Nitrofurantoin-Associated Acute Pulmonary Toxicity 
A Review of Three Cases 
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INTRODUCTION 
Nitrofurantoin is a synthetic nitrofuran that is used for the prevention and treatment of urinary tract infections (UTIs). Several adverse drug reactions have been associated with nitrofurantoin including gastrointestinal reactions, blood dyscrasias, peripheral neuropathy, and acute and chronic pulmonary reactions. We report three cases of nitrofurantoin-associated acute pulmonary toxicity which required admission to our hospital to illustrate the substantial morbidity associated with this adverse drug reaction. 

CASE 1 
A 44-year-old female with a 24 hour history of urinary frequency was prescribed Macroclantin® (nitrofurantoin) for a suspected UTI. She had an allergy to nitrofurantoin (reaction unknown), but did not recognize the trade name product. She was also reportedly allergic to sulpha, codeine and meperidine, but no details of the allergy were available. Approximately 24 hours after the first nitrofurantoin dose, she presented to the emergency room with nausea, vomiting, diarrhea, right-sided chest tightness, dyspnea, chills, lightheadedness and mild headache. There were no complaints of wheezing, swelling of the tongue or lips, or pruritis. On examination, the patient was afebrile, hypotensive with a recorded blood pressure of 80/50 mmHg, tachycardic at 100 beats/minute, and had a respiratory rate of 16–18 per minute. She had bibasilar crackles, normal heart sounds and a fine, nonpruritic, blanching erythematous total body rash. Chest x-ray (CXR) revealed bilateral small effusions, which initially were thought to be due to fluid overload and lung volume loss. Laboratory values were normal with the exception of elevated leukocytes $15.2 \times 10^9/L$ (Normal: 4–10) (normal eosinophils, elevated neutrophils), urea 8.1 mmol/L (Normal: 3.5–7.0) alkaline phosphatase 95 U/L (Normal: 25–94) and aspartate transaminase 180 U/L (Normal: 7–40). Her serum bicarbonate was low at 20 mmol/L (Normal: 24–31). Blood gases on 50% oxygen by mask were pH 7.37 (Normal: 7.35–7.45), PaCO$_2$ 29 mmHg (Normal: 35–45), PaO$_2$ 124 mmHg (Normal: 70–100), HCO$_3$ 16 mmol/L (Normal: 21–28) and oxygen saturation 99% (Normal: >92%). Urinalysis and 12-lead electrocardiogram (ECG) were normal. The patient was diagnosed with an allergic reaction to nitrofurantoin. Past medical history was noncontributory, and the patient was not on any other medications. In the ER, the patient was treated with subcutaneous epinephrine, intravenous diphenhydramine, and fluids, and transferred to the floor where methylprednisolone 125 mg IV q6h was ordered. Within two days the patient's leukocyte count had decreased, she was ambulating, eating well, and had an oxygen saturation of 92% on room air. On discharge, she was normotensive and her laboratory values had either normalized or were correcting. Unfortunately, the next day the patient returned to the ER with increasing dyspnea, and was found to be in mild congestive heart failure and atrial fibrillation. Significant laboratory findings on second admission included an elevated lactate dehydrogenase 207 U/L (Normal: 88–177), chloride 108 mmol/L (Normal: 95–105), CO$_2$ 32 mmol/L (Normal: 24–31), and leukocytes $12.2 \times 10^9/L$ (Normal: 4–10) with eosinophils of $1.3 \times 10^9/L$. Serum potassium was low at 3.2 mmol/L (Normal: 3.5–5.5). Blood gases on admission were pH 7.53, PaCO$_2$ 32 mmHg, PaO$_2$ 53 mmHg, HCO$_3$ 27 mmol/L, oxygen saturation was 92% on room air.
The patient was treated with furosemide. Within two days, the patient had improved enough to again be discharged home.

