

SHORT REPORT

Pericardial, retroperitoneal, and pleural fibrosis induced by pergolide

S Shaunak, A Wilkins, J B Pilling, D J Dick

Abstract

Three patients with Parkinson's disease are described who developed pericardial, retroperitoneal, and pleural fibrosis associated with pergolide treatment. Surgical intervention was required in all three cases, either to reach a tissue diagnosis or for potentially life threatening complications. Symptoms emerged on average 2 years after the institution of treatment, and were sufficiently non-specific to cause significant delays in diagnosis in all cases. The erythrocyte sedimentation rate (ESR) was raised in the two patients in whom it was measured. Serosal fibrosis is a rarely reported adverse effect of pergolide treatment, although it is well described with other dopamine agonists. We suggest that patients with Parkinson's disease who receive pergolide treatment should be regularly monitored for the development of such complications.

(*J Neurol Neurosurg Psychiatry* 1999;66:79–81)

Keywords: pergolide; Parkinson's disease; ergot; serosal fibrosis

Dopamine agonists such as pergolide and bromocriptine are widely used in the management of Parkinson's disease to treat motor fluctuations during chronic levodopa therapy. In addition, the early use of these drugs as monotherapy is increasingly advocated, particularly in younger patients, to delay or reduce the development of late motor fluctuations and dyskinesia. Although fibrotic reactions are well documented after bromocriptine therapy,^{1–4} there are relatively few reports of these complications arising during treatment with pergolide. We describe three patients who developed pronounced serosal fibrosis after treatment with pergolide, which in one case was life threatening, and review the literature on this condition.

Case reports

CASE 1

This 63 year old man presented in 1976 at the age of 41 with asymmetric tremor and rigidity. A diagnosis of Parkinson's disease was made and therapy with a levodopa/benserazide preparation (Madopar 250, 1.25 g/day) was instituted with good symptomatic relief. In

1992, the emergence of motor fluctuations led to the introduction of pergolide, and the dose of this was gradually increased to a maximum of 1mg/day. In 1994, 2 years after the introduction of pergolide, the patient developed left flank pain with weight loss, and was found to have a mild anaemia (haemoglobin 10.4 g/dl), with indices suggesting iron deficiency, and an ESR of 40 mm/h. Upper gastrointestinal endoscopy and barium enema gave negative results. Seven months later right sided chest pain and a non-productive cough developed; investigations confirmed persistent anaemia, an ESR of 55 mm/h, and bilateral pleural thickening on chest radiography and CT. Lung function tests showed a reduction in total lung capacity of 36% with no fall in transfer factor, consistent with pleural fibrosis without parenchymal involvement.

Seven months later the patient presented with exertional dyspnoea, paroxysmal atrial fibrillation, and signs of gross right ventricular failure. Echocardiography suggested pericardial thickening, with a dyskinetic septum but relatively good left ventricular function. Digoxin and diuretics were added without benefit. Constrictive pericarditis was suspected, and this was confirmed at cardiac catheterisation where right atrial pressure was found to be raised with equalisation of right and left ventricular pressures in diastole. At exploration, the heart was encased in thick, calcified pericardium, with tight bands around the superior and inferior vena cavae. Total pericardectomy with freeing of the vena cavae was performed, with an immediate fall in right atrial pressure to normal values, and resolution of the patient's cardiac failure. Subsequently, pergolide was stopped, and the patient is currently maintained on a combination of levodopa/benserazide and tolcapone.

CASE 2

This 61 year old man was diagnosed with Parkinson's disease in 1990 at the age of 53, and initially treated with a levodopa/benserazide preparation (Madopar 125, 0.5 g/day). Pergolide was introduced 2 years later and the dose increased over the course of 12 months to a total of 3 mg/day. Two years after the introduction of pergolide, the patient developed marked oedema of the left leg, associated with urinary frequency, nocturia, and loin pain;

Department of
Neurology, Norfolk and
Norwich Hospital,
Brunswick Road,
Norwich NR1 3SR, UK
S Shaunak
A Wilkins
J B Pilling
D J Dick

Correspondence to:
Dr S Shaunak, Department
of Neurology, Addenbrookes
Hospital, Hills Road,
Cambridge, CB2 2QQ, UK.

