Pleuropulmonary Fibrosis After Long-term Treatment With the Dopamine Agonist Pergolide for Parkinson Disease

Ron Tintner, MD; Prasad Manian, MD; Polly Gauthier, MD; Joseph Jankovic, MD

Dopamine agonists are increasingly used in the treatment of Parkinson disease, but they may cause serious adverse effects. In December 1983, symptoms of Parkinson disease developed in a 55-year-old man with no history of pulmonary disease, smoking, or asbestos exposure. He began treatment with dopamine agonists bromocriptine mesylate (in 1984) and pergolide mesylate (in 1989). In late 2000, pulmonary symptoms developed. Chest radiographs and computed tomographic findings showed a mass in the right upper lobe and effusion. A biopsy specimen showed pleural and parenchymal fibrosis. This syndrome resolved after cessation of pergolide therapy and a switch to pramipexole dihydrochloride. This case draws attention to the association of long-term ergot dopamine agonist therapy with pleuropulmonary fibrosis, which can develop as late as 11 years after the initiation of therapy. We also review evidence that the risk of this complication is substantially lower with the newer nonergot dopamine agonists.

REPORT OF A CASE

In December 1983, a man aged 55 years complained of left arm stiffness, soreness, and paresthesias. On examination, he had decreased blink frequency, poverty of spontaneous movement in general and especially of the left upper extremity, stiff gait, and en bloc turning. His left arm was kept in slight flexion and had increased tone with cogwheel rigidity and decreased rapid alternating movements. A diagnosis of PD was made, but no treatment was started until September 1984, when bromocriptine mesylate therapy was started and the dosage was titrated to 22.5 mg/d with moderate improvement in left arm symptoms. In July 1985, the bromocriptine mesylate dosage was reduced to 15 mg/d and carbidopa and levodopa therapy were started and increased to 3 divided doses of 75 and 300 mg, respec-
tively, with marked symptomatic improvement. Slight deterioration ensued over the next years, and in October 1987, amantadine hydrochloride therapy at a dosage of 200 mg/d was added with minimal symptomatic benefit. In June 1989, after stopping amantadine therapy because of ankle edema, his left-sided PD symptoms increased, and subsequently improved partially when amantadine therapy was re-started. In August 1989, bromocriptine therapy was discontinued and pergolide mesylate therapy at a dosage of 1.5 mg/d was initiated. His parkinsonism progressed, necessitating adjustment of the levodopa dosage. In August 2000, a cough and shortness of breath developed that led to the diagnosis of pleural effusion (Figure 2A). At that time, he also received daily treatment with tolterodine tartrate, 2 mg; lisinopril, 5 mg; spironolactone, 25 mg; furosemide, 40 mg; and aspirin, 81 mg.

Computed tomography of the chest showed a mass in the right upper lobe of the lung and pleural plaques (Figure 2B and C). Because of coronary artery disease (with a previous inferior myocardial infarction) and evidence of congestive heart failure (an ejection fraction of 40%), a stent was placed in the left anterior descending coronary artery. He underwent multiple thoracenteses for recurrent bloody pleural effusions and multiple computed tomography–guided biopsies with a final diagnosis of fibrosis. He was readmitted to the hospital in October 2000 and underwent thoracotomy and biopsy of the right lung and pleura. The biopsy results showed fibrotic changes in the pleura with mild chronic inflammation (Figure 3).

Pramipexole dihydrochloride was substituted for pergolide, and the dosage was gradually increased to 3 mg/d in November 2000.
In July 2001 he had mild motor fluctuations related to long-term levodopa therapy, but his parkinsonism was relatively well controlled. In addition to 3 mg/d of pramipexole, he was receiving 50 mg of carbidopa and 200 mg of levodopa 5 times per day and half of a tablet of combined 50-mg carbidopa and 200-mg levodopa (controlled-release Sinemet) at bedtime. He has continued to do well without recurrence of pulmonary signs or symptoms through July 2002.

