A follow-up study of the prevalence of valvular heart abnormalities in hyperprolactinemic patients treated with cabergoline

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CONTEXT

Uncertainty exists whether the long-term use of ergot-derived dopamine agonist (DA) drugs for the treatment of hyperprolactinemia may be associated with clinically significant valvular heart disease; and whether current regulatory authority guidelines for echocardiographic screening are clinically appropriate.

OBJECTIVE

To provide follow-up echocardiographic data on a previously described cohort of patients treated with DA for lactotrope pituitary tumors; and to explore possible associations between structural and functional valve abnormalities with the cumulative dose of drug used.

DESIGN

Follow-up echocardiographic data were collected from a proportion of our previously reported cohort of patients; all had received continuous DA therapy for at least 2 years in the intervening period. Studies were performed according to British Society of Echocardiography minimum standards for adult transthoracic echocardiography. Generalised estimating equations with backward selection were used to determine odds ratios of valvular heart abnormalities according to tertiles of cumulative cabergoline dose, using the lowest tertile as the reference group.

SETTING

Thirteen centers of secondary/tertiary endocrine care across the United Kingdom.

RESULTS

There were 192 patients (81 males; median age, 51 years; interquartile range [IQR], 42–62). Median (IQR) cumulative cabergoline doses at the first and second echocardiograms were 97mg (20-377) and 232mg (91-551) respectively. Median (IQR) duration of uninterrupted cabergoline therapy between echocardiograms was 34 months (24-42). No associations were observed between cumulative doses of dopamine agonist used and the age-corrected prevalence of any valvular abnormality.

CONCLUSION

This large UK follow-up study does not support a clinically significant association between the use of DA for the treatment of hyperprolactinemia and cardiac valvulopathy.

INTRODUCTION

Patients with lactotrope pituitary tumors who require medical therapy are typically treated with dopamine agonists (DAs). Amongst the ergot-derived DAs in common use, cabergoline is most widely prescribed because of its greater efficacy and better side-effect profile than bromocriptine, although some physicians still favor the latter drug for use in women attempting conception and for those in established pregnancy who require treatment to control tumor size.

Following the publication of a number of case reports, cohort studies and case-controlled series describing the association of short-term, intensive high dose cabergoline therapy for Parkinson's disease with cardiac valvulopathy[1,2,2,3], guidance was issued by various medicines regulatory authorities recommending screening with transthoracic echocardiography (TTE) for all patients with hyperprolactinemic states on maintenance treatment with this class of drug[4].

Since then, a number of groups have contributed data to the literature in order to guide practice in this area. Most studies have reported TTE findings in modest numbers of patients with prolactinomas and compared them with healthy controls[5-7,7-15]. We have previously reported TTE data from a large (747 patients), multi-center, cross-sectional UK study of patients with hyperprolactinemia treated with DAs[16]. Patients were divided into quartiles according to cumulative DA dose, with the lowest quartile acting as the 'reference group' against which higher quartiles of DA 'exposure' were compared[16]. Here, longitudinal TTE findings are reported in a proportion of those patients, all of whom had received continuous DA therapy for at least 2 years in the intervening period.

MATERIALS AND METHODS

Patients

All 28 centers participating in our original study were contacted and invited to contribute data to this follow-up study. Thirteen centers contributed anonymized data from 192 patients (median age, 51 years; interquartile range [IQR], 42–62), of which 81 were males. The remaining fifteen centres cited time and/or local financial resource constraints as the reasons for not participating in this follow-up study. Inclusion criteria for this study were that all patients must have had two TTEs, separated temporally by at least two years and that all patients should have received uninterrupted cabergoline therapy between those two studies. Demographic and clinical data collected previously was cross-checked again for this study, included age, gender, duration of treatment, maintenance dose of drug, whether the tumor was a microadenoma (≤10 mm) or macroadenoma (≥10 mm), and the presence or absence of any previous cardiac history or risk factors for cardiac disease (smoking, hypertension, diabetes mellitus, hyperlipidemia, history of rheumatic fever). Cumulative doses of cabergoline were calculated by multiplying the weekly dose by the duration of therapy; this calculation was repeated each time the patient's dose was adjusted by the supervising physician and allowed the calculation of a total cumulative cabergoline exposure dose.

