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Systemic Inflammatory Response Syndrome Secondary to Nitrofurantoin

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Abstract

Nitrofurantoin is considered optimal treatment for acute uncomplicated cystitis by the Infectious Diseases Society of America and is being increasingly recommended due to microbial resistance to sulfamethoxazole/trimethoprim and various fluoroquinolone antibiotics. Adverse effects of nitrofurantoin are generally considered mild, with gastrointestinal complaints being the most common. However, there have been isolated case reports describing a more severe systemic inflammatory response syndrome–like reaction, which leads to diagnostic challenges and treatment complications. We report the case of a patient with repeat episodes of systemic inflammatory response syndrome secondary to nitrofurantoin, which was initially attributed to recurrent urinary tract infections.

Keywords

nitrofurantoin, systemic inflammatory response syndrome, urinary tract infections, drug-related side effects, adverse reactions

Introduction

Nitrofurantoin is considered optimal treatment for acute uncomplicated cystitis by the Infectious Diseases Society of America (IDSA) and is being increasingly recommended due to microbial resistance to sulfamethoxazole/trimethoprim and various fluoroquinolone antibiotics.[1] Nitrofurantoin is also a commonly used medication for prophylaxis of acute urinary tract infections (UTIs). Gastrointestinal complaints, including nausea and vomiting, are the most commonly reported adverse events with nitrofurantoin.[2] Although less common, more severe reactions including peripheral neuropathy, hemolytic anemia, hepatitis, cholestatic jaundice syndrome, interstitial lung disease, and pulmonary fibrosis have been described. Hypersensitivity reactions, including anaphylaxis and drug-induced fever, have also been documented after administration of nitrofurantoin.[2,3] There have been isolated case reports describing systemic inflammatory response syndrome (SIRS) after nitrofurantoin administration with associated abrupt onset of fever, malaise, leukocytosis, and occasionally pleuritis.[4-7] This often leads to a diagnostic challenge to determine if SIRS is due to transition to a more complicated UTI, such as acute pyelonephritis, or to a drug-associated adverse event.

In this case report, the patient developed SIRS with abrupt onset of fever, leukocytosis, and hypotension in less than 24 hours after nitrofurantoin administration, which had been prescribed for uncomplicated urgency and frequency. Symptoms rapidly resolved after discontinuation of the medication. The patient developed similar symptoms of frequency and dysuria 2 months later, and was re-challenged with nitrofurantoin, which led to a similar episode of SIRS in less than 24 hours. Symptoms again rapidly resolved after discontinuing nitrofurantoin. All bacterial cultures were negative during both exposures to nitrofurantoin.

Case Presentation

This 58-year-old postmenopausal Caucasian female has a past medical history significant for hypothyroidism and cochlear hydrops and surgical history of partial thyroidectomy, cholecystectomy, benign breast nodule removal, adenoidectomy, and tonsillectomy. Home medications include levothyroxine 75 μg once daily, hydrochlorothiazide/triamterene 25 mg/37.5 mg once daily, a multivitamin once daily, and cholecalciferol 1000 units once daily. Her only known allergies are to yellowfin tuna and a possible reaction to

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shellfish. Family history was significant for type 2 diabetes mellitus and myocardial infarction in her mother and colon cancer in her father. The patient drinks alcohol socially, is a nonsmoker, and denies any illicit drug use. The patient reports that she had previously received sulfamethoxazole/trimethoprim for a previous uncomplicated UTI with no adverse events.

