Fatal Liver Necrosis Associated with the Use of Nitrofurantoin

Yeouda Edoute MD PhD, Yuval Karmon MD, Ariel Roguin MD and Haim Ben-Ami MD

Department of Internal Medicine C, Rambam Medical Center and Rappaport Faculty of Medicine, Technion–Israel Institute of Technology, Haifa, Israel

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Nitrofurantoin, a furan derivative, is used primarily in the treatment of urinary tract infection. It has also been found to be appropriate for use in long-term prophylaxis of recurrent UTI in view of its efficacy, favorable safety and tolerability profile [1]. It is rapidly and completely absorbed from the gastrointestinal tract. Reducing enzymes appear to be crucial for its activation. However, it may cause a wide range of adverse reactions. Chronic hepatitis and ensuing liver damage caused by nitrofurantoin toxicity is very rare.

We report the case of a 73 year old woman who had been taking nitrofurantoin as a prophylactic measure for 14 months and developed fatal hepatic necrosis. Another notable feature was positive antinuclear antibodies. Drug-induced hepatic toxicity is reviewed, with emphasis on early consideration in the differential diagnosis to allow reversibility and avoid fatal outcome.

Patient Description

In September 1998, a 73 year old woman with a 1 week history of postprandial vomiting, progressive jaundice, dark urine and pruritus was admitted to our department. The patient denied any past history of jaundice, alcohol consumption or exposure to blood components. Her past history was unremarkable except for hypertension treated for over 2 years with atenolol 50 mg four times daily and nifedipine 10 mg twice daily. During the previous 14 months the patient had also been taking nitrofurantoin 100 mg four times a day as a prophylaxis against recurrent UTI and denied having any side effects.

Physical findings were remarkable for moderate jaundice and scratch marks on her abdomen. No ascites, edema, masses or hepatosplenomegaly were noted. The pertinent laboratory tests were: hemoglobin 13 g/dl, normal leukocyte count and differential, platelet count 133 x 10^9/L, blood urea nitrogen 53 mg/dl, creatinine 2.7 mg/dl, total bilirubin 14.5 mg/dl (direct 9.8 mg/dl), aspartate aminotransferase 1,160 U/L (normal <40), alanine aminotransferase 884 U/L (normal <45), alkaline phosphatase 190 U/L (normal 30–110), gamma-glutamyl transpeptidase 155 U/L (normal <40), lactic dehydrogenase 235 U/L (normal <225), albumin 3.1 g/dl, globulin 3 g/dl, international normalized ratio =1.36, partial thromboplastin time 39 seconds. Glucose, electrolytes and amylase were normal. Urine analysis showed increased direct bilirubin.

Serology for hepatitis A, B, and C, cytomegalovirus, Epstein-Barr virus, *Toxoplasma* and *Mycoplasma* were all negative. Autoimmune serology demonstrated positive anti-nuclear antibodies 271 U (normal <97), negative dsDNA, anti-smooth muscle, and anti-mitochondrial antibodies.

Abdominal ultrasound displayed a normal liver and pancreas and a thickened gallbladder wall. All drugs were discontinued on admission and systemic methylprednisolone (1 mg/kg) was administered. The patient's jaundice became pronounced with total bilirubin of 30 mg/dl (direct 27 mg/dl), and the liver enzymes AST, ALT and GGT progressively declined to 171, 270 and 66 U/L respectively. INR was 1.65, albumin 2.9 g/dl.

During the following 2 weeks, massive symptomatic ascites developed. Paracentesis revealed an acellular transudate sterile fluid that was negative for acid-ast bacilli. Concomitantly, acute tubular necrosis developed (serum creatinine 5.7mg/dl and BUN 86 mg/dl). The patient's clinical condition deteriorated, and on the 13th hospital day she expired due to liver encephalopathy and clinical sepsis. Histopathological findings of liver needle biopsy revealed necrotic hepatic tissue with mononuclear cell infiltrates that stained negative for CD8.

Comment

Although there is no definitive way of establishing the diagnosis of drug-induced hepatitis other than excluding other causes such as infective, toxic and ischemic, we believe this patient suffered from nitrofurantoin-induced hepatitis. Other causes of acute liver failure (i.e., viral hepatitis, acetaminophen ingestion, ischemic liver cell necrosis, Budd-Chiari syndrome, and infection with Epstein-Barr virus, herpes simplex virus, or cytomegalovirus) were ruled out. While atenolol and nifedipine have been reported to induce liver injury [2,3], it is unlikely that these medications induced acute hepatitis after more than 2 years of continuous use.

Nitrofurantoin is a broad-spectrum antimicrobial agent, widely used in Israel to treat acute UTI and also administered as a prophylaxis for patients with recurrent UTI. Adverse effects are uncommon but may be serious, such as peripheral neuropathy, anemia, agranulocytosis, interstitial pneumonitis, multisystem failure and both acute and chronic forms of hepatitis.

Drug-induced hepatitis as a complication of nitrofurantoin treatment was first reported in 1961 [4]. The incidence of hepatic side effects is estimated to be 0.3–3.3 cases per 100,000 individuals exposed to the drug. Nitrofurantoin-induced acute hepatitis is three times more frequent in women, and its incidence increases with advancing age.

The characteristics of nitrofurantoin-induced acute hepatitis are typical of an immunoallergic type of idiosyncratic hepatic drug reaction. The symptoms usually begin within 6 weeks of starting treatment; most of the patients with acute hepatitis recover, with a mortality rate of 2% [5]. Chronic hepatitis is characterized by a different time course. In these patients, the time interval between administration of the drug and the development of chronic hepatitis is never less than 6 weeks, and generally longer than 6 months. This reaction has recently been described to involve CD8+ cytotoxic lymphocytes, which was found negative in our patient.

Our patient did not respond to steroid therapy and developed a fatal liver necrosis without any previous evidence of chronic liver disease. In conclusion, nitrofurantoin-induced hepatitis should be considered in any patient undergoing treatment with nitrofurantoin, especially among elderly women.

References

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Correspondence: Dr. H. Ben-Ami, Dept. of Internal Medicine C, Rambam Medical Center, P.O.Box 9602, Haifa 31096, Israel. Phone: (972-4) 854-3309, Fax: (972-4) 854-2260, email: mdhaim@tx.technion.ac.il

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John Lennon and (Sir) Paul McCartney, British singers and songwriters (1940–80) and (1942–)