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Pergolide-Induced Pleuropulmonary Fibrosis

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Summary: Pleuropulmonary fibrosis is a rare, but well-recognized adverse effect of ergot alkaloids. We report on four patients who developed pleural and/or pulmonary fibrosis during treatment with pergolide and give characteristics of 87 cases with one or more symptoms of serosal fibrosis. Retroperitoneal and pleuropulmonary fibrosis are serious conditions, which are often irreversible after drug withdrawal. Increased awareness may help to diagnose these complications at an earlier stage and to minimize any permanent damage to the patient. **Key Words:** Pergolide—Pleural fibrosis—Pulmonary fibrosis

Pergolide is a short acting ergot alkaloid used in the treatment of patients with Parkinson disease (PD). It was introduced on the Dutch market in 1991. Pergolide acts as a dopamine receptor agonist for D1 and D2 receptors (1). Common adverse events are gastrointestinal complaints, hallucinations, and confusion (2).

Serosal fibrosis is a well-recognized complication of treatment with ergot derivatives, such as bromocriptine and methysergide (3). For pergolide, some cases of retroperitoneal fibrosis have been reported (4,5). Since its introduction, the Uppsala Monitoring Center of the World Health Organization has received a total of 87 reports on serosal fibrosis attributed to the use of pergolide, including retroperitoneal, pulmonary, and pleural fibrosis. This accounts for approximately 5% of the total number of adverse drug reaction reports on pergolide. We report on four patients who developed pleural and/or pulmonary fibrosis during long-term treatment with pergolide and present characteristics of the case reports found in the Uppsala database.

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CASE 1

A 64-year-old man was diagnosed with PD in 1988 and treated with pergolide since October 1993. In June 1994, he developed symptoms of increasing shortness of breath and a dry cough, especially when lying down, which progressed towards September 1994. He had no fever and did not report ankle oedema. He had stopped smoking in 1954. Other medications included levodopa/benserazide, orphenadrine, selegiline, and diazepam. He had no medical history of pulmonary complaints, chronic obstructive pulmonary disease, pneumonia, contact with tuberculosis, or heart disease. A chest radiograph in June revealed a trace of pleural effusion. In September, a larger amount of pleural fluid was seen on both sides, with normal heart size. Pergolide-induced pleurisy was suspected, and pergolide was subsequently discontinued. Two months after discontinuation of pergolide, the patient's symptoms improved dramatically. He only had mild exertional dyspnoea, although symptoms of his PD had worsened. Chest radiography showed substantial reduction of pleural fluid.

CASE 2

This 63-year-old man presented in October 2000 with shortness of breath, cough, and atypical chest pain

of the left flank of unknown duration. The electrocardiogram showed no abnormalities, and cardiac enzymes were not elevated. The patient had been exposed to asbestos in his job as a plumber and had been using pergolide in increasing dosage since June 1995 for the treatment of PD. Since October 1998, he was using 5 mg/day. Other medications included levodopa/carbidopa 250 mg one tablet three times daily, metoprolol 100 mg one tablet daily, omeprazole 20 mg one tablet daily, and alfuzosine 5 mg one tablet two times daily. Microscopic examination of a percutaneous biopsy revealed chronic nonspecific fibrous pleuritis; no signs of mesothelioma. According to a ventilation/perfusion scan of the lungs, pulmonary embolism was unlikely. Because the percutaneous biopsy was inconclusive, an open pleural biopsy was undertaken. Histologic examination of the pleura showed a fibrous, granulomatous, nonspecific inflammation. No malignant cells or indications for asbestosis were found. It was concluded that the findings were suggestive of a unilateral left-sided pergolide-induced pleuritis. Pergolide was subsequently discontinued. Upon follow-up on January 15, 2001, symptoms of his respiratory disorder had diminished, while his symptoms of PD had worsened.

