

Bromocriptine induced pleuropulmonary fibrosis

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Bromocriptine is an ergot derivative with dopaminergic properties that is of value in the treatment of Parkinsonism. The development of pleuropulmonary fibrosis during treatment with bromocriptine has been reported,¹⁻⁴ but a causal relationship has been questioned.^{5,6} We describe a patient who developed a systemic illness, including pleuropulmonary fibrosis, during treatment with bromocriptine for Parkinsonism, and in whom cessation of the drug was followed by weight gain, reversal of anaemia, a fall in the raised serum IgG concentration and erythrocyte sedimentation rate, and disappearance of neutrophil leucocytosis in lung lavage fluid, strongly supporting a causal relationship with bromocriptine.

Case report

A 55 year old male machine operator presented with

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Parkinsonism in 1978. Thirty five years previously he had temporarily set up presses for manufacture of asbestos containing cylinder head gaskets. He was treated initially with incremental doses of levodopa, reaching 5 g daily. This caused bradykinesia with involuntary movements, and in 1981 the dose was reduced to 2 g daily, with bromocriptine 20 mg twice daily added. His weight was 66 kg. His blood count was normal. Chest radiography showed slight lower zone pleural thickening (fig 1a).

In January 1984, after 27 months of bromocriptine treatment (maximum daily dose 47.5 mg), he developed dyspnoea, subcostal chest pain, and weight loss. His weight was 55 kg, the haemoglobin concentration was 12.7 g/dl, and the erythrocyte sedimentation rate (ESR) was 54 mm in one hour, and there was a polyclonal increase in serum IgG (21.8 g/l)—see figure 2. A chest radiograph in 1984 showed extensive bilateral lower zone pleuropulmonary shadowing. He was referred to the thoracic medicine department in June 1984. The chest radiograph and weight were unchanged, the haemoglobin concentration was 11.7 g/dl, and ESR 85 mm in one hour. Computed tomography showed extensive pleural thickening with numerous tissue strands extending

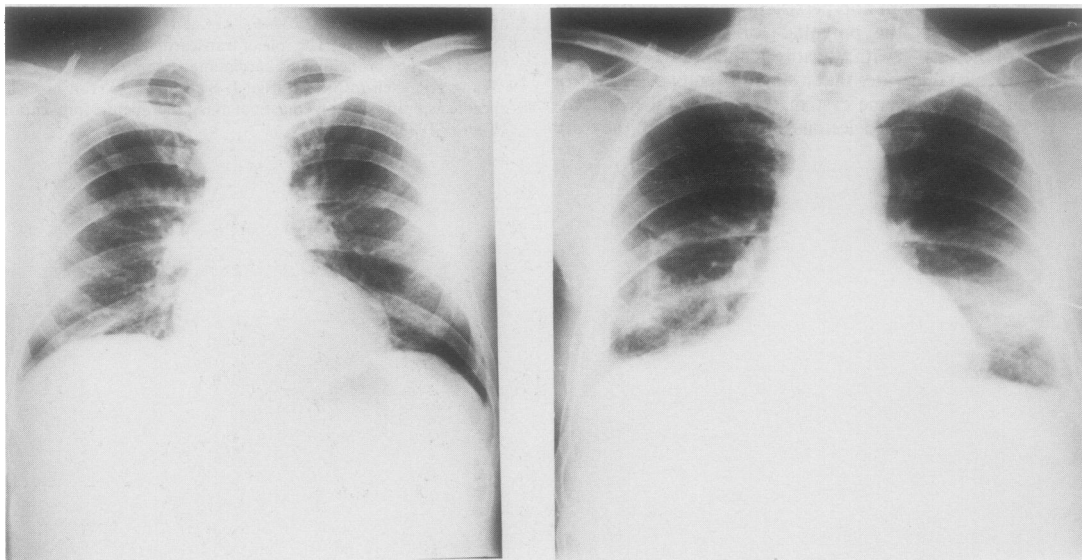


Fig 1 Chest radiograph before (a) bromocriptine treatment and (b) three months after it had finished, showing the development of widespread pleuropulmonary shadowing.

