Editor's key points

- Many clinicians are less familiar with the potential hepatic toxicity of nitrofurantoin than they are with other adverse events associated with the medication. Hepatic toxicity is rare, but it can be fatal, and it might be overlooked in the clinical setting.
- Risk factors for nitrofurantoin-induced liver injury include older age, female sex, and prolonged use. A genetic predisposition has also been suggested.
- If the decision to use nitrofurantoin for the prevention of recurrent cystitis is made, appropriate monitoring should include routine liver enzyme panels. Upon recognition of enzyme elevation, nitrofurantoin should be discontinued to prevent further inflammation and damage. Nitrofurantoin should not be re-challenged.

Points de repère du rédacteur

- De nombreux cliniciens connaissent moins bien la toxicité hépatique potentielle de la nitrofurantoïne que d'autres événements indésirables associés à ce médicament. La toxicité hépatique est rare, mais elle peut être fatale et pourrait passer inaperçue dans le milieu clinique.
- Parmi les facteurs de risque de lésions hépatiques induites par la nitrofurantoïne figurent un âge avancé, le sexe féminin et un usage prolongé. Une prédisposition génétique a aussi été évoquée.
- Si une décision est prise d'utiliser la nitrofurantoïne en prévention de cystites récurrentes, la surveillance appropriée devrait inclure des dosages systématiques des enzymes hépatiques. Si une élévation des enzymes est observée, il faudrait discontinuer la nitrofurantoïne pour prévenir davantage d'inflammation et de dommages. Il ne faut pas faire d'autres tentatives thérapeutiques avec la nitrofurantoïne.

Nitrofurantoin-induced liver failure

A fatal yet forgotten complication

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Nitrofurantoin is recommended as first-line therapy for uncomplicated cystitis owing to its comparable efficacy to cotrimoxazole, minimal resistance, and reduced risk of inducing resistance.[1] It has also been recommended as prophylaxis for recurrent cystitis.[2]

Most clinicians are familiar with the risk of peripheral neuropathy and pulmonary toxicity as adverse effects of nitrofurantoin; however, hepatotoxicity, which might present after acute or chronic use and which can be fatal, might be overlooked.[3]

Here we describe the fatal course of a patient with a drug-induced liver injury secondary to chronic nitrofurantoin use. We highlight the potential manifestations of nitrofurantoin-induced liver injury and offer suggestions for monitoring should chronic use be initiated.

Case

A 53-year-old woman presented to the hospital with jaundice and dark-coloured urine. On presentation, she was also noted to have scleral icterus; however, other physical examination findings were noncontributory, and she was afebrile with all vital signs within normal limits. Her past medical history included multiple sclerosis, chronic obstructive pulmonary disease, depression, recurrent urinary tract infections, and a remote cholecystectomy. The patient was an ex-smoker and did not consume alcohol or use illicit drugs. Her home medications included standard doses of clonazepam, paroxetine, zopiclone, and inhaled umeclidinium, in addition to a higher-than-standard dose of nitrofurantoin at 100 mg twice daily. She had begun therapy with nitrofurantoin 12 months earlier, and there had been no medication changes since then. She denied using over-the-counter medications or herbal products. Upon admission, nitrofurantoin was discontinued, and clonazepam was changed to lorazepam, as lorazepam does not depend on hepatic metabolism. All other home medications were continued. Bloodwork findings on admission are outlined in **Table 1** and were notable for transaminitis, direct hyperbilirubinemia, and elevated international normalized ratio.

Findings of her liver panel were normal 7 years before admission, without interval bloodwork. Test results for hepatitis A, B, and C viruses, HIV, antimitochondrial antibody, anti–smooth muscle antibody, and an Autoimmune Liver Disease panel (Mitogen Advanced Diagnostics Laboratory, Calgary, Alta) were all negative. α_1-Antitrypsin and ceruloplasmin levels were normal. Her immunoglobulin (Ig) A levels were mildly elevated (4.26 g/L; normal 0.6-4.2 g/L), IgG levels were normal, and she had positive antinuclear antibody (ANA) results (1:160).

Findings of abdominal imaging, including computed tomography and ultrasound, demonstrated patent portal-hepatic vasculature and noted hepatic nodularity suggestive of cirrhosis but without splenomegaly or other features of portal hypertension. Given the low suspicion of infectious, ischemic, autoimmune, and metabolic causes of her jaundice, hepatology was consulted. A liver biopsy on day 4 of admission demonstrated active

hepatitis with prominent parenchymal necrosis and collapse and accompanying cholestatic elements, without definite bridging fibrosis, compatible with drug-induced (nitrofurantoin) liver injury.

The patient rapidly declined over the next 7 days, developing refractory hepatic encephalopathy and ascites. Upon discussion with hepatology, given her expressed goals of care and wheelchair-using status, she was deemed unsuitable for transplant. Owing to a poor prognosis, and following a goals-of-care discussion with her family, we transitioned her to a comfort level of care. The patient passed away on day 24.

