CASE REPORT

Nitrofurantoin-Induced Pulmonary Reaction Involving Respiratory Symptoms: Case Report

Zahra Kanji, Victoria C H Su, and Raj Mainra

INTRODUCTION

Nitrofurantoin is an antimicrobial agent that is commonly used to treat urinary tract infections. It may also be used prophylactically for patients with recurrent urinary tract infection. Several cases and various clinical manifestations of pulmonary reactions to nitrofurantoin have been described in the literature.[1] Early recognition of such reactions may prevent disability and death.[2] This article describes a patient with an acute pulmonary reaction, specifically bronchiolitis obliterans organizing pneumonia (BOOP), which occurred after exposure to nitrofurantoin. The patient required intubation, and the condition was responsive to withdrawal of the drug followed by steroid therapy.

CASE REPORT

An 82-year-old man presented with worsening shortness of breath and nonproductive cough of new onset over the previous 6 days.* He had no other symptoms of an upper respiratory infection. His medical history was significant for mild cognitive impairment, gastroesophageal reflux, benign prostatic hyperplasia requiring transurethral prostatic repair, and remote cholecystectomy. Cystitis had been diagnosed 15 days before admission and was initially treated with trimethoprim 100 mg twice daily. Five days later, he was switched to nitrofurantoin 100 mg twice daily because of lack of improvement with the original drug. After the first 7-day course of nitrofurantoin therapy, the patient immediately began a second course of nitrofurantoin with a projected duration of 7 days. The patient presented to hospital 4 days after starting the second course (i.e., 11 days after initiation of nitrofurantoin therapy). He reported that his shortness of breath had begun roughly 5 days after initiation of nitrofurantoin. He had no known drug allergies and no history of smoking. He was taking only one other medication before admission, esomeprazole 40 mg daily, and he had been taking this drug for about 9 months.

On admission, the patient's blood pressure was 143/68 mm Hg, pulse was 102/min, and respiratory rate was 30/min. Because oxygen saturation was only 77%–80% on 4 L/min oxygen via nasal prongs, the patient was switched to high-flow oxygen. His work of breathing was increased, as indicated by supraclavicular indrawing, a tracheal tug, and paradoxical abdominal breathing. He also had signs of peripheral cyanosis. There were no signs of ankle edema, leg swelling, or elevated jugular venous pressure. He had slightly decreased lung sounds in the right upper lobe and diffuse crackles bilaterally. He denied decreased appetite, weight loss, night sweats, fever, or chills.

A complete blood count showed elevation of white blood cells (13.4×10^9/L; normal 4×10^9/L to 11×10^9/L), neutrophilia (neutrophil count 11.3×10^9/L), low hemoglobin (116 g/L; normal 135–170 g/L), and platelet count within normal range (353×10^9/L; normal 150×10^9/L to 400×10^9/L). There was no evidence of peripheral eosinophilia. Urinalysis showed a small amount of protein, but the urine was negative for red blood cells, white blood cells, and nitrites. Concentrations of liver enzymes, serum creatinine, electrolytes, and troponin were normal. Electrocardiography showed normal sinus rhythm and no evidence of myocardial ischemia. No other cardiac investigations were performed. Chest radiography showed diffuse interstitial infiltrates bilaterally, with slightly more infiltrates in the right upper lobe and small lung volumes. Arterial blood gas testing on admission yielded the following results: pH 7.45, partial pressure of carbon dioxide 34 mm Hg, partial pressure of oxygen 48 mm Hg, bicarbonate 23 mmol/L, and oxygen saturation 82%. Computed tomography (CT) of the chest demonstrated diffuse ground-glass opacification with

*The patient's consent was not obtained for publication of this case report. To protect the privacy of the individual and his family, all unique identifying information not pertinent to the case has been omitted from this report.

marked consolidative changes in both upper and lower lung zones. Small bilateral pleural effusions were also present. Markers for autoimmune disease, including antinuclear antibody, antineutrophilic cytoplasmic antibody, and rheumatoid factor, were absent.

