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Captopril in heart failure
A double blind controlled trial

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SUMMARY The effect of the converting enzyme inhibitor captopril as long term treatment was investigated in 14 patients with severe congestive heart failure in a double blind trial. Captopril reduced plasma concentrations of angiotensin II and noradrenaline, with a converse increase in active renin concentration. Effective renal plasma flow increased and renal vascular resistance fell; glomerular filtration rate did not change. Serum urea and creatinine concentrations rose. Both serum and total body potassium contents increased; there were no long term changes in serum concentration or total body content of sodium. Exercise tolerance was appreciably improved, and dyspnoea and fatigue lessened. Left ventricular end systolic and end diastolic dimensions were reduced. There was an appreciable reduction in complex ventricular ectopic rhythms.

Adverse effects were few: weight gain and fluid retention were evident in five patients when captopril was introduced and two patients initially experienced mild postural dizziness; rashes in two patients did not recur when the drug was reintroduced at a lower dose; there was a significant reduction in white cell count overall, but the lowest individual white cell count was 4000×10^6/l. Captopril thus seemed to be of considerable value in the long term treatment of severe cardiac failure.

Severe congestive cardiac failure entails a heavy burden of symptoms and carries a grave prognosis. Although mortality is proportional to the extent of depression of cardiac function, many patients do not die with steadily progressive heart failure[1 2] and are often presumed to have succumbed to arrhythmias. Vasodilator drugs can increase cardiac performance, but there is little evidence that they improve prognosis.[3 4]

Captopril would be expected to have all the advantageous properties of conventional vasodilators in severe heart failure and also to have substantial additional benefits. Converting enzyme inhibition should overcome the possibly adverse direct renal effects of the renin-angiotensin system in severe heart failure as well as lowering secretion of antidiuretic hormone and aldosterone.[5]

Several open studies have indicated benefit from treatment with captopril[6–8]; a double blind trial is, however, critical in assessing the long term effect of any drug in a disease with such prominent symptoms and fluctuating natural history. Three controlled studies of captopril have all shown distinct improvement in exercise tolerance and dyspnoea.[9–11]

We report a double blind controlled trial of prolonged treatment with captopril in patients with severe congestive heart failure. In addition to evaluating symptoms, we measured body sodium and potassium contents and recorded 24 hour ambulatory electrocardiograms. (Preliminary reports of some parts of this study have already been made.[12 13])

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Patients and methods

Fourteen men and six women (mean age 62 years) with severe congestive heart failure (New York Heart

Table 1 *Protocol of treadmill testing*

Stage	*Time (min)*	*Speed (mph)*	*Gradients (%)*	*Predicted oxygen consumption (ml/min)*
1	3	2	0	7
2	3	2·5	4	14
3	3	3	8	21
4	3	3	12	28
5	3	3	16	33
6	3	3	20	39

Association classes III or IV) of more than six months' duration were studied. Thirteen had ischaemic heart disease, four congestive cardiomyopathy, and three severe left ventricular dysfunction associated with valvar regurgitation. All were receiving digoxin together with frusemide (mean dose 375 mg/day); three were also receiving bendrofluazide 5 mg daily, and two others had been taking amiodarone 200 mg daily for more than a year. Six patients had atrial fibrillation. None had angina, significant respiratory disease, or serum creatinine concentrations >200 μmol/l (2·26 mg/100 ml). All gave written consent to the trial, which was approved by the hospital's ethical supervisory committee.

The study was in four phases, full patient assessment being performed at the end of each. Firstly, during a run in phase of two weeks, treatment with digoxin, diuretics, potassium supplements, and amiodarone was stabilised and the patient made familiar with the procedures, including treadmill exercise. Secondly, captopril was introduced at a dose of 6·25 mg three times daily and titrated to a fixed thrice daily dose for each patient (mean total daily dose 93·75 mg; range 37·5–150 mg) for an open study of six weeks' duration. Thirdly, patients were randomly allocated double blind to receive either the same dose of captopril as in the second phase or a matching placebo for six weeks. Fourthly, for a final six weeks patients were crossed over double blind to the alternative treatment to that given in the third phase. All treatment other than captopril was maintained without change throughout the third and fourth phases.

