Angiotensin converting enzyme inhibition in heart failure

J. G. F. CLELAND, H. J. DARGIE & J. I. S. ROBERTSON

Department of Cardiology and MRC Blood Pressure Unit, Western Infirmary, Glasgow, UK

- 1 Captopril, the first orally effective converting enzyme inhibitor, was administered to 14 patients with chronic heart failure for 6 week periods, in a double-blind crossover comparison with placebo.
- 2 Captopril improved symptoms and exercise performance, while left ventricular internal dimensions were reduced.
- 3 The fall in blood pressure induced by captopril was well tolerated.
- 4 Glomerular filtration rate was reduced and effective renal plasma flow increased on captopril.
- 5 No decline in body weight or total body sodium was seen, suggesting that a natriuresis had not occurred.
- 6 Serum and total body potassium rose.
- 7 Ventricular arrhythmias declined.

Keywords captopril heart failure exercise performance renal function arrhythmias total body potassium

Introduction

Heart failure is a clinical syndrome in which breathlessness, tiredness and ankle swelling are the dominant symptoms. It also carries a poor prognosis since less than half of those with New York Heart Association (NYHA) Grade III or IV heart failure will survive the following 12 months (Wilson *et al.*, 1982). Most patients appear to die suddenly rather than from steadily worsening heart failure (Meinertz *et al.*, 1984), and this has been related to ventricular ectopic activity on 24 h ambulatory echocardiographic (ECG) monitoring.

While the aim of treatment is to relieve symptoms primarily it should also be noted whether the prognosis has been favourably affected by treatment or otherwise. Although vasodilator therapy has been successful in improving haemodynamics acutely, and relieving the symptoms of acute left ventricular failure, the results of chronic oral therapy have been less impressive. In well-controlled studies only oral nitrates, prazosin and trimazosin have been shown to improve exercise performance, and symptomatic response is variable. Problems of tolerance also exist (Aronow *et al.*,

1977; Franciosa *et al.*, 1978; Colucci *et al.*, 1980).

The advent of orally-active angiotensin converting enzyme (ACE) inhibitors has led to promising results in several open studies. However, these drugs cannot be regarded solely as vasodilators. Although they do have vasodilator activity [more prominent on the venous side of the circulation (Packer *et al.*, 1980)], their selective effects on renal haemodynamics, their ability to suppress plasma aldosterone and catecholamines (Wenting *et al.*, 1983) and other possible effects on prostaglandins, antidiuretic hormone and kinins render these agents different from conventional vasodilators. Several placebo-controlled studies of ACE inhibitors have suggested benefit in heart failure (Captopril Multicentre Research Group, 1983; Kramer *et al.*, 1983; Cleland *et al.*, 1984). The following study describes the response of 14 patients with severe heart failure in a double-blind crossover comparison of placebo and captopril in 6 week treatment periods, after an initial 6 week open study on captopril. Using the patient as his own control we hoped to

Table 1 Baseline characteristics of the patients studied

<i>n</i>	20
Age	62 ± 9 years (s.d.)
Sex	14 male, 6 female
Frusemide dose	375 ± 128 mg/day
New York Heart Association Classification	3.6 (range 3–4)
Exercise time	5.3 ± 3.4 min
Echocardiography	
End-diastolic dimension	6.8 ± 0.8 cm
End-systolic dimension	5.6 ± 0.4 cm

reduce the wide inter-individual response often seen with vasodilators. Visual analogue scores for breathlessness, ankle swelling and tiredness were used to assess symptoms. Treadmill exercise performance and ECG left ventricular

dimensions were used to assess the response to therapy in a more objective manner. We also investigated renal function with isotope clearance techniques, whole body sodium by *in vivo* activation analysis and whole body potassium

Table 2 Comparison between the end of the double-blind placebo and captopril periods

