Phenformin and pulmonary hypertension

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Two cases with clinical signs of pulmonary hypertension and right heart failure developing during phenformin treatment are reported. The patients were clinically improved on withdrawal of phenformin. Two possible explanations for the pulmonary hypertension were considered: cellular anaerobiosis or alphareceptor stimulation of the pulmonary vessels. The 4 patients so far reported direct attention to the possibility that pulmonary hypertension might appear as a side effect to treatment with biguanides.

There have been several reports of severe lactic acidosis in patients treated with biguanides and a relation has been inferred (Marble, 1961; Bernier, Miller, and Springate, 1963; Johnson and Waterhouse, 1968). In addition in 2 patients who were being treated with phenformin clinical signs of pulmonary hypertension were attributed to a concomitant raised blood lactate content (Sproule *et al.*, 1966; Duwoos *et al.*, 1970). Animal experiments have shown pulmonary vasoconstriction induced by the infusion of lactic acid into the pulmonary artery (Bergofsky, Lehr, and Fishman, 1962). Furthermore, it has been proposed that an intrapulmonary release of lactic acid causes the vascular constriction during hypoxia (Liljestrand, 1958). We have observed 2 patients who developed pulmonary hypertension during phenformin treatment and who improved clinically after phenformin was stopped.

Case reports

Case 1

The patient was a 60-year-old man who was healthy until the onset of diabetes mellitus in 1966. Subsequently the diabetes was well controlled with phenformin 150 mg daily. Examination one year later revealed normal physical findings. Blood pressure 140/90 mmHg. Electrocardiogram normal. Chest x-ray normal with heart size 670/390 ml/m² BSA (Jonsell, 1939).

Three years after the onset of diabetes in March 1969 there was a gradual onset of dyspnoea on effort, tiredness, and, thereafter, intermittent slight ankle oedema. He was admitted to hospital, and physical examination was normal. Electrocardiogram showed slight signs of right ventricular strain; the chest x-ray was normal. The patient was given medical treatment for heart failure. The patient's physical state, however, continued

to deteriorate with increasing dyspnoea, tiredness, and then anorexia. A chest x-ray two months after being admitted (July) showed normal lung fields but increasing heart size (950/540 ml/m² BSA). A complete picture of right ventricular hypertrophy and some right-sided intraventricular conduction defect had developed on the electrocardiogram. Orthopnoea and breathlessness while talking were noted from November 1969 together with ankle oedema and peripheral cyanosis. He could hardly manage to walk more than 40 metres or up one flight of stairs before the onset of severe dyspnoea. There were pulsations at the left sternal border. The pulmonary component of the second heart sound was sufficiently pronounced to be palpable. A fourth heart sound was heard at the third and fourth intercostal space at the left sternal border. These findings were confirmed by phonocardiography in February 1970 (Fig. 1a). The blood pressure was 140/70 mmHg. The electrocardiographic pattern was unchanged as compared to that of July 1969 but an intermittent sinoatrial block and some premature beats of ventricular origin were added. A vectorcardiogram showed pronounced right ventricular hypertrophy (Fig. 2). The heart size had increased to 1210/680 ml/m² BSA, while the lungs were normal. The vital capacity was decreased to 2.9 litres. FEV_{1.0} was normal as was intrapulmonary gas mixing (single breath). At right-sided catheterization the pulmonary artery pressure was 72/16:32 mmHg (Table). There was no shunt. Blood gas estimation revealed slight alveolar hyperventilation. Pulmonary angiography, lung-scanning, and ¹³³Xe studies of the pulmonary perfusion did not give any evidence of pulmonary embolism. Angiography of the leg, pelvic, and inferior caval veins did not show any signs of earlier or present thromboses. There were no signs of increased blood coagulability. Hepatic and renal function tests were normal.

At the end of February 1970 phenformin was stopped. Thereafter the patient was treated with a sulphonylurea and a diuretic was administered intermittently. Gradual relief of symptoms ensued and one month after with-

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drawal of the drug the patient was able to walk about two kilometres and managed 400 kpm/hour on a bicycle ergometer.

