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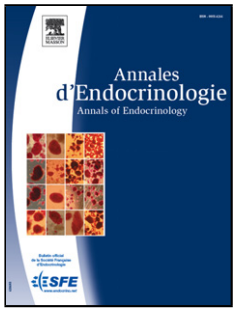

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Monitoring patients receiving dopamine agonist therapy for hyperprolactinaemia

Surveillance des patients sous agonistes dopaminergiques pour hyperprolactinémie

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Abstract

The surveillance strategy for patients taking low dose cabergoline for hyperprolactinaemia is controversial. As more evidence has emerged that the risks of cardiac valvulopathy in this population of patients are low, fewer and fewer endocrinologists adhere strictly to the original Medicines and Healthcare products Agency MHRA guidance of 'at least' annual echocardiography. Strict adherence to this guidance would be costly in monetary terms (£5.76 million/year in the UK) and also in resource use (90,000 extra echocardiograms/year).

This article reviews the proposed pathophysiological mechanism underlying the phenomenon of dopamine agonist valvulopathy, the characteristic echocardiographic changes seen, summarises the published literature on the incidence of valvulopathy with low dose cabergoline and examines the previous and current evidence-based screening guidelines.

Resumé

La stratégie de surveillance des patients prenant de la cabergoline à faible dose pour l'hyperprolactinémie est controversée. Comme de plus en plus de preuves ont montré que les risques de valvulopathie cardiaque dans cette population de patients sont faibles, de moins en moins d'endocrinologues adhèrent strictement aux recommandations originelles de la "Medicines and Healthcare products Agency" d'au moins une échocardiographie cardiaque annuelle.

Le strict respect de ces directives coûterait trop cher aussi bien en terme financier (5,76millions de livres sterling par an au Royaume Uni) qu'en terme d'utilisation des ressources (90,000 échocardiographies supplémentaires par an rien qu'au Royaume-Uni).

Cet article a pour objectif de préciser les mécanisme physiopathologiques qui sous-tendent l'apparition d'une valvulopathie liée à la prise d'agonistes dopaminergiques, de rappeler les changements échocardiographiques caractéristiques observés, de résumer la littérature sur le taux d'incidence des valvulopathie chez les patients recevant de la cabergoline à faible dose et d'examiner les approches factuelles de dépistage.

Keywords: Dopamine agonist, cabergoline, valvulopathy, echocardiogram, hyperprolactinaemia, prolactinoma.

Mots clés: Agoniste dopaminergique, cabergoline, valvulopathie cardiaque, échocardiographie, hyperprolactinémie, prolactinome.

1. Introduction

The dopamine agonist Cabergoline is a highly effective treatment for hyperprolactinaemia and is first line treatment. However, since the 2007 papers of Schade (1) and Zanettini (2) confirming an association between the use of cabergoline in the treatment of Parkinson's disease and the development of cardiac valvulopathy, its use has been closely scrutinised. Cabergoline is no longer used in the treatment of Parkinson's Disease and its use at low doses (~0.5-1mcg/week) in hyperprolactinaemia is subject to stringent guidelines on echocardiographic monitoring (MHRA guidelines).

2.1 Pathophysiology

The proposed mechanism by which dopamine agonists cause fibrotic valvulopathy is through agonist action at $5HT_{2B}$ G protein coupled receptors on vascular interstitial cells (3), resulting in mitogenesis (4). Vascular interstitial cells are the most common cell type found in cardiac valves and have the morphologic and functional features of fibroblasts and smooth muscle cells. They are responsible for maintaining the structure of the valve, through their production of extracellular matrix (proteoglycans, collagens and elastin) and for regulating valve repair, through their ability to enzymatically degrade, reorganise and resynthesize extracellular matrix (5). Drug stimulation of the $5HT_{2B}$ receptors leads to increased deposition of extracellular matrix (6).

