Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.

ETIOLOGY

Pergolide and cabergoline were associated with increased risk for newly diagnosed cardiac valve regurgitation

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.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Cardiology ★★★★★★☆ Neurology ★★★★★★☆

QUESTION

In patients taking antiparkinsonian drugs, do dopamine agonists (DAs) (in particular, pergolide and cabergoline) increase risk for newly diagnosed cardiac valve regurgitation?

METHODS

Design: Nested, case–control study within a cohort of 11 417 patients from the U.K. General Practice Research Database (1988 to 2005) with mean follow-up of 4.2 years.

Setting: > 350 general practices in the United Kingdom.

Patients: 694 patients (31 cases, 663 controls) 40 to 80 years of age (mean age 74 y, 67% men) who had received ≥ 2 prescriptions for antiparkinsonian medications, including the dopamine precursor levodopa; the monoamine oxidase inhibitor selegiline; and the DAs bromocriptine, lisuride, cabergoline, pergolide, pramipexole, and ropinirole. 90% of patients had Parkinson disease, 4% had the restless legs syndrome, and 3% had hyperprolactinemia. Exclusion criteria included history of rheumatic heart disease, congenital heart disease, congestive heart failure, dilated cardiomyopathy, endocarditis or myocarditis, the carcinoid syndrome, or heart valve abnormalities; and receipt of phentermine, ergotamine, dihydroergotamine, fenfluramine, dexfenfluramine, or methylsergide.

Risk factors: Use of individual DAs within 12 months before the index date (current use). Results were adjusted for use of other DAs or amantadine.

Outcomes: Newly diagnosed cardiac valve regurgitation.

MAIN RESULTS

Current use of pergolide (19% of cases, 4% of controls) or cabergoline (19% of cases, 5% of controls) led to higher risk for newly diagnosed cardiac valve regurgitation than did no DA use in the previous 12 months (Table). Daily doses of pergolide or cabergoline > 3 mg and duration of use ≥ 6 months further increased risk (Table). Other DAs did not increase risk for newly diagnosed cardiac valve regurgitation.

CONCLUSION

Antiparkinsonian drugs, pergolide and cabergoline, but not other dopamine agonists, were associated with increased risk for newly diagnosed cardiac valve regurgitation.

Sources of funding: Canadian Foundation for Innovation and Canadian Institute of Health Research.

For correspondence: Dr. R. Schade, Charité-Universitäts Medizin Berlin, Berlin, Germany. E-mail ruediger.schade@charite.de. ■

*See Glossary.

Association between use of dopamine agonists (pergolide and cabergoline) and risk for newly diagnosed cardiac valve regurgitation†

Risk factors	Adjusted incidence–rate ratio (95% CI)	
	Pergolide	Cabergoline
Current use	7.1 (2.3 to 22)	4.9 (1.5 to 16)
Last daily dose > 3 mg	37 (5.1 to 271)	50 (6.6 to 381)
Cumulative duration of use ≥ 6 mo	9.8 (2.9 to 33)	7.8 (2.2 to 27)

†CI defined in Glossary. Incidence–rate ratio adjusted for use of other dopamine agonists or amantadine.

COMMENTARY

How is it that randomized controlled trials (RCTs) of pergolide and cabergoline have failed to detect the possibility of serious valvular pathology? First, most RCTs are designed to show benefit for 1 treatment over another or controls; statistical power and sample sizes are based on this premise. Even large, well-conducted RCTs are usually too small to detect rare serious adverse events. Second, adverse effects may be related to dose or treatment duration and patients may not have had sufficient exposure to the drug in RCTs. Third, patient populations (and thus their underlying risk for adverse events) may be quite different in the "real world." Finally, it is a truism that you will not find what you do not look for. Thus, cursory clinical evaluation alone in patients without cardiac symptoms would have been unlikely to detect subtle regurgitant murmurs.

Could the association between ergot-derived DAs and valvular disease shown in the studies by Schade and colleagues and Zanettini and colleagues have been predicted? Yes. Carcinoid tumors have an associated valvular pathology caused by paraneoplastic effects of such vasoactive substances as 5-hydroxytryptamine (5-HT or serotonin) and histamine released by the malignant cells (1). Similar valvular abnormalities were described for both fenfluramine and dexfenfluramine, both of which are serotonin-receptor agonists (2). In an editorial accompanying the 2 current studies, Roth described how drug agonists to 5-HT_{2B} receptors can be implicated in drug-induced valvular heart disease and discussed potential molecular mechanisms (3). In comparison with other DAs, both pergolide and cabergoline are potent 5-HT_{2B} agonists.

If predictable, why were the RCTs of pergolide and cabergoline not designed to monitor valvular disease? First, they were small and typically involved < 1000 patients. More important, however, is timing. The trials were either designed or completed before the first description of serotonin agonist valvular disease (2) or the involvement of 5-HT_{2B} receptors (4). Even Cochrane reviews of these 2 drugs did not discuss the possibility of valvular disease (5).