**COMMENT**

This case draws attention to a potentially life-threatening complication associated with the use of ergot drugs, particularly pergolide, in the treatment of PD. Pleural effusion and pleuropulmonary fibrosis, confirmed by biopsy findings, developed while the patient received pergolide. He had no prior exposures or risk factors for development of pleuropulmonary fibrosis except for an earlier 5-year exposure to bromocriptine. Because this ergot drug is also associated with fibrotic syndromes, it may have played a contributory role, but the fact that the pleuropulmonary fibrosis occurred 11 years after discontinuation of bromocriptine therapy and resolved immediately after discontinuation of pergolide therapy strongly suggests that pergolide was the causative agent.

Ten cases of fibrosis of serosal membranes associated with pergolide use have been reported in the literature (Table). In addition, 3 cases of restrictive pericarditis have been reported in an abstract form but without documentation of latency or dosage (Table). In all of the reported cases of pergolide-induced fibrotic reactions, the symptoms occurred within 3 years of initiation of treatment. Our case differs from the published reports in that the complication took 11 years to develop; however, since the initial report of this case in abstract form, development of pericardial fibrosis in another patient after 11 years has been reported in the Japanese literature. A recent newsletter has reported fibrosing alveolitis in a 48-year-old woman who had been taking pergolide for more than 6 years before development of shortness of breath and reduced exercise tolerance with computed tomographic evidence of hypersensitivity pneumonitis and fibrosing alveolitis. However, no dosage or response to discontinuation of therapy data were documented.

Serosal fibrosis syndromes have been associated not only with ergot dopamine agonists such as bromocriptine, pergolide, lisuride, cabergoline, mesulergine, and dihydroergocryptine used in the treatment of PD, but...
also with other ergots not used in PD. In particular, methysergide maleate has been reported to have rates of fibrosis estimated at 1 for every 5000 treated patients. The newest dopamine agonists used for PD, pramipexole and ropinirole, are not ergolines (Figure 1B). Because these drugs have not been associated with fibrotic reactions, it has been postulated that mechanisms other than dopamine activation play a role in the development of dopamine agonist–associated fibrosis. Apomorphine hydrochloride, a nonergot agonist at the D1 and D2 dopamine receptors, has also not been associated with fibrotic reactions.

Furthermore, cases have now been reported of restrictive valvular heart disease associated with pergolide. Three of these cases report histologically confirmed changes consisting of endocardial plaque formation overlying normal valvular architecture, ie, serosal fibrosis. This resembles the valvular pathology of carcinoid valve disease, as well as that seen with ergots such as methysergide and ergotamine tartrate and the anorexic agents fenfluramine hydrochloride and dexfenfluramine hydrochloride. A case of bromocriptine-associated valvular disease has now also been associated with fibrotic reactions.

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The mechanism of fibrotic reaction by ergot alkaloids is unknown. Proposed mechanisms include an idiosyncratic immune reaction and modulation at peripheral neurotransmitter or humoral receptor sites. These compounds all share the ergoline nucleus, similar to that of lysergic acid, with structurally different peptides attached to the C8 region of the ergoline ring (Figure 1A). The ergots are all antagonists at serotonin 2 receptors, although pergolide and even bromocriptine are less potent in this action than methysergide; in addition, this drug-receptor interaction may not constitute pure antagonism. Pergolide and other ergots may also modulate other serotonergic receptors. The ergots have cytostatic, endocrine, and immunosuppressant actions besides neurotransmitter modulation. It has been suggested that the fibrotic complications are dose related or seen with recent increases in dosage, although that does not seem to be the case in our patient.

Fibrosis probably results from fibroblast stimulation by various factors. Connective tissue growth factor has recently been described as a fibrogenic factor that induces collagen type I and fibronectin, and the deposition of such molecules leads to fibrotic disease in many tissues. Connective tissue growth factor is believed to play a crucial role in fibrotic disease formation in many tis-

<table>
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<tr>
<th>Source</th>
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<th>Maximum Dosage, mg/d</th>
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Abbreviation: NA, not available.
*Indicates pneumonitis/fibrosing alveolitis.
†Indicates valvular.

Table. Literature Reports of Serosal Fibrosis Syndromes Associated With Pergolide
sues. Connective tissue growth factor in turn is regulated by many factors, including transforming growth factor β, dexamethasone, and serotonin. Furthermore, transforming growth factor β stimulates pleural fibrosis and pleural effusions via pathways in series and parallel with connective tissue growth factor.

