Haemodynamic and hormonal effects of captopril in primary pulmonary hypertension

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SUMMARY The treatment of primary pulmonary hypertension is unsatisfactory. Since, in animals, experimental pulmonary vasoconstriction may be mediated in part by angiotensin II, we treated five primary pulmonary hypertensive patients with captopril for four days. To ensure accuracy of haemodynamic and hormone data, the patients were studied under conditions of constant body posture, regulated dietary sodium and potassium intake, and unchanged diuretic therapy. Captopril reduced mean pulmonary arterial pressure in parallel with plasma angiotensin II levels. Right ventricular ejection fraction recordings increased considerably in three of four patients. Systemic arterial pressure fell, but there was no change in right atrial pressure, cardiac output, or heart rate. The decline in plasma (and urine) aldosterone levels presumably contributed to the positive cumulative potassium balance and the rise in plasma potassium (mean 0.7 mmol/l). These encouraging results suggest that converting enzyme inhibitors warrant a formal trial with prolonged follow up in the treatment of primary pulmonary hypertension.

Primary pulmonary hypertension is a chronic progressive disorder of unknown aetiology. With the exception of very rare cases who survive for long periods¹ or show regression,² most die within 10 years from the time of diagnosis.³ No consistently effective treatment either curative or palliative has been discovered.

Animal studies have suggested firstly that the renin-angiotensin system may play a central role in the development of experimental pulmonary vasoconstriction,⁴ and secondly that inhibition of angiotensin II formation can prevent the pulmonary vascular changes induced by chronic hypoxia.⁵ The scant clinical data available indicate that converting-enzyme inhibitor therapy might prove beneficial in patients with raised pulmonary resistance.^{6,7}

This communication presents detailed haemodynamic and hormone responses to the oral converting-enzyme inhibitor captopril in five patients with primary pulmonary hypertension.

Subjects and methods

Five patients (Table 1) with pulmonary hypertension were studied. All had formal diagnostic catheter studies previously to exclude left sided cardiac disease or intracardiac shunts. Four had no lung disease on

respiratory function testing. One (case 4 Table 1) had evidence of small airways obstruction on computerised spirometry but no significant airways obstruction was demonstrable on routine spirometry. Informed consent was obtained from each patient, and the procedure was approved by the hospital ethical committee.

The study was carried out exactly as described earlier for patients with congestive heart failure.⁸ In brief, a two day control period was followed by four days of captopril treatment; frusemide and digoxin, administered at 0800 h (Table 1) were continued unchanged; strict metabolic balance conditions were adhered to and dietary sodium (32 to 40 mmol/day) and potassium (50 to 98 mmol/day) were constant; urine was collected via an indwelling bladder catheter; haemodynamic recordings using a triple lumen Swan Ganz catheter and an arterial cannula were performed daily at 0830 h and 1530 h at which time arterial samples were drawn for hormone and electrolyte analysis as previously described.⁸ Captopril was started after two control days at a dose of 6.25 mg, increasing to a maximum of 150 mg per dose by the penultimate study day. The drug was given three times daily, at exactly 0730 h, 1430 h, and 2330 h. Digoxin, frusemide, captopril, and potassium chloride (which was added to achieve a total potassium intake of 50 to 98 mmol/day) were the only drugs taken, any others

Table 1 Clinical and haemodynamic data

		Case No.				
		1	2	3	4	5
Sex		F	M	M	M	F
Age		42	62	76	26	55
Duration of symptoms (y)		7	5	2	3	2
Mean pulmonary arterial pressure (mmHg)	Control	29	61.5	38	41	44.5
	Final day	26	53	32	33	37
Mean arterial pressure (mmHg)	Control	80	92	76	99	98
	Final day	63	73	51	82	77
Cardiac output (l/min)	Control	5.4	4.2	10.1	5.4	3.4
	Final day	6.6	3.7	9.3	6.0	3.1
Daily drugs		Frusemide 160 mg Digoxin 0.25 mg	Frusemide 40 mg	Frusemide 120 mg Digoxin 0.0625 mg	Frusemide 120 mg Digoxin 0.125 mg	Frusemide 40 mg

Data for pressures and cardiac output represent the mean of two recordings (0830 and 1530h) from the control (pre-captopril) day and from the final study day (during captopril treatment) for each patient.

having been stopped at least five days before starting the study.

