Severe nitrofurantoin lung disease resolving without the use of steroids

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ABSTRACT

We report a case of an elderly woman who developed a severe, chronic pulmonary reaction to nitrofurantoin therapy that she had taken continuously for three years to prevent urinary tract infections. The patient was taking no other drug known to cause lung disease but the diagnosis was delayed by failure to recognize the association between nitrofurantoin and adverse drug reactions affecting the lung. When originally seen, the patient was unable to care for herself due to dyspnea. Bronchoscopy with biopsy ruled out other causes of her pulmonary disease. Immediate withdrawal of nitrofurantoin led to substantial, sustained improvement and disappearance of symptoms over several months without administration of corticosteroids. Nitrofurantoin toxicity should always be considered in any person taking that drug who develops bilateral infiltrates.

**KEY WORDS:** Abnormalities, drug hypersensitivity, drug-induced, interstitial, lung diseases

Nitrofurantoin is an antimicrobial drug that is most commonly used as a prophylactic agent against urinary tract infections (UTIs), (long and short-term) and for the treatment of acute or recurrent cystitis. Pulmonary toxicity is a potentially serious and even fatal adverse drug reaction of nitrofurantoin treatment[1-5], and although it occurs infrequently, nitrofurantoin is one of the most common medications associated with lung injury.[6]

**Case History**

A 71-year-old female presented with symptoms of dyspnea on exertion and productive cough with clear sputum that had intensified over the past three years. At the time of the initial visit, she had difficulties with activities of daily living, such as going to the bathroom independently and cooking for herself. She was a retired nurse with no known occupational exposures, previous lung disease and no significant smoking history. She had one dog at home and no other pets. Her only other significant medical problem was chronic urinary tract infections and she had been placed on suppressive therapy with nitrofurantoin, 100 mg, every other day for the past three years. Her other regular medications were omeprazole 20 mg and aspirin 81 mg both given daily.

Physical exam revealed a well developed, well nourished female in mild respiratory distress at rest. Her vital signs were stable and room air oxygen saturation was 95%. Examination of the chest revealed vesicular lung sounds with fine crackles at the bases without wheezes, rales or rhonchi. The remainder of her examination was unremarkable. A chest radiograph [Figure 1] and computerized tomographic scan of the chest [Figure 2] obtained approximately one week before the examination revealed patchy airspace disease and prominent calcified hilar lymphadenopathy. A recent cardiac catheterization performed because of suspicion of heart failure, showed no evidence of coronary artery disease and normal heart function.

An adverse drug reaction to nitrofurantoin was considered and the drug was stopped. However, other conditions were also considered and a bronchoscopy with multiple transbronchial lung biopsies was performed the following week. Pathological evaluation of the biopsy specimens showed organizing pneumonia [Figure 3]. No granulomas, vasculitis or viral changes were appreciated. A Gomori methenamine silver stain was negative for fungal organisms. Pulmonary
function tests were performed three weeks after stopping nitrofurantoin [see inset in Figure 3] and revealed a restrictive pattern of lung function (forced vital capacity (FVC) diminished to 57% predicted, total lung capacity (TLC) of 70% predicted) with a carbon monoxide diffusing capacity (DLco) of 28% of predicted.

The pathologic findings, clinical course and long-time treatment with nitrofurantoin were most consistent with a chronic adverse drug reaction (ADR) to nitrofurantoin and the patient was warned not to restart the medication. Due to her advanced age and history of untreated positive tuberculin skin test, the decision was made to withhold corticosteroid therapy and monitor her clinically. She felt some subjective improvement within one week and after several months, her symptoms markedly improved and the airspace infiltrates seen on her chest radiographs began to clear [Figure 5]. Pulmonary function tests showed normalization of her FVC (rising to over 90% predicted) within five months and more gradual but progressive improvement in her DLco [Figure 4]. She was able to resume her usual activities without cough or dyspnea.

**Discussion**

In two large Swedish surveys, Holmberg et al found that most patients who develop pulmonary reactions to nitrofurantoin are women with a median age of 60 to 70 years of age. Historically, two different types of pulmonary injury are attributed to nitrofurantoin use: acute and chronic. The acute manifestation of this process is the most common and is
thought to be due to a hypersensitivity reaction from the drug. Symptoms that develop after six months of therapy are generally considered to be chronic manifestation of the disease and have been thought to be the result of toxicity rather than hypersensitivity. However, over the past 30 years, there have been case reports that suggest that other types of pulmonary reactions can be caused by exposure to nitrofurantoin. These include pulmonary fibrosis[6-12] and bronchiolitis obliterans organizing pneumonia.[13,14] While the timing and mechanisms of injury are varied, the treatment of chronic pulmonary injury from nitrofurantoin is usually the same: cessation of the drug combined with corticosteroid therapy.

Nitrofurantoin is one of the most common causes of medication-induced lung toxicity and its early recognition and treatment is essential to avoid permanent disability or death. The chronic presentations are often associated with a gradual onset of dyspnea on exertion that can be misdiagnosed as other conditions such as congestive heart failure.

Cessation of nitrofurantoin is recommended in all types of nitrofurantoin-induced lung injury. In one study, acute pulmonary reactions improved within 15 days and about half of the patients were asymptomatic within 24h and 88% within 72h.[8] Recovery from chronic reactions may take from months to a year.[15-17] In chronic reactions, not all patients respond to withdrawal of the drug. In this subset of patients, corticosteroids are sometimes used to lessen the inflammatory response. Even then the damage may be permanent although, in a recently published series of 18 patients, half treated with corticosteroids and half not, most patients recovered.[18]

Our patient appeared to have a chronic nitrofurantoin reaction (Naranjo ADR probability scale of 7=probable)[9] that caused severe incapacitation to the point that she needed assistance in caring for herself. Were it not for her history of a positive tuberculin skin test, we would have administered corticosteroids. However, we elected to stop the nitrofurantoin and watch the patient’s condition closely. Within the first week, she felt improved and serial pulmonary function tests documented reversal of the restrictive impairment. Our experience and other recent case descriptions[14,15,17] suggest that the older classification of nitrofurantoin lung as either acute or chronic, with the latter frequently irreversible, is incomplete and corticosteroids may be less necessary than previously thought. Nevertheless, it remains very important to suspect a drug reaction whenever a patient taking nitrofurantoin develops respiratory symptoms and lung infiltrates.

References

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