Retrospective evaluation of cardio-pulmonary fibrotic side effects in symptomatic patients from a group of 234 Parkinson’s disease patients treated with cabergoline

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Summary. Background: Cardiac valvulopathy has been recently associated with the use of the ergot dopamine agonist (EDA) pergolide in Parkinson’s disease (PD). Cabergoline a widely used, well-tolerated EDA which has also been recently implicated in relation to fibrotic side effects although the evidence base for this is not sound.

Aims: In PD patients on chronic cabergoline therapy, do symptoms suggestive of serosal/cardiac fibrosis imply underlying fibrotic lesions?

Methods: A retrospective data review of 234 PD cases from three UK centres, on chronic cabergoline monotherapy or adjunctive treatment to identify symptoms suggestive of pleuro-pulmonary, cardiac or retroperitoneal fibrosis. These causes were thereafter selectively examined by appropriate specialists with relevant investigations.

Conclusions: Out of 234 cases, 15 were identified with symptoms suggestive of respiratory, cardiac or abdominal systems involvement although subsequent investigations failed to reveal definite association with cabergoline except two cases with probable alveolitis and a possible association with cardiac murmur in one case. In spite of the deficiencies of a retrospective study, the results suggest a low risk of fibrotic side effects with cabergoline, particularly cardiac valvulopathy.

Keywords: Cabergoline, pleuropulmonary fibrosis, cardiac, pergolide, Parkinson’s disease.
Abbreviations

AR aortic regurgitation, AS aortic stenosis, BAL broncho-alveolar lavage, Cbg cabergoline, CCF congestive cardiac failure, CXR chest X-ray, DA dopamine agonists, DLCO diffusion capacity (carbon monoxide), ESR erythrocyte sedimentation rate, FEV\textsubscript{1} forced expiratory volume in 1, FVC sec/forced vital capacity, IHD ischaemic heart disease, LV left ventricle, LVH left ventricular hypertrophy, MR mitral regurgitation, PR pulmonary regurgitation, PFT pulmonary function tests, RAS refractory ankle swelling, RPF retro-peritoneal fibrosis, RV right ventricle, Rx treatment, SOBE shortness of breath on exertion, TR tricuspid regurgitation.

Introduction

Recently concern has been voiced regarding the use of EDA and their association with serosal and cardiac valvular fibrosis, emphasised by reports of restrictive cardiac valvulopathy induced by high dose pergolide therapy (Van Kamp et al., 2003, 2004). A recent report also suggested association of noninflammatory fibrotic degeneration of cardiac valves occurring with the use of cabergoline based on four cases (Horvath et al., 2002, 2004). Prior to this, based on the ‘yellow card’ drug side-effect notification system in the UK, the Committee on Safety of Medicines (CSM) issued warnings about occurrence of possible adverse events in the form of pleuro-pulmonary, cardiac and retroperitoneal fibrosis related to use of ergot dopamine agonists, bromocriptine, pergolide and cabergoline in Parkinson’s disease (PD), and recommended screening tests including lung function tests in PD patients, whenever chronic therapy with such DA is envisaged (Committee on Safety of Medicines, 2002). Horvath et al. (2004) and others (Van Camp et al., 2003, 2004) have now suggested adding cardiac monitoring with echocardiography to the list of screening investigations before EDA treatment is started. These recommendations have considerable cost implications and furthermore the evidence base for such recommendations appear unsound apart from pergolide use. The implications for cabergoline, a widely used long acting dopamine agonist with half life of 68 hours and an excellent tolerability profile in the young and the old, both as adjunctive therapy and monotherapy are considerable (Di Marco et al., 2002; Appiah-Kubi et al., 2003). Pharmaceutically driven campaigns and the fear of fibrotic side effects may lead to inappropriate cessation of successful treatment with EDA in some cases as has been the case in several of our patients. Formal perusal of published literature reveals only two cases of fibrotic reactions related to cabergoline (Frank et al., 1999; Horvath et al., 2002, 2004) since its use in PD in 1997 although it has been used earlier to treat prolactinomas, at a lower dose, since the 1980s. Two published studies, one in an abstract form, in 1999 and 2002, report cases of cabergoline-induced interstitial pneumonitis and quadrivalvular heart disease respectively, despite 14 million patient days of cabergoline use in the UK. The recent report from Horvath et al. (2004) presumably expands on their previous abstract (Horvath et al., 2002), which described a case of valvular heart disease apparently linked to cabergoline use. Rascol et al. (2004a, b) mentions that there may be a further few cases of cabergoline related cardiac valvulopathy although none of these cases have been reported or published. There