Another possibility is that pergolide- and ergot-induced fibrotic syndromes involve serotonin. Fibrotic complications have been reported with carcinoid syndrome in which there is overproduction of serotonin. Serotonin has also been shown to trigger the transforming growth factor β–mediated cascade via serotonin 2A receptors. Fibroblast stimulation has also been demonstrated through serotonin 1B receptors. Most ergots also have actions at serotonin receptors. Methysergide, the ergot most frequently linked to fibrotic complications, is an antagonist at serotonin 2A receptors, which one would predict would interfere with the fibrotic cascade. The pharmacology of the ergot drugs at the serotonin receptors of the immune system has not been fully elucidated, and thus an action of the ergots at serotonin receptors remains at least a possible explanation for these fibrotic complications. In addition, atypical antipsychotics such as olanzapine and clozapine are fairly potent serotonin 2A antagonists and have not been associated with fibrosis.

Another related hypothesis is that this occurs because of interference with pineal function, which is profoundly affected by serotonergic function. Pinealectomy leads to increased formation of fibrous tissue in the abdominal cavity. It also leads to reduced formation and/or action of prostaglandin E₂ and thromboxane A₂. Prostaglandin E₂ plays an important role in enhancing function of T-suppressor lymphocytes that control overactive antibody-producing B lymphocytes in situations such as collagen diseases, lithium-induced fibrosis, and cardiomyopathies.

An immunologic or hypersensitivity reaction has also been proposed as a mechanism for ergot-induced fibrosis. It is possible that the ergoline ring structure acts as a hapten to induce an immune response. Fibrotic reactions have been hypothesized to occur as a result of a hypersensitivity reaction to antigens, eg, leaking into the retroperitoneum from atheromatous plaques in the aorta or the common iliac arteries. Mast cells are hypothesized to participate in processes leading to tissue fibrosis in human lung and skin. There is evidence that asbestos-mediated pulmonary fibrosis may be mediated through mast cell–released serotonin and histamine. Human mast cell tryptase is a potent inducer of DNA synthesis in fibroblasts from multiple sources, including human lung but with target cell specificity.

Delayed drug reactions can be immune or nonimmune mediated. Both types are generally not due to the parent compounds but to their metabolites, and it is possible that the fibrotic process is not caused by the parent compound but by a metabolite. Altered pathways of xenobiotic metabolism can have profound effects on metabolic activation of pulmonary drug toxicity. At least 10 metabolites of pergolide have been detected, including N-despropylpergolide, pergolide sulfoxide, and pergolide sulfone. Pergolide sulfoxide and pergolide sulfoxide are dopamine agonists in animals. The other detected metabolites have not been identified, and it is not known whether any other metabolites are active pharmacologically. The late onset of serosal fibrosis could be triggered by the appearance or increased concentration of a pergolide (or other ergot) metabolite due to induction or inhibition of an alternate metabolic pathway, as has been shown in the case of phenobarbital-potentiating carbon tetrachloride toxicity.

Our report provides evidence that ergot dopamine agonists such as pergolide can induce pulmonary fibrosis and possibly other serosal fibrotic syndromes, even after more than a decade of treatment. Therefore, patients presenting with symptoms of pleural, pericardial, or retroperitoneal fibrosis while taking ergot dopamine agonists should switch to a nonergot dopamine agonist. On the other hand, the risk of fibrosis even with long-term ergot exposure is so minimal and usually reversible that it should not outweigh the potential benefits. However, because there is no evidence that the ergot dopamine agonists currently licensed in the United States are clinically superior to the nonergot dopamine agonists, any increased risk should be balanced by increased benefit. A high level of vigilance of this potential complication, however, is prudent.

Accepted for Publication: August 2, 2004.

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Author Contributions: Study concept and design: Tintner, Manian, and Jankovic. Acquisition of data: Tintner and Manian. Analysis and interpretation of data: Tintner, Manian, Gauthier, and Jankovic. Drafting of the manuscript: Tintner and Jankovic. Critical revision of the manuscript for important intellectual content: Tintner, Manian, and Gauthier. Administrative, technical, and material support: Tintner, Manian, and Jankovic. Study supervision: Gauthier and Jankovic.

REFERENCES


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