CASE REPORT

Pergolide-induced lung disease in patients with Parkinson’s disease

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INTRODUCTION

Synthetic dopamine agonists including pergolide have acquired wide usage in the management of Parkinson’s disease (1). These agents have been associated with a number of side effects including nausea, orthostatic hypotension, confusion, paranoia and visual hallucinations (1,2). In addition, they can cause unusual but severe complications such as pericarditis, retroperitoneal and pleural fibrosis (3). However, they have not been known to produce interstitial lung disease. We report on two patients who developed reversible interstitial lung injury whilst taking pergolide.

CASE 1

A 52-year-old woman presented in 1999, with an 18-month history of gradually worsening non-productive cough. She had developed Parkinson’s disease in 1993 and pergolide was introduced 2 years later as her symptoms were not controlled with levodopa. At the time of presentation, her therapy consisted of pergolide 4.5 mg daily (approximate cumulative dose of 5.9 g) and a combination of carbidopa and levodopa.

Examination showed mild Parkinsonism, aortic and mitral regurgitation, and no abnormal respiratory signs. Blood count, biochemical profile and autoantibody screen were unremarkable. The chest radiograph was normal but the high-resolution computed tomograph (HRCT) scan showed diffuse ground-glass shadowing suggestive of acute alveolitis (Fig. 1). The bronchoscopy and limited transbronchial biopsies were normal. Lung function tests showed a restrictive defect with an FEV1 of 1.83 l (predicted 2.44 l), FVC of 2.18 l (predicted 2.87 l), and a residual volume of 1.15 l (predicted 1.71 l). However, the gas transfer factor was preserved. A diagnosis of drug-induced alveolitis due to pergolide was made.

On stopping pergolide, the patient’s cough decreased and this was confirmed objectively by measuring reduction in cough sensitivity using serial inhalation cough challenges with citric acid (Fig. 2). Following an initial improvement, the patient’s symptoms recurred with an associated increase in cough sensitivity on repeated cough challenge testing. Immunosuppression with prednisolone 1 mg/kg and cyclophosphamide 100 mg daily was started. This change in therapy resulted in resolution of symptoms within 3 months (Fig. 2). Immunosuppressive therapy was stopped 3 months later. Repeat HRCT scan showed resolution without fibrosis and lung function revealed FEV1, FVC and transfer factor, all within the normal range. The patient remains stable on a combination of entacapone, carbidopa and levodopa.

CASE 2

A 64-year-old man known to have Parkinson’s disease for 15 years was admitted with a 1-week history of lethargy, breathlessness and dry cough. Pergolide had been introduced 4 years previously (a maintenance dose of 1.5 mg daily, an approximate cumulative dose of 2.1 g) in addition to amantadine and a combination of benserazide hydrochloride and levodopa.

On examination, the heart sounds were soft with mitral regurgitation. There were bilateral inspiratory crackles with basal dullness. The ESR was 89 mm/h, but the autoimmune screen was normal. The chest radiograph showed an enlarged heart with bilateral interstitial shadowing and pleural effusions [Fig. 3 (a)]. The pleural aspirate was sterile on culture, showed mixed inflammatory cells with predominance of lymphocytes and had a protein content of 27 g/l (serum protein of 59 g/l), and the LDH of 467 µ/l. The echocardiogram revealed normal left ventricular function and the presence of a pericardial effusion but no evidence of right ventricular collapse. The HRCT scan of the thorax showed bilateral upper...
lobe airspace shadowing with areas of confluence and more diffuse patchy ground-glass opacification [Fig. 3 (b)]. The patient was unable to perform lung function measurements.

A diagnosis of pergolide-induced pneumonitis with pleural and pericardial effusions was made. Pergolide was stopped and the patient’s symptoms improved within 2 weeks. The chest radiograph showed improvement of pulmonary shadowing and diminution of the pleural and pericardial effusions. Two months later, he was asymptomatic and the chest radiograph was normal. The patient remains stable on amantadine and a combination of benserazide hydrochloride and levodopa.

DISCUSSION

Pergolide is a synthetic dopamine agonist and, like ergot from which it is derived, has been associated with atypical sclerotic disorders such as retroperitoneal (4,5), pleural, and pericardial fibrosis (3). We report a hitherto undescribed complication of pergolide therapy manifesting as two different forms of interstitial lung disease. Our first patient presented with chronic cough, and ground-glass shadowing on the CT scan, suggesting an alveolitis. The inflammatory process continued despite the cessation of pergolide and only abated following the introduction of corticosteroids and cyclophosphamide. In contrast, the second patient presented with an acute illness and a rapid recovery after stopping pergolide.

While there was a strong cause/effect relationship between the drug and the lung disorders in both described cases, we were unable to obtain confirmatory histological evidence of the underlying pathological process in case 1 and it was not attempted in case 2. The patchy distribution of the inflammatory reaction as seen on CT scans was probably the reason for the lack of histological confirmation from transbronchial sampling in case 1. However, the presence of ground-glass opacification on CT in both cases is strongly suggestive of an underlying alveolitis. In case 2, the CT also showed changes suggestive of bronchiolitis obliterans organising pneumonia (BOOP), an increasingly recognised condition where fibromyxoid connective tissue is deposited within small airways and air spaces (6).

Heightened cough reflex has been described in patients with interstitial lung diseases (7,8), and therefore the assessment of cough response has been suggested as a non-invasive method of monitoring effects of treatment in this condition (7). The clinical application of cough challenge was apparent in our first patient. The

**Fig. 1.** HRCT scan of the thorax in the first patient showing diffuse ground-glass shadowing suggestive of acute alveolitis.

**Fig. 2.** Serial cough challenge testing with citric acid (1 and 1000 mM), using single-breath dosimeter method, in the first patient showing initial response to glucocorticosteroids followed by relapse and the effect of immunosuppressive therapy.
heightened cough response suggested an underlying inflammatory process and the decrease of cough sensitivity as a result of cessation of pergolide preceded the radiographic improvement. The underlying mechanism for the altered regulation of cough reflex observed in case I and other patients with interstitial lung disorders (7,8) is unknown but it may reflect sensitisation of the cough receptor by the inflammatory mediators.

Whilst a rechallenge to pergolide was not undertaken, the presentation of both the described cases would fulfil criteria for attribution of a definite drug-related adverse event, as proposed by Karch and Lasagna (9). A similar long latency period between the commencement of pergolide and the development of symptoms was previously described (3). The adverse reactions corresponded to the known pharmacological profile of pergolide and other synthetic dopamine agonists. The symptoms and radiological abnormalities in both of our patients re­mitted on cessation of pergolide. However, as the aetiology of interstitial lung injury due to pergolide is not known, we could hypothesise that the underlying mechanism is an idiosyncratic immune response (3). Certainly, drug-induced lupus is an unlikely explanation in our patients because the antinuclear factor remained negative. More importantly, cardiac failure or infection would not explain the symptoms of our second patient as the left ventricular function was normal and pleural aspirate was sterile.

In conclusion, clinicians should be aware that pergolide may cause interstitial lung disease which can manifest after a long period of latency. Therefore, we recommend that patients who receive this type of therapy should be advised to report all new respiratory symptoms to their physicians and consideration given to HRCT imaging if symptoms fail to resolve rapidly.

These adverse events were reported to the Medicines Control Agency.

REFERENCES