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Original Research Paper

Toxicology

A CASE REPORT – NITROFURANTOIN TOXICITY MIMICKING PNEUMONIA

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ABSTRACT

Introduction : This Case report describes lung injury due to Nitrofurantoin use which presents as Interstitial Lung Disease. A 70 yrs old presented with dyspnoea ,fatigue and cough. Previously he was given nitrofurantoin for Urinary tract infection a couple of weeks ago. Chest X-ray has shown patchy and confluent air space shadowing in both mid and both lower zones likely due to bilateral bronchopneumonia. There are no pleural effusions. There is no pneumothorax.

Knowledge of adverse effect is essential for the early recognition and withdrawal of the drug. nitrofurantoin-induced lung disease has a benign course and respond fully despite radiographic evidence of established lung fibrosis.Symptomatic improvement was observed following steroid course soon after stopping Nitrofurantoin. A review information obtained from North American and European pharmacological database identified reports on Nitrofurantoin toxicity. We are reporting a case here demonstrating acute toxicity of Nitrofurantoin approximately 7-9 days after a short course of Nitrofurantoin.

KEYWORDS : Nitrofurantoin toxicity, hypersensitivity reaction, pulmonary toxicity

INTRODUCTION:

Nitrofurantoin is frequently use anti-bacterial agent for UTI, especially in uncomplicated cystitis as per Australian therapeutic guidelines (1). The majority of patients presented with nitrofurantoin pulmonary toxicity are elderly women (2).This could be related to women more susceptible to get urinary tract infections than men. The median age for presentation of this illness is 60 to 70 years (3). The prevalence was decreased from high in 1960 to low in 1980 .However, it is rising again due to popularity of its use as urinary antiseptic (4).This happened mainly due to decreased propensity of collateral damage and minimal bacterial resistance (5).The first case of nitrofurantoin toxicity was published in New England Journal of Medicine 1961 , by Isreal and Diamond identifying nitrofurantoin toxicity in the patient presenting recurrent pneumonia in same segment of lungs by intentional rechallenge by drug (6).Nitrofurantoin can induced acute ,subacute and chronic pulmonary reaction .Acute reaction causes mild interstitial inflammation and eosinophilia .In contrast ,diffuse interstitial pneumonitis is observed in chronic reaction due to nitrofurantoin (7). These reactions may be severe which warrants hospitalisation (8).Bronchiolitis obliterans organising pneumonia and chronic eosinophilic pneumonia has been reported with use of nitrofurantoin (9) (10). Acute reactions characterised by symptoms within days to weeks similar to community acquired pneumonia such as fever, dyspnoea, cough and inspiratory crackles, hypotension, chest pain and hypoxia (11).Chronic reaction is typically slow onset of dyspnoea and dry cough develops over months or years improves subsequently after stopping drug ,although corticosteroids are helpful in severely affected patients (12). Histologically, all forms of pulmonary toxicities manifest wide spectrum of pulmonary tissue reactions (13).Nitrofurantoin toxicity largely under-recognized and mistaken as community acquired pneumonia while patient being treated for urinary tract infections bacteraemia which may lead to prolong use of drug and pulmonary tissue damage such as irreversible fibrosis or granulomatous reaction (14). Life threatening condition causing Haemoptysis following pulmonary haemorrhage and respiratory failure has been reported due to Nitrofurantoin toxicity (15).This indicates alternative treatment for patients who carries recurrent urinary tract infections and cystitis, also adding nitrofurantoin in allergy list to prevent its reuse and close monitoring of pulmonary side effects for patients receiving long therapy is warranted .

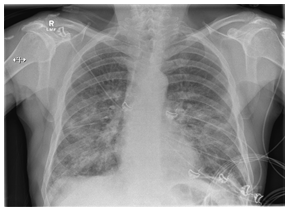
CASE REPORT

A 83 years old independent gentleman, has a background of obstructive sleep apnoea compliant with CPAP, presented with exertional dyspnoea following initiation of Nitrofurantoin for recurrent urinary tract infections.

Onset of symptoms was 6 weeks post nitrofurantoin therapy. There were no infective or other systemic symptoms. He is a non-smoker and worked as a boiler maker in a open pit coal mine where he had asbestos exposure.

His blood tests were unremarkable except CRP was 36 .

