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Case Report

Acute Liver Injury after Three Doses of Nitrofurantoin

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ABSTRACT

A 56-year-old lady presented to the hospital with 2-day history of flu like symptoms. These had begun within a few hours after starting Nitrofurantoin for urinary tract infection that was prescribed by her primary care doctor. Blood tests upon admission revealed elevated aminotransferase levels with normal bilirubin levels. The medication was stopped, and other causes of hepatitis were investigated. Nitrofurantoin induced idiosyncratic drug-induced liver injury (IDILI) was confirmed by excluding all other causes. Patient's symptoms and liver enzymes improved the next day and she was discharged. A follow-up on the laboratory's nine-days later revealed liver enzymes almost back to normal.

Keywords
Nitrofurantoin; Urinary tract infection; Idiosyncratic drug induced liver injury; Acute reversible hepatotoxicity; Flu-like illness; Elevated transaminases.

BACKGROUND

Nitrofurantoin is an antibiotic used for treatment of acute cystitis and for long-term prophylaxis in patients at risk for recurrent urinary tract infections (UTIs). It is a known cause of idiosyncratic drug-induced liver injury (IDILI), a rare adverse drug event that occurs independent of drug dose, route, or duration of administration in susceptible individuals.[1] IDILI from nitrofurantoin has a wide spectrum of presentation from mild elevations in aminotransferase levels to fulminant liver failure.[2] The primary treatment is to discontinue the causative agent. Hepatotoxicity usually presents after a prolonged exposure to the drug and less frequently presents acutely. In this case report, we look at the clinical presentation of hepatotoxicity from only three doses of nitrofurantoin in a patient with no prior history of liver damage or disease.

CASE PRESENTATION

A 56-year-old Caucasian female presented to the emergency department with two days of flu-like symptoms. She complained of worsening chills, subjective fever, myalgia, malaise, cough, and nausea. The symptoms began several hours after taking a first-time dose of nitrofurantoin 100 mg PO BID, which was prescribed by her primary care provider for 7-days due to urinary frequency, urgency, and dysuria for several weeks. She had completed a total of three doses of nitrofurantoin prior to arrival to the hospital.

The patient had a medical history of hypertension, type 2 diabetes, transient ischemic attack, hyperlipidemia, gastroesophageal reflux disease, irritable bowel syndrome, generalized anxiety disorder, depression, lumbago, and convulsions. Surgical history is significant for inguinal hernia repair, tubal ligation, spinal fusion and multiple orthopedic procedures of the ankle, right rotator cuff, and right elbow. There was no family history of liver disease. The patient had no smoking history and no alcohol use. Medications included lisinopril-hydrochlorothiazide, metformin, atorvastatin, clopidogrel, aspirin, esomeprazole, sertraline, buspirone, ondansetron, meclizine, and lamotrigine. On review of systems, the patient endorsed the aforementioned flu-like symptoms in addition to dysuria and some hematuria noted on admission. She denied headache, neck stiffness, congestion, sore throat, chest pain, vomiting and diarrhea.

Vital signs on initial evaluation demonstrated tempera-

ture of 97.5 °F, heart rate of 73 beats per minute, respiratory rate of 16 breaths per minute, blood pressure of 103/62, body mass index (BMI) 23.89 kg/m^2. The patient appeared sickly but was non-toxic in appearance and in no acute distress. She was oriented to person, place, and time. Sclera was anicteric and conjunctiva non-injected. She had no cervical lymphadenopathy or neck stiffness. Lungs were clear to auscultation. Cardiovascular rhythm was normal. Abdomen was soft, non-distended, and non-tender; there was no hepatosplenomegaly. No skin discoloration or rashes were noted. There was no obvious extremity deformity or swelling.

Investigations

Laboratory testing included influenza antigens A and B, strep screen and culture, complete blood count with differential, complete metabolic panel, amylase, lipase, urinalysis, urine culture, magnesium level, and thyroid hormone levels.

The initial results of these studies including Chest X-ray were normal with the exception of the urinalysis, which was positive for nitrite, leucocyte esterase and blood, indicative of UTI, and comprehensive metabolic panel, which demonstrated mild hyponatremia with serum Na 132 mmol/L (Normal 136-145 mmol/L), elevated liver enzymes: alanine aminotransferase (ALT) 1057 U/L (Normal 5-55 U/L), aspartate aminotransferase (AST) 1592 U/L (Normal 5-34 U/L), and alkaline phosphatase (ALP) 174 U/L (40-150 U/L). Total bilirubin was normal at 0.9 mg/dL. These were elevated from previous values approximately 16-months prior: ALT 35 U/L, AST 26 U/L, ALP 93 U/L, and bilirubin 0.4 mg/dL. In addition, ultrasound of the liver was performed and normal. It was felt that the urinary tract infection by itself could cause hepatitis in the absence of severe sepsis.

