forming percutaneous tracheostomy should be aware of occult hypercarbia and the potential for cardiovascular or central nervous system complications secondary to this procedure. Monitoring for and taking steps to minimize hypoventilation is well advised during PET.

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Fluoxetine Hydrochloride (Prozac)-Induced Pulmonary Disease*

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We describe a patient who developed progressive dyspnea, lung infiltrates, and restrictive lung disease in association with the antidepressant fluoxetine hydrochloride (Prozac). The pathologic findings were consistent with hypersensitivity pneumonitis. An associated pulmonary phospholipidosis was also noted.

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Key words: drug-induced lung disease; fluoxetine hydrochloride (Prozac); hypersensitivity pneumonitis; phospholipidosis

Fluoxetine hydrochloride (Prozac; Dista Products; Indianapolis) is a widely used antidepressant. Preclinical studies have shown that this amphilic cationic drug can induce pulmonary and/or systemic phospholipidosis in animals, but to our knowledge, this phenomenon has not been reported in humans. Other amphilic cationic drugs, such as amiodarone, can induce pulmonary alveolitis and phospholipidosis in humans and in animals. We describe the development of hypersensitivity pneumonitis in a patient receiving fluoxetine hydrochloride and demonstrate evidence for phospholipidosis.

CASE REPORT

A 62-year-old woman with manic-depressive illness presented to our outpatient center with dyspnea and nonproductive cough. One and a half years earlier, she had been hospitalized for subacute onset of cough, dyspnea, and fevers. She had been taking fluoxetine hydrochloride (20 to 60 mg daily) for 4 months. On the presumption she had acute bronchitis, she was treated with bronchodilators and antibiotics, with slow symptom resolution. While in the hospital, the fluoxetine hydrochloride therapy was discontinued. In the interim 10 months, after other antidepressants failed to control her depression, treatment with these was discontinued and fluoxetine hydrochloride therapy was eventually restarted at 20 mg daily. Within 5 days of restarting the fluoxetine hydrochloride therapy, she developed progressive dyspnea. She denied chest pain, orthopnea, peripheral edema, or fever. Suspecting that the fluoxetine hydrochloride may have triggered her condition, she discontinued treatment with it.

Four weeks later, she presented to us with unrelenting dry cough, but subjectively less dyspnea. A nonsmoker, she denied any other respiratory or cardiac symptoms, fever, arthralgias, skin tightness or eruptions, Raynaud’s phenomenon, or dysphagia. She

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had handled pathology specimens and was exposed to formaldehyde and xylene throughout her career as a pathologist. Her medical history included a hysterectomy, sinusitis 10 years earlier, and “angioneurotic edema” 12 years prior. She had received blood transfusions for gastrointestinal bleeding 6 years earlier.

She had normal vital signs except for a respiratory rate of 24 breaths/min and was tachypneic during conversation. She had diffuse crackles bilaterally throughout both lung fields, most prominently over the lung bases posteriorly. Results of the remainder of the physical examination were normal except for findings of depression.

Results of laboratory tests, including complete blood cell count, antinuclear antibody test, rheumatoid factor assay, serum IgE, HIV screen, and liver function tests, were all within normal limits or negative. Serologic screens for hypersensitivity antigens, including cat dander, Penicillium notatum, Dermatophyton farinae, Aspergillus fumigatus, Cladosporium herbarum, and Dermatophagoides pteronyssinus were all negative.

A plain chest radiograph showed marked volume reduction with crowding of vessels and an ill-defined interstitial pattern bibasilarly without masses, focal infiltrates, pleural effusions, or mediastinal abnormalities (not shown). High-resolution CT of the chest demonstrated diffuse, bilateral “ground glass” changes with increased pulmonary attenuation (Fig. 1). High-resolution CT of the chest demonstrated diffuse, bilateral “ground glass” changes with increased pulmonary attenuation (density). Noted were “islands” of normal attenuation, corresponding to areas of uninvolved lung (Fig 1). Chest radiograph after prednisone therapy demonstrated resolution (not shown).

Pulmonary function tests showed an FVC and FEV1 of 66 and 77% of predicted, respectively. The FEV1 percent was 88 (predicted, 73). Lung volumes and diffusing capacity were moderately reduced, showing a moderate intrinsic restrictive ventilatory defect. A two-dimensional echocardiogram revealed normal left ventricular function. Fiberoptic bronchoscopy was normal. Bronchoalveolar lavage (BAL) of the middle lobe was performed with three 25-mL aliquots of saline solution. Right upper and lower lobe subsegment biopsy specimens were obtained.

The biopsy specimens revealed patchy infiltration of alveolar septa by lymphocytes, neutrophils, and rare plasma cells (Fig 2). The lymphocytes were predominantly T cells (UCHL-1 positive). A few B cells (L26 positive) were also present. Interstitial fibrosis was mild. Several alveolar spaces contained clusters of foamy macrophages, and some pneumocytes demonstrated foamy cytoplasm. Small granulomas and scattered multinucleated giant cells occasionally containing crystalline material were noted in the interstitium and in the wall of some bronchioles. Some bronchioles showed mild lymphocytic exocytosis. Acid-fast, methenamine silver, and periodic acid-Schiff stains showed no acid-fast organisms, fungi, or Pneumocystis carinii. Viral, fungal, mycobacterial, Legionella, and Mycoplasma cultures were negative.

The BAL fluid contained inflammatory cells (75% lymphocytes, 10% macrophages, 12% neutrophils, and 3% eosinophils), small numbers of respiratory epithelial cells, and occasional multinucleated giant cells. Some macrophages contained multiple small cytoplasmic globules of oil-red-O-positive material.

