CASE REPORT

Nitrofurantoin immune-mediated drug-induced liver injury: a serious complication of a commonly prescribed medication

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SUMMARY

Nitrofurantoin is recommended for first line prophylaxis of recurrent urinary tract infections. Despite a number of side effects it is increasingly prescribed due to its high efficacy, low cost and minimal antimicrobial resistance. Nitrofurantoin-induced immune-mediated liver injury is a particularly serious complication, resulting in both acute hepatic failure and cirrhosis with continued use. We describe the course of two patients who recently presented to our hospital in order to highlight this.

BACKGROUND

We describe the cases of two patients recently admitted to our hospital with an autoimmune-like hepatitis secondary to long-term nitrofurantoin use; the first resulting in a severe acute on chronic hepatitis and jaundice and the second causing cirrhosis and death. Both occurred as a result of continued prescription of nitrofurantoin for many months following an increase in transaminases and could therefore have been prevented. While most physicians are alert to the pulmonary complications of nitrofurantoin, the hepatic sequelae are less well described. Significant hepatic injury is rare following short courses, but prolonged prescription can result in a drug-induced autoimmune hepatitis (AIH) leading to serious adverse events including acute liver failure and cirrhosis, resulting in both liver transplant and death. Presentation is nearly indistinguishable from AIH, making history taking including an accurate drug history and analysis of the time course of events vital. Early withdrawal of the medication nearly always results in rapid normalisation of the liver biochemistry, if not corticosteroids can be life saving. We therefore feel strongly that it is extremely important to highlight this complication given the wider prescription of nitrofurantoin, the severity of the end points and preventable nature of this condition.

CASE PRESENTATION**Case 1**

A 50-year-old woman with type 2 diabetes, chronic back pain and an overactive bladder presented with right upper quadrant pain and jaundice. Examination revealed no features of chronic liver disease. Drug history included nitrofurantoin 50 mg once daily, started 12 months prior to admission, pioglitazone, metformin, amitriptyline, paroxetine, lansoprazole, chlorphenamine, buprenorphine, morphine sulfate, temazepam and lactulose. Admission blood tests

revealed bilirubin 132 $\mu\text{mol/L}$, alanine transaminase (ALT) 747 IU/L, alkaline phosphatase 294 IU/L (figure 1A). The international normalised ratio (INR) was normal and albumin was slightly low at 30 g/L. Liver function was normal 6 months earlier, although her ALT began to rise 5 months prior to admission. Abdominal ultrasound demonstrated gallstones in a thin-walled gallbladder but was otherwise unremarkable. Viral serology was negative. Autoimmune screen revealed elevated IgG levels at 22.2 g/L with negative antinuclear (ANA), smooth muscle (SMA) and antimitochondrial antibodies (AMA). Magnetic resonance cholangiopancreatogram excluded biliary obstruction. Nitrofurantoin was suspended and prednisolone 20 mg daily started 1 day later leading to a decline in ALT. A liver biopsy undertaken shortly afterwards revealed findings consistent with autoimmune chronic active hepatitis with mild fibrosis, in keeping with immune-mediated drug-induced liver injury (DILI; figure 2A). Two months later, the patient remained well on a reducing regime of prednisolone with normal liver function tests.

Case 2

A 75 year-old woman was prescribed nitrofurantoin 50 mg once daily for urinary tract infection prophylaxis. Medical history included hypertension and hypercholesterolaemia for which she took propranolol, ramipril, bendroflumethiazide and atorvastatin. Blood tests were normal prior to the start of nitrofurantoin, however her ALT rose to 145 IU/L 6 months later. Her statin was changed but nitrofurantoin continued until she presented to hospital 6 months later with jaundice and myalgia. Blood tests revealed ALT 868 IU/L, bilirubin 130 $\mu\text{mol/L}$, alkaline phosphatase 130 IU/L, albumin 29 g/L and INR 1.5 (figure 1B). Abdominal ultrasound was normal and a chronic liver screen revealed raised levels of IgA and IgG at 4.5 g/L and 21.9 g/L, with undetectable ANA, SMA, AMA and liver-kidney microsomal antibodies. Serology for hepatitis A to E was negative. A transjugular liver biopsy revealed chronic active hepatitis with a florid inflammatory cell infiltrate consistent with primary or drug-induced AIH on a background of cirrhosis (figure 2B). Nitrofurantoin was discontinued and prednisolone 30 mg once daily started 3 days later following which the liver biochemistry improved (figure 1B). One month postadmission the patient developed a pulmonary embolus. Her INR was normal and she therefore received warfarin but unfortunately developed a

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Figure 1 (A) Liver biochemistry trend (case 1). (B) Liver biochemistry trend (case 2). ALT, alanine transaminase.

fatal spontaneous massive haemorrhage into the abdominal wall soft tissue.