During October to November 1970 the patient managed to walk about 9 kilometres. There were then no signs of cyanosis, oedema, or parasternal pulsations. Only a very slight accentuation of the pulmonary component of the second heart sound and no fourth heart sound could be heard (Fig. 1b); blood pressure 160/90 mmHg. A slight intraventricular conduction defect was still present on the electrocardiogram and vectorcardiogram but there were no signs of right ventricular hypertrophy or strain (Fig. 2). Chest x-ray revealed a decrease in heart size (920/540 ml per m² BSA). Vital capacity was normal (4.1 l.) as well as FEV_{1.0} (3.2 l.). Blood gases were normal. Right-sided catheterization was performed (floating technique) and pulmonary artery pressure was 38/11:22 mmHg (Table).

Subsequently the patient did well until December 1971 when increasing orthopnoea and breathlessness were noted. The patient was admitted to the local hospital with severe systemic hypertension and died suddenly.

At necropsy, evidence of pulmonary hypertension and sarcoidosis was found. Pulmonary oedema, hydrothorax, and signs of stasis in the liver and the spleen were present. The heart (589 g) was enlarged. The right ventricle was dilated and hypertrophied (wall thickness: 4–5 mm). The coronary arteries were only slightly arteriosclerotic and there were no signs of myocardial infarction. The pulmonary artery was dilated to some extent and yellow-white plaques were found indicating

pulmonary arteriosclerosis. The microscopical investigation revealed a wide distribution of more or less fibrous sarcoidotic granulomas in the lung, spleen, and lymph nodes. The granulomas in the lung had a tendency to be sited near the pulmonary blood vessels. In the small arteries of the lung there was a slight proliferation of smooth muscle and reduplication of the internal elastic membranes.

Case 2

A 47-year-old woman was healthy until December 1968 when she suffered from cholelithiasis and became icteric. A cholecystectomy was performed in January 1969. Pre-operatively there were no signs of heart disease and the electrocardiogram was normal. The day after operation there was onset of diabetes and she was treated with insulin. She gained strength normally after the operation

TABLE Catheterization data in Case 1 (pressures in mmHg)

	February 1970	November 1970
Right atrium	2	3
Right ventricle	71/0	37/2
Pulmonary artery	72/16; 32	38/11; 22
Pulmonary capillary venous	4	—

FIG. 1 Phonocardiography in Case 1. a (left), February 1970. Note the obvious right-sided fourth heart sound (IV) and the delayed and pronounced pulmonary component (p) of the second heart sound (II). b (right), October 1970. The amplitude of the pulmonary component is almost normal and no fourth heart sound was recorded.

FIG. 2 Electrocardiogram and vectorcardiogram of Case 1. February 1970; both ECG (a) and VCG (c) (Frank leads, horizontal projection) showed pronounced right ventricular hypertrophy. Eight months later, October 1970 (b and d) only a slight right-sided intraventricular conduction defect can be seen. Calibration signal in (c) and (d) in mV.

and returned to work. Insulin was withdrawn in May 1969 and the diabetes was then controlled with 50 mg phenformin. In November 1970 there was gradual onset of effort dyspnoea and ankle oedema. On examination the blood pressure was 190/130 mmHg and she was treated with diuretics. Despite this her condition gradually worsened and in July 1971 she could not participate in her ordinary farming work. Because of cancerphobia she did not attend hospital until September 1972. On arrival there was jugular venous distension, dyspnoea at rest, hepatomegaly, ascites, and gross oedema of the limbs. The electrocardiogram showed right ventricular strain and right axis deviation. There was an accentuated pulmonary component of the second heart sound. The heart size was 1830/965 ml per m² BSA, with pronounced enlargement of the right atrium and ventricle. Phenformin was withdrawn and digitalis given as well as diuretic therapy. The diabetes was controlled with a sulphonylurea. On this regimen 30 kg of water was lost, the patient gradually improved, and one week later the heart size was 1460/820 ml per m² BSA. Two months after arrival in hospital electrocardiogram, phonocardiogram including jugular venous tracing, carotid pulse

