Valvular heart disease associated with taking low-dose pergolide for restless legs syndrome

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Received 3 February 2008; accepted after revision 30 May 2008; online publish-ahead-of-print 18 June 2008

A 49-year-old female took low-dose pergolide (625 μg daily) for approx. 5 years (approximately cumulative dose 1.140 g/5 years) for the treatment of restless legs syndrome. She developed moderate to severe mitral and aortic valve insufficiency, requiring semi-urgent double-valve replacement. The initial diagnosis of rheumatic valve disease was refuted on histological examination of the valves due to the lack of typical calcification and neovascularization. Valvular heart disease is associated with the use of dopamine agonists for the treatment of Parkinson’s disease and obesity, typically at much higher doses.

KEYWORDS
Pergolide;
Restless legs syndrome;
Valvular heart disease;
Dopamine agonists

Case report

A 49-year-old female garden landscaper presented to a suburban hospital with progressive breathlessness. She had a past medical history of epilepsy, characterized by absence seizures, restless legs syndrome for which she took pergolide, previous heavy alcohol consumption, alcoholic steatohepatitis, depression with prior suicide attempts and heavy smoking, with at least 40 pack year history exposure.

She had been assessed within the previous 2 months by a cardiologist for her breathlessness and had been found to have moderate to severe mitral regurgitation, mild mitral stenosis, and moderate aortic regurgitation. There was no history of rheumatic fever.

Her regular medications consisted of Pergolide 625 μg daily, phenytoin 200 mg nocte, Frusemide 40 mg daily, and dothiepin 150 mg daily.

Her clinical condition deteriorated, and she was referred to a tertiary referral hospital for further evaluation and management. On presentation, she was found to be in acute pulmonary oedema, and required intravenous (IV) Frusemide and approximately 24 h of continuous positive airway pressure ventilation, to stabilize her heart failure. She was reviewed by the cardiothoracic team for consideration of valve replacement. A transthoracic echocardiogram showed normal left and right ventricular size and function with a moderately dilated left atrium. The mitral valve leaflets were thickened with restricted mobility and had a ‘hockey-stick’ appearance, with no calcification present. There was a distinct lack of calcification involving the subvalvular apparatus. There was moderate to severe mitral regurgitation, with reversed systolic flow in the pulmonary veins. Mild mitral stenosis was present with an estimated valve area of ~2 cm². The aortic valve was tri-leaflet with moderate aortic regurgitation with a pressure half time of 316 ms. There was mild tricuspid regurgitation with normal right ventricular systolic pressure (see Figures 1–3). A coronary angiogram showed normal coronary arteries.

She underwent aortic valve and mitral valve replacement within a fortnight, using mechanical valve prostheses. At operation, there was a normal external appearance of the heart with no pericardial fibrosis. The mitral valve was significantly abnormal, with the posterior leaflet fibrotic and retracted along the anteroposterior aspect. The anterior leaflet was more mobile but was still thickened. The subvalvular apparatus was thickened and fibrotic without any pliability and was deemed irreparable. There was no calcification in the valve leaflets or subvalvular apparatus. The aortic valve also showed no calcification in the leaflets or annulus.

Histological examination of the valve showed fibrotic leaflets with myxomatous changes and minimal neovascularization. However, the absence of calcification was striking. The findings were considered atypical for rheumatic valvular disease and pergolide-induced valvular heart disease was confirmed (see Figures 4–7).

Post-operatively, she suffered a culture negative fever. A transoesophageal echocardiogram at this time showed a small mitral valve paravalvular leak. A small echodensity

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doi:10.1093/ejechocard/jen191

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measuring 0.3 cm remote from the valve seat was treated as presumed endocarditis with 6 weeks IV and per orum antibiotics. Owing to concerns about ongoing pergolide-induced damage to her right-side valves, she was referred to a neurologist for help in tapering her pergolide and managing her restless legs syndrome. However, the patient felt so incapacitated by her restless legs syndrome that she was unwilling to give up pergolide treatment. She was discharged on pergolide 625 mg daily, digoxin 250 µg daily, phenytoin 200 mg nocte, clonazepam 0.5 mg nocte, Frusemide 20 mg b.d., warfarin 6 mg daily, and remained afebrile and well 8 weeks following discharge.

