

Nitrofurantoin Pulmonary Toxicity: A Brief Review

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Citation

B Vahid, B Wildemore. *Nitrofurantoin Pulmonary Toxicity: A Brief Review*. The Internet Journal of Pulmonary Medicine. 2005 Volume 6 Number 2.

Abstract

Nitrofurantoin is an antimicrobial agent that is commonly used for treatment of recurrent urinary tract infection. Nitrofurantoin pulmonary toxicity can present as an acute, subacute, or chronic respiratory disease. Common manifestations are dry cough, chest pain, dyspnea, and hypoxemia. Skin rash, arthralgia, and abnormal transaminases are occasionally present. Chest imaging shows patchy infiltrates and fibrosis. Treatment includes stopping the medication and occasionally a course of corticosteroid therapy.

INTRODUCTION

Nitrofurantoin is a broad-spectrum antimicrobial agent. Nitrofurantoin is commonly used to treat acute and recurrent urinary tract infection (UTI) in women, and it is an effective chemotherapeutic agent for patients with recurrent UTIs. Eighty five percent of patients who present with nitrofurantoin-associated pulmonary reactions are women. This observation may be related to the fact that women are more susceptible to recurrent UTI^{1, 2}. Nitrofurantoin-associated pulmonary reactions are reported in less than 1% of patients treated with nitrofurantoin. Acute and severe pulmonary toxicity is even less common. In one study acute pulmonary toxicity that required hospitalization occurred only 3 times among 16101 first courses of treatment with nitrofurantoin³. Patients who present acutely are usually younger with median age of 59 years as compared to those with a chronic presentation with median age of 68 years².

NITROFURANTOIN PULMONARY TOXICITY

Various clinical manifestations of nitrofurantoin pulmonary toxicity have been described in the literature:

1. Acute presentation is the most common clinical presentation (83%). The acute reaction is characterized by marked constitutional symptoms including fever, maculopapular rash, arthralgia, and fatigue. Common pulmonary symptoms are dry cough, chest pain, and dyspnea. Peripheral eosinophilia is common. Eosinophilia is often absent initially; becoming more frequent with subsequent episodes or after treatment for several days. Pulmonary reactions to nitrofurantoin do not

appear to be dose related. Eight percent of acute reactions manifest in the first 8 to 9 days and all acute reactions occur within 1 month on nitrofurantoin therapy. Acute reactions may recur in a much shorter period (within 24 hours) following repeated treatment^{4,5,6}. Acute pulmonary toxicity after starting fluconazole in combination with chronic nitrofurantoin has been reported⁷. Acute pulmonary toxicity has been described in patients who showed no pulmonary reaction with previous nitrofurantoin exposures⁸.

2. Subacute presentation have more insidious onset of symptoms, with most reported cases having received nitrofurantoin for periods ranging at least from 1 month to 6 months. Common symptoms include dry cough, dyspnea, low grade fever, and cyanosis. Laboratory findings may show elevated erythrocyte sedimentation rate, increased IgG levels, and increased antinuclear antibody (ANA) titers^{2,4, 5}.
3. Chronic presentation and pulmonary fibrosis is seen in patients on nitrofurantoin therapy for 6 months to 6 years. The usual presenting symptoms are progressive dyspnea and dry cough over weeks to years^{9,10,11}.
4. Fulminant pulmonary hemorrhage presenting with hemoptysis and respiratory failure has also been described^{12,13}.

LABORATORY FINDINGS AND BRONCHOALVEOLAR LAVAGE

Table 1 summarizes the laboratory findings in acute and chronic nitrofurantoin pulmonary toxicity. Although bronchoalveolar lavage (BAL) is helpful to exclude infectious etiologies of pulmonary disease, BAL findings in nitrofurantoin-associated lung injury are nonspecific^{2,3,4,5}.

PATHOLOGY

Pathologic findings of acute nitrofurantoin pulmonary toxicity include mild interstitial inflammation, interstitial infiltration of eosinophils, reactive type II pneumocytes, alveolitis, fibrinous alveolar exudates, focal hemorrhage, and vasculitis. Characteristic pathologic finding in chronic nitrofurantoin pulmonary toxicity are diffuse interstitial fibrosis, vascular sclerosis, fibrosis and thickening of the alveolar septa, interstitial inflammation, and bronchiolitis obliterans with organizing pneumonia^{2,3,4, 14,15,16} (Figure1). Desquamative interstitial pneumonia, hypersensitivity pneumonitis, and giant cell interstitial pneumonia have been rarely reported in nitrofurantoin lung toxicity^{17, 18}.

RADIOGRAPHIC FINDINGS

Parenchymal changes due to nitrofurantoin pulmonary toxicity are almost always bilateral and are localized predominantly in the lower lung zones on chest radiographs (Figure2). Although unilateral pleural effusions may be accompanied by parenchymal changes, these findings are rare. High resolution computed tomography (CT) scan of the chest may show ground glass opacities, patchy consolidation, and subpleural irregular linear opacities (Figure3)^{11, 16, 19}. Reticular pattern and traction bronchiectasis are also commonly seen in chronic nitrofurantoin toxicity. Although widespread reticular pattern and associated distortion of the lung parenchyma commonly means established and irreversible fibrosis, resolution of these changes have been observed after 6 weeks to 1 year after withdrawing the drug²⁰.

