RAPID COMMUNICATION

Low dose cabergoline for hyperprolactinaemia is not associated with clinically significant valvular heart disease

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Abstract

Objective: Recent trials suggest that using ergot-derived dopamine agonists such as cabergoline in the treatment of Parkinson’s disease is associated with an increased risk of valvular heart disease. However, the dose of cabergoline used to treat hyperprolactinaemia is considerably less than that used in Parkinson’s disease.

Design and methods: A cross-sectional comparative assessment. Forty-four patients treated with cabergoline for hyperprolactinaemia underwent transthoracic echocardiography and were compared with 566 sequential subjects complaining of palpitations, taken from a contemporary echocardiography database.

Results: The mean cumulative dose of cabergoline in the cases was 311 mg. There was no significant, severe or moderate, right- or left-sided valvular regurgitation in either group. Left heart: in the mitral and aortic valves, the rate of mild and trivial valvular regurgitation was not different between the two groups. Right heart: mild tricuspid and pulmonary regurgitation on colour Doppler alone was increased significantly in the cabergoline group, odds ratios of 3.1 and 7.8 respectively (95% confidence interval 1.0–9.6 and 0.8–78.4, \( P < 0.04 \) and \( P < 0.0001 \) respectively).

Conclusion: Cabergoline at doses sufficient to suppress hyperprolactinaemia for a period of 3–4 years is not associated with an increased risk of clinically significant valvular regurgitation.

Introduction

Cabergoline, a D2-specific ergot-derived dopamine agonist, is indicated for the treatment of Parkinson’s disease and hyperprolactinaemia (1, 2). Recent reports have highlighted a high risk of clinically significant valvular heart disease in patients with Parkinson’s disease treated with ergot-derived dopamine agonists including cabergoline at a dose of more than 3 mg daily, whilst the dose used to treat hyperprolactinaemia is often between 0.5 and 1 mg twice weekly (1–3). However, it is unknown whether patients with hyperprolactinaemia treated with smaller doses of cabergoline are also at risk of clinically significant valvular regurgitation. The mechanism underlying the valvular defect has been suggested to be due to ergot-derived dopamine agonist initiation of abnormal fibrogenesis through activation of serotonin receptors 5-HT2B, that are abundant in the fibroblasts of heart valves (4).

Subjects and methods

Forty-four subjects prescribed cabergoline for isolated excess prolactin secretion of any cause that had been treated for at least 6 months were identified and agreed to participate. None had the exclusion criteria of co-secretion of growth hormone, known cardiac disease, including rheumatic heart disease, myocardial infarction within 6 months, diabetes, connective tissue disease, Parkinson’s disease, carcinoid syndrome and the use of homeopathic medication, anorectic or other ergot-derived therapy. No subject was taking antihypertensive or lipid-lowering medication. All subjects underwent transthoracic echocardiography between May and September 2007. The comparison group was selected from a contemporary echocardiographic database. They were consecutive control subjects presenting with a complaint of palpitations with no other known underlying cardiac diagnosis or other past medical history. None of the control had the above exclusion criteria. Controls were included in this analysis only if the heart was morphologically normal and had normal left ventricular systolic function. Ethical permission was given by Hull and East Riding Local Research Ethics Committee (LREC).

Routine echocardiographic assessment was performed on all patients including M-mode, 2D images and colour flow Doppler recordings using a ‘Vivid 5’ (GE Healthcare, Chalfont St. Giles, UK) system operating at

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3.4 MHz. Measurements were taken in accordance with American Echocardiography Society/European Association of Echocardiography guidelines (5, 6). All echocardiography was carried out by one non-blinded trained operator who was blind to the reason for the scan other than for a query of valvular regurgitation and the patients were part of the normal procedure list as for the control population. Echocardiograms were reread by an expert in the field (ALC). The duration and total cumulative dose of cabergoline were calculated from a retrospective analysis of clinical records.

**Statistical analysis**

The cases and controls were analysed by calculating odds ratios (ORs) with 95% confidence intervals (CIs). The OR is an approximation to the relative risk (7). The \( \chi^2 \)-test was used to compare group differences on two degrees of freedom. An arbitrary level of 5% statistical significance (two-tailed) was assumed.

