 6.25 mg, 12.5 mg, and 25 mg at 90-minute intervals. This was equivalent to cumulative doses of 6.25 mg, 12.5 mg, and 25 mg. On the second day, hydralazine was given in doses of 50 mg, 100 mg, and 200 mg again at 90-minute intervals, equivalent to cumulative doses of 50 mg, 100 mg, and 200 mg. Haemodynamic measurements and plasma renin activity estimations (Sealey et al., 1972) were recorded twice at 30-minute intervals before and 90 minutes after each dose of the drugs. Haemodynamic measurements included the right atrial and pulmonary capillary wedge pressures, recorded through a balloon-tipped triple-lumen catheter. Cardiac output was measured in triplicate by thermodilution (Gould cardiac output computer). Blood pressure was measured by a conventional mercury sphygmomanometer and heart rate from the electrocardiogram. The dose of each drug was increased to maximum or until systemic vascular resistance fell by 40% or mean arterial pressure by 20 mm Hg.

Long-term study Maintenance therapy was started with the dose of drug found to be optimally effective during the acute study. Each drug was administered for eight weeks, captopril being given in the first period three times daily and hydralazine in the second period twice daily. The drugs were administered as placebo and active drug (double-dummy) so that patients were unaware of the change over. A symptom-limited exercise tolerance test, using a modified Bruce protocol, and left ventricular ejection fraction, by gated radionuclide technique, were recorded after one and eight weeks of each treatment period. Those carrying out the tests were unaware of the patients' medication. The ejection fraction could be measured in only nine patients as two patients were in atrial fibrillation. Clinical assessment was made at two weekly intervals and diuretics altered as clinically indicated.

Analysis of results by Student's t test for paired data and by analysis of variance for the comparison between drugs at peak dose.

Results

Acute study

The optimal dose of hydralazine was 200 mg in seven patients and 100 mg in four patients. The optimal dose of captopril was 25 mg in eight patients and 12.5 mg in three. Both drugs increased cardiac index significantly (Figure 1). Although this appeared to be more definite for hydralazine, the difference between drugs was not significant. Captopril reduced

<table>
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pulmonary capillary wedge and right atrial pressures, which decreased only slightly on hydralazine, and appeared to decrease mean arterial pressure more than hydralazine (−14% v −10%). Captopril also induced a fall in heart rate, while hydralazine increased heart rate.

**Chronic study**

Eleven patients completed the long-term captopril phase. One patient died suddenly while taking captopril two weeks after he had withdrawn from the trial. He had responded poorly to captopril during both acute and long-term administration and had required a prolonged period in hospital. Eight patients have now completed the hydralazine phase, one of whom died suddenly after responding poorly to both drugs during long-term administration.

Exercise tolerance improved initially in six of the 11 patients on captopril (mean ± SEM 4.4 ± 0.5 min v 2.9 ± 0.8 min, p < 0.05) and by week 8 had improved in eight patients (4.8 ± 0.7 min, p < 0.01). Exercise tolerance was also increased above baseline during hydralazine therapy though this was only significant at eight weeks (4.1 ± 0.8 min, p < 0.05). There was no relationship between acute haemodynamic and exercise responses to captopril. The improvement in exercise tolerance at the first and eighth week of the hydralazine treatment phase however, correlated positively with peak rise in cardiac index during acute administration, although this was significant only for the eighth week (r = 0.75; p < 0.05). Left ventricular ejection fraction improved during treatment with both captopril (0.44 ± 0.04 v 0.39 ± 0.04, p < 0.05) and hydralazine (0.46 ± 0.04, p < 0.02).

Although clinical improvement occurred initially
groups were small and the differences not statistically significant. In only one patient could the deterioration be reversed with increasing diuretics. Captopril was restarted at previous doses in the remaining four patients, three of whom regained their clinical status. The remaining patient had responded poorly to captopril in the first eight weeks and continued in severe cardiac failure even with higher doses of captopril and diuretics.

**Discussion**

The acute haemodynamic comparison of captopril and hydralazine confirms results of studies in separate patient groups (Faxon et al., 1981; Franciosa et al., 1977). Captopril reduces both cardiac preload and afterload, while hydralazine reduces cardiac afterload predominantly. The effect of hydralazine on heart rate, although unexpected, has been shown in patients with chronic heart failure (Franciosa et al., 1977; Packer et al., 1980; Chatterjee et al., 1978). Although theoretically undesirable, the frequency of angina did not increase with hydralazine.

Long-term treatment with both drugs improved exercise tolerance and ejection fraction, this improvement being maintained at two months. Although preliminary studies would suggest a relationship between resting haemodynamics and exercise tolerance (Massie & Kramer, 1982; Packer et al., 1978), drug-induced acute changes in resting haemodynamics appear poorly predictive of improvement in exercise tolerance during long-term treatment. In this study no relationship could be shown between acute alteration of resting haemodynamics with captopril and improvement in exercise tolerance. There was, however, a direct correlation between increased exercise capacity and increase in cardiac index at rest with hydralazine, possibly reflecting the wider response of cardiac output with this drug than with captopril. Although changes in pulmonary capillary wedge pressure did not predict exercise responses, clinical improvement failed to occur in patients on captopril whose pulmonary capillary wedge pressure did not decrease by more than 25%. This shows the lack of agreement between clinical improvement with vasodilators and increase in exercise tolerance, which has been noted before (Adler et al., 1980; Fitchett et al., 1979). Although this may be due to exercise tests being performed remote from clinical deterioration during a period of relative stability, another possible explanation is that maximum exercise tolerance and clinical improvement reflect two different haemodynamic variables, the former depending on cardiac index and oxygen utilisation (Massie & Kramer, 1982; Chatterjee et al., 1978), the latter on changes in pulmonary capillary wedge pressure at rest and at sub-optimal exercise.
The long-term study may be criticised as it was not
cross over or double blind. As acute deterioration can
occur on withdrawal of hydralazine (Black & Mehta,
1979) but not captopril (Maslowskiet al., 1981) a
cross-over trial was not considered justified.
Although worsening of the underlying disease may
have caused the clinical deterioration seen on
hydralazine, the fact that patients improved again on
reintroduction of captopril suggests that there are
important differences between these two drugs.
In conclusion, captopril improved both exercise
tolerance and clinical state, the latter depending on a
reduction in cardiac preload. Although hydralazine
improved exercise tolerance to the same extent, an
effect related to increased resting cardiac index, it
cau sed a less pronounced clinical improvement.
Thus, the theoretical advantage of combining preload
and afterload reduction in patients with severe con-
gestive heart failure is borne out in this study.
Changes in resting haemodynamics may help to
predict the long-term responses to chronic vaso-
dilator therapy.

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