It was previously found that the use of the anorexigenic agents such as fenfluramine and phentermine was a significant risk factor for the development of cardiac valvulopathy (5, 6). Histological examination of the valves of affected patients showed that there were changes similar to those seen in carcinoid heart disease, or in ergot alkaloid drug induced valvulopathy (7, 8). Macroscopically, there was irregular leaflet thickening with plaque-like deposits and nodules. Microscopically, there was patchy fibromyxoid proliferation, disruption of elastic tissue, some disruption of elastic fibres and some lymphocytic infiltration (7, 8). These changes result in valve stiffening and leaflet retraction, preventing proper leaflet closure and allowing regurgitant flow.

2.2 Echocardiographic appearances of drug induced valvulopathy

The echocardiographic appearances of drug induced cardiac valvulopathy have been described as "indistinguishable from those seen in patients with chronic rheumatic valvular disease". There is thickening of the valve and shortening and thickening of the chordae tendineae (8). In the tricuspid and mitral valves, this results in leaflet retraction, displacement of the point of leaflet co-aptation towards the cardiac apex ('tenting'), reduced mobility during systole and consequent regurgitation (9).

3. Current literature, controversies and meta-analysis

Our 2019 meta-analysis (10) summarised all the case-control studies published up until Jan 2017 (summarised in Table 1). Thirteen studies were included and the tricuspid valve was the only valve in which there was a suggestion of an association between low-dose cabergoline therapy and valvulopathy. Few studies reported on valve thickening or valve tenting, and assessment was qualitative rather than quantitative. For moderate or severe tricuspid regurgitation (clinically significant valvulopathy), only 3/13 studies (11-13) had any cases to allow for the calculation of an odds ratio (OR), possibly making the accuracy of the summary statistic less reliable but also reflecting the rarity of this particular outcome. Two of these studies (12, 13) spanned the line of 'no effect'. One study (11) showed a significant association and greatly influenced the summary measure to show a net positive association between low-dose cabergoline use and tricuspid valve disease. This study had a much greater incidence of clinically significant tricuspid regurgitation (27/50 cabergoline cases vs 9/50 controls) than was observed in any of the other studies. It used a different echocardiographic method for grading the tricuspid regurgitation severity to other papers, relying on "the extent to which retrograde flow filled the atrium or ventricle" (11), a method which is known to be error prone (14). The blinding conditions for the echocardiographers was not stated. It should also be noted that a follow-up study by the same group did not return the same findings, neither regarding the incidence of tricuspid regurgitation nor the association with low dose cabergoline therapy (15).

Nevertheless, when the case for non-clinically significant (mild) tricuspid regurgitation is considered, eleven papers reported cases and produced an OR. This resulted in an overall significant effect in favour of increased incidence of valvulopathy in patients taking low-dose cabergoline, both after 6 months (OR 1.49 95%CI 1.09-2.03 p=0.013) and 12 months treatment (OR 1.91, 95%CI 1.28-2.87, p=0.02).

These observations raise an interesting question. Although the association with clinically significant valvulopathy is suggested, albeit with queries over some of the contributing data, the case presented by the non-clinically significant valve lesions is far more convincing. It is possible that cases of valvulopathy in evolution are being documented and that the patients have either insufficient cumulative cabergoline dosage or insufficient time to develop significant valve lesions and that therefore continued surveillance of these patients is imperative. However, if this were the case then one might expect the established literature to contain multiple case reports of patients with clinical presentations with heart failure secondary to cabergoline related valvulopathy. In contrast, not a single case of clinical illness was reported in the meta-analysed papers. Examining the wider literature there are 5 case reports in which cabergoline is the proposed mechanism behind cardiac valvulopathy and in which there is clinically significant cardiac failure (16-20). Whilst other mechanisms (co-existent gut carcinoid, previous bromocriptine therapy, growth hormone excess and prior, undiagnosed valvulopathy) remain plausible in some of these reports, it is important not to discount the possibility that cabergoline is, at least in part, implicated pathogenetically, particularly when administered in relatively high doses over long periods of time (21) .

