

## COMMENTARY

# Cabergoline and cardiac valve disease in prolactinoma patients: additional studies during long-term treatment are required

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## Abstract

The increased risk of cardiac valve disease in patients treated for Parkinson's disease with cabergoline has raised concerns about the safety of treatment with ergot-derived dopamine agonists in patients with endocrine diseases, especially prolactinoma. Six cross-sectional studies have been published recently, of which five studies do not show an association between the treatment of prolactinoma with cabergoline during 45–79 months and clinically relevant valvular regurgitation in a total of 413 patients. Nonetheless, concern is raised because the use of cabergoline was associated in one study with an increased prevalence of moderate tricuspid regurgitation, and in two other studies with mild tricuspid regurgitation. Furthermore, the use of cabergoline was associated with increased frequencies of valvular thickening, calcifications and increased mitral tenting area. At present, the clinical relevance of these findings is still uncertain, but concern is raised with respect to the safety of the use of cabergoline in the long-term treatment of prolactinomas. Echocardiographic evaluation should be considered in patients, who require long-term treatment with cabergoline, especially in high doses. There is a need for larger, preferably prospective, studies with careful echocardiographic assessment and with longer durations of follow-up than the currently available studies.

*European Journal of Endocrinology* 159 363–367

## Introduction

Recently, the safety of cabergoline treatment has been questioned by two population-based studies in patients with Parkinson's disease, showing an increased risk of valve regurgitation after treatment with pergolide and cabergoline (1, 2). Studies in patients with Parkinson's disease also observed that cabergoline is associated with an increased risk of fibrotic changes in cardiac valve leaflets. These fibrotic changes cause thickening, retraction and stiffening of the valves, which result in incomplete leaflet closure with poor coaptation, and, mostly asymptomatic, clinically relevant regurgitation.

Ergot-derived dopamine agonists, and especially cabergoline, are efficacious and well tolerated drugs in the treatment of prolactinoma by reducing both hyperprolactinaemia and pituitary adenoma volume. Cabergoline has a high affinity for 5-hydroxytryptamine (serotonin) receptor 2B (HTR2B) located on heart valves. Activation of these receptors might lead to mitogenesis and fibroblast proliferation. Histopathological investigations of cardiac valves obtained from patients after treatment with pergolide or cabergoline for Parkinson's disease resemble the histological abnormalities observed in the valves from patients

with carcinoid disease and from patients taking antimigraine ergot alkaloid drugs (ergotamine, methysergide) or anorectic drugs (fenfluramine) (3–8).

In the evaluation of the severity of regurgitated cardiac valve disease, three different aspects of valvular function and morphology should be assessed. First, in the case of the presence of regurgitation, the degree of regurgitation should be assessed, e.g. rated in mild, moderate or severe regurgitation according to the recommendations of the American Society of Echocardiography (9); ideally quantitative assessment of valvular regurgitation should be performed. Second, the presence of morphological changes such as thickening and/or calcification of the valves should be evaluated, and third, the mitral tenting area and leaflet coaptation should be measured.

After the publication of the papers, which showed an increased risk of valve regurgitation after treatment with pergolide and cabergoline in patients with Parkinson's disease, six cross-sectional studies have evaluated the association between valve regurgitation and the use of cabergoline in patients treated for prolactinoma, including the study by Wakil *et al.* published in this edition of the *European Journal of Endocrinology* (Table 1) (10–15). These studies included a total of 413 patients, treated with cabergoline for

