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ORIGINAL ARTICLE

Prospective, long-term study of the effect of cabergoline on valvular status in patients with prolactinoma and idiopathic hyperprolactinemia

Laurent Vroonen[1] · Patrizio Lancellotti[2] · Monica Tomé Garcia[1] · Raluca Dulgheru[2] · Matilde Almanza[1] · Ibrahima Maiga[1] · Julien Magne[2] · Patrick Petrossians[1] · Renata Auriemma[1] · Adrian F. Daly[1] · Albert Beckers[1]

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Abstract Since the 1990's cabergoline has been the treatment of choice in prolactinoma, as it permits rapid and effective hormonal and tumor control in most cases. Evidence of cardiac valvulopathy was demonstrated in Parkinson's disease patients treated with dopamine agonists. Retrospective studies in prolactinoma patients treated with cabergoline at lower doses did not show such an effect. However, few prospective data with long-term follow-up are available. The aim of this study was to assess the safety of cabergoline regarding cardiac valvular status during prospective follow-up in patients treated for prolactinoma or idiopathic hyperprolactinemia. We report here a series of 100 patients (71F; median age at diagnosis: 41.5 years) treated with cabergoline for endocrine diseases (prolactinoma $n = 89$, idiopathic hyperprolactinemia $n = 11$). All patients underwent complete transthoracic echocardiographic studies at baseline and during long-term prospective surveillance using the same equipment and performed by the same technicians. The median interval between baseline and last follow-up echocardiographic studies while on cabergoline was 62.5 months (interquartile range: 34.75–77.0). The median total duration of cabergoline treatment was 124.5 months (interquartile range: 80.75–188.75) and the median cumulative total dose of cabergoline was 277.8 mg (interquartile range : 121.4–437.8 mg) at last follow-up. We found no clinically relevant alterations in cardiac valve function or valvular calcifications with cabergoline treatment. Our data suggest that findings from retrospective analyses are correct and that cabergoline is a safe chronic treatment at the doses used typically in endocrinology.

Keywords Cabergoline · Echocardiography · Prolactinoma · Hyperprolactinemia · Cardiac valve

Introduction

An increased risk of cardiac valve disease has been seen in patients treated for Parkinson's disease using high doses of ergot-derived dopamine agonists like cabergoline and pergolide [1]. The mechanisms underlying this effect have been studied widely [2–4]. In Parkinson's disease a correlation between the cumulative dose of dopamine agonists and the severity of cardiac valve regurgitation has been reported [5–8].

Since the 1990's, cabergoline has become the first line treatment for hyperprolactinemia [9–12]. Its widespread use raised questions about its safety in the endocrine setting, as it is used chronically, although the doses used in endocrinology are lower than those used in Parkinson's disease. Our first cross-sectional study in 2008 did not find any relevant valvulopathy in patients treated with dopamine agonists at doses typically used in the endocrine setting [13]. While these results were reassuring, relatively little information on long term use of cabergoline and cardiac valve status are available. We report here a prospective follow-up study of 100 patients treated with cabergoline for

✉ Albert Beckers
albert.beckers@chu.ulg.ac.be

[1] Department of Endocrinology, Center Hospitalier Universitaire de Liège, University of Liège, Domaine Universitaire du Sart-Tilman, Liège 4000, Belgium

[2] Department of Cardiology, Center Hospitalier Universitaire de Liège, University of Liège, Domaine Universitaire du Sart-Tilman, Liège 4000, Belgium

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hyperprolactinemia, in which there was at least one year of follow-up between echocardiographic studies.

Methods

Patient population

The study population consisted of 100 subjects who received cabergoline treatment for prolactin secreting microadenomas ($n = 46$), macroadenomas ($n = 43$) or idiopathic hyperprolactinemia ($n = 11$) and underwent echocardiographic surveillance as part of the standard hospital protocol. Three patients included in the study had not previously received cabergoline before the first cardiac echography whereas the other 97 patients had already been treated. The cumulative dose of cabergoline was calculated for each patient. Data on other risk factors for cardiac valve disease were collected with particular attention paid to hypertension, diabetes mellitus, obesity, hypercholesterolemia and smoking.