Nitrofurantoin-induced lung disease was suspected on the day of admission, and the drug was discontinued. Corticosteroid therapy (methylprednisolone 100 mg IV twice daily) was initiated. After 5 days, the dose of methylprednisolone was decreased to 50 mg IV twice daily, and tapering continued over the next 5 days, after which the patient began a maintenance dose equivalent of prednisone 40 mg daily. Empiric treatment for community-acquired pneumonia (piperacillin–tazobactam 3.375 g IV every 6 hours) was started and then stopped on day 3. Moxifloxacin 400 mg daily was added to the regimen (starting on the same day as piperacillin–tazobactam) for additional atypical coverage to complete a treatment course of 8 days. Oxygen was initially administered by nasal prongs, but increasing oxygen requirements necessitated a change to high-flow oxygen, followed by intubation on day 2.

Bronchoscopy, which was performed after intubation, revealed features consistent with BOOP (aggregation of histiocytes, focal proliferation of fibrous tissue, and type II pneumocyte hyperplasia). Fungal and Ziehl-Neelsen staining yielded negative results, and no malignant cells were observed. Culture of blood, sputum, and bronchial washings also yielded negative results. Nitrofurantoin-induced BOOP was diagnosed on the basis of CT and bronchoscopy findings and the timing of symptom onset in relation to initiation of nitrofurantoin treatment.

The patient was extubated on day 8 after admission and was transferred to the general medicine ward on day 13. His in-hospital course was complicated by gastrointestinal bleeding secondary to gastric erosions. He was discharged to home without complications after 25 days on the general medicine ward. At outpatient follow-up 1 month later, the patient was doing well. He was still short of breath on exertion but was able to walk 1 or 2 blocks and could climb a flight of stairs (dyspnea level 3, according to the Breathlessness Scale of the UK Medical Research Council[3]). He no longer required oxygen and was taking prednisone 40 mg daily with a plan to taper the dose, for a total duration of prednisone therapy of 3 months. At the time of writing (3 months after discharge), pulmonary function tests and follow-up chest radiography were pending.

DISCUSSION

Pulmonary reaction secondary to nitrofurantoin is a potentially serious, even fatal, adverse drug reaction.[1,4] Both acute and chronic forms of nitrofurantoin-induced pulmonary injury have been reported. The estimated incidence of the acute reaction is less than 1%,[1] and those affected are typically relatively younger women (age range 40 to 50 years).[5] Acute pulmonary reactions occur within 1 month of initiating nitrofurantoin therapy, and about 8% of cases present in the first 8 or 9 days.[1] Acute reactions may recur more rapidly after repeated courses of therapy with this drug.[1]

The clinical presentation of nitrofurantoin-induced pulmonary injury is variable, making diagnosis a challenge. The acute presentation is characterized by fever, maculopapular rash, arthralgia, and fatigue, in addition to dry cough, chest pain, and dyspnea. Peripheral eosinophilia is also common.[1]

Chronic reactions are reportedly 10 to 20 times less frequent than acute reactions, and they tend to affect elderly patients.[5] Chronic pulmonary reaction is characterized by progressive dry cough and dyspnea over weeks to years and often occurs in patients who have been taking nitrofurantoin for 6 months or longer.[1]

In addition to these acute and chronic forms of reaction, there have also been reports of pulmonary hemorrhage, pulmonary fibrosis, and BOOP occurring in association with nitrofurantoin.[1,6-9] BOOP is an inflammatory lung disease involving both the distal airways and the alveoli. It is characterized by deposition of granulation tissue in the bronchiolar lumens, alveolar ducts, and alveoli, and by infiltration of mononuclear cells and foamy macrophages in the interstitial tissue and air space.[10,11] Common clinical manifestations of BOOP include nonproductive cough, dyspnea, fever, malaise, weight loss, and hypoxemia.[10] There are several known causes of BOOP, including drug-related causes, and nitrofurantoin-related BOOP has been reported.[1,6-9] According to available case reports, nitrofurantoin-induced BOOP is associated with long-term therapy ranging from 6 months to 4 years and is often characterized by delayed onset of symptoms.[6-9,12]

In the case reported here, the score of 5 on the Naranjo Adverse Drug Reaction Probability Scale[13] indicated that the patient's BOOP was probably related to the use of nitrofurantoin. The patient had a 6-day history of nonproductive cough and dyspnea before presenting to the hospital with hypoxia and had received a total of 11 days of nitrofurantoin therapy at the time of presentation. Early presentations of respiratory symptoms secondary to nitrofurantoin therapy have been reported[4,14,15]; however, this appears to be one of the earliest reported presentations of BOOP secondary to nitrofurantoin. The patient was also taking esomeprazole before admission; however, this drug has not been associated with pulmonary adverse effects. Co-trimoxazole (trimethoprim–sulfamethoxazole) has been associated with acute interstitial lung disease or pneumonia, but BOOP has not been reported.[16] It is unlikely that the patient's symptoms were secondary to trimethoprim, as he had received only a 5-day course of this drug, and the onset of his shortness of breath began 5 days after discontinuation of trimethoprim therapy.

