Cardiac Valve Regurgitation With Pergolide Compared With Nonergot Agonists in Parkinson Disease

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Background: Although most studies have suggested an increased risk of valvulopathy (primarily regurgitation) with pergolide mesylate use, one study suggested that this problem may also occur with use of the non–ergot-derived dopamine agonists pramipexole dihydrochloride and ropinirole hydrochloride.

Objective: To determine if cardiac valve regurgitation occurs more commonly in patients with Parkinson disease (PD) treated with pergolide than in those treated with nonergot agonists at a comparable dose.

Design: A case-control study of echocardiographic findings of valve function in patients receiving dopamine agonists for PD.

Setting: University-based referral center.

Patients: Thirty-six patients with idiopathic PD taking pergolide were compared with a matched control group of patients taking nonergot agonists with regard to the frequency and severity of cardiac valve regurgitation.

Main Outcome Measure: Valve scores (1 indicates trace; 2, mild; 3, moderate; and 4, severe) for the pergolide group were compared with those for the nonergot agonist control group.

Results: The mean ± SD valve regurgitation scores in the matched pergolide group compared with the nonergot group were as follows: aortic, 0.83 ± 1.23 vs 0.19 ± 0.53 (P = .01); mitral, 1.42 ± 1.0 vs 0.39 ± 0.65 (P < .001); and tricuspid, 1.43 ± 1.0 vs 0.19 ± 0.53 (P < .001). Lifetime exposure to a dopamine agonist was not statistically different between the pergolide and nonergot agonist groups (P = .18).

Conclusions: These data strengthen the conclusion that pergolide contributes to cardiac valve regurgitation when used in the long term as a treatment for PD. There appears to be low risk of cardiac valve regurgitation when using non–ergot-derived dopamine agonists.

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Following the original description of pergolide-associated valvular heart disease by Pritchett et al1 in 2002, several studies of this phenomenon have been reported as summarized in a recent review article.2 Although most studies have suggested an increased risk of valvulopathy (primarily regurgitation) with pergolide mesylate use, one study suggested that this problem may also occur with use of the non–ergot-derived dopamine agonists pramipexole dihydrochloride and ropinirole hydrochloride.3 In our previous study, we showed that valvar regurgitation was 2 to 3 times more common in pergolide-treated patients with Parkinson disease (PD) than in the aged-matched general population.4 Since our study lacked a control group of patients with PD who were not treated with pergolide, it remained possible that the observed difference in valvular heart disease was due to some factor inherent to PD rather than to pergolide exposure. The present study was designed to address this limitation by prospectively collecting a conceptually ideal control group for comparison with the previously described pergolide-treated cohort. Our hypothesis was that if pergolide itself was the cause of pergolide-associated valvular heart disease, then the frequency of valvular regurgitation in pergolide-treated patients would exceed that in patients with PD of a similar age who were treated with non–ergot-derived dopamine agonists.

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METHODS

We searched our clinical documentation system for patients with PD who had been treated by 1 of us and who were taking a nonergot dopamine agonist (pramipexole or ropinirole); these 336 patients were listed by age, sex, and dose of dopamine agonist. For each of our original pergolide-treated patients, 2 to 3 patients identified by this search who were of similar age and agonist dose and of the same sex were listed as potential controls. It was important to control for age because valvular regurgitation increases with age, and agonist dose was controlled because we found a dose-response relationship between lifetime pergolide exposure and risk of regurgitation in our original study. Our research nursing staff then attempted to contact potential control patients by telephone and, after several months of this effort, 36 patients (matching 36 patients from the original pergolide cohort of 46 patients) were identified who agreed to undergo a transthoracic echocardiogram with attention to valve function. Patients were not selected as controls if they had a significant history of exposure to pergolide. All 36 control echocardiograms were read by the same cardiologist (S.C.R.), who was blinded to patient identity and agonist treatment. Cardiac valve regurgitation was rated semiquantitatively after the method described in the Framingham Heart Study and expressed numerically according to the following method: 1 indicates trace; 2, mild; 3, moderate; and 4, severe. Valvular regurgitation in the original pergolide cohort was rated using the same scale, and half of these 46 patients had echocardiography performed and the results read at another institution. For some such patients, echocardiographic reports indicated an intermediate degree of valve regurgitation (such as mild to moderate), in which case an intermediate score (such as 2.5) was assigned.

