Effects of captopril (SQ 14,225) in a patient with primary pulmonary hypertension

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Summary

In a 33-year-old patient with severe primary pulmonary hypertension, the acute administration of the angiotensin-converting-enzyme inhibitor captopril (SQ 14,225) induced a rise in cardiac output, and a fall in both pulmonary and systemic vascular resistance. Subsequent chronic oral administration of captopril induced only transient clinical improvement, and the patient died. Captopril may nevertheless be useful in the treatment of less advanced cases of this disease.

Case report

A 33-year-old married woman with 2 children was admitted to hospital in February, 1979 for management of right heart failure due to primary pulmonary hypertension. There was a past history of Raynaud's phenomenon and mild systemic hypertension. Oral contraceptives had last been used 18 months previously.

Exertional dyspnoea had been present for 15 months. Physical examination revealed signs of severe pulmonary hypertension with no evidence of intracardiac shunt. Pulmonary arteriography in September 1978 revealed no evidence of embolic disease. The pulmonary artery pressure was 70/32 mmHg (mean 50 mm). Pulmonary artery saturation was 53%.

The patient's course between April 1978 and February 1979 was marked by gradual clinical deterioration with incapacitating dyspnoea on minimal exertion and stress.

On examination in February 1979 she was dyspnoeic at rest, with central cyanosis. Systemic BP was 80/50 mmHg, and the jugular venous pressure was elevated 15 cm. There was poor peripheral perfusion, with a prominent right ventricular impulse and a left parasternal fourth heart sound. Hepatomegaly, gross ascites, and peripheral oedema were present.

The patient was treated with bed rest, frusemide (40 mg/day) and amiloride (5 mg twice/day). Chest X-ray showed cardiomegaly with a large right ventricle and oligemic lung fields. Haemoglobin was 14.9 g/dl with normal white cell and platelet counts. Arterial blood gases (while breathing air) were PO_2 , 35; PCO_2 , 34; pH 7.39.

In view of the patient's deteriorating clinical status, a trial of captopril (SQ 14,225) was arranged. Informed consent was obtained, and treatment with indomethacin (125 mg/day) was commenced before the initiation of treatment with captopril.

A Swan-Ganz thermodilution catheter was inserted for monitoring of the haemodynamic effects before and after the initial dose of captopril (6 mg). These are summarized in Table 1. Valid pulmonary wedge pressure tracings could not be obtained. The maximum increase in cardiac output occurred 1.25 hr after the administration of captopril and persisted for 2.5 hr. A subsequent dose of 12.5 mg failed to produce a further response.

In view of the acute response to oral captopril, long-term treatment was commenced, in a dose of 12.5 mg 8-hourly. There was some reduction in dyspnoea at rest, and the patient became less cyanosed, with a concomitant improvement in hypoxaemia (PO_2 , 53; PCO_2 , 34; pH, 7.51 while

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TABLE 1. Haemodynamic response to initial 6 mg oral dose of captopril (SQ 14,225)

	Before captopril	After captopril
Heart rate (beats/min)	92	98
Systemic blood pressure (mmHg)	82/55	90/55
Mean right atrial pressure	37	36
Pulmonary arterial pressure	95/42	92/40
Pulmonary arterial pressure (mean)	59	57
Cardiac output (l/min)	1.78	3.04
Systemic vascular resistance (dyn-sec-cm ⁻⁵)	2650	1500
Pulmonary vascular resistance (dyn-sec-cm ⁻⁵)	1210	820

breathing air). However, gross right heart failure persisted in spite of continued use of diuretics.

After captopril had been used for 16 days, a decision was made to stop all active treatment because of the patient's continued gross disability.

Thereafter, clinical deterioration was rapid, with falling urine output and reduced peripheral perfusion, and the patient died 8 days later.

Post-mortem examination demonstrated gross right ventricular hypertrophy, and hepatic congestion. There was neither macroscopic nor histological evidence of pulmonary embolism or infarction. Intimal proliferation and laminar fibrosis with areas of fibrinoid necrosis were seen in the pulmonary arterioles.

Discussion

While the prognosis of patients with primary pulmonary hypertension has generally been poor in the past (Sleeper, Orgain and McIntosh, 1962), recent studies of the vasodilator drugs such as hydralazine (Rubin and Peter, 1980), phentolamine (Ruskin and Hutter, 1979) and diazoxide (Wang *et al.*, 1978), raise hopes that the course of the disease may be significantly altered (Reeves, 1980).

A number of studies suggested that captopril and other angiotensin-converting-enzyme inhibitors might be particularly effective in reducing elevated pulmonary vascular resistance. Teprotide (SQ 20,881), a related drug, has been shown to produce a fall in pulmonary vascular resistance which is more marked than its effects on systemic vascular resistance in patients with hypertension (Niarchos, Roberts and Laragh, 1979) and congestive cardiac failure (Curtiss *et al.*, 1978). Whether this effect is primarily due to inhibition of angiotensin II formation, decreased inactivation of plasma kinins, or secondary changes in the formation of vasodilator prostaglandins and prostacyclin, remains to be determined.

The present report is the first one of the use of captopril for this clinical condition. The patient was unfortunately in a moribund state at the start of the study, with clinical evidence of gross right heart failure associated with gross depression of cardiac output. Captopril was made available on the condition that the patient be pre-treated with indomethacin, because of fears of a possible bronchoconstrictor effect mediated by kinin and prostaglandin release (Greenberg *et al.*, 1979). However, it is also possible that the pulmonary vasodilator effects of captopril which might be mediated by prostacyclin release, were significantly attenuated by indomethacin (Murthy, Waldron and Goldberg, 1978).

Acute administration of a very small dose of captopril was associated with a rise in cardiac output, and a fall in both pulmonary and systemic vascular resistance. Prolonged oral administration of captopril induced minor reduction in dyspnoea and improvement in hypoxaemia. However, these limited results suggest that further investigation of the effects of captopril in patients with primary pulmonary hypertension appears to be justified.

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