

Nitrofurantoin-Induced Chronic Active Hepatitis

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Abstract

Background: Nitrofurantoin is a commonly prescribed urinary antiseptic. Hepatic injury has been associated with its use.

Objectives: To present three patients in whom long-term exposure to the drug resulted in chronic active hepatitis; and to review the epidemiology, clinical immunology, histopathology, pathogenetic features and treatment of previously reported cases.

Results: Withdrawing nitrofurantoin once the diagnosis was suspected did not lead to remission of the liver disease and glucocorticoids had to be administered. One patient died of liver failure.

Conclusions: Awareness of this unusual side effect of nitrofurantoin is important and caution should be taken before prescribing it. Over the past years new insight into the immune nature of this drug has emerged.

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Nitrofurantoin is used for the treatment and prevention of urinary tract infections. Hepatic injury after either short or long-term use of the drug has been described [1-3]. Recently we encountered three women with chronic active hepatitis after long-term exposure to nitrofurantoin. In one of the patients the disease was fatal. We describe the cases and review the literature.

Patients

Patient 1

A 64 year old woman was admitted following 3 days of jaundice, rash and pruritus. She had been suffering from long-standing and slowly progressive olivopontocerebellar atrophy. There was no history of liver disease. Owing to recurrent urinary tract infections she was treated with nitrofurantoin for 5 years (100 mg daily). On examination she appeared icteric, with a maculopapular skin rash covering the lower abdomen and both legs. A non-tender liver tip was palpated. The spleen was not enlarged and there were no stigmata of chronic liver disease. Laboratory data showed bilirubin of 252 M/L (mostly conjugated, NI<17 M/L), aspartate aminotransferase 300 U/L (NI<60 U/L), alanine aminotransferase 1,700 U/L (NI<60 U/L), alkaline phosphatase 300 U/L (NI<140 U/L), lactate dehydrogenase 1,600 U/L (NI<620 U/L) and serum albumin 29 g/L (N 35-55 g/L). White blood cell count was $15.6 \times 10^9/L$ without eosinophilia. Serologic tests for hepatitis B surface antigen, anti-hepatitis A virus immunoglobulin M, anti-hepatitis C virus, anti-Ebstein-Barr virus IgM and anti-cytomegalovirus were negative. Serum ceruloplasmin and urinary 24 hour copper extraction values

were within normal range. Autoimmune serology for antinuclear antibody was positive (2/4); anti-mitochondrial, anti-smooth muscle antibodies were negative. Liver biopsy revealed a mononuclear cell inflammatory infiltrate with bridging necrosis between portal spaces. The portal spaces were enlarged, filled with inflammatory cells, including eosinophils, and there was bile duct proliferation. Nitrofurantoin treatment was discontinued and the patient was given hydrocortisone intravenously. Nevertheless, signs of fulminate hepatic failure developed rapidly and the patient died 21 days after admission. Gram-negative bacteria were recovered from blood and peritoneum.

Patient 2

A 72 year old woman was admitted because of deteriorating jaundice. One month prior to admission she began complaining of nausea and 2 weeks later she became icteric. Her past medical history included hypertension, diabetes mellitus type 2 and recurrent urinary tract infections. There was no history of liver disease. She had been taking atenolol, disothiazide and glibenclamide for a number of years and nitrofurantoin for one year. On examination she was icteric with otherwise normal examination results. Laboratory tests showed AST 960 U/L, ALT 515 U/L, alkaline phosphatase 390 U/L, LDH 1,300 U/L, total bilirubin 263 M/L (direct 230 M/L), albumin 25 g/L, INR 2.07. Abdominal ultrasound revealed normal bile ducts. Serology was negative for acute infection of hepatitis viruses A, B or C, EBV or cytomegalovirus. There were low complement factor levels: C4 18 mg/dl (NI 20-50 mg/dl), C3 trace (50-120 mg/dl), ANA and AMA were negative, anti-SMA was positive (1/4). Liver biopsy showed inflammatory infiltrate consisting of mono- and polymorphonuclear cells with mild eosinophilia primarily confined to the portal spaces with piecemeal necrosis. Bile ductuli proliferation and portal fibrosis, lobular hepatocyte necrosis and anisocytosis were also noted. Nitrofurantoin was discontinued. Notwithstanding, there was no improvement in liver function tests and enzymes 3 weeks thereafter and the patient was started on prednisone 60 mg/day. On follow-up, impaired liver function tests and enzymes normalized slowly over one year, after which steroids were withdrawn successfully.

AST = aspartate aminotransferase

ALT = alanine aminotransferase

LHD = lactate dehydrogenase

EBV = Epstein-Barr virus

ANA = antinuclear antibody

AMA = anti-mitochondrial antibodies

SMA = smooth muscle antibodies

Ig = immunoglobulin

Patient 3

A 76 year old woman was admitted for investigation of abdominal pain of 2 months duration. For the previous 2 years she had been treated with nitrofurantoin for recurrent urinary tract infections. Nitrofurantoin was discontinued 2 months prior to admission and was replaced with ciprofloxacin for one week because of urinary tract infection. Her previous medical history also included cholecystectomy, Billroth type 2 operation for peptic ulcer disease 15 years before the admission, as well as an episode of hepatitis 11 years before the admission (unknown etiology). Three years before admission her liver function tests were reported normal. One month prior to admission she was found to have elevated liver enzymes. The patient was afebrile on admission and the physical examination was remarkable for an enlarged and tender liver without splenomegaly. Laboratory results showed AST 830 U/L, ALT 850 U/L, alkaline phosphatase 110 U/L, LDH 1,300 U/L, total bilirubin 37 M/L, albumin 33 g/L, INR 1.66. Complete blood count was normal without eosinophilia. Serology was positive for anti-HBc IgG antibody but negative for hepatitis B surface antigen, anti-HCV antibody, AMA and anti-SMA. ANA titer was positive on one assay but negative on the repeat assay one week later. Liver biopsy showed inflammatory infiltrate of the portal spaces composed of lymphocytes and eosinophils, mild bile ductal proliferation and piecemeal necrosis of the liver parenchyma. After 8 weeks of observation the liver enzymes still indicated active inflammation; the patient was started on corticosteroids with rapid resolution of her abdominal pain and normalization of her liver function over 8 more weeks, after which the steroids were tapered.