	<i>Placebo</i>		<i>Captopril</i>
New York Heart Association Classification			
Average	2.5		2.0
Range	2–4	<i>P</i> < 0.02	1–3
Visual analogue scores			
Breathlessness (mm)	34 ± 22	<i>P</i> < 0.02	16 ± 17
Tiredness (mm)	28 ± 23	<i>P</i> < 0.02	12 ± 14
Ankle swelling (mm)	8 ± 8	*	8 ± 14
Blood pressure			
Systolic (mm Hg)	130 ± 27	<i>P</i> < 0.001	110 ± 18
Diastolic (mm Hg)	83 ± 16	<i>P</i> < 0.001	64 ± 13
Heart rate (beats/min)	79 ± 11	*	75 ± 11
Weight (kg)	67 ± 9.1	NS	67 ± 9.2
Exercise time (min)	7.6 ± 4.3	<i>P</i> < 0.007	9.1 ± 5.3
End-diastolic dimension (cm)	6.7 ± 1.0	<i>P</i> < 0.06	6.4 ± 1.0
End-systolic dimension (cm)	5.5 ± 1.0	<i>P</i> < 0.04	5.2 ± 1.0
Serum potassium (mmol/l)	3.4 ± 0.4	<i>P</i> < 0.001	3.9 ± 0.4
Serum creatinine (mmol/l)	113 ± 32	<i>P</i> < 0.02	133 ± 42
Glomerular filtration rate (ml/min)	53 ± 19	NS	48 ± 18
Effective renal plasma flow (ml/min)	241 ± 72	<i>P</i> < 0.05	287 ± 100
Total body sodium (mmol)	3200 ± 367	NS	3195 ± 447
Total body potassium (mmol)	2543 ± 135	<i>P</i> < 0.03	2667 ± 111
Plasma active renin concentration (μU/ml)			
Mean	262		405
Range	(12–1501)	*	(46–2289)
Angiotensin II (pmol/l)			
Mean	80		21
Range	(10–292)	<i>P</i> < 0.01	(6–47)
Aldosterone (ng/dl)			
Mean	18		11
Range	(3–74)	NS	(2–56)
Noradrenaline (nmol/l)	5.1 ± 2.6	<i>P</i> < 0.05	3.2 ± 1.7
Ventricular extrasystoles (per 24 h)			
Mean	1897		1387
Range	0–11,416	<i>P</i> < 0.05	0–10,445
Ventricular tachycardia (per 24 h)			
Mean	7		4
Range	0–86	<i>P</i> < 0.05	0–49

Figures are mean ± s.d. unless otherwise stated, and analysed by repeated measures* analysis of variance from the end of the open study unless an order effect was noted. NS = not significant.

by estimation of the endogenous ^{40}K . Cardiac rhythm was monitored using 24 h ambulatory ECG recording. Plasma renin concentration, angiotensin II, aldosterone and catecholamines were also measured. The baseline characteristics of the patients are shown in Table 1. Only the comparison between the end of the double-blind placebo and captopril periods are shown in Table 2 on the 14 patients who completed the study. Five patients died, only two of these on captopril, and a further patient was withdrawn for mitral valve replacement after a dramatic improvement on captopril. Detailed results are reported elsewhere (Cleland *et al.*, in press).

Results

Symptomatic improvement occurred as shown by the improvement in the NYHA score and the visual analogue scores for breathlessness and tiredness. Exercise performance improved and although the difference between placebo and captopril was only 90 seconds, as a graded treadmill test was used, this represents approximately a 50% increase in total work done as based on standard predictions of total oxygen consumption from the treadmill protocol. ECG dimensions were reduced. Both systolic and diastolic blood pressures fell while heart rate showed an insignificant decline on captopril.

Although isotopically determined glomerular filtration rate showed a statistically insignificant decline, 24 h creatinine clearance did fall significantly. Effective renal plasma flow rose. Serum sodium and total body sodium were unchanged, but both serum and total body potassium increased. Ventricular arrhythmias were less frequent during the captopril phase of the study.

The expected changes on the renin angiotensin axis were noted with a rise in plasma renin concentration and a fall in angiotensin II. While plasma aldosterone was reduced, this did not

reach statistical significance. However, plasma noradrenaline and adrenaline were lower on chronic captopril therapy.

Discussion

In a double-blind placebo-controlled study, captopril reduced heart size and improved symptoms and exercise capacity in a group of patients with severe cardiac failure. The fall in blood pressure was generally well tolerated and the fall in renovascular resistance suggested that improvement was associated with a reduction in systemic vascular resistance. However, we have noted syncope with the first dose of captopril. This can occur with doses as small as 6.25 mg, and is generally associated with bradycardia and a rise in plasma adrenaline, without a rise in plasma noradrenaline. Syncope occurs at the time of suppression of angiotensin II but is poorly predicted by either the initial plasma active renin concentration or by the serum sodium. Despite a reduction in plasma aldosterone and renal vasodilatation, no long-term natriuresis could be demonstrated. Ventricular extrasystoles and complex ventricular arrhythmias decreased in frequency. While these effects were not dramatic, the previously demonstrated relation of sudden death in heart failure to 24 h ECG arrhythmias suggest that captopril might not only improve symptoms but may also improve prognosis.

There are several reasons why arrhythmias might have been reduced, including a reduction in pre-load and after-load leading to reduced cardiac size and left ventricular filling pressure, a rise in serum potassium and cellular potassium repletion and a reduction in sympathetic activity. We await with interest the results of properly designed and controlled studies of the effect of captopril on the prognosis of patients with heart failure.

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