In four patients, radionuclide ejection fractions of the right and left ventricles were determined by the first pass technique⁹ using technetium-labelled pyrophosphate, firstly before the study, and again three to eight days after completion of the formal procedure during maintenance captopril treatment.

Our previous experience indicates that haemodynamic and hormone indices are often unstable on the first study day as the patients adjust to the procedure requirements and come into electrolyte balance on the controlled metabolic diet. To avoid spurious results therefore, data from the second day were taken as control (pre-captopril) values.

Statistical methods used were analysis of variance and product moment correlation coefficient. Results in the text and figure are presented as mean $\pm$ SEM.

Results

Clinical details, drugs, and pre-captopril pulmonary artery pressures are shown in Table 1.

HAEMODYNAMICS

Captopril induced highly significant decrements in arterial pressure and in pulmonary arterial pressure ($p < 0.001$, analysis of variance) (Fig.). Mean arterial pressure reached its nadir 18.8 mmHg below baseline levels on the second day of captopril, whereas mean pulmonary artery pressure declined by 6.4 mmHg to its lowest level on the final study day (Fig.). A fall in pulmonary arterial pressure was seen in each patient, the initial (pre-captopril) level and those on the final day being shown in Table 1. Cardiac output changes were minor (Fig. 1 and Table 1) and were not statistically significant. Likewise, baseline right atrial

Fig. Haemodynamic, hormone, and electrolyte results from five patients with primary pulmonary hypertension (mean $\pm$ SEM). Pre-captopril values (open symbols) represent the mean of two readings on the second study day, and are extended as discontinuous horizontal lines for the period of captopril treatment. Conversion to mass units: Plasma renin activity 1 nmol/l per h $\approx$ 1.3 ng/ml per h; Angiotensin II 1 pmol/l $\approx$ 1.04 pg/ml; Plasma aldosterone 1 nmol/l $\approx$ 36 ng/100 ml.

pressure (8.4 ± 1.9 mmHg, mean $\pm$ SEM) and initial heart rates (86.6 ± 3.5 beats per minute) were not altered in any systematic fashion by captopril therapy. Since reliable measurements of pulmonary capillary wedge pressures are virtually impossible in pulmonary hypertension, and since extrapolation to left atrial pressure may be inaccurate,¹⁰ pulmonary vascular "resistance" was not calculated. Right ventricular ejection fractions had increased conspicuously in three

Table 2 Radionuclide ejection fractions before and after captopril

Case No.	Right ventricular ejection fraction		Left ventricular ejection fraction	
	Before captopril	After captopril	Before captopril	After captopril
1	49%	67%	61%	80%
2	51%	43%	38%	46%
4	41%	89%	74%	84%
5	17%	40%	56%	80%
Mean	39.5%	59.8%	57.3%	72.5%

of the four patients three to eight days after completion of the study during continued captopril therapy, while left ventricular ejection fractions showed a more modest increment (Table 2).

HORMONES

Plasma angiotensin II fell steadily during captopril treatment, while plasma renin activity increased in a stepwise fashion to reach a peak on the penultimate study day which was tenfold higher than pre-captopril levels (Fig.). Plasma aldosterone declined rapidly and stabilised at approximately half baseline levels (Fig.). Overall, plasma aldosterone correlated significantly with concurrent plasma angiotensin II ($r=0.53$, $p<0.001$, $n=50$). Urine aldosterone excretion diminished gradually from a control of 38.4 ± 6.2 nmol/24h to 29.2 ± 2.8 nmol/24h on the final study day. Baseline levels of plasma noradrenaline 3570 ± 727 pmol/l (604 ± 123 pg/ml), plasma cortisol 469 ± 64 nmol/l, and urine cortisol 275 ± 19 nmol/24h and were not altered by the introduction of captopril.