Differential Diagnosis

The new finding of elevated serum aminotransferases prompted further evaluation. Infectious, autoimmune, and iatrogenic etiologies were investigated. Hepatitis screen and urine drug screen were both negative. Autoimmune panel was negative for antinuclear antibodies, anti-smooth muscle antibodies, and anti-mitochondrial antibodies. Ceruloplasmin was within normal limits. There were no elevations in lipid panel. Coagulation panel was not performed. Computed tomography of the abdomen and pelvis with contrast showed no obvious pathology. Chest X-ray was negative.

At this point, iatrogenic etiology of hepatic injury was high on the differential. Nitrofurantoin, lamotrigine, and atorvastatin were outpatient medications that had well-known potential for hepatotoxicity. For at least nine months prior to our evaluation, the patient was on a regimen of alternating lamotrigine 25 mg 1 tablet daily for 1-week then 2 tablets daily for 3-weeks. Her records also indicate that she has taken atorvastatin 80 mg at bedtime for the last 5-years. Per the patient's history, a 7-day course of nitrofurantoin 100 mg PO BID was initiated just two-days prior to hospital admission with no prior history of use. Considering these timelines in the context of acute clinical presentation, our focus was placed on nitrofurantoin and its potential contribution to hepatotoxicity.

Treatment

Nitrofurantoin was discontinued on admission. Atorvastatin was placed on hold. The patient was given intravenous fluids for mild hyponatremia and the hyponatremia resolved. She was initiated on intravenous ceftriaxone 1 g for UTI without sepsis. Ibuprofen and Benzonatate were provided as needed for myalgias and cough.

Outcome and Follow-Up

She clinically improved. Her myalgias were much better. Her blood tests next day revealed reduced aminotransferase levels: ALT 573 U/L and AST 357 U/L. ALP increased to 221 U/L. Total bilirubin was normal at 0.4 mg/dL. She was clinically stable for discharge. She was provided instructions to start Cefuroxime 500 mg PO BID for 7-days and to discontinue the atorvastatin in addition to nitrofurantoin.

The patient saw her primary care provider nine days later. She had follow-up comprehensive metabolic panel while she continued to take the Atorvastatin and Metformin. Tests revealed that there was complete resolution on liver function tests: ALT 85 U/L, AST 29 U/L, ALP 153 U/L, and bilirubin 0.5 mg/dL. The roussel uclaf casualty assessment method (RUCAM) for drug-related liver injury score was 9 indicating highly probable case of DILI.

DISCUSSION AND CONCLUSION

Approximately 44,000 individuals develop DILI in USA annually.[3] Up to 50% of all causes of acute liver failure in Western countries can be attributed to DILI.[4,5] Mortality is higher in patients with chronic liver disease who develop DILI than those who do not have chronic liver disease, 16% *vs.* 5.2% respectively.[6,7] Besides genetics, female sex, older age and concomitant use of other drugs have been implicated as possible risk factors in the development of DILI. The mechanism of DILI is idiosyncratic in majority of cases, which could be immune or non-immune mediated liver injury. In non-immune injury, metabolites of drugs bind covalently to the structures inside the cell causing cell death. On the other hand, in immune-mediated idiosyncratic reactions there is an interaction of drug, its metabolites and immune system of the host that could lead to hepatocyte necrosis and/or apoptosis with release of cytokines causing cell damage or create immune-modulating effects.[8,9]

IDILI is a diagnosis of exclusion requiring thorough investigation of medical history focused on time intervals between each suspected xenobiotic administration, onset of signs and symptoms, and total dosage intervals.[10] The acute presentation of the patient after having completed a total of three doses of nitrofurantoin over the period of two days provides a unique timeline for nitrofurantoin-induced IDILI that warrants further discussion on the latency of nitrofurantoin-induced DILI.

In 2003, the drug-induced liver injury network (DILIN) conducted a prospective study of patients with DILI in the United States (n=1257) and found that nitrofurantoin is among the top causes of DILI with long latency (>365-days) while it had a minor

role in DILI with short latency (<7-days).[7] This finding is proportionate to much of the currently available literature on nitrofurantoin-induced DILI as there is a far greater number of case reports demonstrating the long-term consequences of nitrofurantoin on the liver than reports on hepatotoxicity after short-term use.

In searching for cases of nitrofurantoin-induced DILI with comparably short latency (<7-days), we were found only one other report,[11] which discussed a 69-year-old man who noticed jaundice after 3-4-days of drug exposure and presented after 5-days with laboratory evidence of liver injury. Some key comparisons are outlined in the Table 1.

