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The Effects of Low-Dose Pergolide on the Valves of the Heart in Japanese Patients

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Abstract

Background

High-dose pergolide has been reported to induce valvular heart disease. It has not been fully determined whether valvular heart disease is elicited by low-dose pergolide, similar to high-dose pergolide in Japanese patients.

Methods

Fifty-two consecutive patients (20 males, mean age 70±7 years) with Parkinson's disease were enrolled in our study. Twenty-three patients had been treated with low-dose pergolide (less than 1.5 mg/day) before enrollment. Of these 23 patients, 8 had been treated with pergolide and L-dopa without other ergot-derived dopamine receptor agonists (OE) and defined as the pergolide group without OE (P without OE). Fifteen patients had been treated with pergolide, L-dopa, and OE and defined as the pergolide group with OE (P with OE). The other 29 patients had not been treated with pergolide. Of these 29 patients, 15 had been treated with L-dopa alone and defined as the non-pergolide group without OE (NP without OE), while 14 patients had been treated with L-dopa and OE and defined as the non-pergolide group with OE (NP with OE). P without OE and NP without OE were compared to examine the effects of pergolide administration. And P with OE and NP with OE were compared to assess the additive effects of pergolide administration on OE. Clinical characteristics and echocardiographic parameters were compared between the groups.

Results

No significant differences in valvular abnormalities were observed between P without OE and NP without OE. No significant differences in valvular abnormalities were observed between P with OE and NP with OE, either.

Conclusions

The incidence of valvular heart disease did not differ significantly between patients with

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Parkinson's disease taking low-dose pergolide and those not taking low-dose pergolide, either with or without other ergot-derived dopamine receptor agonists.

Key Words: Parkinson's disease; Valvular heart disease; Ergot-derived dopamine receptor agonists Pergolide; L-dopa

Introduction

Ergot-derived dopamine agonists are now commonly used in the treatment of Parkinson's disease. Pergolide is also a widely used ergot-derived dopamine agonist, and is usually used for patients with Parkinson's disease. Retroperitoneal, pericardial, or pleural fibrosis has long been considered the most serious potential uncommon complication of pergolide use[1-3]. Several recent reports have suggested that valvular heart disease might be induced in patients taking high-dose pergolide, in addition to the complications previously described[1,4-6] and that the prevalence of high-dose pergolide-related valvular heart disease may be higher than initially estimated[1,4,5,7,8]. However, most Parkinson's disease patients administered low-dose pergolide in Japan exhibit clinically sufficient effects[9]. It has not been fully determined whether valvular heart disease is elicited by low-dose pergolide, similar to high-dose pergolide.

Accordingly, this study examined whether low-dose pergolide induces valvular heart disease in patients with Parkinson's disease.

Methods

Study Population

This study enrolled 52 consecutive patients (20 males, mean age 70±7 years) with Parkinson's disease who were treated at the Department of Neurology of Osaka City University Hospital between August 2004 and January 2006. Informed consent was obtained from all patients at enrollment. Twenty-three patients had been treated with low-dose pergolide (less than 1.5 mg/day, mean treatment period 42±29 months) before enrollment. Of these 23 patients, 8 had been treated with pergolide and L-dopa without other ergot-derived dopamine receptor agonists (OE) and defined as the pergolide group without OE (P without OE). Fifteen patients had been treated with pergolide and L-dopa with OE, and defined as the pergolide group with OE (P with OE). The other 29 patients had not been treated with pergolide but treated with L-dopa. Of these 29 patients, 15 had been treated with L-dopa alone and defined as the non-pergolide group without OE (NP without OE), while 14 patients had been treated with L-dopa and OE and defined as the non-pergolide group with OE (NP with OE). P without OE and NP without OE were compared to examine the effects of pergolide administration. And P with OE and NP with OE were compared to assess the additive effects of pergolide administration on other ergot-derived dopamine receptor agonists.

Echocardiographic Examination

All patients underwent comprehensive transthoracic echocardiographic examinations with evaluation of both global and regional left ventricular function and valvular and pericardial status using a VIVID 7 ultrasound system (GE Ultrasound, Horten, Norway). The presence of thickening of the leaflets, calcification, restrictive valvular motion, and significant regurgitation (more than moderate regurgitation) were assessed. The presence of valvular tenting of the

mitral and tricuspid valves was also evaluated. The transvalvular pressure gradients of the aortic and mitral valve and pressure gradient of tricuspid regurgitation were measured. All clips of echocardiographic images were stored digitally on magneto-optical (MO) disks for analysis by one experienced echocardiographer and one independent investigator blind to all patient data who performed all measurements and evaluations. Thickening, sclerosis, calcification, and restriction of motion of the mitral, aortic, and tricuspid valves were assessed from multiple views with the zoom function. All semiquantitative and quantitative measurements for determination of regurgitant valvular disease were performed using continuous-wave, pulsed-wave, and color Doppler examinations. For evaluation of the mitral valve, tenting areas and tenting distances were measured, as well. Systolic pulmonary artery pressures were also evaluated using the tricuspid regurgitant jet.