Few studies give data regarding valve morphology and none have used advanced 3D methodology that can now be used to track changes in leaflet mobility and annular distortion through the cardiac cycle, so ascertainment of the role of cabergoline is difficult.

4. Screening guidelines

Following the work of Schade and Zanettini, the MHRA guidelines recommended that, in addition to clinical examination, all patients taking cabergoline undergo echocardiography within 3-6 months of commencing the drug and then every 6-12 months thereafter. It has been estimated that strict adherence to this policy would entail an extra 90,000 echocardiograms/year (22). Based on the NHS tariff for an adult echocardiogram in 2019 this would cost £5.76million/year (~€6.8 million/year). The effects on patient anxiety are hard to quantify but likely to be significant.

Following the MHRA's published guidance, the Endocrine Society briefly mentioned in their 2011 hyperprolactinaemia guideline (23) that they believed that doses of 1-2mg/week of cabergoline would not require regular echocardiographic screening, though they did not grade the evidence for this. It was stated that echocardiography "may be necessary" for patients "requiring a high dose for prolonged periods" to check for valvulopathy, but the society were unable to identify a threshold time or dose of treatment above which this would be required.

By 2014, the publication of many more cross-sectional studies, case-control studies, retrospective studies and some case reports allowed Caputo et al (18) to make a first attempt at an evidenced-based approach to guidelines. This paper highlighted the very low rate of cabergoline associated valvulopathy in the published literature. Though an estimate of the prevalence of cabergoline associated valvulopathy was made (0.17%), this is likely to be a substantial overestimate. Individual case studies were included as 'cases' (the numerator) without any apparent adjustments being made to reflect the population (the denominator) from which they were drawn.

Caputo et al highlighted the importance of clinical examination in the diagnosis of detecting valvular disease. They contend that cardiac auscultation reliably detects valve lesions. Amongst other studies, they cite a 20-year old study (24) involving patients taking dexfenfluramine, a serotoninergic anorectic drug previously used in weight control which is thought to cause a mechanistically similar valvulopathy to that of cabergoline. In this study, the absence of a murmur on clinical examination was highly specific (89%) and gave a high negative predictive value (85%) for excluding a mild or more severe valvular regurgitation. This study employed highly experienced board-qualified physicians with an average 19+/-7 years' experience, yet sensitivity for valve disease was below 40% and positive predictive value below 20%. These data are consistent with a more recent study comparing experienced physicians with echocardiography that confirmed clinical examination alone lacks sensitivity and may miss up to a third of patients with significant valve disease (25). Suggesting a screening tool that lacks sensitivity means those that are picked up are fortunate.

The principal recommendations were;

- Annual cardiovascular examination of patients taking cabergoline for a prolactinoma

Echocardiography should be reserved for;

- Those with an audible murmur on clinical examination
- Those treated with ≥3mg/week for 5 years (or equivalent time to 720mg cumulative dose)
- Those remaining on cabergoline after the age of 50

The cumulative dose of 720mg was a conservative threshold based on the lower standard deviation of the mean cumulative dose associated with cabergoline associated valvulopathy in patients with Parkinson's Disease from Zanettini et al's original work in this area (2), where the mean cumulative dose of cabergoline in patients with moderate/severe valvulopathy was 4015mg, with a standard deviation of +/- 3208mg. An age of 50 years was considered significant because of an increased prevalence of valvular regurgitation found in the Framingham Heart Study above this age (26).

The next, and most recent, set of guidelines followed on from the publication of the biggest meta-analysis to date (10) of single institution, cross-sectional case-control studies examining the link between 'endocrine dose' cabergoline for the treatment of hyperprolactinaemia and cardiac valvulopathy.