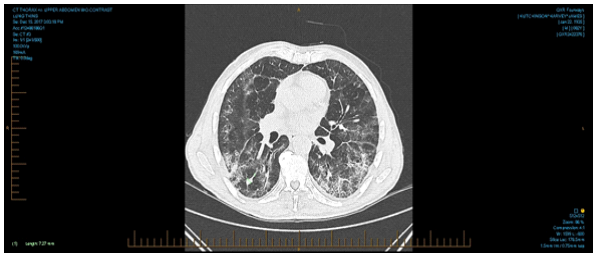
CXR



There is patchy and confluent air space shadowing in both mid and both lower zones likely due to bilateral bronchopneumonia. There are no pleural effusions. There is no pneumothorax.

CT Chest (QLD Xray): Extensive pulmonary interstitial changes with ground glass opacities has appearance suggesting chronic hypersensitivity pneumonitis rather than UIP.

Thickening interlobular, intralobular septa, severity worse in lower lobes. ?early honeycombing posteriorly in RLL. No Mass. Normal LN. No pleural plaques.



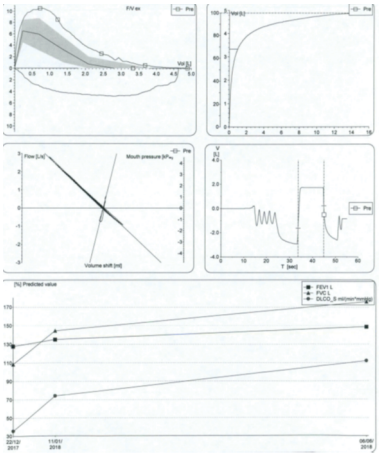
PFT (18.12.17): FEV1 2.9 pre, FVC 3.1 pre, FEV1/ FVC ratio 94, TLC 5.86, DLCO 6.96, KCO 1.51. Reversibility not tested.

6min walk test on RA (22.12.17): Test ceased after 2min and 35seconds (SpO2 sustained <85% and patient complained of lightheadedness). Applied 4LO2 via N.P post test. SpO2 increased to 91% within 1min. O2 decreased to 2LO2 via N.P. SpO2 maintained above 93%. Returned to RIB via attendant propelled W/C

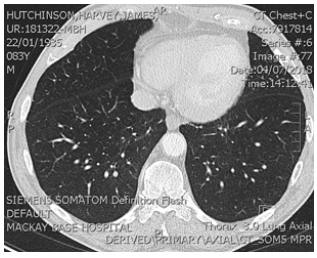
*6min walk test on 2L O2/min (22.12.17): Test Ceased after 4min 30seconds (SpO2 sustained <85% and pt c/o lightheadedness). Required seated rest. SpO2 increased to 90% within 2 mins post test. Lightheadedness resolved.

On prednisolone 50mg PO for 2/52 He was started on Prednisone and continued on this for a few weeks. His lung function initially showed FEV1 of 2.5 (115% predicted), FEVC of 3.10 (93% predicted). His total lung capacity was 5.86 (96% predicted). His corrected diffusion capacity was 1.151 which is 36% of predicted. Following steroid introduction his corrected diffusion capacity has improved to 62% of predicted.

The last lung function has shown normal FEV1 and FVC with some airflow limitation. Total lung capacity is 7.15 which is 123% of predicted along with corrected diffusion capacity normalising.



Repeat CT chest: Has shown near resolution of symptoms.



Echo was normal.

Looking at the whole picture, he had Nitrofurantoin induced pulmonary toxicity with CT proven interstitial changes which are predominantly radicular and interstitial pattern along with some distorted parenchymal architecture which is more consistent with the interstitial pneumonitis. With Nitrofurantoin induced toxicity we see nearly 10 – 30% of patients showed response to corticosteroids usually with a few months of treatment. In this case however complete remission following the use of corticosteroid with both HRCT wise and lung function wise. This patient has shown complete confirmed laboratory recovery from severe Nitrofurantoin induced interstitial lung disease, pulmonary function parameters have also improved.

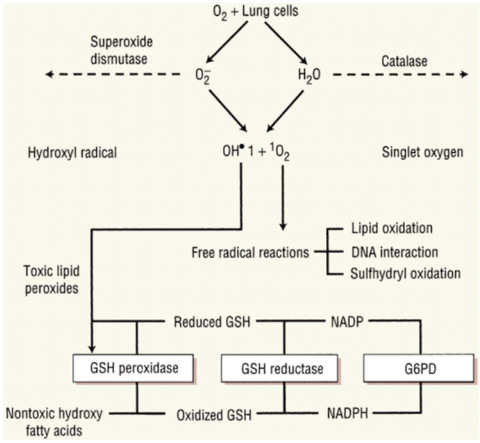
DISCUSSION:

Nitrofurantoin's chemical name: 1-(5-nitrofurfurylideneamino) hydantoin, is first line option for uncomplicated cystitis and is a long term suppressive agent prophylaxis in recurrent UTIs as per Australian Therapeutic Guidelines. Macrodantin is bacteriostatic at low concentration and is bactericidal in vitro at higher concentration. It affects bacterial wall synthesis by inhibiting bacterial proteins, DNA, RNA (16) (17). It is thought to be acute toxicity of Nitrofurantoin through hypersensitivity reaction Type I or III, chronic form through oxygen mediated tissue injury either toxic response or cell mediated response (18). Loffler's syndrome is associated with Nitrofurantoin evident on histology suggestive of peri-vasculitis with eosinophil infiltrates, macrophages and proteinaceous oedema fluid in alveoli. It is also associated with pulmonary fibrosis infrequently(19).

Apart from pulmonary toxicity, Nitrofurantoin is associated with hepatic reaction, impaired renal function, metabolic acidosis, hematolytic anaemia, colitis, carcinogenicity(20).

Pathophysiology behind Nitrofurantoin Lung toxicity is also documented in details following injury due to highly reactive oxygen species and nitrite radicals. One of the cell's key antioxidant such as NADPH get consumed in redox cycling and free radicals forms which causes lipid peroxidation, mitochondrial damage ,apoptosis(21).

Schematic of the interaction of oxygen radicals and the antioxidant system. (GSH, glutathione; G6PD, glucose-6-phosphate dehydrogenase; NADP, nicotinamide-adenine dinucleotide phosphate; NADPH, reduced NADP.)(19)



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, Ninth Edition*: www.accesspharmacy.com

Clinical Features of acute reactions occurs rarely, 1 in 5000 patients after first exposure .More common in middle age /elderly females with recurrent UTIs following structural anomalies of genitourinary tract (22). Acute pulmonary hypersensitivity reaction to nitrofurantoin presents as cough, dyspnoea and fever often manifests within 3 to 8 days .However, it may appear within few hours to 4 weeks .In subacute or chronic reactions , dyspnoea and cough are most common symptoms generally develops after a month of exposure to drug(23).

Patient having acute toxicity presents to Emergency department appearing unwell, cyanosed due to Type II Respiratory distress. These patients are febrile with tachycardia, tachypnoea and hypotension.

Respiratory examination showed bi-basal crepitation .CXR shows normal lung field or pulmonary oedema including diffuse parenchymal changes or interstitial alveolar shadowing in lower lobes of lungs in 90% of affected patients

and pleural effusion commonly present (23). Blood test shows leucocytosis with eosinophilia for weeks which slowly resolves post cessation of nitrofurantoin generally after 6 weeks .ESR can be elevated up-to 80 mm/h (23). A variety of positive sexologies including ANCA, ANA, Anti-smooth muscle antibody , RA factor have been reported in these patients (24) (25).

Pulmonary function test shows moderate gas impairment, with no reduction in FEV1 or vital capacity. Chronic forms shows restrictive pattern with reduced lung volumes (2) (7).

HRCT shows bilateral ground glass consolidation in acute form and asymmetrical mixed pattern of consolidation and fibrosis in chronic form (7). Imaging findings and histopathology picture mimics organising pneumonia (9).

Broncho-alveolar lavage is nonspecific but may be helpful in proving immunological response characterise by presence of lymphocytosis, eosinophilia and neutrophilia (26).

Lung biopsy not often necessary. When obtained, it shows variation among pathologies suggestive of interstitial inflammation, interstitial pneumonia of non-specific pattern, organizing pneumonia or chronic eosinophilic pneumonia (12) (10).

Re-challenging with nitrofurantoin is not advised due to recurrence of lung toxicity (11).

Diagnosis of nitrofurantoin pulmonary toxicity is challenging. Differential diagnosis includes pulmonary oedema, cryptogenic organizing pneumonia and idiopathic interstitial pneumonia (27).

Treatment of acute pulmonary toxicity includes cessation of nitrofurantoin which leads to clinical improvement. Prognosis of this condition is good when correctly diagnosed.

Chronic presentation takes weeks to months to recover fully. Oral glucocorticoid is not useful routinely. It may be beneficial in case of severe respiratory impairment (2) (28). Careful initiation of steroid after ruling out infection shows rapid improvement though few cases of severe pulmonary toxicity resolved without steroid (29).

Follow up needed in certain cases who has persistent symptoms, pulmonary fibrosis, and persistent blood eosinophilia.

Conclusion

Nitrofurantoin has a value in treatment of urinary tract infection. Unfortunately, it is associated with adverse effects such as pulmonary toxicity which is often mistaken as infection.

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