Each patient underwent at least two cardiac ultrasound evaluations, with a minimum of 12 months between assessments. The retrospective period was defined as the period up to the first ultrasound evaluation (baseline findings) while the prospective period extended from the first to the last echocardiography (follow-up findings). All the patients and controls consented to the performance of echocardiographic surveillance and the study was approved by the Ethics Committee of the Center Hospitalier Universitaire de Liège

Controls

As previous studies have not addressed baseline valvular status as compared to healthy (non-cardiac disease) controls, we recruited a cohort of 60 anonymized healthy individuals that were matched for age and sex with the patient population. In the control group, the rates of valvular regurgitation for the four cardiac valves were as follows: tricuspid valve–grade 0 ($n = 30$), grade 1 ($n = 25$), grade 2 ($n = 5$); mitral valve–grade 0 ($n = 33$), grade 1 ($n = 27$), grade 2 ($n = 0$); aortic valve–grade 0 ($n = 53$), grade 1 ($n = 7$), grade 2 ($n = 0$); pulmonary valve–grade 0 ($n = 34$), grade 1 ($n = 24$), grade 2 ($n = 2$). None of the control subjects had evidence of calcification or grade 3 valvular insufficiencies at baseline. The mitral valve tenting area was normal in all control subjects (median: 1.20 cm^2 (IQR: 1.10–1.40 cm^2)). The echocardiographic results of this control group were compared with the patient cohort in terms of valve characteristics at baseline.

Echocardiographic measurements

All patients and controls underwent a complete transthoracic echocardiographic examination using the same equipment (Vivid 7 GE, Vingmed Ultrasound, Horten, Norway). All echocardiograms were performed by two experienced echocardiographers, with special attention towards valvular status and these cardiograms were interpreted by a third echocardiographer. Echocardiographic and Doppler data were obtained in digital format and stored on optical disks for off-line analysis. Valvular regurgitation was diagnosed using color-coded doppler and by imaging multiple views. Quantification of regurgitant valve disease was made according to the guidelines of the American Society of Echocardiography [14]. Valve regurgitation was graded on a 0–3 scale as absent, mild (not significant), moderate, or severe. Abnormal leaflet or cusp thickening was judged to be present when the thickness (localized or widespread) exceeded 5 mm [6, 8]. Mitral and tricuspid valves were regarded as restrictive if leaflet stiffening and retraction towards the apex was identified. Mitral valvular tenting area —a marker of the apical displacement of mitral leaflets— was obtained from the parasternal long axis view at mid-systole and measured the area enclosed between the annular plane and the mitral leaflets [15, 16]. The aortic valve was judged as being restrictive if the valve opened with visibly evident doming of the leaflets. Systolic pulmonary artery pressure was estimated from the systolic trans-tricuspid pressure gradient (in mmHg) using the simplified Bernoulli equation. Classification of valvular status was made according to the American Society of Echocardiography and was summarized as follows [14]:

grade 0: no dysfunction

grade 1: mild regurgitation (grade 1 regurgitation is considered not clinically significant)

grade 2: moderate regurgitation

grade 3: severe regurgitation

Statistical analysis

Data were imported into the R statistical package. Continuous variables were tested for normality. Since none of the continuous variables showed a normal distribution, they were described in the article as medians and inter-quartiles ranges (IQR). The total range was also reported where relevant. The control and cabergoline treated subjects were divided in subgroups based on sex and current age (<30, 30–40, 41–50, 51–60, >60 years).