Valve scores of the matched control patients were compared with those of the pergolide cohort using the Wilcoxon signed rank test. Since 10 of the original pergolide cohort members could not be matched to controls, we compared valve scores of this group with those of the 36 pergolide-treated patients.
who were successfully matched to controls using the Mann-
Whitney U test to determine if these groups were substantially
similar. To determine if nonergot agonist–treated control pa-
tients were exposed to a similar dose of agonist as the per-
golide cohort, we first converted the nonergot agonist dose to
pergolide equivalents using the following formula, as sug-
gested by Grosset et al: 1 mg of pramipexole dihydrochlo-
ride=1 mg of pergolide mesylate=4 mg of ropinirole hydro-
chloride. Lifetime agonist dose in the nonergot agonist cohort
was compared with the lifetime agonist dose in the pergolide
cohort using the paired t test. All control patients who partici-
pated in this study provided written informed consent before
undergoing echocardiography, and the study was approved by
the University of Texas Southwestern institutional review board.

The 36 control patients (25 men and 11 women) taking
nonergot agonists are compared with the pergolide co-
hort in the Table. All but 1 pair of patients had PD, and
the age matching was reasonably successful. Valve scores
are shown in Figure 1 for the aortic, mitral, and tricus-
pid valves. No significant difference was found between
the mean±SD valve scores in the matched (n=36) and un-
matched (n=10) pergolide groups: aortic, 0.83±1.2 vs
0.80±0.92 (P=.80); mitral, 1.42±1.0 vs 0.90±0.88 (P=.17);
and tricuspid, 1.43±1.0 vs 1.3±0.82 (P=.74). By con-
trast, the mean±SD valve scores of the matched per-
golide group differed significantly from those of the non-
ergot agonist control group: aortic, 0.83±1.23 vs 0.19±0.53
(P=.01); mitral, 1.42±1.0 vs 0.39±0.65 (P<.001); and tri-
cuspid, 1.43±1.0 vs 0.19±0.53 (P<.001).

No statistically significant difference was found be-
tween the pergolide and nonergot agonist groups for pul-
monic regurgitation. The mean±SD lifetime agonist dose
comparing the pergolide cohort with the nonergot co-
hort expressed in pergolide equivalents was similar
(5307±3880 vs 4356±3342; P=.18), as shown in
Figure 2. Although 20 of the nonergot agonist–treated
patients had nonzero scores for 1 or more valves (56%),
in no case were these abnormalities symptomatic. No pa-
tients taking nonergot agonists had worse than mild re-
gurgitation in any valve, whereas regurgitation of this se-
verity was seen in at least 1 valve in 11 pergolide-treated
patients.

This study strengthens the conclusion we drew from
our earlier work that pergolide most likely injures car-
diac valves in patients with PD who take this drug in
the long term. Our present data suggest that pergolide
itself is the most likely offending agent (rather than
some other unknown factor associated with PD) and
that nonergot agonists are much less likely to cause
regurgitant valvulopathy. This conclusion is concordant
with the recent publication of Peralta et al. This induc-
tion of valve regurgitation is plausibly related to the
stimulation of serotonin receptors by pergolide, a fea-
ture it shares with fenfluramine hydrochloride, a drug
associated with valvulopathy. Although we have shown
that pergolide is associated with more valve regurgita-
tion than the nonergot dopamine agonists, most of our
affected pergolide-treated patients had mild regurgita-
tion, which was asymptomatic. Whether continued treat-
ment with pergolide would have produced clinically important valvulopathy in these individuals is unknown.

The strength of our study is the matching of non-ergot agonist–treated patients with those in the pergolide cohort by age, sex, diagnosis, and lifetime dose of agonist. This matching reduces the likelihood that some unknown factor is the underlying cause of valvular regurgitation seen in pergolide-treated patients. Our study has 1 important limitation in that echocardiography of half the pergolide cohort was performed and the results read at other institutions, and despite significant efforts to obtain these outside studies for our own internal review, we were unsuccessful in obtaining a sufficient number of them to address this limitation. Nevertheless, since the valve scoring method we used is that typically used by most echocardiographers in the routine use of this test clinically, we doubt that this limitation significantly affected the results.

On the basis of the current data and those of our previous report,⁴ we continue to advise patients who are taking pergolide to stop taking the drug if possible and, if not, to undergo yearly echocardiography looking for valve regurgitation. Our practice of recommending nonergot dopamine agonists as first-line therapy for patients needing a dopamine agonist appears to be relatively safe from the standpoint of cardiac valve function.

Of course, pergolide-associated valvular heart disease is only 1 of the drug complications to be considered when treating PD. Dopamine agonists are associated with several other potentially serious adverse events, including sedation,¹² sleep attacks,¹³ hallucinations,¹⁴ pathological gambling,¹⁵ and other compulsive behaviors.¹⁶ We believe that patients should be counseled regarding all of these risks and carefully monitored for the development of problems during therapy. Nevertheless, valvular regurgitation is the only potentially serious adverse effect convincingly demonstrated to be differentially associated with pergolide compared with the non-ergot dopamine agonists.

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