CASE 3

A 65-year-old man was diagnosed with PD in 1997 and was treated with pergolide 0.25 mg one tablet three times daily as of December 1997. The dose had been increased to three times daily 0.5 mg in September 1999. He was also treated with selegiline 5 mg one tablet two times daily. In the past, he had been exposed to asbestos in his work as a carpenter. He presented with dyspnoea in February 2000. Chest radiography revealed bilateral pleural thickening and pleural fluid, suggestive of mesothelioma. A CT scan showed bilateral pleural thickening on several levels (Fig. 1). Initially, the patient refrained from thoracoscopy, but in September 2000 he gave consent to the procedure. Histologic examination of a pleural biopsy showed reactive fibrous pleuritis, however, without the presence of malignant cells. It was concluded that findings were suggestive of pergolide-induced pleural fibrosis, while other causes were excluded. Pergolide was discontinued, and the patient was managed on a levodopa/carbidopa combination alone. There have been no clinical improvement or a resolution of radiologic findings since the cessation of pergolide therapy.

CASE 4

This 63-year-old man presented in August 2000 with exertional dyspnoea and dry cough for 9 months. He had been using pergolide 3 mg/d for 3.5 years for the treatment of PD. The dose had been increased to 4.5 mg/day, 6 months before the start of his symptoms. The patient had no history of pulmonary disease or heart disease, had not smoked, and did not keep birds. His other medications included propranolol 180 mg one tablet daily. Physical examination showed no abnormalities. Laboratory tests showed raised ESR at 96 mm/h, increased LDH (lactate dehydrogenase) of 136 U/L, and eosinophilia of 0.51×10^9/L (normal $< 0.44 \times 10^9$/L). Arterial blood gasses were: PaO_2 64 mmHg (normal 75–100 mm Hg), $PaCO_2$ 44 mm Hg, and pH 7.42. Rheumafactor, antinuclear antibodies (ANA),

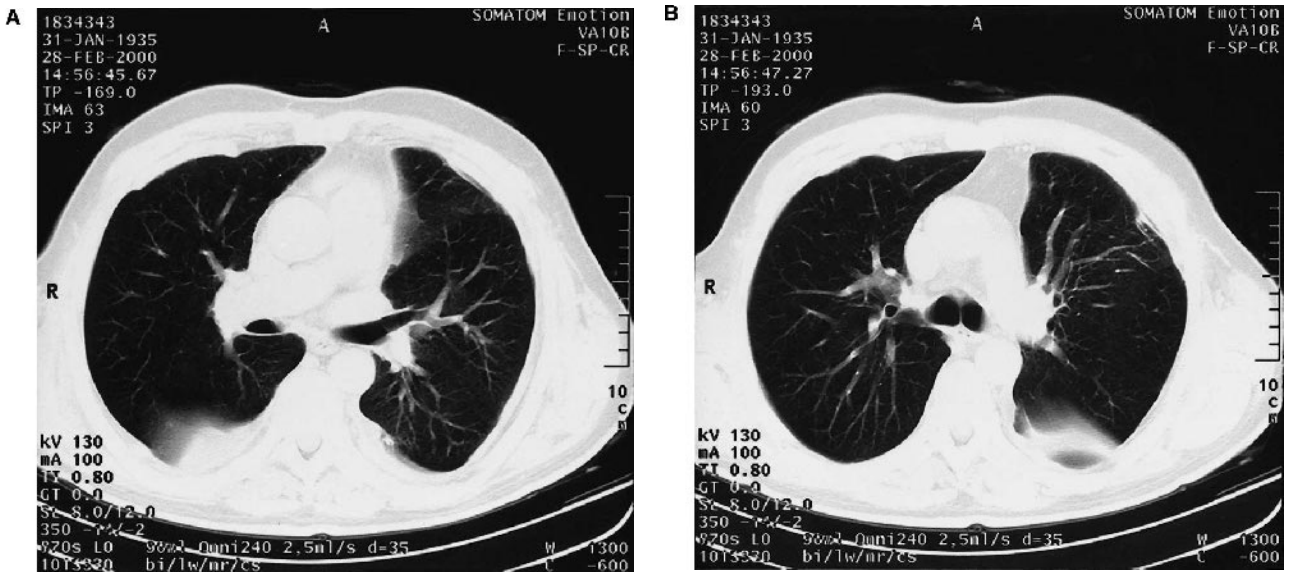

FIG. 1. **(A** and **B)** CT scans of Patient 3. Bilateral pleural thickening on several levels.