These guidelines were written by a group, comprising cardiologists with an interest in echocardiography/valvular disease and endocrinologists with an interest in the pituitary. They utilise the pathophysiological similarities between cabergoline induced valvulopathy and carcinoid heart disease, where there are already validated scoring systems in place (27), to propose a scoring system (28) (Table 2) that takes into account changes to the mobility and morphology in valve leaflets, right ventricular structure and function and the degree of valvular regurgitation or stenosis. An echocardiogram taken before commencing cabergoline allows for a baseline score to be given and provides a point of reference against which future echocardiograms can be compared. It also allows any changes in valve morphology to be set into the context of cumulative drug exposure but also to determine which changes are a result of age and other co-morbidities.

A joint position statement between the British Society of Echocardiography, British Heart Valve Society and the Society for Endocrinology recommended the following (14);

1. All patients should undergo echocardiography before commencing dopamine agonist therapy
2. Patients taking a dose of cabergoline ≤2mg/week should undergo surveillance echocardiography at 5 years.
3. Patients taking a dose of cabergoline >2mg/week should undergo annual echocardiography
4. Patients taking a dose of ≤2mg/week who develop a change in valve function should undergo annual echocardiography if treatment is to continue
5. Decisions regarding discontinuation of medication should only be made after review of serial imaging by an echocardiographer experienced in analysing drug-induced valvulopathy or carcinoid heart disease.

These recommendations were a conservative approach based on previous work (29) examining cabergoline treated patients who had had two echocardiograms separated in time. From this follow-up data, it was felt that doses of ≤2mg/week of cabergoline were unlikely to cause significant heart valve deterioration within a 5-year period and so therefore the date for first screening on this dose was set at 5 years. Applying the same logic, patients without a change on this echocardiogram and continuing on ≤2mg/week of cabergoline could also be imaged again in a further 5 years. For patients taking 2mg/week, 5 years represents a cumulative cabergoline dose of 520mg, just over 25% lower than that suggested by Caputo et al (18).

For higher doses >2mg/week, the established literature has been unable to exclude an association with cardiac valvulopathy. This dose is still distant from the 'tipping point' of 3mg/day described in the original Parkinson's disease work, but despite many studies trying to ascertain a critical duration of treatment or cumulative dose, none has been found. For this reason and because existing studies cannot exclude the possibility of a small effect, a recommendation was made for annual screening in these patients. However, the number taking >2mg/week is very small. Recent (unpublished) data from the primary care medical records of 646 patients in North East London taking cabergoline as treatment for hyperprolactinaemia, for >6 months, suggests that only 24 (3.7%) were taking a mean dose of

≥2mg/week and so this recommendation is less onerous than that made by the MHRA which entailed all patients being screened at least annually.

Provided that no significant valve lesions have been observed during cabergoline treatment, no further surveillance is required after its cessation (14).

Although these guidelines (and the MHRA predecessor) place an importance on periodic surveillance with echocardiography, we do not believe that imaging replaces clinical examination; rather it is complementary (30). There are well documented inconsistencies with echocardiography, particularly in the area of inter-observer variability. Some measurements are subjective, particularly those relating to thickening and retraction, and there is a proven risk of ascertainment bias when the ultrasound operator is aware that patients are on drugs that may cause valvulopathy (31). In clinical practice, blinding operators to previous results is probably not feasible. Were the latter set of guidelines and scoring system to be adopted, establishing a pool of operators with experience in echocardiography of carcinoid/drug induced heart disease so that variability is minimised may be a useful strategy. Similarly, clinicians using echocardiogram images or reports to advise on continuation or cessation of cabergoline therapy should be aware that the degree of regurgitation itself should not necessarily be a deciding factor and that other morphological aspects (e.g valve thickness and restricted valve mobility) should be carefully evaluated (14). It is recommended that a decision to stop cabergoline treatment should be considered if there is a change of >2 points (Table 2) on serial imaging after review by an operator with experience of drug induced or carcinoid valvulopathy. A decision should then be made collectively with the involvement of the patient and their endocrinologist.