Discussion

Nitrofurantoin, a furan derivative, is used to treat and prevent urinary tract infections. Adverse effects include chills, fever, leukopenia, hemolysis (in G6PD-deficient patients), pneumonitis and neuropathy [1]. Hepatic injury after both acute and chronic exposure to the drug has been described [2,3]. The true incidence of hepatic injury secondary to nitrofurantoin is difficult to obtain. In a study comparing the adverse reaction to the drug between countries [1], it was estimated that adverse reaction to nitrofurantoin accounted for 0.5% to 8% of all annually reported side effects of all drugs. It was estimated in one country (Sweden) to be 0.9–1.2 reports/prescriptions but 0.07–0.08 reports/prescriptions in another (Britain). Of these adverse events 5.4–16% were related to the liver. Most reported cases of chronic active hepatitis from nitrofurantoin occurred in women [4], but there is also a report of such a reaction in a man [5].

The clinical features vary from self-limited acute anicteric hepatitis [6] to chronic hepatitis and hepatic failure [7]. All three patients described in our report had clinical hepatitis. Features of hypersensitivity reaction such as rash, eosinophilia and arthralgia occur in some patients after chronic exposure to the drug [2], as seen in patient 1.

Chronic active hepatitis has been reported after both a short exposure of 6 weeks with 100–200 mg nitrofurantoin daily [2] and as

long as 4 years daily exposure [8]. Chronic active hepatitis after rechallenge with nitrofurantoin was reported in three patients. One patient suffered recurrent hepatitis and eosinophilia 2 weeks after rechallenge. His liver function tests continued to be disturbed and inflammation was found on liver biopsy even 5 months after discontinuation of the drug [2]. Another patient developed hepatitis 9 weeks after rechallenge [4]. Recurrent hypersensitivity reactions, including hepatitis, occurred in a patient even 17 years after the last exposure [9]. Thus, it appears that rechallenge with nitrofurantoin may be dangerous and is not recommended. Once hepatotoxicity from the drug is suspected it should be promptly discontinued. Continuation of the drug can lead to ongoing liver inflammation and decompensation [7].

Liver histopathology shows an inflammatory process in the portal spaces and varying degrees of hepatic necrosis or hepatocyte degeneration [4,7,10] with or without eosinophilic infiltration. In some cases of chronic exposure there were signs of cirrhosis [4,11].

Stricker et al. [4] found positive ANA and positive SMA in 11 of 13 patients after chronic exposure to nitrofurantoin, and hepatic injury. No direct correlation was found between the presence of autoimmune markers and the severity of histologic findings. The presence of anti-SMA antibodies together with hypergammaglobulinemia was reported in 70% and hypergammaglobulinemia alone in 88% of patients [4].

The pathogenesis of liver injury from nitrofurantoin is not known. It has been speculated, however, that it is an immunoallergic rather than a metabolic reaction [12]. Supporting an immunoallergic reaction are the following findings: a) the female/male ratio in patients with adverse reactions to nitrofurantoin is higher than the female/male prescription rate [12]; b) the occurrence of chronic active hepatitis and lupus erythematosus-like disease after exposure to the drug includes vasculitic lung injury [3,13]; c) the presence of ANA, ASM antibodies and hypergammaglobulinemia resembles the findings in patients with autoimmune chronic active hepatitis [14,15]; d) the presence of chronic active hepatitis on liver histology, as well as the predominance of cytotoxic lymphocytes in the hepatic parenchyma as seen in autoimmune chronic active hepatitis [16] was also reported in nitrofurantoin liver toxicity [17]; and e) susceptibility to autoimmune chronic active hepatitis is genetically mediated [15]. One patient presenting with nitrofurantoin-induced chronic active hepatitis was found to have human leukocyte antigen A1-B8 (18), known to be a risk factor for developing autoimmune chronic active hepatitis [19]. No human leukocyte antigen studies were reported in patients with nitrofurantoin-induced chronic active hepatitis.

Discontinuation of the drug led to clinical and biochemical improvement in most cases [7,10,20]. In some patients, withdrawing nitrofurantoin did not have a beneficial effect and steroids had to be added to the treatment regimen [4]. In others, especially those with continued exposure to the drug, the result was fatal despite the addition of steroids [7].

In conclusion, long-term exposure to nitrofurantoin may cause chronic active hepatitis. This adverse reaction shares a number of features with autoimmune hepatitis, including histopathology and immune markers and possibly the response to glucocorticoids.

HCV = hepatitis C virus

Unrecognized, it can be fatal. Awareness of this uncommon side effect is important, and other urinary tract infection preventive measures, such as vaginal estrogen creams, should be considered before prescribing a drug with potentially rare but serious adverse reactions.

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