CASE REPORT

Fatal Nitrofurantoin Lung

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Abstract

Nitrofurantoin is a drug commonly used for urinary tract infections. It acts by damaging bacterial DNA. It is given in dose of 50-100 mg orally and is generally considered a safe drug but has occasionally been known to cause pulmonary toxicity which is usually reversible and only rarely fatal. We present a case of an elderly lady receiving nitrofurantoin for her urinary tract infection who developed sudden acute lung injury to which she finally succumbed within a few weeks.

Introduction

Nitrofurantoin is a drug commonly used for urinary tract infections. It acts by damaging bacterial DNA. There is rapid reduction of nitrofurantoin inside the bacterial cell by flavoproteins (nitrofuran reductase) to multiple reactive intermediates that attack bacterial ribosomal proteins, DNA, and inhibit pyruvate metabolism and other macromolecules within the cell. It is given in dose of 50-100 mg orally and is generally considered a safe drug but has occasionally been known to cause pulmonary toxicity which is usually reversible and only rarely fatal. We present a case of an elderly lady receiving nitrofurantoin for her urinary tract infection who developed sudden acute lung injury to which she finally succumbed within a few weeks.

Case

The patient was a 67 year old female having hypertension, diabetes, and hypothyroidism. She presented with the chief complaints of dyspnoea since 1 week which was of sudden onset and which rapidly progressed to dyspnoea at rest. A week prior to admission, she had a good effort tolerance and could climb 2-3 flights of stairs without difficulty. As her breathlessness worsened, she was admitted to Hinduja hospital for further evaluation and management. On examination, she was afebrile, severely tachypnoeic (Respiratory rate of 38 breaths per minute) and hypoxic with an oxygen saturation by pulse oximetry (SpO2) of 40% while breathing ambient air. She was haemodynamically stable. Auscultation revealed extensive bilateral crackles. Clinically, the differential diagnoses were acute interstitial pneumonia vs. acute hypersensitivity pneumonitis.

A detailed history revealed prolonged nitrofurantoin use for 1 month prior to admission with a similar prolonged course one year earlier. There were no other environmental or occupational allergen exposures.

An X-ray chest done on admission (Figure 1) showed bilateral reticular shadows. A High resolution computed tomography (HRCT) scan of the chest (Figure 2) was done which showed extensive ground glass opacities, interstitial thickening and reticular shadows which suggested hypersensitivity pneumonitis.

Other investigations done were as follows: Blood gas analysis showed pH-7.478, PCO2-25.4; PO2-41.8, bicarbonate-21.1. Complete blood count showed Hemoglobin-10.8 gm%, Platelets- 548000/mcl and Total leucocyte count-17200/mcl. Routine biochemistry was unremarkable. 2D Echo was normal with a Left Ventricular Ejection Fraction of
The working diagnosis was hypersensitivity pneumonitis secondary to nitrofurantoin use. She was started on intravenous methylprednisolone 500 mg for 3 consecutive days. There was marginal improvement and the patient was now able to swallow and speak short sentences at rest and there was reduction in crackles in bilateral interscapular area.

On a non-rebreathing mask (NRBM) with a high flow of 15 litres/minute of oxygen, her SpO2 fluctuated between 85 – 93%. However, after about a week, she had an episode of severe breathlessness and could not maintain SpO2 on NRBM and became cyanotic. She was transferred to the ICU and started on non-invasive ventilation. Initially she required FiO2 of 70% which later increased to 100%. An HRCT scan of the chest (Figure 3) was repeated which showed fibrotic changes with areas of traction bronchiectasis and honeycombing - resembling a usual interstitial pneumonia (UIP) pattern.

Pirfenidone, a novel antifibrotic agent, was started along with N-acetyl-cysteine for its antioxidant properties as oxidative stress has shown to contribute to nitrofurantoin induced lung injury. She continued to deteriorate and expired about a month after hospitalization due to progressive respiratory failure.

**Discussion**

Nitrofurantoin associated pulmonary reactions are reported in less than 1% of patients receiving the drug. The mechanism of nitrofurantoin-induced lung injury is through direct injury of lung parenchymal cells through oxidant mechanisms. Nitrofurantoin also stimulates lymphocyte-mediated alveolar epithelial injury. Pulmonary endothelial cell injury, immune-complex mediated reactions and hypersensitivity reactions are also supposed to contribute to its toxicity. Nitrofurantoin-induced injury is accelerated in the presence of hyperoxia.

The pulmonary reaction can be acute, subacute or chronic. The most common presentation is acute which occurs in more than 80% of the cases. The acute reaction is characterised by dry cough, chest pain and dyspnoea. Constitutional symptoms such as fever, chest pain, fatigue and rash are common. Eosinophilia is usually present. Almost all acute reactions occur within 1 month of starting nitrofurantoin treatment (usually between 3 - 8 days). Subacute presentations have a more insidious onset with most cases having nitrofurantoin exposure ranging 1 - 6 months. Common symptoms include dry cough, dyspnoea, low grade fever and cyanosis. Patients with more than 6 months of exposure usually have a chronic presentation with pulmonary fibrosis. It is usually seen in elderly females. This is usually due to toxicity of increased drug administration rather than a hypersensitivity response.

Broncho-alveolar lavage findings in nitrofurantoin-induced lung toxicity are generally nonspecific. Histopathologic presentations of acute nitrofurantoin pulmonary toxicity include mild...
interstitial inflammation, eosinophilic interstitial infiltration, reactive type II pneumocytes, alveolitis, fibrinous alveolar exudates, focal haemorrhage, 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 organising pneumonia. Rarely presentations include desquamative interstitial pneumonia (DIP), hypersensitivity pneumonitis, and giant cell interstitial pneumonia. Pleural effusions - following both acute and chronic exposure- have also been reported with nitrofurantoin.

High resolution computed tomography scan of the chest may show ground glass opacities, patchy consolidation, and subpleural, irregular, linear opacities. Chronic nitrofurantoin toxicity may show reticular pattern and traction bronchiectasis. 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 drug.

**Treatment**

Stopping the drug is essential. About 47% of the patients with acute reactions are asymptomatic within 1 day of stopping the drug; 88% respond within 2 days and almost all within 3 days. The chronic reactions usually take a few weeks to respond. However, 60% may have residual disease. Role of corticosteroids is not established. They may be useful in severe cases with hypoxaemia. Mortality with acute nitrofurantoin-induced lung injury is usually less than 0.5% of all cases. It is slightly higher at 8% with chronic pulmonary toxicity.

Our patient had an acute presentation (within one month) of nitrofurantoin-induced lung injury in the form of an acute hypersensitivity pneumonitis which was rapidly progressive. She died despite immediate stopping of the drug as well pulses of steroids. The important lesson from this case is to take a careful drug history in all patients with interstitial lung disease.

**References**