Symptoms were assessed according to the New York Heart Association classification and by visual analogue scales for breathlessness, tiredness, and ankle swelling. Exercise tolerance was tested with a modified Balke treadmill protocol in stages of three minutes (Table 1). End diastolic and end systolic dimensions and fractional shortening were calculated from left ventricular M mode echocardiograms.[14] Twenty four hour ambulatory electrocardiographic monitoring for ventricular couplets (two consecutive complexes), ventricular salvoes (three consecutive complexes), and ventricular tachycardia (three consecutive complexes at rates >120 beats/minute) was performed using a Medilog 1 system.

Venous blood samples were drawn at 0800, the patients having fasted and remained supine overnight, 10 hours after the previous dose of captopril or placebo. Samples were assayed for serum concentrations of electrolytes, urea, and creatinine and for plasma concentrations of active renin, angiotensin II, aldosterone, cortisol, noradrenaline, and adrenaline.[15–18] Blood pressure was measured between 1400 and 1600 with a standard sphygmomanometer lying and after two minutes' standing; heart rate was recorded at the same times. Total body potassium content was measured from endogenous potassium-40, using the whole body counter; total body sodium content was measured similarly after activation analysis.[19–22] Renal plasma flow and glomerular filtration rate were estimated with radioisotope clearance methods, using sodium iodohippurate (^{131}I) and technetium-99m diethylenetriamine penta-acetic acid.[23 24] Urinary creatinine clearance over 24 hours was also measured.

STATISTICAL METHODS

The results of three analyses are presented, each based on standard statistical methods with the data transformed to a logarithmic scale as appropriate. The first comparison was between the start and finish for the open study and the second between the ends of the phases of the double blind study during which placebo or captopril was given. The final comparison used repeated measures analyses of variance to incorporate data from the start of the double blind study together with data from the end of the placebo and captopril phases, and in effect this compared the changes during the two double blind six week periods of treatment. The design of the study shows that this final analysis would be sensitive to any effect of the order of treatment allocation, and the results are not reported in cases where the order effect was significant at the 5% level.

Results

Table 2 gives the results of all the tests undertaken.

Clinical outcome—Of the 20 patients entered, 14 completed the study. Two died in the initial run in phase, two during the open captopril phase, and one in the double blind phase while taking placebo. The condition of a sixth patient with mitral incompetence improved considerably during the open captopril phase, and he was therefore withdrawn for valve replacement. Table 2 gives detailed results only for the 14 patients who completed the study, unless otherwise stated.

Renal and hormonal effects—Captopril reduced plasma angiotensin II concentrations and plasma active renin concentration rose. The fall in mean plasma

Table 2 *Results of tests in 14 patients who completed the double blind study. Values are mean (SD) unless indicated. Mean, median, and range are given for data that were not normally distributed*

