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Authors

Sanna, Maija B.

Braskett, Melinda J.

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CLINICAL VIGNETTE

Nitrofurantoin Induced Hepatotoxicity

Maija B. Sanna, M.D.,¹ and Melinda J. Braskett, M.D.²

¹Department of Medicine, UCLA David Geffen School of Medicine

²Division of Clinical Immunology and Allergy, Keck School of Medicine at University of Southern California

Case

A 65-year-old woman with history of hypertension, dyslipidemia, coronary artery disease, atrial fibrillation, and history of mitral valve replacement presented to urgent care with dysuria and fatigue. Her medications included aspirin, isosorbide dinitrate, lisinopril, metoprolol, simvastatin, pantoprazole, warfarin, and tramadol. She was married, did not smoke or drink alcohol, and had no recent travel. Urine dipstick was positive for urinary tract infection, and nitrofurantoin 100mg BID for 5 days was prescribed. Symptoms resolved and she had no adverse effects from the medication.

Two weeks later, her dysuria recurred and nitrofurantoin at the same dose and duration was prescribed. Laboratory investigations revealed creatinine of 0.6 mg/dL and normal values for liver function tests and CK. She developed symptoms of nausea and decreased appetite and continued the full course of antibiotics. Four days later, she presented to her doctor's office where she was afebrile with normal blood pressure and benign abdominal exam. Urinalysis was negative. She continued to have nausea and decreased appetite and developed mid-back pain and abdominal bloating. She was seen in urgent care where she was given a GI cocktail (calcium carbonate and viscous lidocaine).

Five days later, she re-presented to urgent care with ongoing back pain, nausea, decreased appetite, and recorded home low blood pressure of 85/56 mmHg. Her abdominal exam was unchanged. Blood pressure medications were reduced, and labs were drawn showing a normal CBC without eosinophilia, creatinine of 0.7mg/dL, and elevated liver function tests (AST 690 U/L, ALT 881 U/L, Alk Phos 686 U/L, TB 3.1 mg/dL). Abdominal imaging demonstrated a normal liver and non-dilated bile duct. Repeat testing three days later showed ongoing elevation in liver tests (AST 471 U/L, ALT 580 U/L, Alk Phos 606 U/L, TB 3 mg/dL). Additional testing at that time included negative hepatitis serology, normal ESR, CRP, and CK. ANA was positive at 1:160. Smooth muscle antibody was positive at 1:20 and anti-mitochondrial antibody was negative. Her symptoms gradually resolved, and her liver function tests returned to normal within one month.

Nitrofurantoin is a commonly prescribed antibiotic in primary care used to treat urinary tract infections (UTIs). It is indicated for the acute treatment of UTIs, as well as long-term treatment

for UTI prophylaxis. Common side effects include nausea, diarrhea, rash, dyspepsia, dizziness, and drowsiness. More serious and infrequent side effects include pulmonary toxicity (interstitial pneumonitis), neurotoxicity (peripheral neuropathy), hemolytic anemia, exfoliative dermatitis, lupus-like syndromes, and hepatotoxicity.^{1,2} Risk of nitrofurantoin-induced hepatitis increases with age greater than 64 years.³

Nitrofurantoin is a common culprit in drug-induced liver injury and can produce a varied picture. Patterns of drug induced liver injury can be defined as hepatocellular, cholestatic, or mixed using the R ratio. The R ratio = $[ALT/ULN] \div [AlkP/ULN]$ with $R > 5$ = hepatocellular, < 2 = cholestatic, and $2-5$ = mixed where ULN = upper limit of normal.⁴ Additionally, nitrofurantoin drug-induced liver injury can cause either acute hepatitis or a chronic hepatitis syndrome. Severity of reactions can range from mild elevations in serum liver tests to fulminate liver failure resulting in death.¹

Nitrofurantoin induced acute liver injury typically presents within a few days to weeks after exposure and incidence is reported as about 0.3 cases per 100,000 prescriptions.¹ Fever, rash, nausea, vomiting, anorexia, malaise, and eosinophilia may be present and pattern of injury is predominantly hepatocellular.^{2,5} Chronic hepatitis from nitrofurantoin can be seen months to years after long-term nitrofurantoin initiation and is more common than the acute form (1 per 1500 persons exposed).¹ Patients may present with fatigue, weakness, and jaundice.

There are several proposed mechanisms for nitrofurantoin-induced liver injury. One mechanism involves direct injury to the hepatocyte via oxidative stress.^{5,6} In another proposed mechanism, nitrofurantoin, or a metabolite of the drug combines with endogenous polypeptides and with the HLA class I antigen on hepatocyte membranes, and initiates CD8+ cytotoxic T cells mediated cell death.⁷ Other factors that support an immunologic basis include higher female:male ratio, presence of ANA and anti-smooth muscle antibodies, high gamma globulin levels, and the presence of inflammatory cells on liver biopsy.^{5,6} DeBoer et al⁴ found that most cases of DILI from nitrofurantoin had a phenotype of autoimmunity similar to autoimmune hepatitis that occurred in 70% of the nitrofurantoin related cases.

Diagnosis of nitrofurantoin-induced hepatotoxicity is a clinical diagnosis of exclusion. Removal of the offending agent and subsequent resolution of liver abnormalities strengthens the clinical diagnosis. Re-challenge is not recommended given risk for recurrence. While withdrawal of the medication is usually sufficient in treating nitrofurantoin induced liver injury, more severe cases, especially those with strong autoimmune features, may benefit from the use of corticosteroids.⁶

In summary, this case illustrates the uncommon, though well-described phenomenon of nitrofurantoin induced hepatitis. The importance of recognizing nitrofurantoin induced liver injury cannot be overstated, especially since fatalities have occurred in cases where the drug was continued despite clinical illness.⁸

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