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).[1] Several adverse drug reactions have been associated with nitrofurantoin including gastrointestinal reactions, blood dyscrasias, peripheral neuropathy, and acute and chronic pulmonary reactions.[2,3] 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 Macrodantin® (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 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 × 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 × 10^9/L (Normal: 4–10) with eosinophils of 1.3 × 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 cortrimoxazole, 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 10.8×10^9/L with eosinophils of 0.34×10^9/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 94g/L (Normal: 115–160) and 0.29 (Normal: 35–47) respectively. Urinalysis and thyroid function tests were normal. Blood gases on admission were pH 7.46, $PaCO_2$ 33 mmHg, PaO_2 43 mmHg, and HCO_3 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 FEV 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 0.69×10^9/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, pO_2 68 mmHg, pCO_2 41 mmHg, and HCO_3 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, but review of past health records revealed a reported allergic reaction to nitrofurantoin, however no details were available. Her heart rate was 67 and irregularly regular, blood pressure was 105/70 mmHg, respiratory rate 18 per minute, and she was afebrile. Heart sounds were normal and coarse diffuse crackles were heard on auscultation throughout the lung. Her CXR showed small bilateral pleural effusions and a mild interstitial pattern. An ECG showed second degree heart block with a heart rate of 67. All laboratory parameters except for leukocytes 17.1×10^9/L (Normal: 4–10), urea 10.8 mmol (Normal: 3.5–7.0), creatinine 121 µmol/L (Normal: 70–120) and albumin 33 g/L (Normal: 35–50) were normal. Blood gases on admission were pH 7.4, PaO_2 46 mmHg, $PaCO_2$ 39 mmHg and CO_3 25 mmol/L with an oxygen saturation of 82% on room air. Nitrofurantoin and digoxin were discontinued. The patient had low grade fevers (up to 38°C) for the first few days. White blood cell count normalized with 6% eosinophils. Oxygenation improved with time with a PaO_2 of 77 mmHg being recorded on day 6 of hospital stay. The patient was discharged home on that day.

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,[4] other toxicities including chronic pulmonary fibrosis have been documented in the literature.[2]

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.[5] 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.[5] 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.[5]

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.[3] Typical symptoms include fever, dyspnea, chills and cough (dry or productive). Chest pain is common and may be pleuritic, although it has also been described as dull, squeezing or similar to pain experienced during a myocardial infarction. Epigastric or back pain may also be present. A pruritic rash may be experienced by some patients either early or late in the reaction. The physical examination shows a patient in acute distress, tachypneic, tachycardic, usually febrile and sometimes hypotensive. Chest examination usually reveals bibasilar rales and rarely wheezing. The white blood cell count may be normal or high, with a left shift seen early in the episode. Eosinophilia is common, however it is often not evident until the second exposure to nitrofurantoin. Blood gas determinations often show hypoxemia and hypocapnea. Pulmonary function testing demonstrates a decrease in diffusion capacity of carbon monoxide and a mild restrictive pattern, however obstruction is not generally evident unless underlying obstructive lung disease is also present. The CXR classically demonstrates a lower lobe bilateral interstitial pattern which resembles pulmonary edema, however pleural effusions may also be seen.[3–5]

Treatment is supportive including discontinuation of the drug. Patients presenting with more severe symptoms may benefit from additional symptomatic treatment including oxygen, intubation or vasopressors. Steroids, bronchodilators and antihistamines have been used, but the role of these agents is unclear.[3,5]

Cases of nitrofurantoin-induced pulmonary toxicity have been reported in the literature for many years. In 1980, Holmberg et al published an analysis of 921 adverse reactions to nitrofurantoin. The analysis divided the adverse reactions into several categories, with the most frequent adverse reaction being acute pulmonary reactions (43% of all reactions).[2] Jick et al published a study looking at hospitalizations secondary to nitrofurantoin use.[4] Both acute and chronic reactions were reported, however only three were attributed to the acute-onset type. In one case, a 74-year-old woman was admitted to hospital after taking nitrofurantoin for three weeks. She developed dyspnea on exertion and pleuritic back pain which worsened with cough. Her leukocyte count was elevated with a significant left shift and increased eosinophils. A CXR showed bilateral abnormality, which appeared consistent with congestive heart failure. On the fourth day of hospitalization, the chest x-ray had normalized and leukocyte count had lowered. A second case involved a 57-year-old man who had taken nitrofurantoin for 16 days. One day prior to admission, he developed chills, chest pain, nonproductive cough, fever to 39.4°C, tachypnea and mild shortness of breath. The lungs had generalized bibasilar coarse rales. The leukocyte count was elevated with no eosinophilia. The patient improved rapidly and was subsequently discharged with a diagnosis of pleuritis possibly secondary to nitrofurantoin.

Our patients all demonstrated notable similarities to both documented case reports and to summary literature.[2–5] 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.[4] 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

1. Hardman JG, Limbird LE. Goodman and Gilman's — The pharmacological basis of therapeutics. 9th ed. New York: McGraw-Hill, 1996.
2. Holmberg L, Boman G, Bottiger LE, Eriksson B, Spross R, Wessling A. Adverse reactions to nitrofurantoin: analysis of 921 reports. Am J Med 1980;69:733–8.
3. Chudnofsky CR, Otten EJ. Acute pulmonary toxicity to nitrofurantoin. J Emerg Med 1989;7:15–9.
4. Jick SS, Jick H, Walker AM, Hunter JR. Hospitalizations for pulmonary reactions following nitrofurantoin use. Chest 1989;96:512–5.
5. Lauterburn BH, Smith CV, Mitchell JR. Molecular mechanisms involved in drug-induced pulmonary injuries. Sem Resp Med 1980;2:45–50.

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