**Table 1** Cabergoline and cardiac valve disease in patients with Parkinson's disease or prolactinoma.

Author (year)	Disease	No. of patients	No. of controls	Gender, F/M	Age, years	Cumulative dose of cabergoline, mg	Duration of cabergoline use, months	Clinically, relevant regurgitation	Valvular thickening/calcification	Mitral tenting area
Peralta (2006)(32)	M. Parkinson	13	49	4/9	65	2579	30	Sign. more moderate and severe regurgitation	NS	NA
Yamamoto (2006) (33)	M. Parkinson	16	85	11/5	65	4318	35	Sign. more MR, AR, and TR	NS	NA
Junghanns (2007) (34)	M. Parkinson	24	38	8/16	64	6677	53	Sign. more mild and moderate AR and moderate MR	NA	NS
Schade <i>et al.</i> (2007) (2)	M. Parkinson	6	31	NA	73	NA	NA	Sign. more regurgitation	NA	NA
Zanettini <i>et al.</i> (2007) (1)	M. Parkinson	49	90	22/27	62	2820	24	Sign. more MR, AR, and TR	Sign. more thickening	Sign. increased
Kenangil (2007) <sup>a</sup> (35)	M. Parkinson	46	49	26/20	64	NA	46	Sign. more moderate AR, MR, and TR, sign. more mild AR	Sign. more mitral and aortic calcification	NA
Rasmussen (2008) (36)	M. Parkinson	56	53	20/36	63	NA	43 <sup>b</sup>	Sign. more moderate regurgitation and more AR	Sign. more thickening	NS
Yamashiro <i>et al.</i> (2008) (22)	M. Parkinson	153	79	86/67	65	3000	36	Sign. more AR	NA	NA
Lancellotti <i>et al.</i> (2008) (10)	Prolactinoma	102	51	73/29	51	204 <sup>b</sup>	79 <sup>b</sup>	NS	NS	Sign. increased
Bogazzi <i>et al.</i> (2008) (11)	Prolactinoma	100	100	79/21	41	279	67	NS	NA	NA
Vallette <i>et al.</i> (2008) (13)	Prolactinoma	70	70	37/33	44	282	55	NS	NS	NA
Kars <i>et al.</i> (2008) (12)	Prolactinoma	47	78	34/13	46	363	62	NS (but sign. more mild TR)	Sign. more mitral and aortic calcification, sign. more tricuspid thickening	NA
Wakil <i>et al.</i> (2008) (14)	Prolactinoma	44	566	32/12	42	311	45	NS (but sign. more mild TR and PR)	NS	NA
Colao <i>et al.</i> (2008) (15)	Prolactinoma	50	50	44/6	37	414	NA	Sign. more moderate TR	NS	NA

Data are expressed as mean, unless otherwise mentioned. NA, not available; NS, non significant; AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; PR, pulmonalis regurgitation.

<sup>a</sup>Patients used either pergolide or cabergoline.

<sup>b</sup>Median.

45–79 months. Five of these studies did not find an association between clinically relevant valve regurgitation and treatment with cabergoline for prolactinoma. However, in one study moderate tricuspid regurgitation was more prevalent in patients when compared with controls (15), and two other studies showed an increased prevalence of mild tricuspid regurgitation (12, 14). Moreover, Colao *et al.* documented that moderate tricuspid regurgitation was significantly more prevalent in treated subjects than in *de novo* patients and in patients receiving a cumulative dose of cabergoline above the mean (72%) than in those receiving a lower dose (36%,  $P=0.036$ ) (15). These observations are in agreement with potential effects of cabergoline on the valvular serotonin receptor, like in the manifestations of the classical right-sided carcinoid heart syndrome (16, 17). Four other studies, published in abstract form only, did not find clinically relevant valve disease, in line with the above-mentioned six publications (18–21).

The present study by Wakil *et al.* compared the echocardiographic data of 44 patients treated with cabergoline for prolactinoma with 566 controls from a database (14). With a mean cumulative dose of 311 mg cabergoline, they found no increased risk in clinically relevant valve regurgitation or changes in valve morphology. However, mild tricuspid and pulmonary regurgitation were more prevalent in patients when compared with controls. Although the authors conclude, that this could be due to differences in interpretation of echocardiographic data by the observer between the two groups, whereas the ultrasounds of patients treated with cabergoline were more accurately evaluated for regurgitation than those of the control group. However, this observation is in line with two other previous studies (12, 15). Therefore, the observations on the association between the use of cabergoline and subclinical tricuspid regurgitation in three out of the six currently available studies raise serious concern with respect to the safety of the long-term use of cabergoline, and possibly of other ergot-derived dopamine agonists.

There are a number of methodological considerations in the interpretation of the data presented in the studies. The number of patients and controls was relatively small in these studies. Moreover, minor degrees of regurgitation were also found in some of the controls. Some studies used controls from echocardiographic data bases, which may be subject to selection bias. In general, the studies had a low power to detect small effects of cabergoline on valve characteristics. Double-blind randomized controlled trials are considered the most rigorous to document the benefits of a certain therapeutic approach. However, rare adverse effects are likely to be missed in these trials, especially in the case of smaller studies in relatively rare diseases like prolactinoma, and especially when these adverse effects take many years to develop. Therefore, the combination of

data warrant more studies with a longer follow-up and more patients to interpret with certainty the clinical relevance of the effects of cabergoline on the right side of the heart.

