Urine Discoloration Associated With Metronidazole: A Rare Occurrence

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Jane Y. Revollo, PharmD¹, Jeffrey C. Lowder, MD²,
Andrew S. Pierce, MD^{1,2}, and Jennifer D. Twilla, PharmD^{1,3}

Abstract

Objective: To report a case of metronidazole-induced urine discoloration in a patient with *Clostridium difficile* sepsis. **Case Summary:** A 52-year old man was admitted with sepsis secondary to *C difficile* colitis, which developed after he had been recently treated with broad-spectrum antibiotics for community-acquired pneumonia. The *C difficile* infection was treated with metronidazole, and the patient subsequently developed cola-colored urine. When metronidazole was inadvertently stopped for 34 hours, the urine color returned to normal, but again darkened when the medication was restarted. The patient suffered no clinically adverse effects from the abnormal urine color. He completed the treatment course for colitis and was discharged to home. **Discussion:** Urine discoloration is a known side of metronidazole. However, it has been poorly reported in the literature, and many clinicians are unaware that it may happen. Here we report the case of a patient who developed dark urine while receiving treatment with metronidazole. Other potential causes of the urine discoloration were explored, including hemolysis, rhabdomyolysis, or adverse reactions to other medications, with no clear positive findings. An objective causality assessment (Naranjo probability scale) revealed that the urine discoloration was probably due to metronidazole. **Conclusions:** Metronidazole can cause urine discoloration without otherwise harming the patient. Clinicians should be aware of this potential side effect and provide reassurance to patients who develop abnormal urine that there are no clinically relevant adverse outcomes.

Keywords

metronidazole, Flagyl, dark urine, urine discoloration, adverse effect

Introduction

Metronidazole is a nitroimidazole antibiotic, which is bactericidal against gram-positive and gram-negative anaerobic bacteria. It is frequently used for infections caused by anaerobic and protozoal organisms, including *Clostridium difficile*. Common adverse effects of metronidazole include gastrointestinal upset, headache, and taste disturbances.¹ More rarely, discoloration of urine has been reported with metronidazole use.^{1–7} Although urine discoloration is listed in the package insert, only 2 case reports have been published in the primary literature linking metronidazole to this adverse effect.^{2,4}

Here we report the case of a patient receiving intravenous metronidazole, who developed urine discoloration after 2 days of therapy that reappeared after rechallenge with the medication.

Case Report

The patient was a 52-year-old Caucasian male with a past medical history of hypertension, coronary artery disease

(status post-percutaneous coronary intervention and stent placement), hyperlipidemia, and depression. His home medications included aspirin, omeprazole, atenolol, losartan, isosorbide mononitrate, rosuvastatin, paroxetine, niacin, and prasugrel. The patient had been previously admitted to the hospital for community-acquired pneumonia. He was treated with broad-spectrum antibiotics, vancomycin and piperacillin-tazobactam, and discharged on azithromycin and moxifloxacin. The patient subsequently developed *C difficile* colitis and was readmitted to the intensive care unit at an outside hospital with severe sepsis. On admission he was started on intravenous metronidazole 500 mg q8h and

¹Methodist University Hospital, Memphis, TN, USA

²University of Tennessee Health Science Center College of Medicine, Memphis, TN, USA

³University of Tennessee Health Science Center College of Pharmacy, Memphis, TN, USA

Corresponding Author:

Jennifer D. Twilla, PharmD, Department of Pharmacy, Methodist University Hospital, 1265 Union Ave, Memphis, TN 38104, USA.
Email: jennifer.twilla@mlh.org

Figure 1. A. Urine color after initial administration of metronidazole. B. Urine color after discontinuation of metronidazole. C. Urine color after readministration of metronidazole.

oral vancomycin (unknown dose). While in the hospital, he was continued on rosuvastatin, paroxetine, and niacin and started lactobacillus acidophilus, oxybutynin, and hydromorphone, in addition to the antibiotics.

When the patient was transferred to our hospital, he was found to be hypotensive with acute kidney injury (serum creatinine 2.3, baseline 1.0) and had tea-colored urine. The presumed cause of the kidney injury was sepsis related to the *C difficile* colitis. With aggressive intravenous hydration and antibiotics (IV metronidazole 500 mg q6h, oral fidaxomicin 100 mg twice daily), the acute renal injury resolved, and the patient became normotensive. However, his urine continued to darken to cola colored (Figure 1A). The urine discoloration was initially attributed to hemolysis secondary to postulated disseminated intravascular coagulation in the setting of ongoing sepsis. However, urine and serum workup for hemolysis was negative. Urinalysis was positive for low levels of bilirubin but negative for blood. Creatine kinase was 81 (normal range = 35-232), thereby ruling out rhabdomyolysis. After 7 days of treatment with metronidazole at our hospital, the medication was inadvertently stopped and not resumed for 34 hours. During this window, the patient's urine dramatically cleared and returned to a yellow-gold color (Figure 1B). Metronidazole has a half-life of ~8 hours; therefore, the medication would have been almost completely eliminated during this period.¹ After the 34-hour hiatus, metronidazole was restarted, and within 8 hours, the patient's urine had become cola colored again (Figure 1C). Due to the negative hemolysis findings and the timing of urine discoloration with regard to metronidazole administration, the cause of the urine discoloration was linked to the medication.

Discussion

In this article, we document the third reported case of urine discoloration due to metronidazole use. While the first report linking metronidazole to urine discoloration was reported in the literature more than 40 years ago,² it was not

until 2001 that this topic resurfaced. Geeting and Roberts reported urine discoloration in a patient who overdosed on metronidazole tablets in a suicide attempt.⁴ On presentation to the emergency department, the patient had dark brown urine but was otherwise asymptomatic. In this letter, the authors stated the medication manufacturer, G.D. Searle & Co, reported urine discoloration most commonly occurred with medication overdose or in patients with hepatic dysfunction.⁴

Abnormal urine color is a known side effect of a number of drugs. Medications including rifampin, doxorubicin, and propofol can cause urine discoloration ranging from red or orange to blue-green. Dark brown or black urine has been associated with drugs such as nitrofurantoin, acetaminophen overdose, and metronidazole.⁵ While the exact mechanism is unknown, it has been hypothesized that the pigment of an azometabolite is responsible for metronidazole-induced urine discoloration.¹ Despite the changes in urine color, no adverse clinical events have been reported.

Our patient developed urine discoloration after 2 days of metronidazole therapy. Full workup of alternative causes for urine discoloration was conducted. Urinalysis did not reveal an explanation for the dark-colored urine. Other etiologies were considered, including hemolysis and rhabdomyolysis. However, urinalysis was negative for blood. The creatine kinase level was within normal limits and the statin was the continuation of a home medication, and it is unlikely that the urine discoloration was due to statin-induced rhabdomyolysis. The abnormal urine coloration resolved on discontinuation of the medication but returned within 8 hours when the drug was restarted. According to the Naranjo adverse drug reaction probability scale, metronidazole was likely responsible for the change in urine color (score 8-10). The patient had no hepatic dysfunction and received approved doses of the medication. Furthermore, he denied any adverse effects, such as pain or dysuria, with the urine discoloration.

Although urine discoloration is listed as an adverse effect of metronidazole, it occurs rarely. However, it is visually alarming and may be upsetting to the patient or family members. Clinicians should be aware of this adverse effect and provide reassurance that no clinical events occur due to this effect.

Declaration of Conflicting Interests

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