Statistical analysis

Comparisons of continuous variables between two groups were made by the Mann-Whitney U test. Differences between groups were assessed by the χ^2 test for categorical variables. A value of $p<0.05$ was considered to indicate statistically significance.

Results

The clinical characteristics and echocardiographic parameters of P without OE and NP without OE are given in Table 1. There were no significant differences in clinical characteristics or echocardiographic parameters between the 2 groups. Echocardiographic assessments of valvular abnormalities in both P without OE and NP without OE are summarized in Table 2. No significant differences in valvular abnormalities were noted between the 2 groups.

Table 3 shows the clinical characteristics and echocardiographic parameters of P with OE and NP with OE. No significant differences in clinical characteristics or echocardiographic parameters were observed between the 2 groups, except for gender. Table 4 shows echocardiographic assessments of valvular abnormalities in these two groups. There were no

Table 1. Clinical characteristics and echocardiographic parameters in patients who did not use other ergot-derived dopamine agonists

	P without OE n=8	NP without OE n=15	p value
Gender (male/female)	5/3	6/9	0.10
Age (years old)	72±7.6	73±7.2	0.60
Cumulative dose of pergolide (mg)	1429±824		
Echocardiographic parameters			
LVDd (mm)	45±3.7	42±4.7	0.20
LVDs (mm)	27±6.0	28±6.5	0.92
IVS (mm)	9.3±1.5	9.5±1.2	0.80
PW (mm)	8.6±1.2	8.9±1.2	0.67
LAD (mm)	32±4.1	35±4.2	0.08
EF (%)	61±7.4	62±7.1	0.50
IVC (mm)	13±1.4	13±3.2	>0.99

P, pergolide; NP, non pergolide; OE, other ergot-derived dopamine receptor agonists; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; IVS, interventricular septal thickness; PW, left ventricular posterobasal wall thickness; LAD, left atrial dimension; EF, ejection fraction; and IVC, dimension of inferior vena cava.

Table 2. Echocardiographic assessment of valvular abnormalities in patients who did not use other ergot-derived dopamine agonists

	P without OE n=8	NP without OE n=15	p value
AV thickening of the leaflets	3 (38%)	2 (13%)	0.78
Calcification	1 (13%)	0	0.46
Restriction of valve motion	0	0	
Regurgitation	2 (25%)	0	0.28
Trans AV PG (mm Hg)	7.6±2.9	6.5±2.2	0.45
MV thickening of the leaflets	2 (25%)	2 (13%)	0.48
Calcification	0	1 (7%)	0.16
Restriction of valve motion	3 (38%)	1 (7%)	0.65
Valvular tenting	0	1 (7%)	0.16
Regurgitation	0	0	
Trans MV PG (mm Hg)	2.6±1.1	2.4±0.9	0.93
Tenting area (cm^2)	0.98±0.43	0.82±0.29	0.38
Tenting distance (cm)	0.52±0.06	0.47±0.13	0.10
TV thickening of the leaflets	0	0	
Calcification	0	0	
Restriction of valve motion	0	0	
Valvular tenting	0	0	
Regurgitation	0	0	
TV Regurgitation PG (mm Hg)	19.3±7.6	20.7±7.8	0.97
PV thickening of the leaflets	0	0	
Calcification	0	0	
Restriction of valve motion	0	0	
Regurgitation	0	0	

P, pergolide; NP, non pergolide; OE, other ergot-derived dopamine receptor agonists; AV, aortic valve; MV, mitral valve; TV, tricuspid valve; PV, pulmonary artery valve; and PG, pressure gradient.

Table 3. Clinical characteristics and echocardiographic parameters in patients who used other ergot-derived dopamine agonists

	P with OE n=15	NP with OE n=14	p value
Gender (male/female)	3/12	7/7	0.04*
Age (years old)	69±5	66±6	0.11
Cumulative dose of pergolide (mg)	765±865		
Echocardiographic parameters			
LVDd (mm)	42±6.3	45±4.5	0.38
LVDs (mm)	26±5.4	29±4.2	0.18
IVS (mm)	9.1±1.3	8.7±1.6	0.71
PW (mm)	8.1±1.6	8.2±0.9	0.70
LAD (mm)	37±8.6	35±8.2	0.34
EF (%)	65±6.5	62±6.7	0.27
IVC (mm)	14±2.7	14±2.9	0.55