### **Cabergoline and cardiac valve disease: prolactinoma versus Parkinson's disease**

Patients treated with cabergoline for prolactinoma differ in several important aspects from patients treated for Parkinson's disease. They differ in age and gender, and, importantly, in cumulative dose of cabergoline and duration of therapy. As shown in Table 1, patients treated for Parkinson's disease are usually ~65 years of age, compared with ~45 years in prolactinoma patients. In patients with Parkinson's disease there is a more or less equal sex ratio, whereas prolactinoma patients have a female preponderance. The cumulative dose used in Parkinson's disease is probably the most important explanation of discrepancy in the development of cardiac valve disease in patients treated for Parkinson's disease and not in patients treated for prolactinoma. The cumulative dose of cabergoline ranged in several studies between 2600 and 6700 mg in patients with Parkinson's disease, whereas, in patients treated for prolactinoma, the cumulative dose is more than a factor 10 lower: 200–500 mg. This finding is also supported by a study reported by Yamashiro *et al.* (22). They showed that cabergoline use in Parkinson's disease was associated with statistically significant increased frequency of aortic regurgitation. Subgroup analysis of patients treated with higher daily dosages of 2.5 mg, higher cumulative dose of 3 g or longer treatment duration of 35 months showed increased adjusted (for age and sex) odds ratios for aortic regurgitation, which were significantly higher (14.41, 15.29 and 12.99 respectively) in cabergoline users, compared with controls.

Five of the six recently published studies in prolactinoma patients evaluated the relation between the use of cabergoline and morphological changes of the valves, and one study found significantly more frequent thickening and calcifications of cardiac valves in patients treated with cabergoline compared with controls (12). In Parkinson's disease, five studies have evaluated thickening and calcification of valves, and three of these studies found an increased frequency of these fibrotic changes. It should be noted that the echocardiographer needs to be experienced in the evaluation of these, mostly subtle, morphological changes. Moreover, currently there are no specific guidelines available for the scoring of valvular thickening, calcification and/or stiffness. Consequently, this qualitative assessment of valvular morphology most likely will have a significant interobserver variability.

The mitral tenting area is a quantitative index of modification of the valve structure, and is related to the

severity of regurgitation. Leaflet stiffening and the subsequent apical displacement cause an increase in this area, and result in incomplete mitral leaflet closure and valve regurgitation. Several studies in patients with Parkinson's disease have shown an association between treatment with pergolide or cabergoline and an increased mitral tenting area (1, 23, 24). In patients treated for prolactinoma, only Lancellotti *et al.* measured the mitral tenting area, and reported a significantly increased area in patients treated with cabergoline, and, moreover, an association of increased area with more severe mitral regurgitation (10). An increase in mitral tenting area might be an early sign of alterations of cardiac valve structure, and this measurement should be included in future echocardiographic studies in prolactinoma patients.

In contrast to cabergoline, the ergot-derived dopamine agonists lisuride and bromocriptine are potent antagonists of the HTR2B (25, 26), and there is only one case report on fibrotic valve changes during the use of bromocriptine (27). Evaluation of the association between the use of these drugs or non-ergot-derived dopamine agonist quinagolide and cardiac valve disease are scarce in Parkinson's disease and prolactinoma (12, 28). Both studies could not confirm the findings found in patients treated with pergolide or cabergoline. Furthermore, a meta-analysis of seven cross-sectional studies including 477 patients treated with ergot-derived dopamine agonists pergolide or cabergoline and 127 patients treated with non-ergot-derived dopamine agonists for Parkinson's disease performed by Simonis *et al.* showed moderate to severe valvular disease of 26% in patients treated with ergot-derived dopamine agonists, and of 10% in non-ergot-derived dopamine agonists and 10% in controls ( $n=364$ ) (29).

An important question is why certain patients develop cardiac valve disease and other patients not? There seems to be an individual susceptibility of the HTR2B on cardiac valves for the agonist activity or affinity of cabergoline. It is possible that pharmacogenetic mechanisms are involved in the susceptibility of developing valvular complications during the use of dopamine agonists like cabergoline, since polymorphisms of the serotonin receptor have been described (30, 31).

## Conclusion

There are several observations on subclinical cardiac valve disease in patients using cabergoline that raise serious concerns with respect to the safety of the long-term use of cabergoline. These include the documentation of mild and moderate tricuspid regurgitation, and subtle changes in cardiac valves such as calcifications, thickening and increased mitral tenting area, even after a cumulative dose of cabergoline of only 300 mg. We agree with the conclusion of Colao *et al.* that echocardiographic

evaluation is indicated in patients, who require long-term treatment with cabergoline, especially in high doses (15). Furthermore, there is a need for larger, preferably prospective, studies with careful echocardiographic assessment and with longer durations of follow-up than the currently available studies.

## Disclosure statement

All the authors have nothing to declare.

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Received 12 August 2008

Accepted 13 August 2008