For mitral valve tenting area data, statistical comparison of control cases versus cabergoline-treated patients at baseline was made using the Kruskal-Wallis test on each subgroup. Comparison of tenting data in the cohort at baseline and last assessment were performed using the

Table 1 Characteristics of patients with grade 2 (moderate) tricuspid regurgitation ($n = 4$)

Age at diagnosis (yr)	PRL at diagnosis (μU/mL)	Adenoma size at diagnosis	Other treatment	Retrospective treatment period (mo)	Prospective follow-up (mo)	Total follow-up (mo)	Cumulative cabergoline dose (mg)	Severity grade change during follow-up
48	1695	Micro	none	55	51	106	292.0	None (2→2)
43	3830	Macro (invasive)	bromocriptine surgery	144	55	199	256.75	None (2→2)
24	1500	Micro	bromocriptine surgery	180	81	261	273.0	None (2→2)
36	1936	Micro	bromocriptine	21	56	77	256.25	Decrease (2→1)

Micro: microadenoma (<10 mm); Macro: macroadenoma (>10 mm); mo: months; PRL: prolactin

paired version of the Kruskall-Wallis test. For valvular insufficiencies, the score (0–4) was tested by binning the number of patients for each score value, then testing the corresponding contingency table with a chi-square test. This test was performed first for the age and sex-related subgroups of controls versus patients and then for the data of patients at baseline versus their last evaluation. Statistical significance was assessed based on a p-value < 0.05.

Results

The patient cohort consisted of 70 women and 30 men. The median age at the diagnosis was 41.5 years (IQR: 28–51 years). The median total duration of cabergoline treatment was 124.5 months (IQR: 80.7–188.7 months) and the median cumulative dose of cabergoline was 277.8 mg (IQR: 121.4–437.8 mg) at last follow-up. Cardiovascular risk factors at baseline included: dyslipidemia ($n = 25$), obesity ($n = 28$), hypertension ($n = 22$), diabetes mellitus ($n = 10$) and smoking ($n = 19$).

Retrospective period: baseline findings at first echocardiographic evaluation

The median duration of treatment before the baseline echocardiographic examination (the retrospective period) was 62.5 months in the patient population (IQR: 24.75–132.0 months; Range: 0–276 months). The median dose of cabergoline during that period was 139.38 mg (IQR: 31.88–323.75 mg). Moderate mitral valve regurgitation was found in four female cabergoline-treated patients at baseline. None had dilated cardiomyopathy or renal failure. In another four female patients, mild tricuspid insufficiency was present at baseline but none had pulmonary hypertension (Table 1). No patient had aortic or pulmonary valvulopathy at baseline. The median mitral valve tenting area was normal in the patient cohort at baseline (1.26 cm^2 (IQR: 1.10–1.40 cm^2)). As compared to normal controls, there was no significant difference in terms of mitral valve tenting in patient cohort at baseline ($p = $ NS). At baseline, there were no significant differences between the healthy controls as a whole and the patient population in terms of the frequencies of valvular regurgitation; similarly no significant, clinically relevant differences were seen between the healthy controls and the patients when analyzed separately by age and sex ($p = $ NS).

Prospective period: follow-up findings at last echocardiographic evaluation

The median duration of the prospective follow-up period from baseline to last echocardiographic evaluation was 62.5 months (IQR: 34.75–77.0 months; range: 12–92 months). The median dose of cabergoline in the prospective period alone was 85.75 mg (IQR: 35.5–171.5 mg). As noted above, the median cumulative (retrospective plus prospective period) cabergoline dose was 277.8 mg (IQR: 121.4–437.8 mg).

Evolution of valvular status during follow-up of our population is shown in Fig. 1. During the prospective period, one patient developed moderate tricuspid regurgitation. This patient was a 43-year-old female with a macroadenoma at diagnosis. Her PRL levels were 1339 μU/mL at diagnosis and she had surgery and cabergoline treatment with a total cumulative dose of 541.7 mg over the course of 239 months of treatment. Three patients developed a new finding of mild (clinically non significant) aortic insufficiency. Three patients developed mild pulmonary valvular insufficiency (not clinically significant), while two other cases of pre-existing mild insufficiency normalized during prospective follow-up.