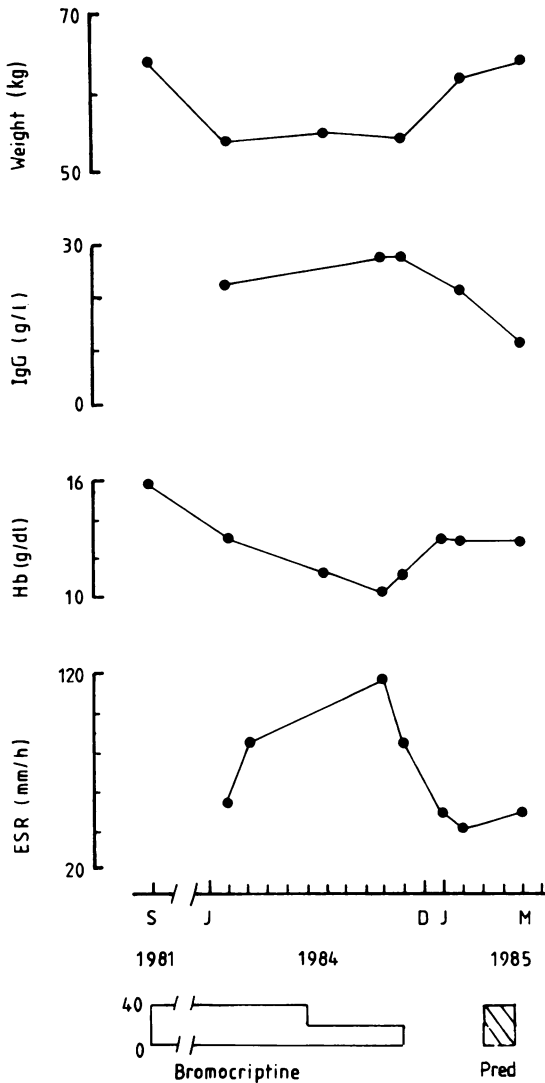


Fig 2 Changes in serum erythrocyte sedimentation rate (ESR), haemoglobin (Hb) and immunoglobulin G (IgG) concentrations, and body weight during and after bromocriptine treatment. Time in months is shown on the horizontal axis (S—September; J—January; M—May). The blocks below the graph represent daily drug doses (in mg) and duration of treatment (pred—prednisolone).

radiographs were unchanged, haemoglobin was 10.1 g/dl, ESR 117 mm in one hour and IgG 27.7 g/l. A gallium lung scan was normal. Bronchoalveolar lavage fluid (lingula) showed slight neutrophil leucocytosis (total cell yield 0.3×10^6 /ml; differential count: neutrophils 9%, macrophages 80%, lymphocytes 5%, epithelial cells 6%). An open biopsy (right lung) was performed; the pleura showed hyaline pleural plaques with a chronic inflammatory infiltrate of lymphocytes and plasma cells, and the lung showed non-specific fibrosis.

Treatment with bromocriptine was tailed off and the patient continued to take levodopa alone. Bronchoalveolar lavage fluid obtained from the same segment two weeks after he had stopped bromocriptine showed a normal differential white blood cell count (total cell yield 0.5×10^6 /ml; differential count neutrophils 2%, macrophages 95%, lymphocytes 3%). Six weeks after he had stopped bromocriptine the chest radiograph and results of lung function tests remained unchanged but his weight had risen to 61.4 kg, the haemoglobin concentration was normal, ESR was 39 mm in one hour, and serum IgG was 21.0 g/l (fig 2). Prednisolone (40 mg daily) was started but after six weeks' treatment there was no change in either chest radiograph (fig 1b) or lung function values. Treatment with prednisolone was stopped. The patient's condition remained static.

Discussion

Various drugs may cause pleuropulmonary changes. With some—for example, methysergide⁷—the relationship is well documented, but in others the association remain unclear. A possible relationship between bromocriptine and pleuropulmonary fibrosis was first suggested by Rinne,¹ who described radiological abnormalities in seven of 123 Parkinsonian patients treated with bromocriptine. The daily dose of the drug ranged from 20 to 90 mg and the maximum duration of treatment before presentation was 27 months. A more detailed report of a single patient² suggested that bromocriptine related pleuropulmonary fibrosis could be associated with a systemic illness, including chest pain, dyspnoea, and abnormalities of ESR and serum immunoglobulins. These symptoms settled when bromocriptine was stopped, and, although there was no response to prednisolone, the chest radiograph and lung function improved progressively over two years.

Although there are other reports of the development of pleuropulmonary fibrosis during bromocriptine treatment,^{3,4} a causal relationship has been challenged.^{5,6} Furthermore, a recent review of 37 patients with Parkinsonism treated with bromocriptine showed no chest radiographic abnormalities,⁸ although the authors cautiously suggested that such patients should have annual radiographs. Information supplied for 1964–85 by the Committee on Safety of Medicine records 313 cases (five fatal) of adverse reactions to bromocriptine. Only 12 cases (non-fatal) are respiratory, and these do not include any cases of pleuropulmonary fibrosis (Committee on Safety of Medicines 1985, personal communication). In the present case cessation of bromocriptine treatment was followed by weight gain, a rise in haemoglobin, a fall in ESR and serum IgG, and disappearance of neutrophil leucocytosis in lung lavage fluid, strongly supporting a causal relationship

into the lung. A Trucut needle biopsy showed pleural fibrosis with patchy non-specific pulmonary fibrosis and no evidence of either asbestos fibres or neoplasia. Lung function tests showed severe restriction of lung volumes (total lung capacity 55%, vital capacity 42% predicted) with normal transfer coefficient.

In October 1984 his symptoms, lung function and chest

between the drug and the pleuropulmonary changes. There may have been slight prior asbestos related pleural fibrosis.

The mechanism of bromocriptine induced lung damage is unknown. Bromocriptine is structurally similar to methysergide,² which is well known to cause pleuropulmonary fibrosis; this process, like bromocriptine induced lung fibrosis, may occur only after prolonged use of the drug and regress after its cessation. Methysergide is a serotonin agonist and serotonin may cause pulmonary fibrosis both in the experimental animal and in man in the carcinoid syndrome;⁹ ergot derivatives, such as bromocriptine, may act at serotonergic synapses.¹⁰

In conclusion, our case provides evidence that bromocriptine may cause pleuropulmonary fibrosis, occurring after several months' treatment at high doses, and that this may be arrested by cessation of the drug. Clinicians using bromocriptine should be aware of this unusual side effect.

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