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CASE REPORT

Pulmonary hypertension and fenfluramine

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Pulmonary hypertension and fenfluramine. H.M.M. Pouwels, J.L.R.M. Smeets, E.C. Cheriex, E.F.M. Wouters.
ABSTRACT: Fenfluramine is a widely prescribed anorectic drug as adjuvant therapy for obesity. Pulmonary vascular hypertension after use of fenfluramine is rarely reported. We present a patient with pulmonary hypertension and right heart failure after treatment with fenfluramine. Pulmonary hypertension resolved after withdrawal of the drug.
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Fenfluramine, a phenylethylamine derivative, is widely prescribed as an anorectic drug in the western world as adjuvant therapy for obesity. The occurrence of pulmonary vascular hypertension after use of fenfluramine is rarely reported [1–4].

We present a patient with pulmonary vascular hypertension and right heart failure after treatment with fenfluramine. Three months after withdrawal of the drug, pulmonary hypertension had resolved.

Case history

A 58 yr old woman was referred to the hospital for investigation of worsening dyspnoea, tiredness and mild chest pain related to exertion for three months. She was known to exhibit Raynaud's phenomenon in the past. She had never smoked and had no history of cardiac or pulmonary disease. For eleven months before admission she had been taking fenfluramine, 120 mg daily.

On admission she was unable to walk because of breathlessness. She weighed 69 kg and had bilateral ankle oedema. Arterial blood pressure was 170/90 mmHg. Jugular venous pressure was raised. The lungs were clear. Right ventricular pulsations were felt. The pulmonary component of the second heart sound was audible at the apex. A systolic ejection murmur was heard over the second intercostal space at the left parasternal edge, consistent with a tricuspid regurgitation.

Laboratory findings, including blood gas analysis, were within the normal range. Lung volumes and carbon monoxide diffusing capacity were within the normal range. A work-up for collagen vascular or autoimmune disease was negative.

A chest radiograph showed an enlarged right ventricle, prominent hilar vessels and clear lung fields. An electrocardiogram showed sinus rhythm, vertical electrical axis and abnormalities with severe right ventricular pressure overload. Echocardiography and Doppler investigation revealed a normal left ventricular function, an enlarged right ventricle and a tricuspid regurgitation measuring 4 $m \cdot sec^{-1}$, indicating right ventricular pressures exceeding 65 mmHg.

Pulmonary arteriography showed no evidence of embolism. At right heart catheterization systolic pulmonary artery pressure was raised to 80 mmHg (table 1). Pulmonary vascular resistance was calculated as 880 $dynes \cdot s \cdot cm^{-5}$.

Table. 1 – Haemodynamic data on admission (A), 8 wks (B) and 3 months (C) after stopping fenfluramine

	A	B	C
RVP mmHg	70/6	50/6	32/4
PAP mmHg	80/30	50/15	30/10
Mean PAP mmHg	47	27	16
PVR $dynes \cdot s \cdot cm^{-5}$	880	480	290

RVP: right ventricular pressure; PAP: pulmonary arterial pressure; PVR: pulmonary vascular resistance calculated with assumed O_2-consumption (Fick method).

Fenfluramine was stopped and the patient was given diuretics. Within three weeks her symptoms disappeared. Noninvasive follow-up by electrocardiography and Doppler echocardiography showed a progressive decline of right ventricular overload. Pulmonary artery pressure, measured after 8 wks by catheterization, had markedly decreased. After three months of fenfluramine withdrawal pulmonary artery pressures were nearly normal (fig. 1).

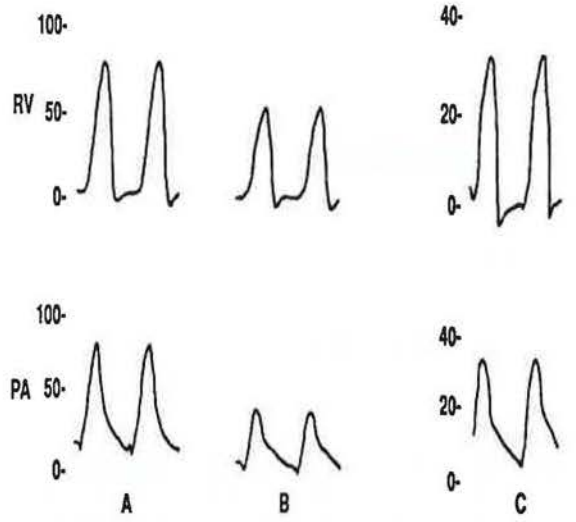

Fig. 1. – Right ventricular (RV) and pulmonary arterial pressure (PA) curves, expressed in mmHg, on admission (A), 8 wks (B) and 3 months (C) after stopping fenfluramine.

Discussion

The interrelationship between the intake of anorectic drugs and the occurrence of primary vascular pulmonary hypertension has been well known for many years. In 1967, about 2 yrs after the drug aminorex-fumarate (an amino-oxazoline derivative) became available to the public, the incidence of pulmonary vascular hypertension suddenly increased in Switzerland, Austria and Germany [5–7]. There was strong epidemiological evidence that the intake of this appetite-suppressant, prescribed for obesity, was related to the development of pulmonary hypertension. Chlorphentermine, another anorectic drug, gave rise to striking changes in the lung parenchyma in animal studies [8].

Pulmonary vascular hypertension associated with fenfluramine is very rare. DOUGLAS *et al.* [1] reported pulmonary hypertension in two patients taking fenfluramine for over eight months; the pulmonary hypertension resolved completely on withdrawal of the drug. In one patient pulmonary hypertension recurred after rechallenge with fenfluramine. GAUL *et al.* [2] described pulmonary vascular hypertension in a woman after completion of three courses of fenfluramine (nine months): nifedipine led to a considerable temporary improvement.

Irreversible pulmonary hypertension was reported by MCMURRAY *et al.* [3] in a patient who had been taking fenfluramine for seven months. Treatment with high flow oxygen, nifedipine, captopril, hydralazine and isoprenaline failed. Histological examination of the lungs at necropsy showed changes of a florid classical plexogenic pulmonary hypertension. Two other cases were described by LOOGEN *et al.* [4].

In the present case, pulmonary hypertension and right heart failure developed after treatment with fenfluramine during eleven months and resolved completely after stopping the anorectic drug. The data of our patient support the earlier reported observation that the prognosis in patients with vascular pulmonary hypertension due to anorectic drug intake critically depends on the interruption of drug intake [4].

The intricate pathophysiological mechanism of pulmonary hypertension after anorectic drug intake remains to be clarified. The structure of these drugs is closely related to amphetamine and a and b sympathomimetic or serotonergic effects on pulmonary vasculature can be supposed [9].

Since severe pulmonary hypertension may result from fenfluramine intake, patients taking this drug must be advised to report the development of exertional breathlessness immediately.

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RÉSUMÉ: La fenfluramine est un anorexigène largement utilisé comme traitement adjuvant de l'obésité. L'hypertension vasculaire pulmonaire après emploi de fenfluramine n'a été signalée que rarement. Nous décrivons une observation d'hypertension pulmonaire et de décompensation cardiaque droite faisant suite au traitement à la fenfluramine. L'hypertension pulmonaire a disparu après cessation de ce traitement.

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