

Reversibility of primary pulmonary hypertension during six years of treatment with oral diazoxide

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SUMMARY A 32 year old woman presented with a syncopal attack and dyspnoea on exertion. A diagnosis of primary pulmonary hypertension was confirmed by clinical examination, cardiac catheterisation, and pulmonary angiography. Her symptoms resolved completely with oral diazoxide and the pulmonary arterial pressure was reduced to normal levels over a period of six years. When diazoxide was discontinued on two separate occasions pulmonary hypertension recurred. This demonstrated the continued presence of the underlying stimulus for vasoconstriction.

The prognosis in primary pulmonary hypertension is grave; the five year survival rate is <25%.¹ Although spontaneous remission has been reported, it is rare.^{2,3} Though various agents including acetylcholine,⁴ nifedipine,⁵ tolazoline,⁶ isoprenaline,⁷ verapamil,⁸ hydralazine,⁹ and diazoxide¹⁰ have been shown to lower pulmonary artery pressure when given by direct intra-pulmonary artery injection or sublingually, the results of long term oral treatment have been disappointing, with success being achieved in only a few patients.

We describe a patient with primary pulmonary hypertension in whom treatment with oral diazoxide caused a sustained reduction of pulmonary artery pressure accompanied by relief of symptoms. When treatment was discontinued on two separate occasions pulmonary hypertension recurred and the patient's symptoms returned. We hope that continued treatment with diazoxide will improve prognosis in this patient.

Case report

A 32 year old woman was admitted to Aberdeen Royal Infirmary in August 1979 after a syncopal episode. She had been in good health until 18 months before when she began to experience exertional dyspnoea and increasing fatigue. She also reported several episodes of central chest pain on exertion that were relieved by rest. At admission she was not

taking oral contraceptive drugs and had never taken anorectic agents. She had had two uncomplicated pregnancies and her medical and family histories were unremarkable.

Physical examination showed that she was dyspnoeic at rest with moderate peripheral cyanosis. The jugular venous pressure was elevated at 7 cm with giant "a" waves. There was a prominent left parasternal heave with a palpable second sound at the pulmonary area. Auscultation revealed a wide physiological splitting of the second sound with a loud pulmonary component. Examination of the chest was normal.

Electrocardiography showed sinus rhythm with right axis deviation and a dominant R wave in lead V1 consistent with right ventricular hypertrophy. A radiograph of the chest demonstrated dilatation of the pulmonary trunk and main pulmonary arteries. An M mode echogram of the pulmonary valve showed loss of the "a" dip and conspicuous mid-systolic notching. There was also dilatation and hypertrophy of the right ventricle. Right heart catheterisation confirmed the presence of pulmonary hypertension with a pulmonary artery pressure of 90/40 mm Hg (mean pressure 66 mm Hg).

Pulmonary capillary wedge pressure was 7 mm Hg. Oxygen saturation studies showed no evidence of cardiac shunt. A pulmonary angiogram showed that the pulmonary trunk and main pulmonary arteries were considerably enlarged but that the peripheral vessels narrowed very rapidly. There was no evidence to suggest thromboembolic disease. Serological tests for antinuclear factor and lupus erythematosus cells were negative.

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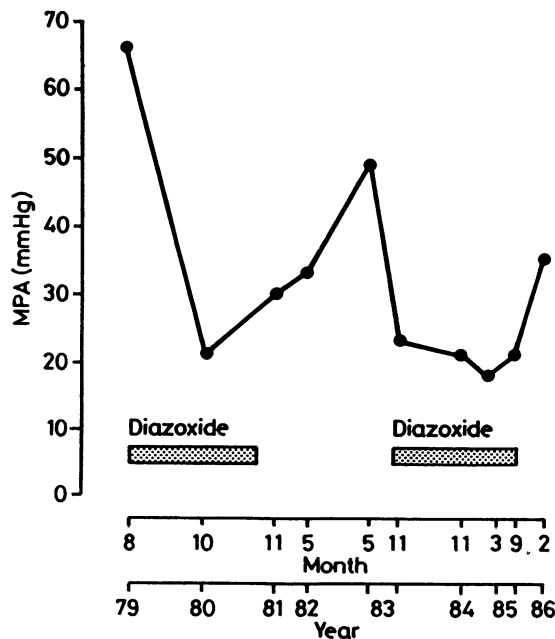


Figure Changes over 6½ years in mean pulmonary arterial pressure (MPA) during diazoxide treatment and when treatment was withdrawn.