HAEMODYNAMIC-HORMONE RELATIONS

The patterns of change in mean pulmonary artery pressure and in circulating angiotensin II were similar (Fig.). A possible relation between these two indices was supported by the close correlation between their concurrent mean values as plotted in the Fig. ($r=0.91$, $p<0.001$, $n=9$). The correlations of mean systemic arterial pressure with angiotensin II ($r=0.69$, $n=9$) and with plasma renin activity ($r=-0.83$, $n=9$) were also statistically significant ($p<0.05$ and $p<0.01$, respectively).

SODIUM AND POTASSIUM

Cumulative sodium balance in individual patients was variable during captopril administration, but overall was slightly negative (-24.4 ± 19.3 mmol). By contrast, cumulative potassium balance was positive, and the mean plasma potassium increased by 0.7 mmol/l ($p<0.001$, analysis of variance; Fig.) from a baseline level of 3.7 mmol/l (range 3.0 - 4.4 mmol/l).

CLINICAL STATUS

The two youngest patients (cases 1 and 4) noted a dramatic clinical improvement during maintenance

captopril therapy. Exercise tolerance using a symptom-limited treadmill test¹¹ improved in case 1 from five minutes 12 seconds before captopril treatment to nine minutes five seconds after three weeks of treatment. Exercise performance was not assessed in case 4. His pulmonary arterial pressure, however, was measured using a Swan Ganz catheter after four months of treatment with captopril, and had declined to $41/13$ mmHg from a pre-captopril level of $51/30$ mmHg. Case 5 increased her exercise tolerance from nine minutes 30 seconds to 14 minutes nine seconds after four weeks of captopril, but has subsequently deteriorated clinically. Case 2, with the highest pulmonary pressure (Table 1), showed no change in exercise tolerance. Case 3 developed symptomatic hypotension, and thus captopril was withdrawn; he died three months later.

Discussion

The treatment of primary pulmonary hypertension is unsatisfactory. Though many drugs have been tried, none has proved uniformly effective. The rationale for the current study may be summarised as follows. In animals and man, angiotensin II can raise pulmonary arterial pressure independent of any action on the systemic arterial circulation.¹²⁻¹⁴ Experimental pulmonary vasoconstriction secondary to hypoxia must be mediated by a vasoactive messenger, since the direct effect of low oxygen levels on pulmonary artery smooth muscle is one of dilatation.¹⁵ Though contrary reports have appeared,¹⁶ there is evidence that this hypoxia-induced pulmonary vasoconstriction in animals is angiotensin II-dependent,^{4,5} and that blockade of angiotensin II formation by converting-enzyme inhibition can limit the development of pulmonary arterial hypertrophy and of right ventricular hypertrophy.⁵

The pathophysiological role of the renin angiotensin system in primary pulmonary hypertension in man is unknown and the effects of blocking angiotensin II formation in this condition have received scant attention. A single case study reported that captopril temporarily reduced dyspnoea and improved arterial oxygen tension,⁷ and more recently Schmengler *et al.*¹⁷ documented a decline in pulmonary arterial pressure after captopril treatment in 15 patients with pulmonary hypertension including five with primary pulmonary

hypertension. Converting-enzyme inhibitor treatment decreased pulmonary arterial pressure and pulmonary vascular resistance in patients with systemic hypertension after coronary artery surgery.⁶ Rich and Rosen,¹⁸ however, failed to show a fall in four cases treated for 48 hours with captopril but noted great variability in the pressures over this period.