Similarities between the two cases include the elevation of serum aminotransferase levels noted <7-days from starting the first dose of a 7-day course of nitrofurantoin 100 mg BID in patients with previously normal liver markers and no history of liver injury. In both cases, the discontinuation of nitrofurantoin led to improvement of liver enzyme levels; however, this statement is limited in that the follow-up laboratory tests were performed at different timeframes [2.5-months *vs.* 1-10-days], making it difficult to compare how quickly liver enzyme levels normalized and what factors contributed to that normalization.

The most notable differences between the two cases include the symptoms, latency of DILI, liver function test results on admission, and results of the investigation of other etiologies contributing to livery injury. Our 56-year-old female patient reported flu-like symptoms several hours after the first dose of nitrofurantoin, which was quicker than the 69-year-old male patient who noticed yellow skin discoloration three days after initial nitrofurantoin use. Unlike this 69-year-old male patient, our patient had neither jaundice nor elevated bilirubin levels, though ALP remained elevated throughout the two-day hospitalization. The 69-year-old male patient had elevated ANA titers and positive smooth muscle antibodies, while our patient had a completely negative autoimmune antibody panel.

The examination into these two cases provides a platform for further investigation into nitrofurantoin-induced liver injury with short latency (<7-days). Further reports on acute reversible hepatotoxicity from nitrofurantoin should be encouraged to bring awareness to clinical providers and increase discussion and research regarding nitrofurantoin and its short-term hepatotoxic effects.

Learning Points

- This case highlights an acute presentation of Nitrofurantoin induced idiosyncratic drug-induced liver injury (IDILI).
- Nitrofurantoin induced hepatotoxicity should be suspected in anyone presenting with elevated flu- like symptoms and elevated liver enzymes within a few days (less than a week) of commencement of treatment with Nitrofurantoin.
- This is a reversible condition and discontinuation of the medication will yield instant results.

Table 1. *Comparison of Case Reports of Drug Induced Liver Injury (DILI) with Short Latency*

	Case Report 1[10]	Case Report 2
Age, gender, past medical history, reason for admission	69-year-old male with a history of chronic obstructive pulmonary disease (COPD), coronary artery disease, hypertension, hyperlipidemia, and congestive heart failure admitted for COPD exacerbation and jaundice	56-year-old female with a history of hypertension, type 2 diabetes, transient ischemic attack, hyperlipidemia, gastroesophageal reflux disease, irritable bowel syndrome, generalized anxiety disorder, depression, lumbago, and convulsions admitted for UTI and elevated liver enzymes with chills and myalgias.
Prescribed nitrofurantoin dosage	7-day course of nitrofurantoin 100 mg BID prior to admission	7-day course of nitrofurantoin 100 mg BID prior to admission
Latency (First dose of nitrofurantoin to onset of symptoms)	3-days	several hours
Initial symptoms post nitrofurantoin use	Jaundice	Flu-like symptoms including chills, subjective fever, malaise, cough, and nausea
Days from first nitrofurantoin dose to discontinuation	5-days	2-days
Days from first nitrofurantoin dose to admit	8-days	2-days
Liver function test results on admit	ALT 608 U/L; AST 1260 U/L; ALP 2640 U/L; bilirubin 12.4 mg/dL	ALT 1057 U/L; AST 1592 U/L; ALP 174 U/L; bilirubin 0.9 mg/dL
Previous liver function test results	A year prior, normal liver function tests with ALT 25 U/L; AST 23 U/L; ALP 113 U/L; bilirubin 0.8 mg/dL.	16 months prior, normal liver function tests with ALT 35 U/L; AST 26 U/L; ALP 93 U/L; bilirubin 0.4 mg/dL
Results of other investigation	Elevated anti-neutrophil titers (1:160) and positive anti-smooth muscle antibodies. Ultrasound of the abdomen showed	Autoimmune panel negative for antinuclear antibodies. Ultrasound of the liver was normal.
Treatment and Course	Nitrofurantoin was discontinued 3-days prior to admission. He received 10-days of 40 mg IV methylprednisolone and demonstrated significant improvement. He was subsequently discharged.	Nitrofurantoin was discontinued on admission. The patient was given IV fluids for mild hyponatremia and IV ceftriaxone 1 g for UTI without sepsis. She clinically improved over treatment overnight and was discharged the following day.
Repeat lab results after nitrofurantoin discontinuation	Approximately 2.5-months after discontinuation, the patient had normal liver function tests with ALT 20 U/L; AST 20 U/L; ALP 73 U/L; bilirubin 0.6 mg/dL	1 day after discontinuation, the patient had ALT 573 U/L (45.8% decrease from admit); AST 357 U/L (77.6% decrease from admit); ALP 221 U/L (27.0% increase from admit); bilirubin 0.4 mg/dL 10-days after discontinuation, the patient had normal liver function tests with ALT 85 U/L; AST 29 U/L; ALP 153 U/L; and bilirubin 0.5 mg/dL

CONSENT

The authors have received written informed consent from the patient.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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