TREATMENT AND PROGRESS

In view of favourable reports of the use of diazoxide in primary pulmonary hypertension,¹⁰ the patient was treated with a dose of 150 mg daily which was gradually increased to 600 mg daily. At this dosage, however, postprandial nausea, facial oedema, and severe postural hypotension developed; the dose was reduced to 350 mg daily which gave a plasma concentration of 75 µg/ml (325 µmol/l).

She was discharged from hospital and was reviewed a month later. Although the findings on physical examination were unchanged, she reported improvement in her exercise tolerance, and her fatigue and chest pain had resolved completely. She had had no further syncope.

The electrocardiogram continued to show evidence of right ventricular hypertrophy but the total voltage of the R wave in V1 and the S wave in V6 was less than before.

Treatment was continued and in October 1980 she was admitted for repeat cardiac catheterisation. Her pulmonary artery pressure was now 27/14 mm Hg (mean 20 mm Hg). In view of this dramatic reduction in pulmonary artery pressure we initially thought that this must be a rare example of spontaneous regression and we gradually decreased the dose of diazoxide and stopped the drug completely in July 1981. Subsequent follow up, including serial

measurements of pulmonary artery pressure, showed a gradual rise in pressure (figure) and this was accompanied by the return of her symptoms. Oral diazoxide (150 mg/day) was started again in July 1983 and again she responded favourably. Her pulmonary artery pressure remained within normal limits while she was on treatment and she was able to lead a normal active life with no major side effects.

In October 1985 a further attempt was made to withdraw treatment and diazoxide was discontinued. Repeat cardiac catheterisation in February 1986 again showed a further rise in pulmonary artery pressure (figure) and this was accompanied by a return of exertional dyspnoea. Treatment was started again at a dose of 150 mg a day and her symptoms disappeared.

Discussion

Diazoxide is a thiazide derivative which has a potent vasodilator effect on both the pulmonary and systemic arterial systems, but it is not a diuretic. The drug is thought to cause direct vasodilatation of the small pulmonary resistance vessels, reducing right ventricular afterload and thereby allowing a rise in cardiac output with corresponding relief of symptoms in primary pulmonary hypertension. Unfortunately a proportionately greater decrease in systemic vascular resistance may occur at the same time and this may be responsible for some of the reported dangers, including sudden death, of the use of vasodilators in this condition.^{11 12} In our patient symptomatic postural hypotension developed when she was taking a high dose (600 mg/day), of diazoxide, but this disappeared when the dose was reduced to 350 mg a day. Initially she experienced nausea, fluid retention, and hirsutism; these ceased when the dose was reduced to 150 mg/day. Diabetes mellitus did not develop at any time.

Paul Wood first suggested that the initial event in primary pulmonary hypertension is sustained pulmonary arterial vasoconstriction of unknown cause that eventually results in the development of fixed obliterative vascular disease.¹³ This view has been further supported by Wagenvoort and Wagenvoort¹⁴ and Edwards and Edwards.¹⁵ Such irreversible anatomical changes have been held to be responsible for the failure of vasodilator treatment but it has been postulated that such treatment might be effective if it were used before these permanent changes occur. The findings in our case support this concept and demonstrate that in some patients at least the vasoconstriction remains potentially reversible with long term treatment. This case also shows, however, that the stimulus to the development of pulmonary hypertension, whatever it may be, per-

sists on withdrawal of treatment even after several years.

Spontaneous regression of the disease is rare.^{2 3} Two cases have been reported; these patients were found to have had primary hypertension at the ages of 11 and 12 years. This had regressed by the time they reached early adult life; but most series show relentless progress of the condition¹ with most patients dying within five years of diagnosis. Long term oral treatment with vasodilators or other drugs, such as anticoagulants, has usually been disappointing except in a very small proportion of patients with primary pulmonary hypertension. A recent report demonstrated sustained improvement in primary pulmonary hypertension in a patient who was treated with sublingual isoproterenol for six years.¹⁶ A sustained beneficial response to diazoxide was reported elsewhere,^{10 17 18} but the maintenance of the efficacy of the drug over a six year period has not been shown before and raises the hope that early treatment may be effective in some cases. The patient might have responded beneficially to other agents with fewer side effects. Since her pulmonary hypertension was controlled with diazoxide at a dose less than that which caused side effects, however, we felt justified in continuing treatment with this drug.

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