Pergolide is an ergot-derived dopamine agonist, which has been used since 1989 as an adjunct to levodopa/carbidopa in the treatment Parkinson’s disease, and as single therapeutic agent in restless legs syndrome. Its association with valvular heart disease has led to its voluntary withdrawal from the market in March 2007.1
Valvular heart disease has been described with ergot-derived drugs since the mid-1990s, with the most common agents being anorectic agents, such as fenfluramine and dexfenfluramine, the anti-migraine drugs, such as ergotamine and methysergide, and the dopamine agonists, such as pergolide and cabergoline.\textsuperscript{5,6}

The pathogenesis is remarkably similar to that which occurs in carcinoid valvular heart disease. The anorectic drugs fenfluramine and dexfenfluramine augment serotonin activity, while the dopamine agonists are structurally similar to serotonin. Excess levels of circulating serotonin or analogues stimulate fibroblast growth and fibrogenesis through the 5HT\textsubscript{2B} receptors on valvular endocardium.\textsuperscript{7}

The pathology described is thickening of the leaflets and subvalvular apparatus. The echocardiographic abnormalities of the mitral valve are similar to that of rheumatic valve disease, with thickening and diastolic doming of the anterior mitral leaflet, immobility of the posterior mitral valve leaflet, thickening and shortening of the chordae tendineae, but very little valve stenosis\textsuperscript{9} as was noted in our patient (mitral valve area of \(\sim 2\) cm\(^2\)). The histopathology is characterized by preservation of valve structure, myofibroblast proliferation, excess extracellular matrix deposition, and a distinct lack of calcification, as opposed to that which is seen more commonly in rheumatic valve disease, as was demonstrated in this case.

Van Camp \textit{et al.}\textsuperscript{8} in an initial case series of 10 patients found that the valvular disease was associated with high doses of pergolide (>5 mg/day). This was subsequently assessed by the same authors using a larger cohort of 96 patients with Parkinson’s disease. Seventy-eight patients were treated with pergolide, both high dose (>5 mg/day) and low dose (<5 mg/day), and 18 had never been treated with pergolide.\textsuperscript{9} The three groups were blindly assessed for echocardiographic features of restrictive valvopathy of the mitral and tricuspid valves, using leaflet tenting distance and areas as the key measures of restriction. There was a direct relationship between the degree of restrictive valvopathy and the mean cumulative dose of pergolide, in grams, and mean duration of therapy, with evidence of restrictive valve disease found in 42, 29, and 0%, respectively, of the high dose (4403 g, 15.5 months), low dose (2220 g, 20.9 months), and control groups (\(P = 0.0025\) vs. all patients given pergolide). Further evidence of dose-related response was demonstrated by almost complete regression of the valve abnormalities upon cessation of the pergolide therapy in two of six patients within 6 months. This regression of severity has also been observed with cessation of other anorectic and dopamine agonists.\textsuperscript{10}

A study conducted by Zanettine \textit{et al.},\textsuperscript{11} focusing on patients on therapy for Parkinson’s disease, showed that both pergolide and cabergoline had similar risk for the development of valvular disease (23.4% of 64 patients in the pergolide group and 28.6% of 34 patients in the cabergoline group developed moderate to severe valvular insufficiency). However, in this study, cumulative doses were >6 and >4 g respectively, which are considerably lower than doses noted in the study by Van Camp \textit{et al.}. Development of significant valvular involvement in our patient with only approximately 1.14 g cumulative exposure suggests that even at lower doses, treatment with these agents may have deleterious effect. Alternatively, it raises the possibility that an alternate process may have additionally contributed to the valvular damage, although we were unable to obtain a past history of rheumatic heart disease or previous treatment with dopamine agonists.

Our patient continues to take pergolide for the effective treatment of her restless legs syndrome, despite our concerns regarding ongoing valvular damage. She continues to be closely monitored for any deterioration of her right-side valves from ongoing pergolide treatment.

Acknowledgement

Special thanks go to Dr Winnie Varikat, Westmead Department of Anatomical pathology, for the analysis of the pathological specimens.

References

1. FDA warning. 29 March 2007.