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EDITORIAL

Cabergoline for hyperprolactinemia: getting to the heart of it

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The hypothesis that dopamine agonists cause valvular heart disease stems from prior case reports and clinical studies in men with Parkinson's disease [1, 2]. The finding that subtype 2 5-hydroxy tryptamine (5HT2B) receptor activation is responsible for cardiac valvular disease associated with certain serotonergic drugs, particularly the appetite suppressor, fenfluramine, supports the concept that dopamine agonists might cause cardiac valvular damage via stimulation of the this receptor [3]. The 5HT2B receptor is widely expressed in cardiac valves and its activity results in fibroblast proliferation and structural abnormalities, as demonstrated in heart disease promoted by carcinoid tumors which produce excessive serotonin [4]. Cabergoline, a highly effective drug for the therapy of hyperprolatinemia, while known to activate the 5HT2B receptor [5], was not proven to cause cardiac risk until 2007, when two studies in the New England Journal of Medicine (NEJM) reported that dopamine agonists were associated with valvular regurgitation in men treated for Parkinson's [1, 2]. This revelation caused a stir among endocrinologists and pituitary specialists throughout the world, since the use of dopamine agonists as first-line therapy for the treatment of prolactinomas was the standard of care.

While both cabergoline and bromocriptine had traditionally been thought of as low risk medical therapies, the data reported in Parkinson's disease [1, 2] raised the concern that cabergoline, but not bromocriptine, could cause valvular disease in patients with hyperprolactinemia and/or pituitary disorders, particularly if used in high doses for a long period of time. The idea that dopamine agonists could cause heart disease was particularly alarming since the patients being treated for hyperprolactinemia and/or prolactinomas are typically fairly young, otherwise healthy, and with benign tumors, a group for whom introducing a therapeutic risk, possibly greater than the underlying disease, would be unacceptable. In the wake of the 2007 findings reported in the NEJM that cabergoline and pergolide (now removed from the market because of this concern) were associated with valvular disease in men with Parkinson's [1, 2], several organizations issued warnings and guidelines, mandating echocardiography at baseline and then ongoing throughout follow up in patients receiving cabergoline for pituitary disorders, including a safety label change by the FDA in 2011 suggesting routine echocardiography in cabergoline treated patients with a "recommended frequency every 6 to 12 months or as clinically indicated". Similarly in 2008, in response to the European Medicines Agency's suggestion for a safety update, the Medicines and Healthcare Products Regulatory Authority in the UK recommended that echocardiograms should be followed routinely every 6 to 12 months in patients receiveing cabergoline [6].

Soon after the 2007 NEJM publications on this topic [1, 2], many centers analyzed echocardiographic results in cross-sectional studies among patients with pituitary disease treated for hyperprolactinemia and/or prolactinomas with cabergoline [7–15]. None reported clinically significant valvular heart disease [8–15] with the single exception in a cohort with a high rate of background hypertension [7] and for which the prospective follow up of this cohort receiving ongoing cabergoline therapy, failed to show progressive

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disease [16]. While the preliminary cross-sectional data were essentially negative, including mean cumulative doses in these studies that ranged from 146–443 mg [7–15], long term randomized prospective studies have recently become available [16–18] and the one by Vroonen et al. in this issue is the longest in duration with a median interval between echocardiograms of 62.5 months and a median total duration of therapy with cabergoline of 124.5 months, and this study was unique, among the prospective studies, by virtue of the inclusion a control group of non cardiac patients at baseline [18].

The prospective randomized controlled study by Vroonen et al. from CHU Liège in Belgium, reported in this issue of Endocrine, is reassuring in the lack of clinically relevant valvular heart disease seen in pituitary patients treated with typical doses of dopamine agonists [18] and confirms similar findings among patients with prolactin disorders prospectively evaluated [16, 17] as well as a prior prospective study among patients treated for acromegaly [19]. Given the bulk of data, including the many cross sectional studies and the newly reported perspective studies in patients with prolactin disorders treated with cabergoline, it is not unreasonable to consider baseline echocardiography in patients in whom chronic treatment with cabergoline is planned but to reserve mandating ongoing follow up echocardiography to those with the following: (1) baseline echocardiogram demonstrating significant abnormalities, (2) increased risk of valvular disease, (3) signs or symptoms of valvular disease, (4) high cumulative doses of cabergoline (those who receive higher doses and/or very long duration of therapy). In addition, based on the data to date, it may be reasonable to include a threshold cumulative dose of cabergoline among the criteria to determine when follow up echocardiography is necessary.

What we don't know for sure is whether or not patients with Parkinson's disease may be more susceptible to the impact of valvular dysfunction caused by cabergoline or if it is merely a cumulative dose associated phenomena. The cumulative dose reached after many years in patients treated with cabergoline for prolactin disorders does not nearly approach the critical threshold reported in the studies of Parkinson's patients, in which cumulative doses averaged >2 g (mean was 2820 mg with standard deviation (SD) of 2515 mg) in the group with trace or mild valvular regurgitation and >4 g (mean was 4015 mg with SD of 3208 mg) in those with clinically significant disease (moderate or severe regurgitation) [1]. The mean cumulative dose in the study by Vroonen L et al. was 277.8 mg, interquartile range (IQR) 121.4–427.8 [18], similar to another recent prospective study in which cumulative dose was 232 mg, with IQR 91–551 mg [17], less than one tenth of the mean cumulative dose associated clinically significant valulopathy in men with Parkinson's [1]. The absence of a significant association with cumulative dose of cabergoline among the few hyperprolactinemic patients who developed valvular dysfunction [17, 18], may be due to the fact that the sample size was too small to show this and/or that the cumulative dose was lower than the threshold dose required to see this association. Of note in the prospective study by Drake et al. among 192 patients, even though a significant association of cumulative dose and valvular insufficiency was not found, four of the five patients who had interval progression to grade 3 (moderate) had received a cumulative dose of cabergoline higher than the mean, and in three of these cumulative dose was >1000 mg.

I do not think the question of cabergolines's risk to heart valves in patients with prolactin disorders has yet been put to rest entirely, since in the studies to date, a selected small subgroup of patients did progress from zero to mild or to moderate valvular regurgitation. Even though those with progressive valvular insufficiency were few and their changes were largely clinically insignificant, we cannot entirely exclude the possibility that after an even longer exposure to the drug, valvular dysfunction would progress. The risk of an echocardiogram procedure is minimal and predominantly an issue of cost. Certainly if a patient has any clinical signs or symptoms associated with cardiovascular disease, there's no reason not to pursue an echocardiogram at any point as you would with any patient with such symptoms. However, the requirement for annual or more often ongoing routine echocardiographic screening for asymptomatic patients on typical doses of cabergoline for prolactinoma is unfounded based on the clinical findings to date which fail to reveal substantial evidence of clinical cardiac disease in this context.

Compliance with ethical standards

Conflict of interest The author Dr. L.B.N. declares that she has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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