Our study shows that captopril is capable of causing a significant and sustained fall in pulmonary arterial pressure in primary pulmonary hypertension. The long period of study was designed to minimise the effect of short term fluctuations in pulmonary pressure as reported previously.¹⁸ These patients were all suffering from pulmonary hypertension as evidenced by a resting mean pulmonary pressure clearly exceeding 25 mmHg in accordance with the WHO criteria for the diagnosis of pulmonary hypertension.¹⁹ A mean pressure of 43 mmHg after 24 hours of bedrest represents at least a moderate grade of severity. The resting cardiac output was within the normal range, which is not unusual in cases of moderate severity on digitalis and diuretic treatment. They were all significantly limited on exercise. The important question is whether the modest fall in mean pulmonary pressure we observed was of clinical and haemodynamic benefit. Our data on exercise performance and right ventricular ejection fraction, though limited, indicate that it was. Right ventricular ejection fraction bears a close inverse relation to mean pulmonary arterial pressure.²⁰ Furthermore, a depressed ejection fraction indicates moderate or severe pulmonary hypertension, being normal in mild disease.²⁰ Ellis *et al.*²¹ observed a significant increase in right ventricular ejection fraction with a fall in pulmonary pressure after low flow oxygen therapy in patients with obstruction airways disease. The changes in right ventricular ejection fraction in our cases are compatible with the thesis that captopril was producing a worthwhile relief of pulmonary vasoconstriction. Cardiac output at rest showed a gradual increase but did not attain statistical significance. This may be because of the study design which contrasts with the usual procedures for vasodilator studies which are all short-term acute interventions. Schmengler *et al.*¹⁷ reported falls in pulmonary vascular resistance and right atrial pressure despite a rise in cardiac output, with a fall of 10 mmHg in the mean pulmonary pressure.

Left ventricular ejection fraction improved somewhat in our study though it was within the normal range in the initial diagnostic studies. We are unaware of any previous studies on the effect of vasodilator drugs on left ventricular ejection fraction in this condition. While left ventricular function may be grossly normal in pulmonary hypertension, detailed studies²² have shown depressed contractility and limitation of the Frank-Starling mechanism because the pulmonary

vascular changes impede left ventricular filling. The acute induction of pulmonary hypertension by hypoxia in animals is generally accompanied by a decrease in ejection fraction.²³ The study of Schmengler *et al.*¹⁷ quoted previously also reported a fall in pulmonary wedge pressure with improvement in cardiac output with captopril, indicating improvement in left ventricular function. It is unlikely that the improvement in right ventricular performance in our patients was secondary to alterations in left ventricular function since the magnitude of change in ejection fraction was substantially greater for the right than for the left ventricle.

The close relation between mean pulmonary artery pressure and angiotensin II levels in our study suggests the possibility that the octapeptide was contributing to the pulmonary vasoconstriction. Support for this premise comes from data showing a close association of pretreatment renin levels with changes in pulmonary vascular resistance induced by converting-enzyme inhibitor therapy.^{6,17} Whether long term captopril therapy results in a sustained lowering of pulmonary artery pressure, and if so whether it can be explained fully by the decline in circulating angiotensin II levels, remains to be determined.

The hormonal and metabolic changes were entirely predictable on the basis of converting-enzyme inhibition, that is a fall in angiotensin II and therefore in aldosterone, and a concomitant rise in plasma renin. Likewise, a positive cumulative potassium balance and increase in plasma potassium were not unexpected since similar changes were observed during captopril treatment for cardiac failure.⁸ Presumably these potassium changes resulted in part from the decline in aldosterone levels.

The syndrome of primary pulmonary hypertension is not a homogeneous entity and several mechanisms, some as yet undiscovered, may be implicated. It is highly likely that some patients will either respond poorly or not at all to converting enzyme inhibitors. This has been the experience with other vasodilators in the treatment of primary pulmonary hypertension. Our data suggest that converting-enzyme inhibitors warrant a trial in individual patients where other forms of treatment have failed.

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