	Baseline	*End of open study*	*Captopril double blind phase*	*Placebo double blind phase*	*From end of open study*	
					Response to captopril	*Response to placebo*
New York Heart Association score:						
Mean	3·5	2·0	2·0	2·5	−0·6	+0·2
Median	4	2	2	2		
Range	3–4	1–3	1–3	2–4	−2–0	0–2
		p<0·001		p<0·04		p<0·02
Visual analogue scores:						
Breathlessness (mm)	52(27)	15(12)	16(17)	34(22)	−23(22)	+11(24)
		p<0·001		p<0·02		p<0·02
Tiredness (mm)	48(25)	26(20)	12(14)	28(28)	−2(31)	+10(20)
		p<0·04		p<0·02		p<0·02
Ankle swelling (mm)	20(25)	6(7)	6(8)	8(14)	2(9)	1(3)
		p<0·04		NS		
Supine heart rate (beats/minute)	83(9)	79(10)	75(11)	79(11)	−1(10) *	+1(10)
		p<0·05		NS		
Supine systolic blood pressure (mm Hg)	118(20)	109(16)	110(18)	130(27)	−21(15)	+10(14)
		p<0·01		p<0·001		p<0·001
Supine diastolic blood pressure (mm Hg)	79(14)	68(12)	64(13)	83(16)	−18(9)	+14(8)
		p<0·01		p<0·001		p<0·001
Standing heart rate (beats/minute)	88(12)	83(10)	82(13)	85(14)	3(10)	0(13)
		p<0·05		NS		NS
Standing systolic blood pressure (mm Hg)	115(26)	102(14)	112(17)	127(26)	−18(15)	0(16)
		p<0·01		p<0·005		p<0·03
Standing diastolic blood pressure (mm Hg)	77(21)	71(15)	72(15)	84(16)	−12(11)	+5(12)
		NS		p<0·005		p<0·01
Weight (kg)	66·8(14·7)	66·1(10·2)	67·0(9·2)	67·0(9·1)	+0·2(1·1)	+0·3(1·3)
		NS		NS		NS
Exercise time (min)	5·6(3·8)	9·1(5·0)	9·1(5·3)	7·6(4·3)	+1·7(1·2)	−0·6(1·7)
		p<0·005		p<0·03		p<0·007
End diastolic left ventricular dimension (cm)	6·7(0·8)	6·4(1·2)	6·4(1·0)	6·7(1·0)	−0·2(0·3)	+0·2(0·4)
		p<0·003		p<0·01		p<0·06
End systolic left ventricular dimension (cm)	5·6(1·1)	5·3(1·1)	5·2(1·0)	5·5(1·0)	−0·2(0·4)	+0·1(0·3)
		p<0·03		p<0·001		p<0·04
Fractional shortening	17·2(6·8)	18·3(5·9)	18·7(5·9)	17·3(5·6)	+0·3(3·8)	−0·3(0·4)
		NS		NS		NS
Serum sodium (mmol/l)	140(5)	141(3)	140(3)	140(6)	−1(4)	−1(2)
		NS		NS		NS
Serum potassium (mmol/l)	3·4(0·7)	3·9(0·6)	3·9(0·4)	3·4(0·4)	+0·6(0·6)	−0·4(0·4)
		NS		p<0·003		p<0·001
Serum urea (mmol/l)	9·3(5·7)	10·8(9·7)	11·1(8·4)	7·7(3·6)	+3·0(5·0)	−1·4(4·2)
		NS		p<0·03		p<0·01
Serum creatinine (μmol/l)	116(40)	123(45)	133(42)	113(32)	+13(29)	−14(25)
		NS		p<0·002		p<0·02
White cell count (×10⁶/l)	8100(1400)	7000(6500)	6300(1300)	7400(1100)	−500(1600)	+300(1500)
		p<0·05		NS		NS
Total body sodium content (mmol)		3195(437)	3195(447)	3200(367)	15(140)	−11(157)
				n=12, NS		n=10, NS
Total body potassium content (mmol)		2596(443)	2667(111)	2543(135)	+74(126)	−102(179)
				n=14, p<0·05		n=12, p<0·03
Plasma active renin (μU/ml)						
Mean	168	383	405	262	+120	−76
Median	51	97	104	55	+52	−35
Range	20–1209	28–2287	46–2289	12–1501	−96–788	−290–51
		p<0·05		p<0·004		*
Angiotensin II (pmol/l)						
Mean	53	22	21	80	−62	+16
Median	36	22	17	31	−14	+4
Range	8–178	4–38	6–47	10–292	−259–5	−15–154
		p<0·02		p<0·05		p<0·01
Aldosterone (pmol/l)						
Mean	924	252	308	504	−280	+84
Median	336	196	224	280	−56	+28
Range	112–2100	56–924	56–1568	84–2072	−1652–168	−308–812
		p<0·005		NS		NS
Noradrenaline (nmol/l)	4·1(2·1)	3·0(2·0)	3·2(1·7)	5·1(2·6)	−2·1(1·9)	+0·3(1·5)
		n=13, NS		n=10, p<0·02		n=8, p<0·051
Adrenaline (nmol/l)	0·23(0·28)	0·15(0·34)	0·28(0·19)	0·50(0·39)	−0·37(0·38)	+0·09(0·31)
		n=11, NS		n=10, NS		n=8, p<0·03