No significant variations in mitral function were found across the course of the prospective study. Of the four women that had moderate (grade 2) mitral regurgitation, three remained stable while one decreased in severity during the prospective follow-up. In these patients, the follow up period ranged from 77 to 261 months and the cumulative

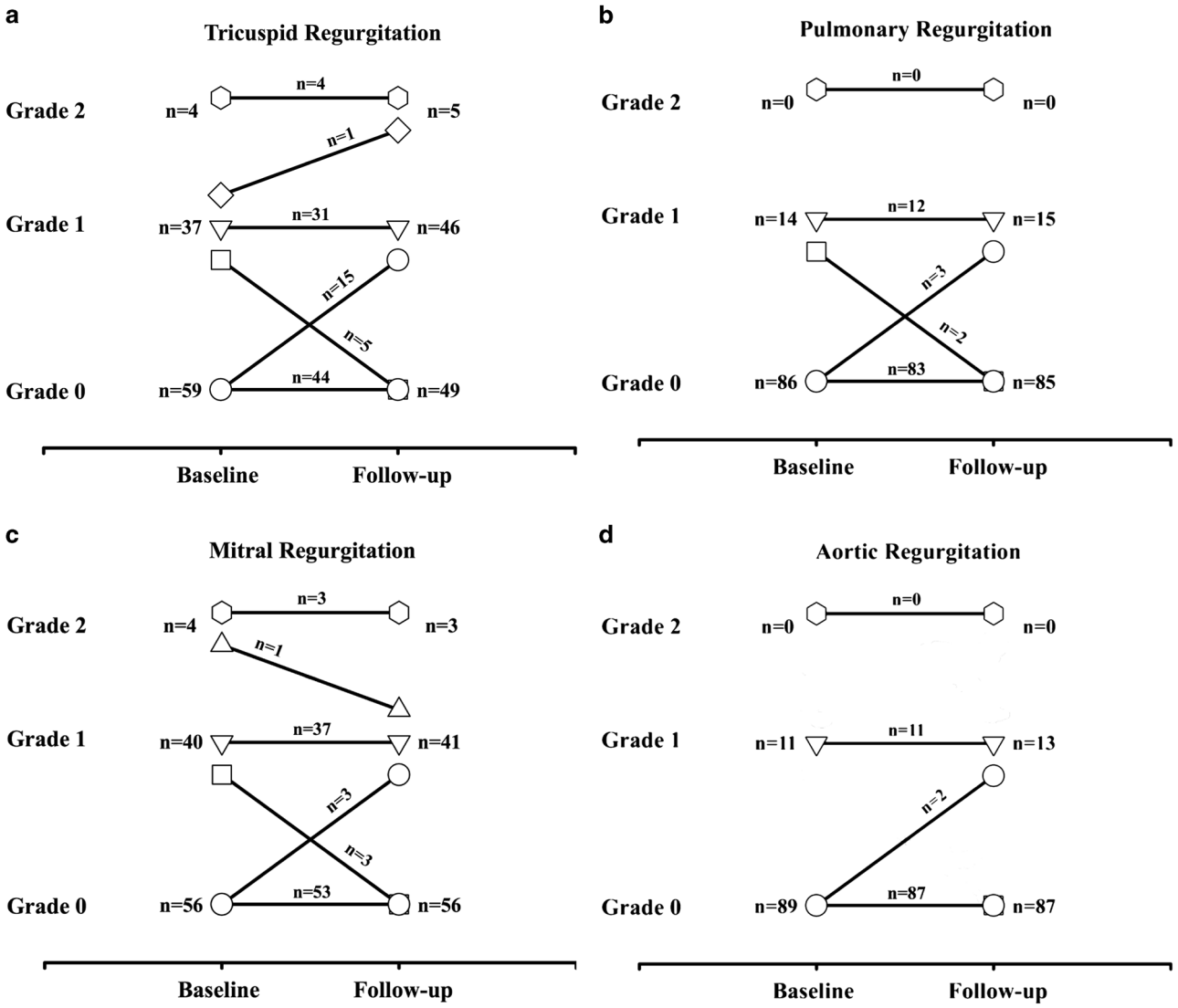

Fig. 1 Frequencies of valvular regurgitation on echocardiography in patients treated with cabergoline at baseline and at last follow-up