curve, apex cardiography and echocardiography suggested severe pulmonary hypertension (probably 60–80 mmHg) with enlargement of the right ventricle. No shunt was shown on indicator dilution curves. In November 1972 the heart size was 1280/760 ml per m² BSA. A further slight improvement was noted in February 1973 and she managed to walk two kilometres. The pulmonary second heart sound was still accentuated but less than it had been previously. The heart size was further reduced to 1070/640 ml per m². The electrocardiogram was unchanged. Clinically there had been no events suggesting pulmonary emboli and no signs of thrombosis; phlebography in February 1973 was normal.

Discussion

Schilling (1960) described 4 cases with chest discomfort during biguanide therapy. Sproule *et al.* (1966) reported a case with lactic acidosis and concomitant pulmonary hypertension during treatment with phenformin. Duwoos *et al.* (1970) also found a case of diabetes treated with phenformin developing

signs of pulmonary hypertension. There was right-sided heart failure with hepatomegaly and oedema of the lower limbs. Concomitantly there was hyperlactataemia and muscle weakness. The clinical and laboratory signs of toxicity regressed on stopping phenformin. In our cases similar clinical pictures were observed with evidence of pulmonary hypertension and right heart failure during treatment with phenformin, and improvement gradually occurring after withdrawal of phenformin. In both cases the situation was confirmed by laboratory investigations.

Pulmonary embolism was a presumptive diagnosis in both cases but no signs of thrombi or pulmonary emboli could be demonstrated. The proliferative changes found in the lung vessels in Case 1 were consistent with primary pulmonary hypertension but were otherwise nonspecific (Wagenvoort and Wagenvoort, 1970).

At necropsy the finding of sarcoidosis in Case 1 was surprising. It is known that sarcoidosis in the lungs, if it is severe with signs of fibrosis, can cause pulmonary hypertension (Svanborg, 1961). The patient, however, had no radiological signs of pulmonary sarcoidosis and it is unlikely that the rapid and pronounced improvement seen in this case fits the natural course of sarcoidosis. Furthermore, sarcoidosis was not considered likely as a cause for the pulmonary hypertension as there was improvement when the drug was withdrawn.

In discussing the role of phenformin in pulmonary hypertension account must first be taken of the fact that there is a great difference in pulmonary vascular reactivity between individuals and that many aetiological factors in pulmonary hypertension are still obscure (Hurst and Logue, 1970).

Several reports have suggested that appetite-depressing drugs, such as aminorex, induce pulmonary hypertension (Gurtner *et al.*, 1968; Gurtner, 1969; Lang *et al.*, 1969). Since the chemical formulas of the anorexants are somewhat similar to noradrenaline, α -receptor stimulation has been suggested as the cause of vasoconstriction, giving rise to pulmonary hypertension (Malmquist *et al.*, 1970). A part of the phenformin molecule shares these similarities with the presence of a phenethyl group linked to nitrogen. However, studies on the metabolism of phenformin have not shown that this part of the molecule is split off (Beckmann, 1967; Hall, Ramachander, and Glassman, 1968).

The exact mechanisms of the action of phenformin in man are not known. Phenformin *in vitro* favours anaerobic metabolism and there is an increase *in vitro* as well as *in vivo* of lactate levels (Steiner and Williams, 1958; Clarke and Forbath, 1960; Craig *et al.*, 1960). This metabolic situation might in the present cases be of pathogenic import-

ance as it is known to precipitate pulmonary vascular constriction and an increase of pulmonary artery pressure (Liljestrand, 1958; Bergofsky *et al.*, 1962).

The present observations and the earlier cases reported (Sproule *et al.*, 1966; Duwoos *et al.*, 1970) indicate the need for watchfulness for the development of pulmonary hypertension in patients taking biguanides.

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