Table 2 *continued*

	Baseline	*End of open study*	*Captopril double blind phase*	*Placebo double blind phase*	*From end of open study*	
					Response to captopril	*Response to placebo*
Creatinine clearance (ml/min)	62(22)	56(20)	56(21)	61(21)	−11(14)	+9(12)
		n=12, NS		n=12, NS	n=10; p<0·01	
Glomerular filtration rate (isotopic assessment) (ml/min)			48(18)	53(19)		
				n=12, NS		
Effective renal plasma flow (ml/min)			287(100)	241(72)		
				n=12, p<0·05		
Ventricular extrasystoles						
Mean	3917	2353	1387	1897	−582	+187
Median	187	107	121	199	−83	+68
Range	3–24570	0–24299	0–10445	0–11416	−7934–4291	−2330 13854
		p<0·01		NS	p<0·05	
Ventricular couplets						
Mean	82	26	8	14	−6	+26
Median	2	1	0	3	−1	+1
Range	3–24750	0–357	0–82	0–103	−24–4	−3 275
		p<0·05		p<0·04	p<0·06	
Ventricular salvoes						
Mean	9	7	5	13	−7	+2
Median	0	0	0	1	−1	0
Range	0–94	0–67	0–70	0–147	−77–2	−3–13
		NS		p<0·02	p<0·02	
Ventricular tachycardia						
Mean	9	5	4	7	−3	+2
Median	0	0	0	1	0	+1
Range	0–94	0–67	0–49	0–86	−37–1	−1–18
		NS		NS	p<0·05	

Conversion: SI to traditional units—Urea: 1 mmol/l≈6·1 mg/100 ml. Creatinine: 1 μmol/l≈11·3 μg/100 ml. Angiotensin II: 1 pmol/l≈10·5 pg/100 ml. Aldosterone: 1 nmol/l≈36·1 ng/100 ml. Noradrenaline: 1 nmol≈16·9 ng/100 ml. Adrenaline: 1 nmol/l≈18·3 ng/100 ml.
*Significant order effect at less than 5%.

aldosterone concentration during the trial proper did not achieve conventional levels of significance, although the value at the end of the open captopril phase was significantly lower than that during the run in phase ($p<0·005$). Plasma noradrenaline and adrenaline concentrations were lower in patients while receiving captopril. During treatment with placebo, mean (SD) total body potassium content was below normal, at 92(14)% of predicted normal, and mean serum potassium concentration was 3·4(0·4) mmol (mEq)/l. Captopril caused significant increases in both total body content ($p<0·05$) and serum concentration ($p<0·003$) of potassium. By contrast, neither total body content nor serum concentration of sodium changed significantly. With captopril there was a rise in effective renal plasma flow. Although the fall in glomerular filtration rate estimated isotopically was not significant, that measured by conventional creatinine clearance was, and both serum urea ($p<0·03$) and creatinine ($p<0·002$) concentrations rose significantly during treatment with captopril.

Blood pressure and heart rate—Both systolic and diastolic pressures, supine and standing, were lower during treatment with captopril; there was no postural fall in blood pressure. Heart rate was not significantly changed in either posture (Table 2).

Weight—With the initiation of captopril in the open phase, mean (SD) body weight rose over the first week from 66·3(2·5) kg to 67·5(2·6) kg ($n=18$; $p<0·05$). This was largely due to distinct retention of fluid in five patients, two of whom required an increase in frusemide dosage. There were thereafter no significant differences in body weight between the mean values at the end of each phase of the study (Table 2).