After a hiking vacation in Yosemite National Park, the patient developed post-coital urgency and frequency, and was prescribed nitrofurantoin 100 mg twice daily for a UTI. The patient had no prior exposure to nitrofurantoin. In less than 24 hours after administration of the first dose of nitrofurantoin, the patient experienced an abrupt onset of fever, chills, lightheadedness, chest congestion, pleuritis, and generalized weakness. She presented to the emergency department at a local hospital and was found to be hypotensive with a blood pressure of 90/51 mm Hg, febrile with a temperature of 101.7 °F, but with normal oxygen saturations at 96% on room air. She required 2 L of normal saline solution to stabilize her blood pressure. Blood and urine cultures were drawn, and she was given 1 g of ceftriaxone IV (intravenous) and ondansetron 4 mg IV. The complete blood count (CBC) was remarkable for leukocytosis with white blood cell (WBC) count of 17.1 $\times$ 10^3/μL with 83% segs and 9% bands. The complete metabolic panel (CMP) was only remarkable for a potassium level of 3.4 mmol/L. Lactate was within normal limits at 1.4 mmol/L. Urinalysis showed 2+ blood, trace leukocyte esterase, 5 to 10 WBCs, 0 to 4 red blood cells, and 1+ bacteria. Blood and urine cultures were collected prior to administration of parenteral antibiotic and subsequently were negative. She was discharged from the local emergency department with a prescription for levofloxacin for suspected acute pyelonephritis. However, all symptoms improved within 24 hours of discharge. The patient completed the 7-day course of levofloxacin. On return home, an extensive workup was completed by her primary care physician due to her travel history and severity of symptoms. The CBC, CMP, C-reactive protein, and erythrocyte sedimentation rate were within normal limits. Lyme disease serology, Lyme immunoglobulin M (IgM), Lyme IgG, *Borrelia burgdorferi* C6 peptide antibody (Ab) total, and CD 57 for Lyme disease were all negative. Ehrlichia, Rocky Mountain spotted fever, and West Nile virus IgG and IgM antibodies were all negative. The symptoms at that time were attributed to a likely bacterial infection, presumably the UTI.

Two months later, the patient experienced another episode of post-coital urinary frequency and urgency and took nitrofurantoin 100 mg twice daily over a 24-hour period. The next morning, the patient experienced an abrupt onset of fevers, chills, myalgia, pleuritis, and weakness, as well as nausea and vomiting. She presented to her primary care physician with a temperature of 102.6 °F, hypotension with a systolic blood pressure of 80 mm Hg, tachycardia with heart rate of 120 beats per minute, and was tilt test positive. She did not have a rash or urticaria and was fully alert and oriented. Her physical examination was unremarkable, except for generalized body aches. She received 2 L of normal saline to stabilize her blood pressure and was prescribed levofloxacin after blood and urine cultures were obtained. Her CBC was remarkable for a WBC count of 22 000 $\times$ 10^3/μL with 94% granulocytes. Urinalysis showed 500 leu/μL and 250 Ery/μL. CMP was only remarkable for a potassium level of 3.2 mmol/L. Within 24 hours, symptoms had resolved once again. The patient returned to her primary care provider and was afebrile and normotensive. A repeat CBC was performed, and her WBC had decreased to 8.5 $\times$ 10^3/μL, although the percentage of granulocytes was still elevated at 86.6%. Her hemoglobin had decreased from 12 g/dL to 10 g/dL and hematocrit had decreased from 38% to 34%. Platelets decreased from 138 $\times$ 10^3/μL to 128 $\times$ 10^3/μL. The patient's D-dimer was slightly elevated at 0.6 (ref $<$ 0.4). Partial thromboplastin time and international normalized ratio were unremarkable. Haptoglobin was also within normal limits at 191 mg/dL. Repeat CMP was only remarkable for a potassium level of 3.0 mmol/L. Within 48 hours, the patient's WBC differential was within normal limits. The patient recognized that she had taken nitrofurantoin both times shortly before the onset of symptoms and reported this to her primary care provider when returning the second day for follow-up examination and blood work. Because all cultures drawn during these 2 occurrences were negative and her symptoms quickly resolved after discontinuation of nitrofurantoin, her SIRS symptoms were believed to be secondary to an adverse drug reaction to nitrofurantoin. Levofloxacin was discontinued. The patient was advised to avoid nitrofurantoin use in the future and nitrofurantoin was listed it as an adverse drug reaction (SIRS) in medical records to prevent recurrence of this reaction. The application of the Naranjo scale (Table 1) identifies this reaction to nitrofurantoin as a definite adverse drug reaction, with a score $\geq$9.[8]

Discussion

Only a few other case reports could be found in the literature, which explicitly document a similar type of reaction to nitrofurantoin as the patient discussed in this case report. Forster and colleagues[4] reported a 77-year-old male patient with bladder cancer status post-radical cystoprostatectomy and ileostomy who was treated with nitrofurantoin prophylaxis for recurrent UTIs. Two weeks after beginning nitrofurantoin therapy, the patient presented to the emergency room with fever, chills, and leukocytosis, which led to a broadening of antibiotic coverage to include tigecycline and aztreonam. The patient was restarted on nitrofurantoin 2 additional times and experienced SIRS each time, which resolved when the nitrofurantoin was discontinued, similar to our patient.[4] In a report published by Gandotra and colleagues,[5] a 74-year-old female was treated with nitrofurantoin for a UTI based on local antibiogram results and a urine culture positive for *Escherichia coli* and subsequently experienced chills, fever,

Table 1. Naranjo ADR Probability Scale[a,8].