P, pergolide; NP, non pergolide; OE, other ergot-derived dopamine receptor agonists; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; IVS, interventricular septal thickness; PW, left ventricular posterobasal wall thickness; LAD, left atrial dimension; EF, ejection fraction; and IVC, dimension of inferior vena cava.
*$p<0.05$

Table 4. Echocardiographic assessment of valvular abnormalities in patients who used other ergot-derived dopamine agonists

	P with OE n=15	NP with OE n=14	p value
AV thickening of the leaflets	3 (20%)	0	0.08
Annular calcification	2 (13%)	2 (14%)	0.95
Restriction of valve motion	2 (13%)	0	0.16
Regurgitation	2 (13%)	0	0.16
Trans AV PG (mm Hg)	6.5±2.9	8.8±5.0	0.25
MV thickening of the leaflets	1 (7%)	1 (7%)	0.29
Annular calcification	2 (13%)	0	0.16
Restriction of valve motion	1 (7%)	2 (14%)	0.50
Valvular tenting	3 (20%)	0	0.08
Regurgitation	0	1 (7%)	0.29
Trans MV PG (mm Hg)	2.87±0.96	3.48±1.00	0.20
Tenting area (cm^2)	1.01±0.52	0.86±0.29	0.53
Tenting distance (cm)	0.43±0.19	0.50±0.13	0.08
TV thickening of the leaflets	0	0	
Annular calcification	0	0	
Restriction of valve motion	0	0	
Valvular tenting	0	0	
Regurgitation	0	0	
TV Regurgitation PG (mm Hg)	23.9±6.9	20.6±6.6	0.27
PV thickening of the leaflets	0	0	
Annular calcification	0	0	
Restriction of valve motion	0	0	
Regurgitation	0	0	

P, pergolide; NP, non pergolide; OE, other ergot-derived dopamine receptor agonists; AV, aortic valve; MV, mitral valve; TV,tricuspid valve; PV, pulmonary artery valve; and PG, pressure gradient.

significant differences in valvular abnormalities between the 2 groups.

Discussion

We found that the incidence of valvular heart disease did not differ significantly between patients with Parkinson's disease taking low-dose pergolide and those not taking low-dose pergolide, either with or without other ergot-derived dopamine receptor agonists. These findings suggest that low-dose pergolide might not induce valvular heart disease.

Pergolide has been reported to be associated with retroperitoneal, pericardial, and pleural fibrosis, as well as restrictive valvular heart disease[1-3]. It was found that some degree of valvular regurgitation was present in one or more valves in 89% of pergolide-treated patients, and an approximately 2- to 3-fold increase in risk of abnormal valves was found in patients taking pergolide, compared to patients not taking it[4-7,10]. In addition, restrictive valvular heart disease of any type was present in 33% patients taking pergolide but no patients not taking pergolide, indicating that restrictive valvular heart disease is not a rare complication in patients treated with pergolide[1,4,5]. High-dose pergolide (more than 5 mg per day) was administered and caused valvular heart diseases in previous investigations[4,10], while low-dose pergolide (less than 1.5 mg per day) was given in our study and our findings show that the incidence of valvular heart disease was not significantly different between patients taking low-dose pergolide and those not

taking low-dose pergolide. The patients with Parkinson's disease who were enrolled in previous investigations required high-dose pergolide for improvement of neurological condition. On the other hand, low-dose pergolide was sufficient for the patients enrolled in the present study. The majority of patients enrolled in the previous investigations were not Japanese, while those enrolled in our study were all Japanese. Differences in race might be related to the differences in dose of pergolide required to treat Parkinson's disease.

Echocardiography is a well-established and useful tool for clinical assessment of heart valve structures, such as calcification, thickening, and heart valve motions[1,4]. Although cardiac CT and MRI have recently emerged as new noninvasive diagnostic tools for heart disease[11-14], echocardiography is still advantageous for real-time evaluation of valvular motion and structure[12,15]. However, echocardiographic assessment of heart valves is not objective, not quantitative, and depends on the echocardiographer's technique and experience. Therefore, in the present study all echocardiographic examinations were performed by one well-experienced echocardiographer and all measurements and evaluations were carried out by one independent investigator blind to all patient data, in order to obtain consistent and accurate echocardiographic assessment. Continuous- and pulsed-wave Doppler examinations were also performed to estimate the severity of valvular heart disease in semi-quantitative fashion.

Implications

According to the recently published guidelines in the United States, no ergot-derived dopamine agonists, including pergolide, should be given to patients with Parkinson's disease[16,17]. However, low-dose pergolide is sufficiently beneficial for such patients, and prohibition of all ergot-derived dopamine agonists, including pergolide, would be profoundly disadvantageous for Japanese patients with Parkinson's disease. Our findings show that the incidence of valvular heart disease was not significantly different between patients with Parkinson's disease taking low-dose pergolide and those not taking low-dose pergolide, either with or without other ergot-derived dopamine agonists. Low-dose pergolide may be able to be administered with observation for development of heart valve disorders, with cooperation between neurologists and cardiologists.

