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Fatal postoperative systemic pulmonary hypertension in benfluorex-induced valvular heart disease surgery

A case report

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Abstract

Rationale: Drug-induced valvular heart disease (DI-VHD) remains an under-recognized entity.

Patient concerns: This report describes a heart valve replacement which was complicated by intractable systemic pulmonary arterial hypertension in a 61-year-old female with severe restrictive mitral and aortic disease. The diagnosis of valvular disease was preceded by a history of unexplained respiratory distress. The patient had been exposed to benfluorex for 6.5 years.

Diagnoses: The diagnostic procedure documented specific drug-induced valvular fibrosis.

Interventions: Surgical mitral and aortic valve replacement was performed.

Outcomes: Heart valve replacement was postoperatively complicated by unanticipated disproportionate pulmonary hypertension. This issue was fatal despite intensive care including prolonged extracorporeal life support.

Lessons: Benfluorex is a fenfluramine derivative which has been marketed between 1976 and 2009. Although norfenfluramine is the common active and toxic metabolite of all fenfluramine derivatives, the valvular and pulmonary arterial toxicity of benfluorex was much less known than that of fenfluramine and dexfenfluramine. The vast majority of benfluorex-induced valvular heart disease remains misdiagnosed as hypothetical rheumatic fever due to similarities between both etiologies. Better recognition of DI-VHD is likely to improve patient outcome.

Abbreviation: DI-VHD = drug-induced valvular heart disease.

Keywords: cardiac surgery, fenfluramin, pulmonary hypertension, valvular heart disease

1. Introduction

Benfluorex, a fenfluramine derivative, induces restrictive drug-induced valvular heart disease (DI-VHD) and seldom pulmonary arterial hypertension. In most cases, the severity of DI-VHD is mild but may be severe and requires valve surgery. The case describes a benfluorex-exposed patient who underwent mitral and aortic valve replacement but died postoperatively because of systemic pulmonary hypertension. Valve pathology analysis demonstrated anorexigen-induced fibrosis. Informed consent was obtained from the mother of the patient.

2. Case presentation

A 61-year-old female patient was referred for mitral and aortic valve replacement. She had a history of obesity, hypothyroidism, hypertension, smoking, type 2-diabetes, and 6.5-years-benfluorex intake that was interrupted 2 years ago. She reported a 4 year history of increasingly severe episodes of acute respiratory distress initially accounted to exacerbation of chronic obstructive pulmonary disease. Doppler echocardiography examination found normal left ventricular end-diastolic diameter (45 mm) with normal ejection fraction (75%), enlarged left atrium, moderate aortic regurgitation with thickened leaflets, and mild restrictive mitral regurgitation with thickened, and shortened leaflet and subvalvular apparatus resulting in significant mitral stenosis (mean gradient 15 mmHg, valve area below 1.3 cm²). Right heart catheterization showed mean pulmonary capillary wedge pressure at 39 mmHg, heightened pulmonary pressures (systolic 82–diastolic 38/mean 56 mmHg) and right atrial pressure (21 mmHg). Lung function tests
Figure 1. Mitral valve. Panel A: Atrial aspect of the mitral valve – both AV and PV are markedly thickened by fibrosis without calcifications. Note the commissural fusion. The gross pathology is typically a rheumatism-like pattern. Panel B: The subvalvular apparatus shows that the chordae tendineae are severely involved presenting fibrous thickening, fusion, and shortening. Panel C: Gross pattern of the aortic cusps showing uneven thickening of the valve (millimeter scale). Panel D: Histopathology of the mitral valve – the structure of the valve is preserved. The endocardium is thickened by fibrosis (arrows). H&E stain. Original ×2.5. Panel E: Histopathology of the mitral valve – elastic stain showing clearly the endocardial fibrosis (arrows). Elastic stain. Original ×2.5. Panel F: Histopathology of a cusp in a thickened area – the structure of the valve is preserved. The endocardium is thickened by fibrosis (arrow). H&E stain. Original ×2.5. Panel G: Histopathology of a cusp – elastic stain showing clearly the endocardial fibrosis (arrow) occupying a half of the valve thickness. Elastic stain. Original ×2.5. AV = anterior valve, PV = posterior valve.

3. Discussion

Since World War II, the incidence of rheumatic fever as a main cause of restrictive valvular disease has declined significantly and has been progressively replaced in Western countries by other etiologies including degenerative, genetic, radiation-induced, or drug-induced valve disease.

Activation of the 5-HT2B receptor by norfenfluramine (the active metabolite of benfluorex as well as fenfluramine and dexfenfluramine) is thought to be the main mechanism of development of DI-VHD.\(^3\) 5-HT2B receptors activation produces valvular endocardial fibrosis with thickened and retracted leaflets associated with chordae tendineae thickening, fusion, and retraction of the subvalvular mitral apparatus. Pathology analysis shows that the valve architecture is well preserved without inflammation or neovascularization.\(^3\) In contrast rheumatic heart disease leads to scarring fibrosis, inflammatory damage with disruption of the valve layers and with neangiogenesis including thick-wall vessels. Finally anorexigen exposure produces distinctive valvular lesions from other valvular disease etiologies.\(^4\) Calcifications may noteworthy be observed in both etiologies.\(^3\)

In clinical practice DI-VHD often produces severe symptoms despite mild or moderate regurgitation due to restrictive valve opening and thereby pulmonary hypertension. The restrictive mitral valve disease may be dynamic with exercise or loading conditions;\(^6\) repeated mitral regurgitation worsening directly impacts on left atrial pressure and thereby pulmonary artery pressures. Of note commissural fusions thought to be specific to rheumatic fever may also be found in benfluorex-induced VHD and further aggravate leaflet opening restriction and symptoms.\(^7\) Dexfenfluramine-related endocardial cardiac fibrosis producing restrictive physiology remains to be demonstrated in benfluorex treated patients.\(^8\) Although preoperative cardiac catheterization showed postcapillary pulmonary hypertension, the patient immediately developed systemic pulmonary hypertension following valve replacement similar to pulmonary arterial hypertension suggesting an additional precapillary component.\(^2\)

showed forced expiratory volume-1 at 74%, Tiffeneau-index 70%, PO\(_2\) 83 mmHg, and PCO\(_2\) at 32 mmHg. No sleep disorder was found. The patient underwent mitral and aortic valve replacement with mechanical bileaflet valves. Peroperative findings were severely enlarged pulmonary trunk, noncalcified funnel-shaped mitral apparatus associated with leaflet thickening and commissural fusion (Fig. 1, panels A, B). Due to extreme chordal tendineae retraction, mitral leaflets were fused with papillary muscles. In contrast aortic leaflets were thin with noncoronary cusp prolapse (Fig. 1, panel C). Intraoperative transesophageal echocardiography showed normal valve prostheses and right and left ventricle function. However, systemic pulmonary hypertension (mean pulmonary artery pressure 53 mmHg, mean systemic arterial pressure 58 mmHg) developed and the patient died despite administration of inotropic agents and nitric oxide as well as prolonged extracorporeal life support. Pathology examination demonstrated drug-induced valvular disease by demonstrating noninflammatory endocardial fibrosis on both mitral (Fig. 1, panels D, E) and aortic valves (Fig. 1, panels F, G).
Interestingly in the present case, in addition to aortic valve cusp prolapse which is common finding in benfluorex-induced VHD,[9] the cusps were found to be intraoperatively normal despite pathological features of DI-VHD.

In conclusion, a history of heart failure or valve replacement related to restrictive valvular disease in a patient without history of rheumatic fever should alert the clinician of potential adverse drug effect.

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References