and extractable nuclear antibodies (ENA) were all negative. Electrocardiography showed normal sinus rhythm with left bundle branch block. Ventilation/perfusion scan of the lungs revealed two minor matched ventilation/perfusion defects. A pulmonary function test showed a restrictive defect, together with a reduced diffusion capacity. A CT scan of the chest revealed extensive intrapulmonary fibrotic lesions on both sides, with pleural thickening, and pleural effusion, especially on the right side (Fig. 2). Histologic examination of a pleural biopsy and a thoracoscopic lung biopsy showed nonspecific fibrous inflammation. No malignant cells were found. Because this was the second patient who developed pleuropulmonary fibrosis during treatment with pergolide in this department of Pulmonary Medicine, this case was also suspected to be related to the use of pergolide, which was discontinued in September 2000. Upon follow-up in February 2001, both his clinical condition and radiologic findings have improved, as has his pulmonary function test.

Analysis Spontaneous Adverse Drug-Reaction Reports in Uppsala Database

Since its introduction, the Uppsala Monitoring Center has received a total of 1902 adverse drug reaction reports on pergolide. Of these reports, 87 (4.6%) refer to one or more symptoms of serosal fibrosis, including pleural effusion (38 reports), pleural fibrosis (21 reports), pulmonary fibrosis (18 reports) and retroperitoneal fibrosis (19 reports) (Table 1). Although pleural effusion does not always occur simultaneously with pleural and/or pulmonary fibrosis, we included this diagnosis in the analyses because it is part of the spectrum of ergot derivative induced pleuropulmonary disease (3). In comparison, of the 6786 received adverse drug reaction reports on another ergot derivative bromocriptine, 159 (2.3%) refer to one or more symptoms of serosal fibrosis. Reports on serosal fibrosis with other antiparkinsonian agents were less frequent, e.g.: amantadine 3 of 3587 reports (0.08%), selegiline 4 of 1955 reports (0.2%), and levodopa/carbidopa 7 of 5887 reports (0.1%).

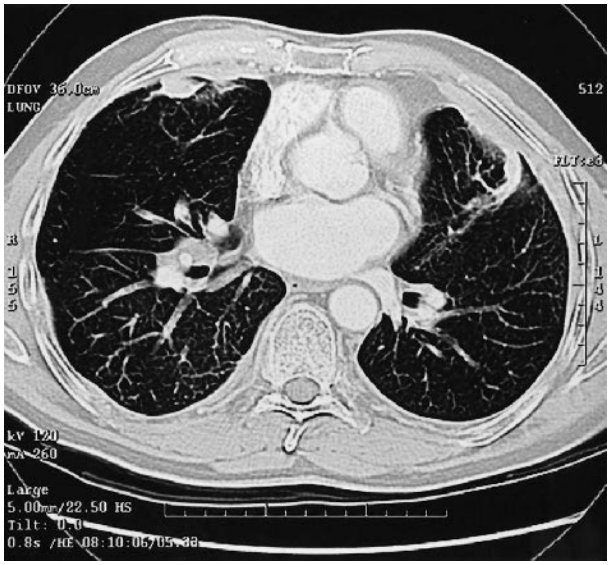

FIG. 2. CT scan of Patient 4. Bilateral intrapulmonary lesions with pleural thickening.

TABLE 1. *Mean age, daily dosage of pergolide, and latency time per diagnostic category*

Diagnosis Variable	Number Number reported	Mean (SD)
Total population	87	
Age (years)	73	64.2 (8.1)
Daily dosage (mg)	54	2.64 (1.51)
Latency time (years)	20	2.19 (1.71)
Pleural effusion	38*	
Age (years)	32	65.4 (8.7)
Daily dosage (mg)	18	2.55 (1.71)
Latency time (years)	5	2.55 (3.25)
Pleural fibrosis	21*	
Age (years)	18	64.7 (8.8)
Daily dosage (mg)	10	1.99 (0.89)
Latency time (years)	8	1.84 (1.00)
Pulmonary fibrosis	18*	
Age (years)	16	59.9 (6.1)
Daily dosage (mg)	14	2.92 (1.58)
Latency time (years)	3	2.54 (1.10)
Retroperitoneal fibrosis	19*	
Age (years)	14	63.6 (6.7)
Daily dosage (mg)	15	3.30 (1.46)
Latency time (years)	5	2.07 (0.70)

* One patient can have more than one diagnosis.