The findings of radiography, CT, and bronchoalveolar lavage in cases of nitrofurantoin-associated lung injury are

typically nonspecific. Nitrofurantoin-induced pulmonary changes are almost always bilateral and are localized primarily to the lower lung zones.[1] Bilateral patchy alveolar infiltration and linear opacities occurring at the bases of the lung, as revealed by chest radiography, are suggestive of BOOP. The CT findings of BOOP include ground-glass opacification in the subpleural or peribronchovascular space and bilateral basal air-space consolidation.[11] The radiographic findings and CT scans for the patient described here were consistent with a diagnosis of BOOP. Bronchoalveolar lavage may be helpful in excluding infectious causes of pulmonary disease.[1]

The exact mechanism of nitrofurantoin-induced pulmonary reaction is unknown. Several mechanisms have been proposed, and hypersensitivity to nitrofurantoin is the most probable cause.[17] Pulmonary injury secondary to hypersensitivity reactions is not dose-related. Lymphocytes are activated by nitrofurantoin to produce mediators that promote the release of cytokines, resulting in lymphocytic alveolitis.[17] In contrast, direct toxicity of nitrofurantoin on the lung parenchymal cells is dose-related. This type of toxicity initially manifests as pulmonary edema and diffuse alveolar damage, which is eventually followed by interstitial fibrosis.[17] Other hypothesized mechanisms include nitrofurantoin-induced production of oxidants and immune complex–mediated reactions.[1]

Nitrofurantoin therapy should be withdrawn as soon as pulmonary injury is suspected. The role of corticosteroids has not been well established. Treatment with corticosteroids has shown inconsistent benefit in nitrofurantoin-induced pulmonary reaction; moreover, patients have improved with drug discontinuation alone.[2,18] Nonetheless, a trial of steroids may be helpful for patients with severe respiratory symptoms or hypoxia.[11,18] Given the inflammatory nature of BOOP, corticosteroids are recommended as the mainstay of therapy. Prednisone is administered at a dose of 1 mg/kg daily for the first 1 to 3 months, with a tapering regimen for a total duration of 1 year.[11] It has been suggested that corticosteroid therapy in patients with BOOP may prevent progression to end-stage fibrosis.[7] In most cases, administration of prednisone 30 to 40 mg daily for 5 weeks to 16 months has been associated with positive outcomes: either complete resolution or partial recovery in terms of clinical symptoms and radiographic imaging.[6,8,9,12] In 2 cases, corticosteroid therapy was ineffective, and the patients died from infectious complications. Both of these patients were ex-smokers, and the corticosteroid was tapered rapidly after initial recovery.[7] In the patient described here, methylprednisolone 100 mg twice daily was administered for the first 5 days after discontinuation of the nitrofurantoin. Subsequently, the steroid therapy was tapered down to prednisone 40 mg daily to complete a 3-month course of therapy.

Although rapid improvement in clinical symptoms after withdrawal of nitrofurantoin has been reported,[1] radiographic resolution may lag, and complete resolution of symptoms may take months.[18] The pulmonary injury may be reversible, or the patients may be left with residual lung damage.[6,9,18] The patient described here was generally doing well after discharge but was still experiencing breathlessness on exertion.

CONCLUSIONS

It is important to monitor patients who are taking nitrofurantoin, either for a short course or as long-term prophylactic therapy, for the occurrence of pulmonary adverse effects. Patients should be instructed to report the onset of new cough or shortness of breath. A high index of suspicion for an adverse drug reaction is warranted when patients taking nitrofurantoin experience respiratory symptoms and pulmonary infiltrates. If nitrofurantoin-induced lung injury is suspected, re-exposure to nitrofurantoin therapy should be avoided.

