Hypersensitivity Pneumonitis Due to Venlafaxine

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Venlafaxine is a selective serotonin, noradrenalin, and dopamine reuptake inhibitor. Although side effects are rare, venlafaxine has very occasionally been associated with hypersensitivity pneumonitis. We report the case of a 61-year-old woman diagnosed with depressive disorder and treated with venlafaxine (Dobupal) at a dose of 150 mg/d for 18 months. When depression worsened, the dose was increased to 255 mg/d. Three weeks later she complained of nonproductive cough, shortness of breath with moderate effort, and asthenia. Clinical and radiologic findings, lung function, bronchoalveolar lavage, and histology of lung biopsies all indicated a diagnosis of hypersensitivity pneumonitis. Other causes were ruled out and venlafaxine was discontinued. Clinical, radiologic, and lung function findings then resolved without the use of corticosteroids or nonsteroid immune modulators. All findings were normal on follow-up after 3 months.

Key words: *Hypersensitivity pneumonitis. Venlafaxine. Adverse effects, drugs.*

Neumonitis por hipersensibilidad debida a venlafaxina

La venlafaxina es un antidepresivo que inhibe de forma selectiva la recaptación de serotonina, noradrenalina y dopamina. Los efectos secundarios son infrecuentes y excepcionalmente se ha asociado a neumonitis por hipersensibilidad. Describimos el caso de una mujer de 61 años diagnosticada de síndrome depresivo y tratada con Dobupal® (venlafaxina), a dosis de 150 mg/24 h, desde hacía 18 meses, que presentó un deterioro de su enfermedad, por lo que se incrementó la dosis de venlafaxina hasta 225 mg/día. Tres semanas después desarrolló síntomas de tos no productiva, disnea a esfuerzos moderados y astenia. El cuadro clinicorradiológico, los hallazgos en la función pulmonar, el lavado broncoalveolar y la histología de las biopsias pulmonares eran indicativos de neumonitis por hipersensibilidad. Se descartaron otras etiologías y se retiró la venlafaxina sin utilizar corticoides ni otros inmunomoduladores, con lo que desaparecieron tanto la clínica como los hallazgos radiológicos y funcionales, que se normalizaron a los 3 meses.

Palabras clave: *Neumonitis por hipersensibilidad. Venlafaxina. Reacción adversa a drogas y fármacos.*

Introduction

Venlafaxine is an antidepressant that selectively inhibits the reuptake of serotonin, noradrenalin, and dopamine without triggering significant muscarinic or α-adrenergic effects; it is metabolized in the liver and both metabolites and unmetabolized drug are cleared by the kidneys.[1,2] Adverse effects are uncommon: anorexia, diarrhea, insomnia, nausea, nervousness, sleepiness, sweating, arrhythmias, and hypertension have been described in fewer than 3% of patients.[1,2] Pulmonary toxicity is considered rare, though a few cases of asthma,[3] pulmonary infiltrates with eosinophilia,[4,5] or interstitial pneumonitis[6,7] have been reported.

Although hypersensitivity pneumonitis is usually associated with inhaling organic substances and certain industrial chemical products, in recent years it has also been linked with certain drugs.[8,9] We report the case of a woman diagnosed with depressive disorder who developed a nonproductive cough and dyspnea at rest after her dosage of venlafaxine was increased. Radiologic, functional, and histologic findings indicative of hypersensitivity pneumonitis were also noted. All signs and symptoms disappeared when the drug was discontinued, and the clinical picture could not be explained by any other cause.

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Case Description

The patient was a 61-year-old woman, an ex-smoker (20 pack-years) with no known allergies who was diagnosed with depressive disorder with psychotic symptoms and treated for 18 months with venlafaxine (Dobupal) at a dose of 150 mg/d. Six months before consulting us, lormetazepam (Loramet) and olanzapine (Zypresa) were added at dosages of 5 mg/d because the patient was experiencing paranoia. When the symptoms persisted, venlafaxine was increased to a dosage of 225 mg/d. Six weeks later the patient complained of nonproductive cough, shortness of breath with moderate effort, and asthenia, all of which had worsened during the previous 3 weeks. On physical

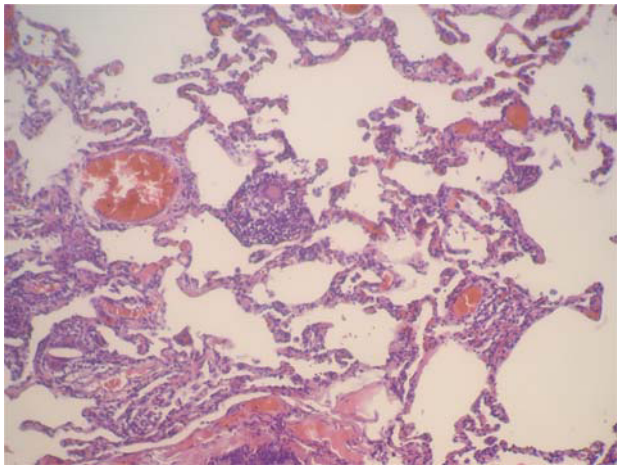

Figure 1. Interstitial pneumonitis without fibrosis of the alveolar wall (hematoxylin-eosin, original magnification ×60).