Mean age of the cases of pergolide-induced serosal fibrosis was 64.2 years (range 45–87), 64.7 years in men and 63.3 years in women. Of the 87 patients, 64 were men, 13 were women, and in 10 cases gender was not reported. In 51 reports the outcome was specified. Three patients died as a result of the adverse event, 32 patients had not recovered at the time of the report, and 16 patients recovered with (4 patients) or without (12 patients) sequelae. Daily pergolide dosage was reported in 54 cases, and varied from 0.05 mg to 6 mg. Mean daily dosage was 2.64 mg. Information on the date of onset of the adverse reaction to pergolide, and the date pergolide intake was initiated, was available in 20 patients. Mean time from initiation of pergolide to the onset of the adverse reaction (latency time) was 2.19 years. Latency time varied from 73 days to 7.92 years. Table 1 shows the means of age, daily pergolide dosage and latency time per diagnostic category. Patients with pulmonary fibrosis attributed to the use of pergolide were on average younger than patients with one of the other diagnoses (independent samples t test $p = 0.014$, 71 df). Daily pergolide dosage was signifi-

cantly higher in patients with retroperitoneal fibrosis, and significantly lower in patients with pleural fibrosis. Cases with pleural effusion did not differ significantly from cases with other diagnoses.

DISCUSSION

The four case reports demonstrate that, besides retroperitoneal fibrosis, pleural and pulmonary fibrosis can be attributed to the long-term use of pergolide. The obvious temporal relation and absence of other causal factors, such as other medications or asbestos exposure, argue strongly for a causal role of pergolide in these cases. Propranolol has been associated with retroperitoneal fibrosis (6), and could have theoretically had a causal role in the onset of pleuropulmonary fibrosis in Patient 4. However, despite continuation of propranolol in this patient, his condition improved dramatically, making it a less likely explanation. In the medical literature we found two reports on pleuropulmonary fibrosis attributed to the use of pergolide (7,8). The first report describes a 70-year-old man, who developed pleural fibrosis 18 months after the introduction of pergolide. His clinical and radiologic condition did not improve after discontinuation of treatment. The second patient, a 65-year-old-man, was diagnosed with pergolide induced pleuropulmonary fibrosis after 3 years of use. Symptoms and signs of this patient dramatically improved after discontinuation of pergolide.

Analysis of the spontaneous adverse reaction reports provided by the Uppsala database revealed that mean age of the cases of serosal fibrosis attributed to the use of pergolide was approximately 64 years, and that a majority of the reported adverse events were seen in men. Signs of serosal fibrosis occurred on average at a daily dose of 2.64 mg pergolide after a mean duration of use of 2.19 years. More than two thirds of patients had not recovered at the time of the spontaneous report. Since the analyses were based on data from a spontaneous reports database, which may be prone to underreporting and selective reporting, the results should be treated with caution and can only raise hypotheses about the causal role of pergolide in the induction of serosal fibrosis. For calculation of relative risks a proper control group is needed. Also, detailed information on other potential causes, such as other medications or asbestos exposure, is missing in these reports.

Pleuropulmonary fibrosis is a well-recognized adverse effect of treatment with ergot derivatives, such as bromocriptine and methysergide, and is often irreversible after drug withdrawal. The onset usually occurs 12 to 48 months after initiation of therapy (3). The diagnosis is often delayed because initial symptoms are non-specific. Since the early use of pergolide as monotherapy is increasingly advocated, this complication may be observed more frequently in the future. The mechanism by which ergot derivatives cause serosal fibrosis is poorly understood. The effects seem to be dose-related (9). It has been suggested that fibrotic changes are due to increased serotonin levels with a subsequent increase in fibroblast activity (3).

In conclusion, retroperitoneal and pulmonary fibrosis are well-recognized adverse effects of ergot derivatives. The long-term use of pergolide also seems to increase the risk of serosal fibrosis. Retroperitoneal and pleuropulmonary fibrosis are serious conditions, which are often irreversible after drug withdrawal. Increased awareness may help to diagnose these complications at an earlier stage and minimize any permanent damage to the patient.

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