In the studies by Schade and colleagues and Zanettini and colleagues, the estimates of drug-induced valvular disease are probably unstable, given the small number of patients with new valvular regurgitation. Furthermore, the evaluation strategies were very different. Therefore, it is not surprising that Schade and colleagues reported a very rare prevalence (12 in 30 000) with clinical case ascertainment and that Zanettini and colleagues reported a more common prevalence among a selected cohort based on echocardiographic case ascertainment.

(continued on page 76)

Pergolide and cabergoline increased risk for valvular heart disease in Parkinson disease

Zanettini R, Antonini A, Gatto G, et al. **Valvular heart disease and the use of dopamine agonists for Parkinson's disease.** N Engl J Med. 2007;356:39-46.

Clinical impact ratings: Cardiology ★★★★★★☆ Neurology ★★★★★★☆

QUESTION

In patients with Parkinson disease, do pergolide, cabergoline, or non–ergot-derived dopamine agonists (DAs) increase risk for valvular heart disease?

METHODS

Design: Cohort study.

Setting: Outpatient clinic at the Parkinson Institute in Milan, Italy.

Patients: 155 patients with Parkinson disease who had been taking pergolide (n = 64), cabergoline (n = 49), or non–ergot-derived DAs (n = 42) for ≥ 12 months and had never taken the other types of DA (mean age 63 y, 63% men), and 90 control participants without Parkinson disease matched to patients for sex, age, and hypertension status (mean age 64 y, 58% men). Groups were also similar for body mass index, diabetes, coronary heart disease, and systolic and diastolic blood pressure. Exclusion criteria were history of cardiac valvular abnormalities, previous use of anorectic or other ergot-derived drugs, valve calcification, valve regurgitation associated with annular dilatation or excessive leaflet motion, and mitral regurgitation associated with left ventricular wall-motion abnormalities or left ventricular dilatation.

Risk factors: Use of pergolide, cabergoline, or non–ergot-derived DAs for ≥ 12 months.

Outcomes: Clinically significant valvular heart disease (moderate-to-severe mitral, aortic, or tricuspid valve regurgitation), composite regurgitation score (range 0 to 12, higher score indicates more severe disease), and mitral valve tenting area.

MAIN RESULTS

The prevalence of moderate-to-severe valve regurgitation was 23% in the pergolide group, 29% in the cabergoline group, 0% in the non–ergot-derived DA group, and 6% in the control group. The pergolide and cabergoline groups had higher risk for moderate-to-severe valve regurgitation (Table) and higher mean composite regurgitation scores than the control group (4.8 and 5.1, respectively vs 3.3, $P < 0.001$). The non–ergot-derived DA and control groups did not differ for these outcomes. The pergolide, cabergoline, and non–ergot-derived DA groups had higher mean mitral valve tenting areas than the control group (3.0, 3.1, and 2.8 cm^2 vs 2.4 cm^2, respectively, $P \leq 0.002$).

CONCLUSION

Pergolide and cabergoline, but not non–ergot-derived dopamine agonists, increased risk for valvular heart disease in patients with Parkinson disease.

Sources of funding: Italian Parkinson Association and Grigioni Foundation for Parkinson Disease.

For correspondence: Dr. R. Zanettini, Istituti Clinici di Perfezionamento, Milan, Italy. E-mail cardriab@icp.mi.it.

Association between use of the dopamine agonists pergolide and cabergoline and risk for moderate-to-severe valve regurgitation in patients with Parkinson disease compared with persons without Parkinson disease*

Outcomes	Relative risk (95% CI)	
	Pergolide	Cabergoline
Mitral valve regurgitation	6.3 (1.4 to 28)	4.6 (0.9 to 23)
Aortic valve regurgitation	4.2 (1.2 to 15)	7.3 (2.2 to 25)
Tricuspid valve regurgitation	5.6 (0.7 to 50)	5.5 (0.6 to 52)

*CI defined in Glossary.

COMMENTARY

(continued from page 75)

These studies provide another reminder that substances capable of producing therapeutic effects are always capable of producing adverse effects. At present, it would be prudent to avoid prescribing either pergolide or cabergoline unless there are absolutely no suitable alternatives. In patients currently stable on these medications, potential valvulopathy should be assessed clinically and with echocardiography; if valvular disease is shown, an alternative nonergot drug should be chosen. While a strategy of serial echocardiographic monitoring during therapy may seem attractive (akin to liver enzyme monitoring when using statins), this strategy has not been proven to favorably affect outcome. Regression of valvular disease after stopping pergolide has been observed, but it cannot be guaranteed.

David Massel, MD
Neville Suskin, MD
London Health Sciences Centre
London, Ontario, Canada

References

1. **Spatz M.** Pathogenetic studies of experimentally induced heart lesions and their relation to carcinoid syndrome. Lab Invest. 1964;13:288-300.
2. **Connolly HM, Crary JL, McGoon MD, et al.** Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med. 1997;337:581-8.
3. **Roth BL.** Drugs and valvular heart disease. N Engl J Med. 2007;356:6-9.
4. **Rothman RB, Baumann MH, Savage JE, et al.** Evidence for possible involvement of 5-HT(2B) receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. Circulation. 2000;102:2836-41.
5. **Clarke CE, Deane KH.** Cabergoline for levodopa-induced complications in Parkinson's disease. Cochrane Database Syst Rev. 2001;(1):CD001518.