Discussion

In the case presented, the likely cause of liver failure was chronic use of nitrofurantoin, supported by liver histology corroborating a drug-induced cause. The Naranjo Adverse Drug Reaction Probability Score was used to assess causality.[4] Although the Naranjo scale is not specific to liver injury, it is the most extensively used adverse drug reaction causality assessment tool.[5] Her Naranjo score was 6 out of 13, indicating a *probable* adverse drug reaction to nitrofurantoin, receiving points for previously documented conclusive reports on this reaction (+1), the adverse event appearing after the suspected drug was administered (+2), there being no alternative causes that on their own could have caused the reaction (+2), and the adverse event being confirmed by objective evidence (+1). Her transaminase levels declined following nitrofurantoin discontinuation, with continued bilirubin level ascension. This likely represented further liver dysfunction secondary to "burnout," and therefore a point was not included for this.

Table 1. Patient laboratory values: *Values in boldface represent abnormal results.*

LABORATORY VARIABLE	PATIENT'S RESULT	NORMAL RESULT
Alanine aminotransferase	**1219** U/L	1-40 U/L
Aspartate aminotransferase	**1497** U/L	8-32 U/L
Alkaline phosphatase	**361** U/L	30-145 U/L
γ-Glutamyltransferase	**511** U/L	8-35 U/L
Total bilirubin	**203** μmol/L	0-24 μmol/L
Direct bilirubin	**161** μmol/L	0-7 μmol/L
Creatinine	40 μmol/L	40-100 μmol/L
Albumin	**30** g/L	33-48 g/L
Glucose	5.7 mmol/L	3.3-11.0 mmol/L
Lactate dehydrogenase	**551** U/L	100-235 U/L
Ferritin	**3480** μg/L	13-375 μg/L
International normalized ratio	**2.1**	0.9-1.1

We used MeSH terms *nitrofurantoin, drug induced liver injury,* and *case reports* to search for previous reports.

The first published report of nitrofurantoin-induced liver injury was in 1961,[6] with an appreciable number of reports since then.[7-15] Nitrofurantoin has been shown to cause a spectrum of hepatic injury ranging from mild hepatitis to fulminant liver failure and death.[9,10] Despite this, the overall incidence of liver injury is very rare, reported at 0.0003%.[16] It is likely this rarity that leads to this reaction being forgotten.

Nitrofurantoin-induced acute liver injury generally presents days to weeks after initiation of the drug.[17,18] It is characterized by a predominant hepatocellular enzyme elevation with possible symptoms of fever, rash, jaundice, abdominal pain, nausea, malaise, and anorexia.[17] Chronic injury is more insidious and usually presents after 6 months of therapy.[16,17] Clinical and laboratory features might resemble acute injury; however, patients generally lack the immunoallergic symptoms of fever and rash.[16] Patients also typically manifest abnormal liver function, including elevated international normalized ratio and bilirubin levels, suggesting greater hepatic damage. Additionally, chronic injury often demonstrates histologic and autoimmune-like serologic features including positive ANA and anti–smooth muscle antibody levels, and hypergammaglobulinemia.[3,19] A thorough medication history is essential, as immunology and histology findings often resemble primary autoimmune hepatitis.[3] Our patient presented with jaundice 1 year after continuous nitrofurantoin therapy and was found to have liver enzyme elevations, and histologic and autoimmune-like serologic features including positive ANA and mildly elevated IgA levels.

Risk factors for nitrofurantoin-induced liver injury include older age, female sex, and duration of use.[3,17,20,21] A genetic predisposition with HLA-B8 has also been suggested.[10,21] Correlation between the dose and development of liver injury is inconsistent. Lower doses of nitrofurantoin appear to be as effective as higher doses for long-term prophylaxis.[22] However, our patient was taking a cystitis-treatment dose (100 mg twice daily) for 1 year for prophylaxis for recurrent cystitis. The prophylactic dose is typically 50 to 100 mg daily for 6 months.[2] This reminds all care providers of the importance of reassessing a patient's medication regimen at each encounter.

The decision to initiate prophylactic antimicrobials for recurrent cystitis is controversial but should be based on individual patient assessment and a discussion of risks versus benefits.[23] Considerations for initiating nitrofurantoin prophylaxis should include the risk of hepatotoxicity and appropriate monitoring, particularly if any of the above risk factors are present. While no guidelines exist, we suggest a pragmatic approach of monitoring hepatic enzymes after 1 month for subacute reactions, followed by every 3 months during continuous therapy.[24,25] Upon recognition of enzyme elevation,

nitrofurantoin should be discontinued to prevent further inflammation and damage, enzyme levels should be monitored for improvement, and alternative explanations should be explored. Hepatotoxicity is reversible if recognized early and nitrofurantoin is stopped; however, continuation of the drug after clinical illness can be fatal.[3,11,18] Nitrofurantoin should not be re-challenged, as accelerated hepatic injury might occur.[3]

Conclusion

This report highlights the potentially fatal hepatic complications of nitrofurantoin. It joins a collection of others documenting this outcome. While rare, hepatotoxicity is a serious complication of nitrofurantoin use, and it might be overlooked in the clinical setting. It seems many clinicians are less familiar with this potential complication, particularly in relation to its oft-quoted neurologic and pulmonary toxicity. Certainly, the relative infrequency of reported reactions is likely the most influential aspect, joining a long list of medications reporting hepatic injury as *possible*. When patients are taking several medications, attributing liver enzyme elevations to one agent poses a challenge. However, the gravity of potential complications necessitates the exploration of nitrofurantoin as the causative agent. Our hope is that this report proves useful in reminding clinicians of this.