CASE 2

A 69-year-old female had been feeling unwell for three days prior to admission. She developed dyspnea and a dry cough which brought her to hospital where she was prescribed cotrimoxazole, then discharged home. Over the following 24 hours, she had increasing dyspnea, fever, chills, sweats and a non-productive cough. This prompted her return and she was admitted to hospital. With further questioning it was discovered that the patient had received nitrofurantoin approximately seven weeks prior which she had discontinued due to the development of a diffuse rash. Unknown to the admitting staff on the previous unit, she had self-administered two doses of nitrofurantoin just prior to the onset of dyspnea several days before. Past medical history was significant for ischemic heart disease, MI, peripheral vascular disease and hypothyroidism. The patient had no history of asthma, pneumonia or tuberculosis, but had been a 1/2 pack per day smoker for many years. Medications on admission included atenolol 100 mg daily, EC ASA 325 mg daily, diltiazem 60 mg three times a day, oxazepam 10 mg at bedtime, levothyroxine 50 mcg, and lithium 300 mg daily. On examination, the patient’s blood pressure was 130/70 mmHg. She was febrile at 38.7°C, tachycardic at 100 beats/minute, and had a respiratory rate of 28–30 per minute. Chest examination revealed dense crackles in both bases and diffuse expiratory wheezes. Her CXR was significant for hyperinflation with a possible infiltrate. Abnormal laboratory values on admission included mildly elevated leukocytes at 10.8 × 10⁹/L, with eosinophils of 0.34 × 10⁹/L, urea of 10.6 mmol/L (Normal: 3.5–7.0), and serum creatinine of 165 umol/L (Normal: 70–120), low albumin of 30 g/L (Normal: 35–50), hemoglobin and hematocrit were decreased at 94 g/L (Normal: 115–160) and 29% (Normal: 35–47) respectively. Urinalysis and thyroid function tests were normal. Blood gases on admission were pH 7.46, PaCO₂ 33 mmHg, PaO₂ 43 mmHg, and HCO₃⁻ 25 mmol/L. In hospital, the patient was started on IV erythromycin and cefuroxime, but there was no significant improvement. A small left-sided effusion and bilateral infiltrates developed on CXR, and a persistent wheeze was noted thus chest medicine was consulted. Pulmonary function testing was ordered demonstrating severe restrictive disease with an FEV₁ of 0.7 L (40% of predicted) and an FVC of 0.83 L (38% predicted) with mild obstruction. Subsequent bronchoscopy found non-specific inflammatory changes and diagnosis of nitrofurantoin pulmonary toxicity was made by chest medicine who prescribed prednisone 50 mg po daily. At this point the patient was afebrile and the eosinophil count was mildly elevated at 0.69 × 10⁹/L. Over the next several days the patient improved and she was discharged by day 11 with a prescription for prednisone. At the time of discharge her blood gases were pH 7.43, PaO₂ 68 mmHg, pCO₂ 41 mmHg, and HCO₃⁻ 27 mmol/L.

CASE 3

An 81-year-old female was admitted to hospital with complaints of decreased energy, weakness, fatigue, progressive dyspnea and pleuritic chest pain of several days duration. She also complained of cough producing white sputum. She denied paroxysmal nocturnal dyspnea, ankle swelling, orthopnea, fever or chills, but had noted a 20 lb weight loss over the past few months. Approximately one week prior to admission, in response to complaints of increased frequency and nocturia, she was prescribed nitrofurantoin without improvement. In addition, the patient was receiving amiloride-hydrochlorothiazide (Moduret®) 1/2 tablet every other day, digoxin 0.25 mg daily and Tylenol #3 as needed. The patient was unaware of any allergies, however no details of a specific IgE sensitized infiltrates are reported.1 Her past medical history was significant for chronic obstructive pulmonary disease and peripheral vascular disease. Her past medical history was significant for chronic obstructive pulmonary disease and peripheral vascular disease. The patient had no history of asthma, pneumonia or tuberculosis, but had been a 1/2 pack per day smoker for many years. Medications on admission included nitrofurantoin 100 mg daily. At this point the patient was afebrile and the eosinophil count was mildly elevated at 0.69 × 10⁹/L. Over the next several days the patient improved and she was discharged by day 11 with a prescription for prednisone. At the time of discharge her blood gases were pH 7.43, PaO₂ 68 mmHg, pCO₂ 41 mmHg, and HCO₃⁻ 27 mmol/L.

DISCUSSION

Several toxic reactions to nitrofurantoin have been reported. Pulmonary reactions, predominantly in 1 in 500 patients, include acute pulmonary disease, chronic pulmonary disease, and hypoproteinemia with respiratory distress.4 The exact mechanism of injury is not defined; however, the reaction is often related to an allergic response and is thought to be mediated by a decrease in circulating IgE levels.5 Several clinical reports have also described a recurrent pattern of sensitized IgE-positive eosinophilic infiltrates and pulmonary symptoms, thus suggesting an allergic reaction to nitrofurantoin.5 However, no details of a specific IgE sensitized infiltrates are reported.1

Toxicity has been reported to occur in patients with various conditions including chronic obstructive pulmonary disease, chronic renal failure, and chronic pulmonary disease. The reaction has been postulated to be related to an allergic response and is thought to be mediated by a decrease in circulating IgE levels.5 Several clinical reports have also described a recurrent pattern of sensitized IgE-positive eosinophilic infiltrates and pulmonary symptoms, thus suggesting an allergic reaction to nitrofurantoin.5 However, no details of a specific IgE sensitized infiltrates are reported.1

