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Clinical Study

Valvular heart disease in patients with Parkinson's disease treated with pergolide, levodopa or both

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Abstract

Cardiac valvulopathy has been reported in patients with Parkinson's disease treated with pergolide. The aim of this study was to clarify the frequency and severity of valvular heart disease (VHD) in patients treated with pergolide, levodopa or both. We evaluated VHD by transthoracic echocardiography in 25 patients who were taking pergolide, 29 patients taking levodopa and 20 patients taking both levodopa and pergolide. All groups were compared with two separate age-matched control groups. There was no increase in the frequency of any type of echocardiographically-significant valvulopathy in the pergolide groups. Echocardiographically significant aortic regurgitation was found in 8% of the patients in the pergolide group and in 37.9% of the patients in the levodopa group. There was no correlation between VHD and pergolide dose, cumulative dose or duration of therapy. The mean pergolide dose was 2.6 ± 1.4 mg/day in the pergolide monotherapy group. We did not find any unequivocal evidence that pergolide causes significant valvular regurgitation. However, the mean pergolide dosage in our study was lower than in previous studies.

Keywords: Levodopa; Parkinson's disease; Pergolide; Valvulopathy

1. Introduction

Ergot derivatives have been shown to cause retroperitoneal, pleural and pericardial fibrosis.[1] Recently, cardiac valvulopathy has been reported in Parkinson's disease (PD) patients treated with pergolide.[2–6] The valvular lesions identified in these patients receiving pergolide were strikingly similar to those seen in patients receiving ergot derivates such as methysergide and ergotamine, or the anorectic drugs fenfluramine and dexfluramine, and in patients with carcinoid heart disease.[7–10]

The underlying mechanisms that lead to valvulopathies remain unclear. These drugs stimulate the 5-hydroxytryptamine 2B (5-HT2B) receptors, which are notably expressed in heart valves and induce fibroblast mitogenesis. This may partly explain how 5-HT2B receptor agonists cause valvular lesions.[11] Pergolide has an agonistic effect on serotonergic receptors, and the cardiac side effects are claimed to be due to the activation of these serotonergic receptors. The stimulation of the 5-HT2B receptors in the cardiac valves may increase the risk of cardiac valvular fibrosis due to the trophic effect on fibromyoblasts.[12]

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The aim of our study was to clarify the frequency and severity of valvular heart disease (VHD) in patients treated with pergolide and to compare them with patients using levodopa or both levodopa and pergolide.

2. Patients and methods

The study was approved by the local ethics committee. All patients gave written informed consent.

The patients and control subjects were included in the study as five groups: Group 1, PD patients treated with only pergolide ($n = 25$); Group 2, PD patients treated with only levodopa ($n = 29$); Group 3, PD patients treated with both pergolide and levodopa ($n = 20$); Group 4 (control 1), age-matched control group for Groups 2 and 3 ($n = 31$); and Group 5 (control 2), age-matched control group for Group 1 ($n = 26$).

Patients with previous rheumatic VHD and those with coronary heart disease prior to or during antiparkinsonian therapy were excluded from the study, as were patients with hypertension and angina pectoris.

All patients were carefully examined and evaluated according to clinical features, Unified Parkinson's Disease Rating Scale (UPDRS) scores[13] and Hoehn-Yahr stage[14] during the on phase. All patients underwent echocardiographic examination to assess valvular structures. The patients were examined for valvular regurgitation, restrictive valvular disease and pulmonary hypertension. Clinical and demographic features of the groups are presented in Table 1.

2.1. Cardiac assessment

A cardiologist, blind to the patients' diseases and therapies, carried out the cardiac assessments (including physical examination and echocardiography). Transthoracic echocardiography was performed using the Wingmed Vivid 3 echocardiography device (GE Wingmed Ultrasound, Horten, Norway) with 2.5-MHz multiphase images. Parasternal long-axis and parasternal short-axis, apical 4-cavity, apical 5-cavity, apical 2-cavity and subcostal standard imaging methods were used for echocardiographic assessments. Color Doppler, pulsed wave and continuous wave Doppler echocardiography were used to detect and evaluate the severity of valvular regurgitation. The severity of valvular (mitral, aortic, tricuspid and pulmonary) regurgitation was assessed using the indexes of the American Society of Echocardiography.[15,16] The severity of regurgitation was classified as mild, moderate or severe. Moderate or severe regurgitation for mitral and tricuspid valves and mild, moderate or severe regurgitation for aortic and pulmonary valves were regarded as echocardiographically significant. The thickness and mobility of cardiac valves were also assessed; and patients with valves thicker than the internationally accepted 5 mm and limited valvular motion were regarded as having restrictive valvular cardiac disease. Similarly, stenosis was classified as mild, moderate or severe. Pulmonary arterial systolic pressure was calculated from tricuspid regurgitation flow velocity using the Bernoulli equation, and adding right atrial pressure (assumed to be 5 mmHg). Pulmonary arterial pressure was considered normal ($\leqslant$30 mmHg), or classified as mild (30–45 mmHg), moderate (45–60 mmHg) or severe (>60 mmHg).[17]

Patients with valvular lesions possibly resulting from other pathologies (eg rheumatic VHD, valvular calcification, valvular disorders accompanied by left ventricular wall motion disorders, valvular prolapsus, annular dilatation, or congenital valvular abnormalities) were excluded from the study.

Table 1
Clinical and demographic features of the study groups

	Group 1 pergolide ($n = 25$)	Group 2 levodopa ($n = 29$)	Group 3 pergolide + levodopa ($n = 20$)	Group 4 control 1 ($n = 31$)	Group 5 control 2 ($n = 26$)	p
Age (years)	58.3 ± 9.1 (34–75)	71.6 ± 6.6 (55–84)	66.8 ± 9.2 (49–78)	66.6 ± 6.9 (50–80)	57.5 ± 11.1 (35–74)	< 0.001[a,b,c,d]
Gender (male/female)	11/14	15/14	15/5	22/9	16/10	
Age of onset (years)	50.5 ± 9.5	66.2 ± 5.8	56.4 ± 10.5	–	–	< 0.001[b,e]
Duration of disease (years)	7.8 ± 3.7	5.4 ± 3.5	10.4 ± 3.9	–	–	< 0.001[e]
Dosage of pergolide (mg/day)	2.6 ± 1.4 (0.75–5.50)	–	2.3 ± 0.9 (0.75–4.00)	–	–	0.360
Duration of pergolide usage (years)	4.6 ± 2.1 (1–8)	–	6.0 ± 2.4 (1–10)	–	–	0.048[a]
Dosage of levodopa (mg/day)	–	445.7 ± 251.3 (150–1200)	556.5 ± 196.8 (250–900)	–	–	0.105
Duration of levodopa usage (years)	–	3.8 ± 3.1 (1–16)	7.9 ± 2.9 (2–14)	–	–	< 0.001[e]
UPDRS total	23.2 ± 15.4	35.5 ± 16.1	37.0 ± 19.4	–	–	0.010[a,b]
UPDRS motor	13.5 ± 9.0	23.9 ± 10.6	22.6 ± 14.1	–	–	0.002[a,b]
UPDRS daily life	7.2 ± 6.3	8.8 ± 5.3	11.1 ± 6.1	–	–	0.102

Post hoc analysis: [a] statistically significant difference between Groups 1 and 3; [b] statistically significant difference between Groups 1 and 2; [c] statistically significant difference between Groups 1 and 4; [d] no significant difference between Groups 1 and 5; [e] statistically significant difference between Groups 2 and 3.
UPDRS = Unified Parkinson's Disease Rating Scale.