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Competing interests
None declared

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References

1. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* 2011;52(5):e103-20.
2. Epp A, Larochelle A. No. 250—recurrent urinary tract infection. *J Obstet Gynaecol Can* 2017;39(10):e422-31.
3. Hydes T, Wright M, Jaynes E, Nash K. Nitrofurantoin immune-mediated drug-induced liver injury: a serious complication of a commonly prescribed medication. *BMJ Case Rep* 2014;2014:bcr2013203136.
4. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30(2):239-45.
5. Causality. In: *LiverTox: clinical and research information on drug-induced liver injury* [Internet]. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 2019. Available from: **https://www.ncbi.nlm.nih.gov/books/NBK548049/**. Accessed 2019 Apr 1.
6. Ernaelsteen D, Williams R. Jaundice due to nitrofurantoin. *Gastroenterology* 1961;41:590.
7. Hebert MF, Roberts JP. Endstage liver disease associated with nitrofurantoin requiring liver transplantation. *Ann Pharmacother* 1993;27(10):1193-4.
8. Stricker BHC, Blok APR, Claas FHJ, Van Parys GEV, Desmet VJ. Hepatic injury associated with the use of nitrofurans: a clinicopathological study of 52 reported cases. *Hepatology* 1988;8(3):599-606.
9. Schattner A, Von der Walde J, Kozak N, Sokolovskaya N, Knobler H. Nitrofurantoin-induced immune-mediated lung and liver disease. *Am J Med Sci* 1999;317(5):336-40.
10. Burgert SJ, Burke JP, Box TD. Reversible nitrofurantoin-induced chronic active hepatitis and hepatic cirrhosis in a patient awaiting liver transplantation. *Transplantation* 1995;59(3):448-9.
11. Thuluvath PJ, Mckendrick MW. Nitrofurantoin induced chronic liver disease. *J Antimicrob Chemother* 1986;18(2):291-2.
12. Miller ARO, Addis BJ, Clarke PD. Nitrofurantoin and chronic active hepatitis. *Ann Intern Med* 1982;97(3):452.
13. Black M, Rabin L, Schatz N. Nitrofurantoin-induced chronic active hepatitis. *Ann Intern Med* 1980;92(1):62-4.
14. Ramadas P, Krishnan P, Frechette V. An unusual case of nitrofurantoin-associated hepatotoxicity. *Am J Ther* 2018;25(3):e378-9.
15. Kapral N, Saxena R, Sule AA, Markle B. Nitrofurantoin: friend or foe? *BMJ Case Rep* 2018;2018:bcr2018225629.
16. Nitrofurantoin. In: *LiverTox: clinical and research information on drug-induced liver injury* [Internet]. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 2019. Available from: **https://livertox.nih.gov/Nitrofurantoin.htm**. Accessed 2019 Apr 1.
17. Sakaan SA, Twilla JD, Usery JB, Winton JC, Self TH. Nitrofurantoin-induced hepatotoxicity: a rare yet serious complication. *South Med J* 2014;107(2):107-13.
18. Cetti RJ, Venn S, Woodhouse CRJ. The risks of long-term nitrofurantoin prophylaxis in patients with recurrent urinary tract infection: a recent medico-legal case. *BJU Int* 2009;103(5):567-9.
19. Thiim M, Friedman LS. Hepatotoxicity of antibiotics and antifungals. *Clin Liver Dis* 2003;7(2):381-99.
20. Stine JG, Chalasani N. Chronic liver injury induced by drugs: a systematic review. *Liver Int* 2015;35(11):2343-53.
21. Stine JG, Northup PG. Autoimmune-like drug-induced liver injury: a review and update for the clinician. *Expert Opin Drug Metab Toxicol* 2016;12(11):1291-301.
22. Muller AE, Verhaegh EM, Harbarth S, Mouton JW, Huttner A. Nitrofurantoin's efficacy and safety as prophylaxis for urinary tract infections: a systematic review of the literature and meta-analysis of controlled trials. *Clin Microbiol Infect* 2017;23(6):355-62.
23. Byron JK. Urinary tract infection. *Vet Clin North Am Small Anim Pract* 2019;49(2):211-21.
24. *Long-term nitrofurantoin safety monitoring guidance.* London, UK: NHS; 2016. Available from: **https://www.telfordccg.nhs.uk/your-health/medicines-management/prescribing-guidelines/infections/2308-nitrofurantoin-safety-monitoring-guidance-may-2016-1/file**. Accessed 2019 Apr 1.
25. Sherigar JM, Fazio R, Zuang M, Arsura E. Autoimmune hepatitis induced by nitrofurantoin. The importance of the autoantibodies for an early diagnosis of immune disease. *Clin Pract* 2012;2(4):e83.

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