One of the statistical issues that needed to be addressed was that of multiple testing when there are multiple variables to be tested and the possible inflation of a Type I error. There is no consensus among statisticians on what procedure to adopt to allow for multiple comparisons (8, 9). The Bonferroni correction (whereby the threshold for significance is simply reduced by the number of comparisons made) is known to be too conservative (10); therefore, we have followed the recommendations of Perneger (9) and not adjusted for this.

**Results**

Table 1 depicts the patients’ characteristics. Forty-four patients had at least 6 months treatment with cabergoline. All patients had been initiated and maintained on cabergoline alone. There were no significant, severe or moderate, valvular regurgitation in any of the four cardiac valves in either group. Furthermore, none of the patients on cabergoline had abnormal heart morphology on echocardiography.

**Left heart echocardiography**

In the left heart, i.e. mitral and aortic valves, the rate of mild and trivial regurgitation was not different between the two groups. In the cabergoline group, mild mitral regurgitation OR was 0.4 (95% CI 0.04–2.6, \( P=0.5 \)) while mild aortic regurgitation OR was 1.7 (95% CI 0.2–13.7, \( P=0.2 \)) as depicted in Table 2.

**Right heart echocardiography**

In the right heart, the ORs of mild tricuspid regurgitation detectable on colour Doppler alone was 3.1 in the cabergoline group (95% CI 1–9.6, \( P=0.04 \)) while that for mild pulmonary regurgitation was 7.8 (95% CI 0.8–78.4, \( P<0.0001 \)), as depicted in Table 2.

<table>
<thead>
<tr>
<th>Valve findings</th>
<th>Control number, ( N=566 )</th>
<th>Cabergoline number, ( N=44 )</th>
<th>Odds ratios (95% CI)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricuspid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>237</td>
<td>10</td>
<td>1</td>
<td></td>
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<tr>
<td>Trivial regurgitation</td>
<td>291</td>
<td>29</td>
<td>2.4 (1.1–5.0)</td>
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<tr>
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<td>38</td>
<td>5</td>
<td>3.1 (1.0–9.6)</td>
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</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>517</td>
<td>22</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Trivial regurgitation</td>
<td>46</td>
<td>21</td>
<td>10.7 (5.5–21)</td>
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<tr>
<td>Mild regurgitation</td>
<td>3</td>
<td>1</td>
<td>7.8 (0.8–78.4)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Mitral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>255</td>
<td>20</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Trivial regurgitation</td>
<td>273</td>
<td>23</td>
<td>1.1 (0.6–2.0)</td>
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<tr>
<td>Mild regurgitation</td>
<td>38</td>
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<td>0.4 (0.04–2.6)</td>
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<td></td>
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<tr>
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<td>550</td>
<td>41</td>
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<tr>
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<td>2</td>
<td>3.4 (0.7–16.3)</td>
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<tr>
<td>Mild regurgitation</td>
<td>8</td>
<td>1</td>
<td>1.7 (0.2–13.7)</td>
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</table>
Discussion

We found that in patients taking low dose cabergoline for prolactin excess, there was no increased valvular regurgitation, of any grade, in the left heart. In the right heart, there was an increased risk of (clinically insignificant) mild grade tricuspid and pulmonary valves regurgitation in the cabergoline group.