Received 28 May 1998 and
in revised form
4 August 1998
Accepted 10 August 1998

the ESR was raised at 57 mm/h, and there was mild impairment of renal function. A nuclear lymphangiogram was normal, but CT of the abdomen disclosed a severe left hydronephrosis and appearances consistent with retroperitoneal fibrosis. Retrograde ureterography showed an 8 cm stricture in the left mid-ureter, which was stented, and steroids were started at a dosage of 20 mg/day. The patient's loin pain and urinary symptoms subsequently resolved, with a concomitant fall in the ESR, although he has required low dose maintenance steroids since. Pergolide was withdrawn, and the patient is now maintained on an levodopa/benserazide preparation alone. Recent imaging has shown an atrophic, non-functioning left kidney, with evidence of mild pelvicalyceal dilatation on the right.

CASE 3

This 70 year old man developed Parkinson's disease in 1991 at the age of 62, and was initially treated with levodopa/benserazide (Madopar 125, 375 mg/day) and selegiline. Pergolide was introduced 4 years later for motor fluctuations, to a maximal dose of 3.75 mg/day. Eighteen months after the introduction of pergolide, the patient complained of right shoulder pain and mild exertional dyspnoea. Routine haematological investigations were unremarkable, although the ESR was not measured.

Within 6 months the pain had become more severe, involving the anterior chest wall and root of the neck, and the patient complained of increasing dyspnoea. Physical examination now showed reduced air entry at the base of the right lung, and chest radiography showed thickening of the pleura of the right lung, which was confirmed on CT. A percutaneous biopsy was performed, but histology was inconclusive, and open pleural biopsy was therefore undertaken. Histological examination of the pleura showed dense fibrous tissue and cytokeratin positive mesothelial tissue without mitoses, and the appearances were thought to be those of benign pleural fibrosis. Pergolide was subsequently discontinued, and the patient is managed on levodopa alone. There has been no clinical or radiological resolution of his respiratory disease.

Discussion

The three cases reported here serve to illustrate the range of serosal fibrotic reactions that may be caused by treatment with pergolide; as in the first case described such complications may be potentially fatal. The temporal relation of the symptoms to the institution of treatment and absence of any other aetiology, including previous exposure to asbestos, argues strongly for a causal role for pergolide in these cases. Initial symptoms in our patients emerged on average 2 years after the introduction of pergolide, and were often sufficiently non-specific to delay accurate diagnosis. In the first case, a relatively small dose of pergolide was sufficient to cause severe constrictive pericarditis, illustrating that these complications are not necessarily dose dependent.

Serosal fibrosis is a recognised complication of treatment with ergot derivatives, including methysergide, lysergic acid diethylamide (LSD), and ergotamine.⁵ In addition, some reports have linked the use of bromocriptine and cabergoline, also ergot derivatives, with the development of pleuropulmonary and retroperitoneal fibrosis,^{1-4 6} and with constrictive pericarditis³ in patients with Parkinson's disease. These reactions seem to occur more commonly in men than women, may occur after short term and low dose therapy, and are often irreversible after withdrawal of the drug, although a degree of regression may be seen.⁵ In many of the reported cases, inflammatory markers such as the ESR and C reactive protein have been raised,¹⁻⁴ and these findings may be of diagnostic value.

Such complications of pergolide therapy, however, are rarely described, although they may be expected on theoretical grounds given that pergolide is also an ergot derivative. There are two published reports of retroperitoneal fibrosis after pergolide treatment,^{7 8} but we can find no other cases of constrictive pericarditis or pleural fibrosis associated with this drug in the literature. The manufacturers and the Committee on Safety of Medicines have received the following additional reports of cardiac and pulmonary toxicity after pergolide therapy since the launch of the drug in 1991: haemopericardium one, constrictive pericarditis one (fatal outcome), pericarditis (non-specified) one, pulmonary fibrosis one, pleural effusion one, lung infiltration one, and dyspnoea nine (personal communication).