References

1. Vahid B, Wildemore BMM. Nitrofurantoin pulmonary toxicity: a brief review. *Internet J Pulmon Med* 2006 [cited 2011 Aug 4];6(2). Available from: www.ispub.com/journal/the_internet_journal_of_pulmonary_medicine/volume_6_number_2_14/article/nitrofurantoin_pulmonary_toxicity_a_brief_review.html
2. Bhullar S, Lele SM, Kraman S. Severe nitrofurantoin lung disease resolving without the use of steroids. *J Postgrad Med* 2007;53(2):111-113.
3. Fletcher CM. The clinical diagnosis of pulmonary emphysema: an experimental study. *Proc R Soc Med* 1952;45(9):577-584.
4. Holmberg L, Boman G, Böttiger LE, Eriksson B, Spross R, Wessling A. Adverse reactions to nitrofurantoin. Analysis of 921 reports. *Am J Med* 1980;69(5):733-738.
5. Tatley M. Pulmonary reactions with nitrofurantoin. *Prescriber Update* 2002 [cited 2011 Aug 4]:23(2):24-25. Available from: www.medsafe.govt.nz/profs/PUarticles/nitrofurant.htm
6. Cameron RJ, Kolbe J, Wilsher ML, Lambie N. Bronchiolitis obliterans organising pneumonia associated with the use of nitrofurantoin. *Thorax* 2000;55(3):249-251.
7. Cohen AJ, King TE Jr, Downey GP. Rapidly progressive bronchiolitis obliterans with organizing pneumonia. *Am J Respir Crit Care Med* 1994;149(6):1670-1675.
8. Fawcett IW, Ibrahim NB. BOOP associated with nitrofurantoin [letter]. *Thorax* 2001;56(2):161.
9. Fenton ME, Kanthan R, Cockcroft DW. Nitrofurantoin-associated bronchiolitis obliterans organizing pneumonia: report of a case. *Can Respir J* 2008;15(6):311-312.
10. Al-Ghanem S, Al-Jahdali H, Bamefleh H, Khan AN. Bronchiolitis obliterans organizing pneumonia: pathogenesis, clinical features, imaging and therapy review. *Ann Thorac Med* 2008;3(2):67-75.
11. Epler GR. Bronchiolitis obliterans organizing pneumonia. *Arch Intern Med* 2001;161(2):158-164.
12. Robinson C, Nyi PP. Probable nitrofurantoin-induced bronchiolitis obliterans with organizing pneumonia. *Am J Health Syst Pharm* 2009;66(21):1919-1922.
13. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30(2):239-245.
14. Sovijärvi AR, Lemola M, Stenius B, Idänpään-Heikkilä J. Nitrofurantoin induced acute, subacute and chronic pulmonary reaction*s. Scand J Respir Dis* 1977;58(1):41-50.

15. Chudnofsky CR, Otten EJ. Acute pulmonary toxicity to nitrofurantoin. *J Emerg Med* 1989;7(1):15-19.
16. Foucher P, Camus P, GEPPI (Groupe d'Études de la Pathologie Pulmonaire Iatrogène). Pneumotox On Line: The drug-induced lung diseases. Dijon (France): University Hospital; [cited 2011 Apr 20]. Available from: www.pneumotox.com/index.php?fich=accueil&lg=en
17. Goemaere NN, Grijm K, van Hal PT, den Bakker MA. Nitrofurantoin-induced pulmonary fibrosis: a case report. *J Med Case Reports* 2008;2:169.
18. Mendez JL, Nadrous HF, Hartman TE, Ryu JH. Chronic nitrofurantoin-induced lung disease. *Mayo Clin Proc* 2005;80(10):1298-1302.

Zahra Kanji, BSc(Pharm), ACPR, PharmD, is a Clinical Pharmacy Specialist—Critical Care, Pharmacy Department, Lions Gate Hospital, North Vancouver, British Columbia. She is also a Clinical Associate Professor, Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia.

Victoria C H Su, BSc(Pharm), ACPR, is a Doctor of Pharmacy candidate, Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia.

Raj Mainra, MD, FRCPC, FCCP, is a Respirologist and Intensivist with the Department of Respirology, Lions Gate Hospital, Vancouver Coastal Health Authority, North Vancouver, British Columbia.

Address correspondence to:
Dr Zahra Kanji
Pharmacy Department
Lions Gate Hospital
231 East 15th Street
North Vancouver BC V7L 2L7

e-mail: Zahra.Kanji@vch.ca