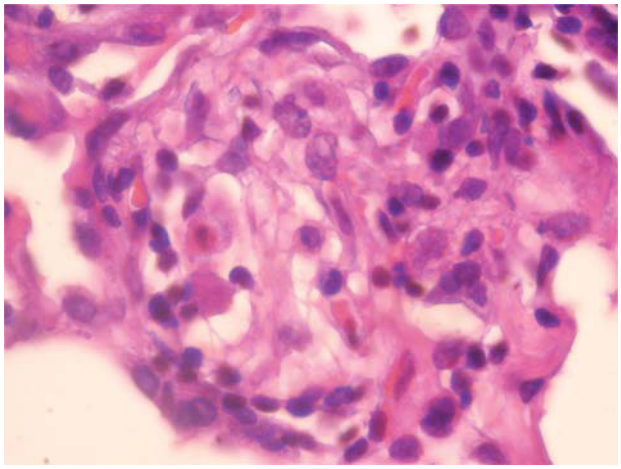

Figure 2. Poorly defined epithelioid granuloma in an alveolar septum (hematoxylin-eosin, original magnification ×1300).

examination, the patient had no fever and blood pressure was 130/85 mm Hg; heart rate, 70 beats/min; and respiratory rate, 22 breaths/min. Auscultation detected rales in the middle and lower zones of both lung fields but no other relevant findings.

Arterial blood gas analysis breathing room air (inspired oxygen fraction, 21%) showed a pH of 7.47, PaO_2 of 66 mm Hg, $PaCO_2$ of 36 mm Hg, and bicarbonate concentration of 26 mEq/L. A blood workup included a coagulation study, which showed a white cell count of 6100/µL (35% neutrophils, 2% eosinophils, and 55% lymphocytes); erythrocyte sedimentation rate of 17 mm in the first hour; angiotensin-converting enzyme concentration, 91 U/mL; rheumatoid factor, 235 U/mL; C-reactive protein, 10 mg/L, and circulating immunocomplex, 5.7 µg/mL. Blood parameters for coagulation, general biochemistry, immunoglobulins, autoantibodies, and tumor markers were all within normal ranges. Blood cultures, urinary antigen testing for *Legionella pneumophila* and *Streptococcus pneumoniae*, serology for atypical microorganisms and respiratory viruses, precipitin testing for bird antigens and fungi, and the Mantoux test were all negative. Sputum bacteriology and cytology gave no relevant findings. An electrocardiogram and echocardiogram revealed no anomalies. Skin tests against a battery of aeroallergens were negative. A chest radiograph revealed a ground-glass pattern and zones with micronodular images. Computed chest tomography showed similar findings, with attenuation at the bases of both lungs and enlarged lymph nodes of 1 cm or less. Lung function tests clearly showed a restrictive pattern: forced vital capacity (FVC) was 1.85 L (58%), forced expiratory volume in 1 second (FEV_1) was 1.76 L/s (75%), FEV_1/FVC was 95%, peak expiratory flow was 250 L/min (85%), total lung capacity was 3.45 L (73%). Diffusion capacity was not measured although after the patient walked 338 meters in the 6-minute walk test, desaturation was evident: at baseline arterial oxygen saturation was 90% and heart rate was 87 beats/min, whereas at the end of the test arterial oxygen saturation was 85% and heart rate was 115 beats/min.

Fiberoptic bronchoscopy revealed no macroscopic abnormalities; microbiological studies that included cultures and gene amplification techniques to detect *Mycobacterium tuberculosis* and viruses were carried out on the bronchial aspirate and bronchoalveolar lavage fluid. The results were negative. The lavage fluid cell count revealed 45% neutrophils, 5% eosinophils, and 50% lymphocytes comprised of 65% CD2 (T cells), 35% CD4, 30% CD8, 20% CD56 (killer cells), and 1% CD22. Thoracoscopic biopsies showed interstitial pneumonitis with no fibrotic thickening of the alveolar wall, zones of bronchiolitis, epithelioid granuloma, and giant cell cholesterol crystals. These manifestations were suggestive of hypersensitivity pneumonitis (Figures 1 and 2). Suspecting venlafaxine, we substituted mirtazapine but made no changes in the other medication (olanzapine and lormetazepam); no corticosteroids or immunodepressants were prescribed. Fifteen days later, clinical improvement was evident, and computed tomography 3 months after discontinuing venlafaxine showed resolution of all images. Lung function was normal and remained unchanged at 9 months.