5. Conclusion

The current lack of a critical threshold for cumulative dose or treatment duration above which the risk for valvulopathy is increased necessitates a cautious approach to surveillance; however, too much screening risks alarming patients and is a burden on healthcare resources. With the benefit of over a decade of clinical studies, it appears that the MHRA guidance probably overstates the risk of valvulopathy in low dose cabergoline treatment and therefore its surveillance recommendations are

most likely to be too conservative. The more recently proposed guidance suggests a combination of clinical examination and careful, nuanced interpretation of echocardiographic surveillance with evidence to support a more widely-spaced imaging schedule for patients taking the lowest doses of cabergoline.

Future studies matching echocardiographic observations with clinical outcomes and the passage of time may provide even better insights into the optimum surveillance strategy.

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Titles for tables

Table 1 Summary of case control studies from Steeds et al (14).

All patients were treated for hyperprolactinaemia with cabergoline for a minimum of 6 months prior to echocardiography. Values rounded to nearest whole number, mean ± SD unless stated.

MV=mitral valve, TR/PR=tricuspid/pulmonary regurgitation & VD=valve disease & AV/MV aortic/mitral valve

Table 1 Summary of case control studies from Steeds et al (14)

Study (year)	Cases (male%)	Controls (male%)	Age Cases + s.d.	Cumulative Dose (mg) + s.d.	Duration Rx (mths) + s.d.	Summary
Bogazzi 2008	100 (21)	100 (16)	41 + 13	279 + 301	67 + 39	No effect
Boguszewski 2012	51 (27)	59 (27)	42.3 + 13.5	239 + 243	38 + 21	↑ MV tenting ↑ mild TR (7.8% v 0%) ↑ mild PR (no statistics presented)
Colao 2008	50 (12)	50 (12)	36.5 + 10.5	414 + 390	81 + 37	↑ mod TR (54% v 18%) No other difference in VD
Cordoba Soriano 2013	8 (25)	11 (34)	38.8 + 10.4	158 (median)	46	No effect
Elenkova 2012	103 (20)	102 (21)	38.6 + 9.93	174 (no SD)	47 + 286	↑ subclinical fibrosis (40 v 23%) No other difference in VD
Halperin 2012	15 (40)	58 (10)	No data	523 (median)	No data	No effect
Herring 2009	50 (60)	50 (60)	51.2 + 15.5	443 + 375	79 + 42	No effect
Kars 2008	47 (28)	78 (26)	46 + 13	363 + 377	62 + 32	↑ mild TR (41% v 26%) ↑ AV calcification
Lancellotti 2008	102 (28)	51 (37)	51 (median)	184 + 105	79 (median)	↑ MV tenting No other difference in VD

Nacthigall 2010	100 (48)	100 (48)	44 + 13	253 + 520	48 + 40	No effect
Tan 2010	72 (26)	72 (28)	36 (median)	126 (median)	53 (median)	No effect
Vallette 2008	70 (47)	70 (47)	44 + 13	282 + 271	55 + 22	No effect
Wakil 2008	44 (27)	566 (32)	41.8 +13.2	279 + 301	44.8	↑ OR mild TR; mild PR No other difference in VD

All patients were treated for hyperprolactinaemia with cabergoline for a minimum of 6 months prior to echocardiography. Values rounded to nearest whole number, mean ± SD unless stated.

MV=mitral valve, TR/PR=tricuspid/pulmonary regurgitation & VD=valve disease & AV/MV aortic/mitral valve

	Normal = 0	**Mild = 1**	**Moderate = 2**	**Severe = 3**
Leaflet thickening	0	+	++	+++
Leaflet mobility	0	↓	↓↓	↓↓↓
Leaflet morphology	Normal	Stiff and straight	Mild retraction	Moderate–severe retraction
Stenosis	0	Mild	Moderate	Severe
Regurgitation	0	Mild	Moderate	Severe
RV dimension	0	>42 mm	RV = LV	RV forming the LV apex
RV function	0	↓	↓↓	↓↓↓

Table 2 Scoring system for patients receiving dopamine agonist therapy from Steeds et al (14) and adapted from Bhattacharyya et al (28).

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