cabergoline dose range ranged from 256.25 to 292.0 mg (Table 1). Table 2 shows the evolution of each cardiac valve between baseline and last follow-up examinations. The median mitral valve tenting area at the last follow up was 1.27 cm^2 (IQR: 1.03–1.47 cm^2), which was not significantly different from baseline ($p = 1.0$).

Discussion

In 1997, Connolly et al. reported a series of 24 cases of unusual valvulopathy in patients treated with fenfluramine and phentermine, two anorectic drugs frequently used in the USA at the time [17]. Both were already known to be responsible, when used alone, for pulmonary hypertension. Regurgitation was found in all patients and echocardiography showed a particular valvular morphology, resulting in thickening of the anterior mitral leaflet, but both the right-sided and left-sided heart valves were involved. As this kind of valvulopathy was already described in patients suffering for carcinoid disease [18, 19] and in patients taking serotonin-like drugs [20], a common pathway for these valvulopathies was suggested. In 2000, Rothman et al. reported that activation of 5-hydroxytryptamine subtype 2 receptor (5-HT2B), which is highly expressed in human cardiac valves, is required to develop this cardiac valvular disease [2]. In consequence, mitogenesis and proliferation of fibroblasts progressively lead to an overgrowth valvulopathy [3, 4]. Since then, particular attention was paid to other ergot dopamine agonists such as bromocriptine, pergolide and cabergoline, usually used in the treatment of Parkinson's disease [1].

Table 2 Comparison of evolution of valve status between baseline and last echocardiographic evaluations in 100 patients

Tricuspid insufficiency	Baseline evaluation	Final evaluation
$p = 0.3655$		
Grade 0 (n)	59	49
Grade 1 (n)	37	46
Grade 2 (n)	4	5
Mitral insufficiency		
$p = 0.9253$		
Grade 0 (n)	56	56
Grade 1 (n)	40	41
Grade 2 (n)	4	3
Aortic insufficiency		
$p = 0.8277$		
Grade 0 (n)	89	87
Grade 1 (n)	11	13
Grade 2 (n)	0	0
Pulmonary insufficiency		
$p = 1.0$		
Grade 0 (n)	86	85
Grade 1 (n)	14	15
Grade 2 (n)	0	0

Indeed, in Parkinson's disease patients taking either cabergoline or pergolide, an increased risk of newly diagnosed degenerative heart valve disease is now well established.