Nitrofurantoin is an antimicrobial agent that is commonly prescribed for urinary tract infections. Its use is contraindicated in patients with known hypersensitivity to nitrofurantoin or its components. The drug is associated with a low incidence of side effects, with the most common being gastrointestinal symptoms such as nausea, vomiting, and diarrhea. However, it has been reported to cause an acute pulmonary reaction, characterized by dyspnea, cough, and fever. This reaction is thought to be mediated by an allergic mechanism and is usually reported in patients with a history of asthma or other allergic conditions.7

The peak incidence of nitrofurantoin-induced pulmonary reactions occurs in patients with a history of asthma or other allergic conditions.7 This suggests that patients with a history of allergy or asthma may be at increased risk for developing these reactions.8 However, the exact mechanism of injury is not clearly defined. The reported cases in the literature suggest that nitrofurantoin-induced pulmonary reactions may be related to an allergic response, with a decrease in circulating IgE levels being a possible contributing factor.5

Nitrofurantoin-induced pulmonary reactions are rare and usually occur in patients with a history of asthma or other allergic conditions. The exact mechanism of injury is not clearly defined, but a decrease in circulating IgE levels has been implicated.5 However, the reported cases in the literature suggest that nitrofurantoin-induced pulmonary reactions may be related to an allergic response, with a decrease in circulating IgE levels being a possible contributing factor.5

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DISCUSSION

Several toxicities have been associated with nitrofurantoin's use. While the focus of this report is acute pulmonary toxicity, which has been reported to occur in 1 in 5000 exposures, other toxicities including chronic pulmonary fibrosis have been documented in the literature.

The exact mechanism of the acute pulmonary damage induced by nitrofurantoin has not been clearly defined; however, several theories have been postulated to explain the clinical manifestations. An immune response appears to be the most likely explanation due to the association with fever and eosinophilia and recurrence within hours after rechallenge in previously sensitized individuals. Rapid clearing of the pulmonary infiltrates after withdrawal of the drug has also been reported. It has been suggested that Type III (immune complex mediated), Type IV (cell mediated) and Type II (cytotoxic) mechanisms are all potential explanations for the reactions. Interestingly, since no nitrofurantoin-specific IgE antibodies have been found, true anaphylaxis is unlikely. One non-immunologic theory for acute pulmonary toxicity involves the formation of nitrofurantoin free-radical metabolites. In animals, nitrofurantoin produces a superoxide which may be responsible for lung damage.

Toxicity is generally seen within 3–8 days after initiation of treatment, however with subsequent treatment, symptoms appear much more quickly and may be seen within 1–12 hours. Typical symptoms include fever, dyspnea, chills and cough (dry or productive). Chest pain is common and may be pleuritic, although no nitrofurantoin-specific IgE antibodies have been found, true anaphylaxis is unlikely. One non-immunologic theory for acute pulmonary toxicity involves the formation of nitrofurantoin free-radical metabolites. In animals, nitrofurantoin produces a superoxide which may be responsible for lung damage.

Our patients all demonstrated notable similarities to both documented case reports and to summary literature. As previously described, onset of symptoms occurs more rapidly in patients with previous adverse reactions to nitrofurantoin. In our series, patients who had been previously sensitized and who had a well established reaction to nitrofurantoin (Cases 1 and 2) presented to hospital one and three days after starting the drug, while the patient in whom the reaction was less well established (Case 3) presented at day 7. The first case is somewhat questionable due to the second admission of congestive heart failure. The nitrofurantoin literature does state that a bilateral interstitial
pattern resembling pulmonary edema may be seen on CXR, potentially confusing the diagnosis in this patient. The presence of eosinophils on the second admission for Case 1 would support the hypersensitivity reaction. In Case 2, the pulmonary function testing demonstrated predominantly restrictive disease along with mild obstructive disease. While restrictive disease is expected, obstructive disease is not usually seen with nitrofurantoin-induced pulmonary toxicity. A very plausible explanation is the patient's significant smoking history which very likely contributed to a longitudinal deterioration of lung function. As well, it is noteworthy that in all of our cases a history of adverse reaction due to nitrofurantoin was noted. Despite that, both the physician prescriber and the pharmacist dispenser failed to detect or react to this prescription. The considerable morbidity and associated costs associated were clearly preventable.

Nitrofurantoin-induced acute pulmonary toxicity has been suggested to occur once in every 5000 first administrations. Despite diminishing use of nitrofurantoin, three potential cases with considerable morbidity have been identified. In light of this, pharmacists should be aware of the potential for pulmonary toxicity from nitrofurantoin.

References