Transmission electron microscopy of tissue and BAL fluid showed cytoplasmic membrane-bound lamellar inclusions of variable size and shape in macrophages (not shown).

**DISCUSSION**

Fluoxetine produces phospholipidosis in animals. Although no such changes have been reported in humans, other similarly amphiphillic drugs such as amiodarone, chlorphentermine, and iprindole produce phospholipidosis in animals and in humans. Reported pathologic findings associated with amiodarone include chronic interstitial pneumonitis, bronchiolitis obliterans with organizing pneumonia, and other changes. Lung lavage profiles reflect a lymphocytic and/or neutrophilic alveolitis. Macrophages with intracytoplasmic lamellar bodies are also described.

A previous communication to the editor by Bass and Colebatch suggested a relationship between fluoxetine and the development of acute respiratory insufficiency in a patient also receiving thyroxine and fluphenazine. A lung biopsy specimen was not obtained, and no inflammatory cells were found on BAL. The illness was attributed to “increased pulmonary capillary leakage” possibly associated with fluoxetine, given that the patient’s condition normalized after discontinuing the drug therapy, and that BAL and serologic study argued against inflammatory or infectious processes. Our patient was receiving only fluoxetine, hydrochloride, and her clinical course and findings were clearly different.
The role of fluoxetine hydrochloride in causing our patient's clinical, physiologic, radiologic, and pathologic abnormalities is secured by the following: (1) histologic and cytologic findings consistent with hypersensitivity pneumonitis; (2) the temporal correlation of symptom onset with fluoxetine hydrochloride, therapy initiation, symptom relief with drug therapy discontinuation, recrudescence with rechallenge, and eventual progression to a chronic disease requiring corticosteroids; and (3) the exclusion of other etiologies.

The lamellar inclusions we observed in macrophages resemble those seen with amiodarone. The clinical importance of these inclusions in the pathogenesis of the patient's pulmonary disease is uncertain, but as with amiodarone, these changes may reflect drug use, and not necessarily drug toxicity.

In view of fluoxetine hydrochloride's increasing use throughout the world, it is important to note the association of a pulmonary disease with this drug. To our knowledge, this is the first report establishing clinicopathologic and roentgenologic documentation of a fluoxetine hydrochloride-associated pulmonary alveolitis. In addition, pulmonary phospholipidosis was found. These two processes may or may not be related. Further studies will be needed to define the relationships between the phospholipidosis-like changes described, drug dosage, and pulmonary symptoms.

REFERENCES

**Acute Myocardial Infarction While Using the Nicotine Patch**

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A 39-year-old man developed an acute myocardial infarction 20 days after starting treatment with nicotine patches. He had not smoked while using the patches. He recovered without complications. Coronary angiography did not reveal coronary stenoses. He had no history of myocardial infarction, hypertension, or diabetes mellitus. Although coincidence cannot be excluded, it is recommended that all patients should be strongly advised not to smoke while using the nicotine patch and to consult a physician if chest pain develops.

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**Key words**: adverse drug reactions; myocardial infarction; nicotine patch; postmarketing surveillance

Smoking increases the risk of cardiovascular events such as acute myocardial infarction, stroke and sudden death, and lung disease. The nicotine transdermal delivery system ("nicotine patch") is a relatively new supportive method for cessation of smoking, and it has an increasing popularity. It was stated that nicotine patches produce a more steady serum level of nicotine, compared with nicotine gum, avoiding peaks in nicotine level. The side effects of the patches in the trials seemed to be relatively modest, with the most frequent side effect being a minor local skin reaction. It was demonstrated that transdermal nicotine has less effect on platelet activation and catecholamine release than does cigarette smoking, and it was suggested that its use in patients with coronary artery disease is safer than cigarette smoking. However, we report on a patient who developed an acute myocardial infarction after starting use of the nicotine patch.

**CASE REPORT**

A 39-year-old fireman had been smoking 50 to 100 cigarettes per day for several years, and he had already made several unsuccessful attempts to quit smoking. The medical history revealed no signs of diabetes mellitus, hypertension, thyroid disease, angina pectoris, or preexisting vascular disease, but 2 years before hospital admission, he was referred with chest pain after a thoracic trauma. Cardiac catheterization at that time demonstrated no abnormalities, and he had never had chest pain since. There was no history of Raynaud's phenomenon, migraine, or Prinzmetal's variant angina. His father had a myocardial infarction at age 60 years. The patient consumed modest amounts of alcohol and coffee. To help him stop smoking, nicotine patches (Nicotinell; Ciba Geigy; Arnhem, The Netherlands) with a dose of 21 mg (20 cm²) per patch were prescribed. He used no other drugs.

He successfully stopped smoking, but 20 days after starting treatment with the nicotine patches, several hours after administrating the patch, he developed severe substernal chest pain, radiating to the left shoulder with subsequent sweating and nausea without vomiting. He presented to the emergency ward. On admission, he was normotensive (140/80 mm Hg), had normal peripheral pulses, and had no signs of cardiac failure. However, ECG showed an acute transmural inferior myocardial infarction with ST elevation in the leads II, III, aVF and ST depression (partly reciprocal) in the leads I, aVL, V2, and V3 (Fig 1). He was treated with intravenous thrombolysis. Creatine kinase level raised to a maximum of 3,277 U/L (normal, <100 U/L). During the next days, the patient recovered without major complications. He was discharged from the hospital in good clinical condition.

Several weeks after discharge from hospital, an exercise thallium 201 myocardial scintigraphy was performed. The patient reached a maximal work load of 200 W, with a normal rise in heart rate and blood pressure. He did not experience anginal pain at any