		Yes	No	Do not know	Case report patient score
1.	Are there previous *conclusive* reports on this reaction?	+1	0	0	+1
2.	Did the adverse event appear after the suspected drug was administered?	+2	−1	0	+2
3.	Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	+1
4.	Did the adverse reaction reappear when the drug was re-administered?	+2	−1	0	+2
5.	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	+2
6.	Did the reaction reappear when a placebo was given?	−1	+1	0	+1
7.	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8.	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0
9.	Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	+1
10.	Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
				Total score	11

[a]Score interpretation[8]: ≥9, definite adverse drug reaction; 5-8, probable adverse drug reaction; 1-4, possible adverse drug reaction; 0, doubtful adverse drug reaction.

tachypnea, and tachycardia. In this particular case report, the patient also developed a left bundle branch block and transaminitis. The patient was re-dosed with nitrofurantoin 2 different times during the same week and experienced SIRS each time, with resolution of symptoms after discontinuation of nitrofurantoin.[5] Gohar and colleagues[6] reported a case of SIRS due to nitrofurantoin use in an 83-year-old female with a history of recurrent UTIs. Within a few hours of receiving nitrofurantoin, the patient developed lethargy, chills, and fever and was treated with presumed sepsis secondary to UTI. After completing treatment with a cephalosporin antibiotic, the patient was restarted on nitrofurantoin for UTI prophylaxis, and developed recurrent malaise, chills, and fever. With no evidence of infection and return of hemodynamic stability after discontinuation of nitrofurantoin, the patient was discharged home and advised against the use of future use of nitrofurantoin.[6] In one final case reported by *Hospital Medicine*, a 79-year-old woman with a history of recurrent UTIs presented with a 1-week history of fever, chills, nausea, vomiting, and abdominal discomfort after treatment with nitrofurantoin for a UTI. With negative cultures, no signs of infection, and symptomatic improvement after nitrofurantoin discontinuation, it was determined that nitrofurantoin was the likely cause of symptoms.[7] Bäck and colleagues also discussed a similar clinical syndrome to our patient. In this study, 18 patients who received nitrofurantoin developed hypersensitivity including fever, cough, malaise, pleuritis, leukocytosis, and occasionally eosinophilia. They were analyzed for various antibodies and for lymphocyte transformation. This patient population was compared with a control group of 33 patients who received nitrofurantoin but did not develop hypersensitivity reactions. Ten of the hypersensitive patients were positive for the lymphocyte transformation test. IgE antibodies were negative in both groups; however, both groups developed IgG antibodies and the hypersensitive patients had higher titers. This study concluded that there seems to be an association between high IgG antibody titers and nitrofurantoin sensitivity.[9]

SIRS is one of several hypersensitivity reactions rarely reported with the use of nitrofurantoin. Anaphylaxis may also occur after administration of nitrofurantoin, which is a rare but severe allergic reaction which typically results in rash, swelling of tongue or throat, shortness of breath, and hypotension. Although the patient described in this case developed hypotension, she showed no other signs that would lead physicians to believe this was an anaphylactic reaction. The presence of fever in this case further distinguishes SIRS from an anaphylactic reaction, as fever is not a sign of anaphylaxis.

Conclusion

Nitrofurantoin is widely available and commonly prescribed for the prophylaxis and treatment of UTIs. With increased utilization of this medication, rare adverse reactions such as SIRS may occur more frequently. The exact mechanism leading to these rare adverse effects, including SIRS, is not completely understood. Understanding these pathways will help clinicians tailor antibiotic choices for patients and minimize adverse effects. SIRS like symptoms can easily complicate the clinical picture for a patient prescribed nitrofurantoin, especially in the inpatient setting where patients may have

several medical comorbidities. A drug reaction of this type could easily be mistaken for a new-onset bacterial infection or worsening of a previous infection, leading to additional and unnecessary antibiotics. A better understanding of the immunologic reactions to nitrofurantoin is needed in order to properly identify these drug reactions and avoid unnecessary tests and therapies. Few articles exist that document a SIRS type reaction to nitrofurantoin; however, it appears it may be a more common phenomenon than previously thought. More research is needed to better understand this phenomenon and bring awareness to this particular type of adverse reaction to nitrofurantoin.

The patient gave informed consent for the case report to be written and submitted for publication.

Authors' Note

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

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