The mechanism of fibrosis induced by ergot derivatives is poorly understood, although it has been suggested that there may be an idiosyncratic immune response, with the drug acting as a haptent.⁹ Pathological studies of drug induced pleural fibrosis have shown a dense fibrotic reaction, with minimal inflammatory infiltrate.⁵ However, a mononuclear cell infiltrate has been reported in biopsied cases of ergot induced retroperitoneal fibrosis, occasionally with eosinophilia and vasculitis, but without evidence of complement or immune complex deposition.¹⁰

Patients with Parkinson's disease treated with ergot derived dopamine agonists, including relatively recently introduced drugs such as pergolide and cabergoline, should be carefully monitored for the development of serosal fibrosis. We suggest that, given the potential severity of these adverse effects, patients should have an annual chest radiograph and measurement of ESR, in addition to monitoring for new systemic symptoms at each clinic visit. It will be of interest to see whether the use of the new non-ergot dopamine agonists ropinirole and pramipexole is associated with serosal fibrosis, although prolonged follow up will be required given the rarity of these reactions.

We are grateful to Mr K Sethia for providing details of the second case.

1 Ward C, Thompson J, Humby M. Pleuropulmonary and retroperitoneal fibrosis associated with bromocriptine treatment. *J Neurol Neurosurg Psychiatry* 1987;50:1706-7.

- 2 Bowler J, Ormerod I, Legg N. Retroperitoneal fibrosis and bromocriptine. *Lancet* 1986;ii:466.
- 3 Saura J, Aguilar M, Alio J. Pleural effusion and pericarditis secondary to bromocriptine treatment. *Neurologica* 1991;6:331-3.
- 4 Rinne U. Pleuropulmonary changes during long term bromocriptine treatment for Parkinson's disease. *Lancet* 1981;i:44.
- 5 Benard A, Guenanen H, Tillie-Leblond I, et al. Drug induced pleurisy. *Rev Mal Resp* 1996;13:227-34.
- 6 Geminiani G, Fetoni V, Genitrini S, et al. Cabergoline in Parkinson's disease complicated by motor fluctuations. *Mov Disord* 1996;11:495-500.
- 7 Jimenez-Jimenez F, Lopez-Alvarez J, Sanchez-Chapado M, et al. Retroperitoneal fibrosis in a patient treated with pergolide. *Clin Neuropharm* 1995;18:277-9.
- 8 Sanchez-Chapado M, Angulo-Cuesta J, Guil-Cid M, et al. Retroperitoneal fibrosis secondary to treatment with L-Dopa analogues for Parkinson's disease. *Arch Esp Urol* 1995;48:979-83.
- 9 Hoffmann W, Trippel O. Retroperitoneal fibrosis: aetiological considerations. *J Urol* 1961;86:222-32.
- 10 Iversen B, Nordahl E, Thunold S, et al. Retroperitoneal fibrosis during treatment with L-Dopa. *Lancet* 1975;iii:303-4.



Pericardial, retroperitoneal, and pleural fibrosis induced by pergolide

S Shaunak, A Wilkins, J B Pilling and D J Dick

J Neurol Neurosurg Psychiatry 1999 66: 79-81
doi: 10.1136/jnnp.66.1.79

Updated information and services can be found at:
<http://jnnp.bmj.com/content/66/1/79>

	<i>These include:</i>
References	This article cites 9 articles, 1 of which you can access for free at: http://jnnp.bmj.com/content/66/1/79#BIBL
Email alerting service	Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections	Articles on similar topics can be found in the following collections Drugs: CNS (not psychiatric) (1945) Parkinson's disease (690)
--------------------------	--

Notes

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>