PULMONARY FUNCTION TESTING

The typical findings are decreased total lung capacity (TLC), forced vital capacity (FVC), and single-breath carbon monoxide diffusion capacity (DLCO). Although DLCO is always reduced, normal lung volumes may be seen^{14, 16, 20}.

RADIONUCLIDE SCANNING

Nitrofurantoin-induced pulmonary toxicity results in inflammation in lung parenchyma. Gallium-67 citrate lung scintigraphy is highly sensitive test for the detection of

pulmonary inflammation. Gallium scans has been used for early detection of nitrofurantoin pulmonary toxicity²¹. Ventilation-perfusion lung imaging may also show a transient reverse ventilation-perfusion mismatch in acute nitrofurantoin lung toxicity. These changes are usually resolved after 24 to 48 hours after stopping the medication^{22, 23}.

COMBINED LUNG AND LIVER TOXICITY

Patients with chronic pulmonary nitrofurantoin toxicity may also present with chronic hepatitis or abnormally elevated hepatic transaminases. Chronic hepatitis in these patients is associated with positive antinuclear and anti-smooth-muscle antibodies^{24, 25}.

PATHOGENESIS

The mechanism of pulmonary toxicity due to nitrofurantoin is not known. Several mechanisms have been suggested based on clinical, experimental, and animal studies:

1. Direct injury of lung parenchymal cells through oxidant mechanisms^{26, 27}.
2. Nitrofurantoin-induced injury is accelerated in the presence of hyperoxia^{27, 28}.
3. Nitrofurantoin-stimulated lymphocytes mediated alveolar epithelial injury^{29, 30}.
4. Pulmonary endothelial cell injury³¹.
5. Immune-complex mediated reactions¹⁴.
6. Hypersensitivity reactions²⁰.

TREATMENT

After stopping nitrofurantoin therapy, about 47% of patients with acute pulmonary reaction are asymptomatic after one day, 88% within 3 days, and almost all patients after 2 weeks. Recovery in patients with subacute or chronic reaction may take from 2 weeks to 3 months. Pulmonary fibrotic changes may persist in about 60% of these patients.

The role of corticosteroids has not been well described, however, in patients with respiratory symptoms or hypoxemia a trial of corticosteroids may be helpful^{2,3,4,5,6}.

MORTALITY

In one study (1966-1976) mortality among 398 patients with acute nitrofurantoin-associated pulmonary toxicity was only 0.5%. In the same study, the mortality associated with

chronic pulmonary toxicity among 49 patients was higher (8%)^{2,3,4}.

Figure 1

Figure 1: Transbronchial biopsy specimen showing bronchiolitis obliterans organizing pneumonia secondary to treatment with nitrofurantoin (hematoxylin and eosin, 200X).

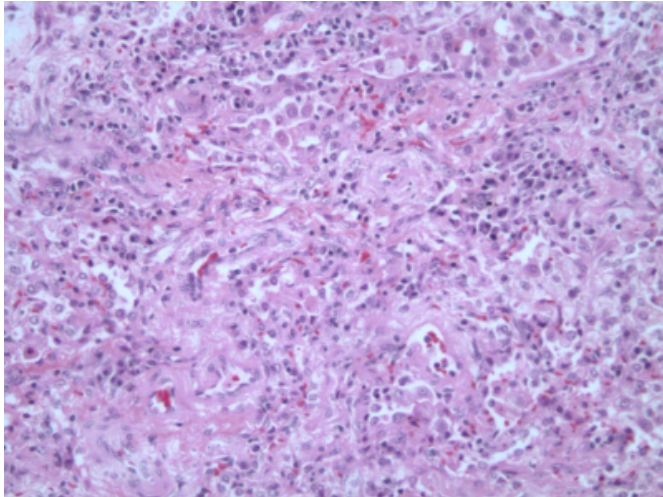


Figure 2

Figure 2: Chest radiograph showing bilateral lower lobe infiltrates in a patient with nitrofurantoin-associated pulmonary toxicity.



Figure 3

Figure 3: CT scan of the chest showing bilateral peripheral patchy consolidations and ground-glass opacities in nitrofurantoin-associated pulmonary toxicity.

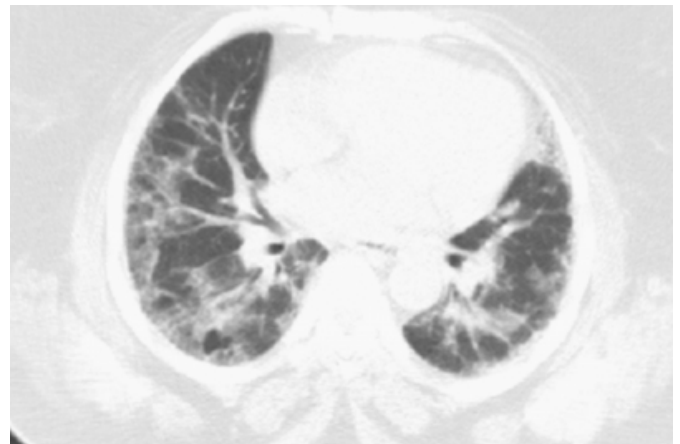


Figure 4

Table 1: Laboratory findings in acute and chronic nitrofurantoin pulmonary toxicity.

	Acute	Chronic
Peripheral Blood Eosinophils>5%	83%	44%
WBCs>9,000/mm ³	52%	15%
Elevated Transaminases	23%	37%
Elevated IgG	30%	80%
ANA (titer>1/10)	25%	60%

ANA: Antinuclear Antibody, WBC: White Blood Cell

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