During the 1990's, cabergoline became the first-line treatment for prolactinomas and hyperprolactinemia. Cabergoline is used at much lower doses in the endocrine setting than those used for Parkinson's disease. Cabergoline is usually well tolerated and highly effective in controlling prolactin hypersecetion and can also reduce tumor size. At doses within the indicated range of about 2 mg per week, resistance to cabergoline treatment is rare. A recent multicenter study in 92 resistant prolactinomas reported that they comprised only about 3.4 % of prolactinomas overall, although this rate rose to 13 % in those with a genetic component to their tumorigenesis [21], such as *AIP* mutation [22, 23]. Cabergoline has a long half-life and its potent D2 receptor affinity leads to a rapid and effective control of many prolactinomas. As this pathology affects people at a young age and as it requires chronic therapy, cumulative doses of cabergoline can be quite high. Our initial retrospective study in prolactinoma patients did not find any relationship between cabergoline dose and the presence or severity of mitral valve regurgitation. In that study, mitral valve tenting area was significantly greater in the cabergoline group when compared with control subjects and mitral valve leaflet thickening was observed in 5.9 % of cabergoline-treated subjects [13]. However, no relationship with the cumulative cabergoline dose was found and none of the patients had aortic or tricuspid valvular restriction [13]. In consequence, our subjects treated with long-term cabergoline therapy did not have a statistically significantly increased risk of clinically relevant cardiac valve disease. These results are concordant with most other studies [24–30]. Only one study found significant tricuspid valve regurgitation in patients receiving high cumulative doses of cabergoline [31]. Significant aortic valvular calcification was also reported in another study [32]. However, prospective data with long-term follow-up are relatively sparse. Maione et al. reported cardiac evaluation of acromegalic patients receiving cabergoline. In that study, a group of 26 patients treated with cabergoline was compared to 26 acromegalic controls not treated with cabergoline and with a similar duration of follow-up [33]. During the follow-up period of at least four years, the incidence of valve regurgitation and remodeling was the same in both groups. Another study reported a higher degree of aortic valvular calcifications in a series of 74 patients treated with cabergoline that were followed for two years [34]. That study was a prospective follow-up evaluation of the previous study by Kars et al., in which a high baseline frequency of aortic valve calcification was noted. In the prospective assessment, no increase of the rate of valve dysfunction or calcification was reported.

In the current cohort of 100 patients treated with cabergoline for prolactinoma and hyperprolactinemia, the risk of developing moderate or significant cardiac valve lesions was not increased. Follow-up was at least one year, but the median follow-up was much longer, at nearly 10 years and the cumulative median dose of cabergoline was >277 mg. None of the handful of moderate mitral or tricuspid regurgitation cases noted at baseline worsened significantly during follow-up. These results are in keeping with other data from prospective analyses [33–35]; however, in contrast to Delgado et al., we did not identify any cases of significant calcification despite similar mean ages at diagnosis in the two studies. Many factors can influence valvular calcifications (dyslipidemia, age, hypertension, renal failure, hyperphosphatemia) and discrepancies between studies might be explained by differences in the populations studied. We had a healthy control group for our baseline comparisons, an important point that is missing from many studies of this type. Information on normative data on the healthy general population would help to set in context whether the very minor variations in clinically non-relevant valve characteristics is related to cabergoline treatment or whether it merely reflects the expected changes that normally occur in the general population over time.

In our series we found tricuspid insufficiency in four cases at baseline. Mild tricuspid regurgitation can be found in approximately 70 % of the general population [14].

Moderate-to-severe regurgitation is rarer and is frequently functional [36], is accompanied by pulmonary hypertension and is associated with a poor survival rate [37]. In our series, none of our patients had risk factors for developing tricuspid regurgitation (apart, theoretically, from cabergoline). Crucially, none had worsening of their tricuspid valvular status during follow-up.

Recently, De Vecchis reported a meta-analysis about the use of cabergoline and the risk of developing cardiac valve disease [38]. Regarding cabergoline use in the endocrine setting, they did find a trend to develop mild to moderate valve regurgitation. In their analysis, they included seven studies [13, 24, 26, 31, 32, 39, 40] comparing data of 444 treated cases versus 954 controls. They conclude that although globally safe, a periodic ultrasound assessment should not be avoided even if cabergoline dose is low. However, as prevalence of valvular abnormality is low, annual evaluation seems not to be necessary except in some selected cases [41].

The involvement of cabergoline in cardiac valvulopathy is now well established in Parkinson's disease. Our prospective study confirms that the use of cabergoline did not increase the risk of valvular disease in our series of patients with prolactinoma and hyperprolactinemia. Taken together with other retrospective, prospective and meta-analytic data, we believe cabergoline therapy at doses used in endocrine practice is safe for the vast majority of patients. Periodic assessments of cardiac valve function may be necessary in patients with other risk factors for valvulopathy and in those with established valve dysfunction at baseline.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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