Case Report

Cabergoline-induced tricuspid regurgitation: Case report and review of literature

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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. 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.

Key words: Cabergoline, prolactinoma, tricuspid regurgitationIntroduction

Introduction

Cabergoline, a dopamine receptor-2 agonist used to treat prolactinomas and Parkinson's disease, is associated with increased risk of cardiac valve disease due to increased frequencies of valvular thickening, calcifications,fibrosis and increased mitral tenting area. 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 but sometimes if unrecognized earlier can lead to symptomatic heart failure. Here we present a case of cabergoline induced symptomatic right heart failure.

Case Report

A 60-year-old woman with insignificant history, who had been taking low-dose Cabergoline 0.25 mg for hyperprolactinemia (micro prolactinoma) from last four years, presented with one and half month history of increasing ankle swelling, abdominal discomfort, and exertional breathlessness. On examination, she had a regular pulse of 88 beats per minute. Her blood pressure was 140/85 mmHg, her jugular venous pressure was elevated, and she was having pitting edema to her mid calves. Heart sounds were dual, with systolic murmurs audible along left sterna border with positive carvello's sign and she was also having tender hepatomegaly. These clinical findings were suggestive of right heart failure. ECG showed sinus rhythm with rate of 90 beats per minute. A chest X-ray showed borderline cardiomegaly with clear lung fields. There was no evidence of interstitial edema or fibrosis or pleural effusions. Blood tests were normal. Echocardiography showed moderate tricuspid regurgitation [Figure 1] and mild pulmonary arterial hypertension, without any regional wall motion abnormality or dilated right ventricle, also no sign of rheumatic heart disease (RHD) and ejection fraction (EF) was 67%. Cabergoline was stopped and patient was put on furosemide and spironolactone. There was an excellent clinical response to this diuretic regimen.

Discussion

Cabergoline, a dopamine receptor-2 agonist used to treat

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prolactinomas, was associated with increased risk of cardiac valve disease in Parkinson's disease. 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 hyperprolactinemia and pituitary adenoma volume. Cabergoline has a high affinity for 5-hdroxytryptamine (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).[3-7]

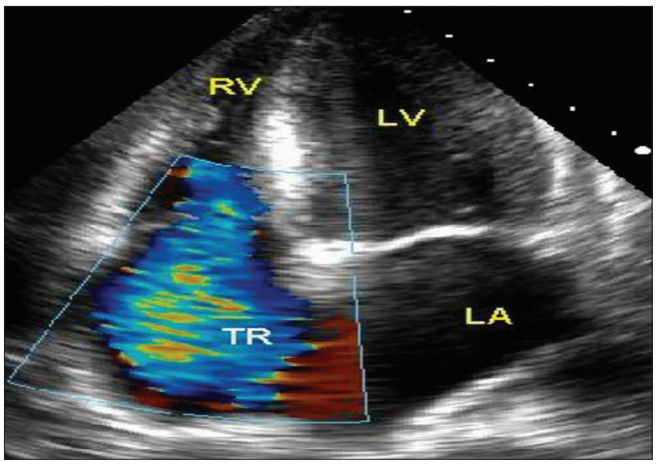

Figure 1: Tricuspid regurgitation on echocardiography

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.[8-13] These studies included a total of 413 patients treated with cabergoline for 45 to 79 months. Five of these studies did not find any 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,[13] and two other studies showed an increased prevalence of mild tricuspid regurgitation[10,12] [Table 1].

There seems to be an individual susceptibility of the HTR2B on cardiac valves for the agonist activity or affinity of cabergoline, that 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.[13-15]

Colao *et al*.[13] found that chronic cabergoline treatment in patients with prolactinoma does not induce any regurgitation of mitral, aortic, or pulmonic valves, but it induces a three times higher prevalence of subclinical moderate tricuspid regurgitation compared with controls and de novo patients. Tricuspid tenting area was significantly greater in treated patients than in controls and de novo patients.

Table 1: Publications on valve regurgitation with cabergoline therapy

Author (years)	Disease	No. of patients	No. of controls	Gender (F/M)	Age, years	Cumulative dose of cabergoline (mg)	Duration of therapy (months)	Clinically relevant regurgitation
Lancelloti *et al.* 2008	Prolactinomas	102	51	73/29	51	204	79	NS
Bogazzi *et al.* 2008	Prolactinomas	100	10	79/21	41	279	67	NS
Vallette *et al*. 2008	Prolactinomas	70	70	37/33	44	282	55	NS
Kars *et al*. 2008	Prolactinomas	47	78	34/13	46	363	62	NS, but sign. More mild TR
Wakil *et al*. 2008	Prolactinomas	44	566	32/12	42	311	45	NS, but sign. More TR and PR
Colao *et al*. 2008	Prolactinomas	50	50	44/6	37	414	NA	Sign. More moderate TR

Tricuspid regurgitation was two times more frequent in patients treated with higher cumulative cabergoline doses. These data should prompt more careful echocardiographic follow-up studies in patients with prolactinoma treated with cabergoline or other ergot-derivative drugs, without any definite cut-off level of cabergoline dosage.

Conclusion

This case shows severe multivalvular pathology, probably as a result of cabergoline. Prescribers need to be aware of the risk of cardiac valvulopathy associated with the use of ergot-derived dopamine agonists. Patients should be warned about the potential adverse events.

We agree with the conclusion of Colao *et al.* that echocardiographic evaluation is indicated in patients who require long-term treatment with cabergoline.[13] 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.

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