Symptoms—Breathlessness, tiredness, and New York Heart Association classification were all significantly improved in the double blind captopril phase of the study; by contrast, ankle swelling was not.

Exercise testing—Exercise time was significantly increased during double blind captopril treatment (Table 2).

Echocardiography—Both end systolic and end diastolic dimensions were reduced by captopril, although fractional shortening was not increased.

24 hour ambulatory monitoring—The incidence of ventricular extrasystoles, couplets, ventricular salvoes, and ventricular tachycardia were all significantly lower with captopril.

Adverse reactions—Two patients developed morbilliform rashes within two weeks of starting captopril.

Both were receiving doses at the upper limit for their level of renal function (captopril 300 mg/day, with creatinine clearances 48 and 43 ml/minute). The rashes cleared on stopping captopril, and in both patients the drug was started again at lower doses without relapse. Two patients had mild postural dizziness without demonstrable hypotension on starting captopril; symptoms resolved spontaneously. Total white cell count showed a slight but significant decline ($p<0.05$) during the open phase of captopril (Table 2). A similar trend in the double blind phase was not significant. The lowest individual white cell count throughout the trial was 4000×10^6/l with a normal differential count.

Discussion

The present double blind study showed clear symptomatic benefit of treatment with captopril in congestive heart failure, with prolongation of exercise time and reduced dyspnoea. These present findings confirm the symptomatic improvement reported with captopril in the two previous double blind trials.[9,10] In our study, echocardiography showed reduction in both end systolic and end diastolic dimensions, effects that would be expected to lead to reduced left ventricular wall tension and hence to lower myocardial oxygen consumption. While several of these indices of benefit are objective, the need for a double blind assessment of symptoms is emphasised. Symptomatic improvement was more pronounced in the open than the blind part of this trial, and some of such benefit could well have been due to effects other than those of captopril.

An initial open phase in which captopril was started was considered to be advisable in the present trial for safety reasons, and the need for this was confirmed by the occurrence of fluid retention with weight gain initially in some patients.

Beneficial effects of captopril may possibly have been carried over into the double blind placebo phase and thus have partly masked the undoubted benefit that was shown. Captopril might thus confer even more advantage than we observed in the present double blind study. Conversely, the design of this trial excluded the possibility of an effect of patient training—for example, in the treadmill procedures—in contributing to the better performance during treatment with captopril rather than with placebo.

Captopril, in a thrice daily schedule and a mean daily dose of 93·75 mg, was clearly effective in sustaining reduction of plasma angiotensin II concentrations. Although we took blood samples 10 hours after the previous dose, when the effect of captopril was probably near its nadir, angiotensin II concentration remained significantly suppressed and active renin concentration appreciably raised. Plasma aldosterone concentration was less obviously reduced at this time but is influenced by several factors other than angiotensin II and these could have been more dominant here. Aldosterone secretion would have been raised, for example, by the captopril induced retention of potassium. In turn, the correction of total body content and serum concentration of potassium, initially below normal, by captopril could have been important for the decrease in ventricular ectopic activity. Other factors that might also have contributed were a reduction in cardiac dimensions and sympathetic activity.

We have argued previously that probably important intrarenal actions of angiotensin II in cardiac failure are preservation of glomerular filtration rate in the face of a fall in renal blood flow; intrarenal angiotensin II also sustained urea excretion.[5,25] The effects of captopril seen here were in accord with this reasoning, with an observed increase in renal plasma flow, a small fall in glomerular filtration rate, and a rise in serum creatinine and urea concentrations. Some caution should, however, be expressed in the interpretation of the clearance of sodium iodohippurate (^{131}I) as renal tubular function could change with converting enzyme inhibition.

The present trial showed clearly that the use of captopril in the treatment of severe cardiac failure corrects many biochemical anomalies, limits arrhythmias, improves cardiac performance, and benefits patients symptomatically. Although several of these aspects would be expected also to improve prognosis, this remains to be confirmed.

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