Echocardiography

As in our previous study, all TTE examinations were performed by fully-trained sonographers in accordance with the British Society of Echocardiography minimum dataset for a standard adult transthoracic echocardiogram[17]. Valve assessment included evaluation of morphology (leaflet thickening, calcification, mobility) and function of the mitral, aortic, pulmonary, and tricuspid valves in multiple views. Two-dimensional imaging was followed by color Doppler echocardiography after optimizing gain (to eliminate random speckle color from non-moving regions) and Nyquist limit (50–60 cm/s)[18]. Standard pulse wave and continuous wave Doppler examinations were performed. Valvular regurgitation was quantified as absent, mild, moderate, or severe by integrating multiple indices of severity[4,19]. As in our previous study, potentially clinically significant valvular disease (morphological or functional) was considered to be moderate or above.

Statistical Analysis

TTE parameters were described using medians and IQRs. The Wilcoxon signed rank test was used to compare parameters between the first and second studies. Generalised estimating equations, to take account of the repeated TTE measurements, were used to determine univariate odds ratios (ORs) for moderate or above abnormalities of any valve according to tertiles of cabergoline dose and patient characteristics. Generalised estimating equations with backwards selection were used to determine multivariate ORs. ORs were also calculated for mild or above valvular abnormalities. Statistical significance was taken as $p<0.05$. All analyses were performed in Stata version 13 (StataCorp, College Station, Texas, USA).

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RESULTS

Of the 192 patients, there were 88 (46%) with a microadenoma, 93 (48) had a macroadenoma and in the remainder it was not specified by the referring physician. Median (IQR) cumulative cabergoline doses at the time of the first and second TTEs were 97mg (20-377) and 232mg (91-551) respectively. Median (IQR) weekly cabergoline dose was 0.5mg (0.5-1.0). Median (IQR) duration of uninterrupted cabergoline therapy between the two studies was 34 months (24-42).

There were 11 echocardiographic abnormalities of moderate severity at the time of the first TTE. Of these, 6 had become mild by the time of the second study, 4 were unchanged and in 1 patient moderate tricuspid regurgitation was reported to have progressed to severe. There were 4 mild echocardiographic abnormalities at the first TTE that had become moderate by the time of the second (table 1). More detailed information on the 9 echocardiographic abnormalities of moderate or above severity at the second study (in 7 patients) is also presented in table 1.

Calculated ORs of any valvular abnormality (thickening, restricted movement, calcification, stenosis, regurgitation, with and without the inclusion of mild lesions) by tertile of exposure to DA are shown graphically in table 2. No associations were observed between cumulative doses of cabergoline and the age-corrected prevalence of any valvular abnormality. ORs were not influenced by the presence or absence of a cardiac history, previous rheumatic fever or any of the risk factors for heart disease and no differences were observed when patients with micro- and macro-adenomas were analysed separately.

DISCUSSION

In this study we have performed detailed, follow-up TTE in a large cohort of patients with hyperprolactinemia who, in addition to being exposed to DA therapy before the first examination, received uninterrupted treatment for at least two years before the second. Compared to our previous report, this cohort of patients contains a greater proportion of men and patients classified as having a macroadenoma. This is likely to reflect the higher background remission rate in women and of microadenomas such that some of these originally reported patients will have discontinued DA at some stage in the intervening period and not have been eligible for inclusion in this study. A patient population enriched with men and patients with macroadenomas is a useful one to study as it contains those most likely to need to continue DA therapy for a prolonged period of time. These data do not suggest a clinically significant effect of DA therapy at 'endocrine doses' on cardiac valvular function during medium-term follow-up and provide further reassurance to physicians using this class of drug for this clinical indication.

The background to the clinical question of the cardiac safety of DA has been extensively documented and summarised. Cabergoline binds to the same receptors ($5\text{-}HT_{2B}$) that mediate carcinoid heart disease, although there is no direct relationship between plasma levels of 5-HT and presence of valvulopathy suggesting that other factors may be required for the pathogenesis of valve dysfunction[20] . Although cardiac valvulopathy may occur in patients with neurological disorders currently treated with doses of cabergoline up to 3mg daily for more than 6 months[1], many endocrine physicians experienced in the management of pituitary disease were surprised by the various regulatory authority recommendations for TTE surveillance in patients with hyperprolactinemia. The doses involved in the treatment of hyperprolactinemia are, typically, approximately $1/20^{th}$ – $1/40^{th}$ of those used in the treatment of Parkinson's disease. Most lactotrope pituitary microadenomas occur in women, for whom either spontaneous remission or intervening pregnancies dictate that the drug is frequently prescribed for a limited period of time. Even if women require prolonged use of cabergoline for hyperprolactinemia, it is often possible to discontinue therapy at the time of the menopause. Our data suggest that the current recommendations (exclusion of cardiac valvulopathy before commencement of DA therapy; second TTE 3–6 months after starting treatment; and serial examinations at 6- to 12-month

intervals while DA therapy is continued) are out of keeping with the risk of developing clinically significant valve disease. Based on estimates of the prevalence of lactotrope pituitary tumors, such a surveillance program would require an estimated 90 000 extra TTEs per year in the United Kingdom[19] at a time when both public and private healthcare providers are seeking to ensure use of cardiovascular imaging is appropriate[21]. Non-financial implications, such as patient anxiety and inconvenience, are harder to quantify.