The increase in right-sided regurgitation was probably due to the inherent under-reporting of trivial and mild valvular regurgitation in the control group that was referred for palpitations, whilst those taking cabergoline were referred for a query of valvular regurgitation. A mild degree of pulmonary regurgitation is a normal variant since it is seen in the majority of adults using modern imaging platforms; in the same way, that the tricuspid valve often exhibits mild degrees of valvular regurgitation (11). The prevalence of right heart valvular regurgitation, both at the pulmonary and tricuspid areas, was 100% in 32 healthy subjects with structurally normal hearts using colour Doppler echocardiography (12). The likelihood is that during a standard echocardiographic examination, the operator may not report minor degrees of right-sided valvular regurgitation as these are ‘normal’. By contrast, because the echocardiograms for the cabergoline group were performed specifically to detect any valvular regurgitation, any regurgitation at all was reported. Even if we accept that rates of regurgitation in the tricuspid and pulmonary valves were significantly different between the two groups, the number of patients was low (giving very wide confidence intervals around the OR) and the regurgitation was clinically insignificant in all subjects. We found no significant difference between the cases and controls for mitral valve disease (Table 2). This is a function of power (13). The prevalence of mild mitral disease in the controls was 38/566 (6.7%) and in the cases was 1/44 (2.3%). We had a power of <5% (5% significance, two-tailed) to detect this difference (our calculations assumed a control:case ratio of 13:1 and make an allowance for rounding errors). This means that a prospective study to show that this difference was statistically significant with adequate power (80%) would require five times the sample size.

Previous reports in Parkinsonian patients have suggested that the principal concern with cabergoline use was left-sided valvular regurgitation, and we have seen no such risk in our patients. Our findings support three of the four published echocardiographic studies on the association between cabergoline in endocrine disease and valvular lesions (14–16). We did not see any clinically significant moderate or severe valvular regurgitation while others reported 1.9, 7 and 5.7% moderate valvular regurgitation in their cabergoline groups though each was not statistically significant in comparison with their reference control groups (14–16). The fourth cross-sectional study observed that a mean duration of treatment with dopamine agonists of 96 months was significantly associated with clinically insignificant (mild) aortic and tricuspid regurgitation, but not with clinically significant (moderate and severe) regurgitation (17). However, in the prolactinoma group, there was no significant difference in the rate of valvular regurgitation between those treated with cabergoline, mean duration of 62 months, and those treated without cabergoline (17). The issue of changes in valvular morphology with cabergoline has been described with emphasis on tenting, thickening and more recently calcifications. The tenting area of the mitral valve was reported to be significantly greater in the cabergoline group and, although this did not correlate with the dose of cabergoline, it correlated with the degree of valve thickening in the cabergoline group (14). Others have reported mixed results of the association between leaflet thickening and cabergoline with one group reporting no evidence of leaflet thickening in those with moderate valvular regurgitation (16), while another reported a significant thickening in the tricuspid valves of patients treated with cabergoline when compared with control (17). The latter group also reported a significantly higher rate of calcifications in the mitral and aortic valves of the cabergoline group compared with control, though the calcifications did not reflect in a mild, moderate or severe valvular regurgitation in the corresponding valves.

In a study of 49 patients treated with cabergoline for Parkinson’s disease, clinically significant mitral regurgitation was seen in 5, aortic regurgitation in 12 patients and tricuspid regurgitation in 3 patients (18). The mean cumulative dose of cabergoline was 2820 mg over a mean duration of 24 months compared with 311 mg over a mean of 44 months in the present study. In Parkinsonian patients, the correlation of cabergoline dose to the echocardiographic findings is unclear, with the adjusted incidence rate ratios for cardiac valve regurgitation for cabergoline being reported to be particularly high at doses above 3 mg daily for 6 months or more (3), though others have not confirmed this (19). There is a correlation between the tenting area of the affected valve and the cumulative dose of dopamine agonists in patients with Parkinson’s disease (20). In our series, patients were screened routinely and no patient had valvular thickening and the tenting area was not measured.

One of the limitations to this study is the selection bias that could have arisen from including the sequential controls investigated for palpitations, as the observers were not blinded, and the indications for the echocardiograms were different between the two groups. This may have potentially caused an overestimation of positive findings in the valves of the cabergoline group, as the observer was directed to look for valvular lesions, and potentially an underestimate of valvular findings in the controls. However, applying the same exclusion criteria to controls and patients would have addressed any confounding effect of this bias in the result.
While the major limitation of this study is that it was not prospective, the number of patients recruited should have demonstrated clinically significant valvular abnormalities if the changes were due to a pharmacological abreaction to cabergoline therapy. As such, these data are reassuring that cabergoline doses of 0.25–4 mg weekly in patients with hyperprolactinemia are safe, though confirmation with a large prospective case-matched trial needs to be undertaken.

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