Discussion

Venlafaxine is used to treat all types of depression including forms related to social anxiety. The drug is metabolized primarily by the hepatic cytochrome P450 enzyme (CYP2D6). Its metabolite, O-desmethylvenlafaxine, inhibits the reuptake of serotonin and has a half-life of 11 hours.[1,2] Although pulmonary toxicity due to venlafaxine seems to be rare, as only a few cases have been reported since 2000,[5-7] the true incidence of such toxicity is unknown. Other antidepressants, however, such as the dothiepin tricyclics and imipramine, have been associated with increased incidence of cryptogenetic fibrosing alveolitis[10,11]; the serotonin reuptake inhibitors fluoxetine and paroxetine have occasionally been associated with pulmonary fibrosis, diffuse alveolar damage,[12] and pneumonitis.[13,14] The mechanisms underlying these associations are unknown although some authors have speculated that some associations may be explained as a hypersensitivity reaction of the host to one of the metabolites[6] and/or the presence of certain genetic polymorphisms of the cytochrome P450 present in 5% to 10% of Caucasian populations. Individuals with this mutation have a slower metabolism and show higher serum concentrations of venlafaxine, thereby favoring toxicity.[15,16] However, in contrast to other authors, we found no toxicity in the heart or other organs.

The appearance of our patient's symptoms coincided with an increase in the prescribed venlafaxine dosage, and the clinical, radiological, and histological findings were consistent with the case described by Turner et al[7] although in our case treatment with corticosteroids was unnecessary. The elevated concentration of circulating

immunocomplexes, the evidence of lymphocytosis in both the blood and bronchoalveolar lavage fluid cell counts, and the histological findings pointed to a hypersensitivity mechanism and were consistent with the characteristics of the few cases in the literature to date. Those cases also reported predominantly lymphocytic interstitial infiltrates, bronchiolitis, and nonnecrotizing giant cell granulomas.[6,7] Such symptoms and findings have also been described with other serotonin reuptake inhibitors, such as fluoxetine.[14]

Pichler[8] has proposed a classification of hypersensitivity reactions to type IV drugs. Typing of the reaction would depend on the differential T-lymphocyte profile, the cytosines involved, and the effector mechanism. Although Pichler's studies have been carried out mainly on skin biopsies, he has suggested that the same mechanisms affect other organs, such as lungs, kidneys, or liver. If Pichler's criteria were applied to our patient's clinical and biopsy findings, the type of response would be classified as a delayed type IVa hypersensitivity response, in which type 1 helper T lymphocytes are involved.[17] Capelozzi et al[18] recently developed an experimental animal model to assess pulmonary toxicity due to antidepressant drugs.

Although our patient had begun treatment with venlafaxine 18 months before consulting us, clinical symptoms appeared 2 weeks after the dose was increased, as in other cases.[7] We decided to perform a biopsy owing to the timing of the patient's psychiatric symptoms, the possible side effects of unnecessary treatment with corticosteroids, the small number of reported cases involving venlafaxine, and the possibility of an alternative diagnosis (eg, sarcoidosis). The disappearance of the clinical, radiological, and functional signs after venlafaxine was discontinued, with no change in other treatments or the prescription of anti-inflammatory drugs, immunodepressants, or immunomodulators, indicated that a cause-effect relationship was highly likely. Although we did not re-prescribe venlafaxine for ethical reasons and in accordance with the probability scale of Naranjo et al,[19] we considered that the association of the adverse effects and the drug had been proven.

Drugs are a frequent cause of iatrogenic effects and lead to considerable morbility and mortality. In a study carried out in the United Kingdom, 6.5% of hospitalizations were related to drug reactions and 2% of such patients died—0.15% of all hospitalizations.[20] The number of drugs that are associated with the appearance of infiltrative lung disease has increased notably in recent years, and the severity of the clinical picture is highly variable. Although diagnosis is often difficult, for any patient with infiltrative lung disease the possibility of a drug reaction should be investigated routinely since discontinuing the drug can lead to improvement or even cure, thus avoiding unnecessary treatments.[9,10]

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