The publication of data regarding valvulopathy in patients with Parkinson's[1] came more than two decades after the first clinical trials of DA agonist use in hyperprolactinemia[22]. There are major problems in designing studies to address the issue of possible cardiac valvulopathy in patients taking 'endocrine doses'. Withholding DA therapy from patients with hyperprolactinemia (particularly women wanting to conceive) in order to perform controlled studies would clearly be unethical; and any postulated cardiac effects of DA therapy (positive or negative) would be hard to separate from any secondary changes that may occur as a consequence of normal gonadal steroid levels being restored to previously hypogonadal patients. Further, with the patent on cabergoline having expired, large-scale multi-center phase IV studies in this area are improbable. Most of the literature in this area therefore comes from single-center studies of modest numbers of DA-treated patients compared to age-matched healthy controls. The majority of those studies have provided reassuring data regarding valve function, with just three reports of increased tricuspid regurgitation (moderate in one, mild in two others) and an inconsistent relationship to the cumulative dose of drug[5,7,8]

To our knowledge, this is the largest follow-up echocardiographic study of hyperprolactinemic patients treated with DA. Although the size is an obvious strength, as in our previous study, an obvious weakness is the lack of a true control group, with the lowest tertile of DA exposure serving as our 'surrogate control'. In an earlier follow-up study, statistically significant increases in aortic valve calcification were observed with DA therapy, although these changes did not translate into any alterations in valve function[7,23]. Moreover, while grading the extent of valve calcification is an important factor in predicting outcome in AS[24], visual estimation on 2D

echocardiography is subjective and has high inter-observer variability[25]. This could simply be that cardiac valvulopathy develops over a prolonged time period and that clinically significant functional changes (defined in most studies as moderate severity or above) cannot be detected over the timescales of the reported studies. It was for this reason that we included an analysis based on 'mild or above severity' as a statistically significant increase in the prevalence of mild valvular abnormalities could provide preliminary evidence of developing clinically relevant valvulopathy. We found no evidence of an increase in mild anatomical or functional valvulopathy with increasing DA exposure.

Reassuring group data can sometimes conceal clinically important effects in small numbers of patients. It is for this reason that we present the details of the 9 moderate or above echocardiographic abnormalities in 7 patients seen at the second TTE; these cases illustrate some of the challenges of interpreting echocardiographic findings in this context. The median age of the 7 patients was 74; all except one patient was older than the median age of the overall cohort. Although this may suggest the observed abnormalities were age-related, this group of patients were also heavily exposed to DA; all except one patient had received a cumulative cabergoline dose above the median for the overall cohort. In case 5, for example, whilst the risk factor profile and documented history of IHD may well have been important factors in the progressive mitral regurgitation, the appearance of thickening of the valve leaflets is also compatible with DA therapy being aetiologically contributory. Determining which echocardiographic abnormalities carry clinical significance is also difficult. Current echocardiography systems such as those used in this study detect 'physiological' tricuspid regurgitation in almost all subjects and 'physiological' mitral regurgitation in more than half[26]. Whilst 'trivial' and 'mild' regurgitation are so common, it is also recognised that significant reporter bias exists when information about the use of DA in patients undergoing surveillance TTE is provided to cardiac technicians[27]. Moreover, quantification, even when using recognised methodology including vena contracta and proximal isovelocity surface area, is only modestly reliable; inter-observer agreement for grading mitral regurgitation as severe or non-severe is only 0.28 between specialists working in academic hospitals[28]. In patients with less severe regurgitation, not only will inter-observer variability be higher but there may well be physiological variation that will cause some change in

categorisation. It is not clear whether newer imaging modalities such as cardiac magnetic resonance imaging will provide more accurate or reproducible assessment of mild degrees of regurgitation[29].

In summary, this follow-up echocardiographic study provides further, reassuring evidence that cardiac valvulopathy is not a major clinical issue in patients with lactotrope pituitary adenomas treated with DA over this timescale. Prospective, case-controlled studies of the size and duration required formally to address this issue are unlikely to be conducted, given their prohibitive cost and logistical challenges. Although the design and duration of the published studies cannot 'exonerate' DA of a possible role in causing cardiac valvulopathy, we suggest that the time is now appropriate for regulatory authorities to consider revising the guidelines for surveillance echocardiography in this group of patients.

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