DISCUSSION

Nitrofurantoin is a commonly prescribed medication in primary care. Side effects include diarrhoea, peripheral neuropathy, pulmonary fibrosis, interstitial pneumonitis and hypersensitivity reactions.^{1 2} Hepatotoxicity accounts for 12% of reported adverse reactions associated with nitrofurantoin and 25% of those resulting in death.² The last study to estimate the

incidence of symptomatic nitrofurantoin-induced hepatic injury was conducted in the late 1980s, quoting 1 in 3000–5000, although the figure is likely to be considerably higher now given wider prescription.³ Significant hepatotoxicity is rare following short courses, although acute hypersensitivity reactions presenting with rash, fever, eosinophilia and raised transaminases, along with cholestasis are well documented in patients taking the medication for less than 6 weeks.^{1 3}

Immune-mediated DILI usually occurs in the setting of long-term nitrofurantoin use. While rarer than acute reactions (approximately 1:9),³ it is often missed and results in grave sequelae if the drug is continued. Nitrofurantoin accounts for 3.4% of cases of AIH⁴ and is one of the most commonly prescribed agents associated with DILI.⁵ In over 85% of cases, DILI occurs 6 months postingestion,³ with some patients presenting 3 years later.⁴ It is nearly always restricted to women and is more common in the elderly.^{3 4} The history is central as immunology and histology are often indistinguishable from primary AIH. In common with primary AIH, mean ALT levels are around 700 and a hypergammaglobulinaemia is usually seen.⁴ In a series of 52 patients ANA and SMA were present in 82% and 73% of cases, respectively.³ Histological examination reveals chronic active hepatitis with a similar severity of inflammation and fibrosis seen at initial diagnosis of primary AIH.³

The prognosis of nitrofurantoin DILI is variable; crucially depending on the stage of disease at diagnosis and appropriate intervention. Early recognition and withdrawal of nitrofurantoin generally results in normalisation of liver biochemistry,^{3 6} however massive hepatic necrosis resulting in acute liver failure, or advanced fibrosis and cirrhosis leading to death and referral for transplantation have been reported.^{1 3 5} Importantly most of these events occurred with continued antibiotic use after the identification of raised transaminases, or reintroduction of the drug.⁶ Jaundice represents a critical stage with a 10% mortality risk.^{7 8} Liver biochemistry should therefore be serially monitored in patients requiring long-term nitrofurantoin prophylaxis and the drug withdrawn if hepatitis occurs.

Corticosteroids improve prognosis where transaminase levels fail to decrease despite drug withdrawal and early initiation may be life saving.⁵ Unlike primary AIH, relapse following immunosuppression withdrawal is rare if the offending drug has been discontinued.⁵ Rechallenges should be avoided as an accelerated hepatic injury usually results.^{3 9}

Figure 2 (A) Percutaneous liver biopsy (case 1). (B) Transjugular liver biopsy (case 2).

Learning points

- ▶ Long-term nitrofurantoin can cause an immune-mediated drug-induced liver injury, which can result in both acute liver failure and cirrhosis.
- ▶ Liver biochemistry, immunological and histological investigations are usually indistinguishable from autoimmune hepatitis and therefore the history is key.
- ▶ Early recognition of raised transaminases and drug withdrawal usually halts inflammation and prevents end-stage, however where transaminase fail to fall prompt introduction of corticosteroids should be initiated.
- ▶ Jaundice represents a critical stage with a 10% mortality risk.
- ▶ Drug rechallenges should be avoided.

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responsible for providing and interpreting the histological images presented and reviewing contents of the study related to the histological findings.

Competing interests None.

Patient consent Obtained.

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