Limitations

The effects of pergolide may differ among races, and further examinations of use of low-dose pergolide in patients of other races are warranted. The differences in dose of pergolide required to treat Parkinson's disease between this study and the previous studies may be attributed to differences of duration and severity of Parkinson's disease. Further comparative studies among different races in a group of patients with homogeneous duration and severity of Parkinson's disease are required. Although this study was limited by its small sample size and was a retrospective study, we consecutively included all patients with Parkinson's disease who were treated at the Department of Neurology of Osaka City University Hospital between August 2004 and January 2006, to minimize patient selection bias. However, potential selection bias by the study design has not been excluded completely. A large-scale prospective randomized study is warranted to confirm our findings. In our study, echocardiographic evaluations of the heart valves were performed once, just after enrollment. Serial echocardiographic assessments of

heart valves may be required to verify our findings.

Conclusions

The incidence of valvular heart disease did not differ significantly between patients with Parkinson's disease taking low-dose pergolide and those not taking low-dose pergolide, either with or without other ergot-derived dopamine receptor agonists. Low-dose pergolide might be able to be administered with careful observation of the heart valves, with cooperation between neurologists and cardiologists.

References

1. Yamamoto M, Uesugi T, Nakayama T. Dopamine agonists and cardiac valvulopathy in Parkinson disease. Neurology 2006;67:1225-29.
2. Connolly HM, Cary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, et al. Valvular heart disease associated with fenfluramine-phentaermine. N Engl J Med 1997;337:581-588.
3. Ling LH, Ahlskog JE, Munger TM, Limper AH, Oh JK. Constrictive pericarditis and pleuropulmonary disease linked to ergot dopamine agonist (cabergoline) for Parkinson's disease. Mayo Clin Proc 1999;74:371-375.
4. Van Camp G, Flamez A, Cosyns B, Weytjens C, Muyldermans L, Van Zandijcke M, et al. Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. Lancet 2004;363: 1179-1183.
5. Van Camp G, Flamez A, Cosyns B, Goldstein J, Perdaens C. Heart valvular disease in patients with Parkinson's disease treated with high-dose pergolide. Neurology 2003;61:859-861.
6. Baseman DG, O'Suilleabhain PE, Reimold SC, Laskar SR, Baseman JG, Dewey RB. Pergolide use in Parkinson disease is associated with cardiac valve regurgitation. Neurology 2004;63:301-304.
7. Horvath J, Fross RD, Kleiner-Fisman G, Lerch R, Stalder H, Liaudat S, et al. Severe multivalvular heart disease: a new complication of the ergot derivative dopamine agonists. Movement Disorders 2004;19:656-662.
8. Waller EA, Kaplan J, Heckman MG. Valvular heart disease in patients taking pergolide. Mayo Clin Proc 2005;80:1016-1020.
9. Narabayashi H, Andoh K, Kowa H, Yanagisawa N, Mizuno Y, Ogawa N, et al. Clinical utility of pergolide mesilate (LY 127808) on Parkinson's disease: double blind study in comparison with bromocriptine. Igaku-to-Yakugaku 1992;27:147-211. (in Japanese)
10. Pritchett AM, Morisson JF, Edwards WD, Schaff HV, Connolly HM, Espinosa RE. Valvular heart disease in patients taking pergolide. Mayo Clin Proc 2002;77:1280-1286.
11. Mahnken AH, Mühlenbruch G, Das M, Wildberger JE, Kühl HP, Günther RW, et al. MDCT detection of mitral valve calcification: prevalence and clinical relevance compared with echocardiography. AJR Am J Roentgenol 2007;188:1264-1269.
12. Feuchtner GM, Dichti W, Friedrich GJ, Frick M, Alber H, Schachner T, et al. Multislice computed tomography for detection of patients with aortic valve stenosis and quantification of severity. J Am Coll Cardiol 2006;47:1410-1417.
13. Boxt LM. CT of valvular heart disease. Int J cardiovasc imaging 2005;21:105-113.
14. Lembcke A, Borqes AC, Dushe S, Dohmen PM, Wiese TH, Rogalla P, et al. Assessment of mitral valve regurgitation at electron-beam CT: comparison with Doppler echocardiography. Radiology 2005;236:47-55.
15. Suzuki J. Cardiac MRI, CT. Naika 2006;97:419-421. (in Japanese)
16. Zanottini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. N Engl J Med 2007;356:39-46.
17. Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. N Engl J Med 2007;356:29-38.