Case Report

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Recurrent Neuropsychiatric Symptoms in a Patient With Repeated Exposure to Metronidazole: A Case Report

Urgent Message: Metronidazole, even during short courses of therapy, can result in disabling neuropsychiatric symptoms. It is important for clinicians to be knowledgeable about these relatively uncommon but serious adverse medication reactions.

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Abstract

Introduction: Metronidazole is a commonly prescribed antibiotic. While gastrointestinal symptoms are the most frequent side effects, adverse neuropsychiatric symptoms have also been well established. Given the relative infrequency of such neuropsychiatric symptoms, clinicians may not consider metronidazole as a possible cause, leading to unnecessary workups.

Clinical Presentation: A 57-year-old man with stable stage IV colorectal cancer and recent hospitalization for hepatic abscess currently being treated with metronidazole had an urgent care (UC) telehealth visit 1-week post-discharge with complaints of 2-3 days of new-onset anxiety and insomnia. He denied systemic symptoms, including fever, and denied headache, vision changes, and seizures.

Physical Exam: His home-measured vital signs were normal. He appeared chronically ill and anxious with notable psychomotor agitation. When palpating his own abdomen, he reported no tenderness. His neurologic and mental status exam revealed no focal deficits.

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Case Resolution: The patient was initially diagnosed with adjustment disorder, and he was started on a selective serotonin reuptake inhibitor (SSRI). At subsequent visits, he developed worsening anxiety and more severe psychomotor agitation. His laboratory assessment was normal. Additional psychotropic medication adjustments were made but provided no relief, and his symptoms persisted until he completed the oral (PO) metronidazole. When the liver abscess recurred months later, similar symptoms returned shortly upon restarting metronidazole and resolved again when the medication was stopped.

Conclusion: While relatively uncommon, metronidazole can cause a variety of neuropsychiatric adverse reactions. Cessation of metronidazole most often results in full resolution of symptoms.

Introduction

Metronidazole is a synthetic antiprotozoal and antibacterial agent prescribed for a wide range of common infectious conditions seen in UC centers.[1] In 2023, nearly 1% of all U.S. UC visits received a metronidazole prescription, resulting in an estimated 1.7 million prescriptions, according to exclusive data analysis provided by Experity for this article. The most frequent and well-known adverse reactions involve gastrointestinal symptoms (eg, nausea, vomiting, diarrhea, cramping). However, a variety of less common adverse reactions involving neuropsychiatric symptoms have also been described, including peripheral neuropathy, confusion, gait instability, dizziness, seizures, acute psychosis, and encephalopathy.[1] Metronidazole-related neuropsychiatric reactions appear to be idiosyncratic and can occur even with short therapeutic courses, although the risk is higher with prolonged duration of treatment.[2]

The largest population study to date examining neurologic adverse outcomes associated with metronidazole found the risk of any severe neurologic event was 0.25%, with central nervous system (CNS) adverse events approximately fourfold more likely than those affecting the peripheral nervous system (PNS).[3] Patients at highest risk are those receiving prolonged courses and intravenous administration as well as those with low body mass index (BMI), cirrhosis or chronic kidney disease.[4]

Clinical Presentation

A 57-year-old man with a history of stable, stage IV colorectal cancer with metastases to the liver and lungs and no history of psychiatric illness presented in a video-based telemedicine UC visit 1 week after being discharged from the hospital where he was treated for a hepatic abscess. During his hospitalization, he was treated with intravenous (IV) ceftriaxone and metronidazole. When his condition stabilized, he was discharged with plans to continue a PO third-generation cephalosporin and PO metronidazole (500mg 3 times daily) until he was able to follow-up with an infectious disease specialist in several weeks. At the telemedicine UC visit, he reported high levels of anxiety and increasing difficulty sleeping. He stated that his fevers related to the abscess had resolved, and he denied abdominal pain, nausea, vomiting, diarrhea, constipation, headaches, and depressive symptoms. He denied any alcohol or drug use.

Physical Exam Findings

The patient's vital signs were taken using equipment he had in his home. He was afebrile and reported a normal heart rate, blood pressure, and oxygen saturation. He appeared thin, but not cachectic, and chronically ill, but in no acute distress. He was speaking in full sentences on video and his face and extremity movements appeared symmetric. The patient was asked to palpate throughout his abdomen and reported no tenderness. His neurologic and mental status exams were notable for visible signs of anxiety, a relatively flat affect, mild-moderate psychomotor agitation and obvious restlessness. There was no apparent rigidity or spontaneous clonus.

Urgent Care Management

The patient was initially diagnosed with adjustment disorder and started on a selective serotonin reuptake inhibitor (SSRI). He and his wife were asked to track his symptoms and check-in with his oncologist to determine if this may be related to his chemotherapeutic regimen.

Case Continuation and Timeline

Five days later, the patient presented for a second telemedicine-based UC visit. He reported that despite starting the SSRI as prescribed, he had noticed progression to a nearly intolerable level of restlessness and anxiety. He had a non-focal neurologic examination and normal vital signs again, so emergency department (ED) referral was not pursued. However, his psychomotor agitation was objectively more severe over video-exam, and he was unable to remain seated during the visit, pacing while his wife spoke for him.

Importantly, the patient and his wife both confirmed that he had never had similar symptoms, and there were no particular thoughts or worries causing him the anxiety. The medication reconciliation did not reveal any obvious culprits for either the anxiety or akathisia. At the second visit, he was diagnosed with anxiety, and the dose of the SSRI was increased. He was also prescribed hydroxyzine to help with severe anxiety/panic, which was preventing him from sleeping. He was provided with an urgent referral to psychiatry at this time and given instructions to seek care in the ED immediately if his symptoms continued to progress.

Given the rapid onset and severity of symptoms in a patient with no prior psychiatric history, the UC clinician ordered outpatient laboratory tests, including thyroid-stimulating hormone and a basic metabolic panel. Both returned results all within normal limits.
On follow-up with his oncologist, the possibility of a rare neuropsychiatric side effect to one of his antibiotics was considered, and the antibiotics were stopped as he had no radiologic evidence of residual abscess in the liver. Over the next few weeks, his symptoms improved dramatically. However, his oncologist felt that his psychotropic medications were more likely resulting in his improvement and discounted the possibility of an antibiotic adverse reaction.

Diagnostic Assessment and Case Conclusion

A few months later, the patient's liver abscess recurred, and he was again started on metronidazole. Within 2 days, the patient had return of restlessness (ie, akathisia) and anxiety. As the cause of his symptoms now became increasingly apparent, the metronidazole was stopped, and his antibiotic therapy was modified. Again, he had quick resolution of his neuropsychiatric symptoms. He decided to taper off the SSRIs as his symptoms had resolved again when the metronidazole was held. With avoidance of metronidazole, his symptoms of anxiety and restlessness did not return.

Discussion

Metronidazole is among the most commonly prescribed antibiotics in the UC setting. While neuropsychiatric adverse reactions occur in only an estimated <1% of cases,[3] it would be expected that over 4,000 cases of such reactions would occur among patients receiving metronidazole from UC centers in the U.S. each year, as per exclusive data analysis provided by Experity for this article. However, given that neurological symptoms tend to resolve for most patients after stopping the antibiotic, it is likely that many subclinical cases of metronidazole-associated neuropsychiatric reactions never reach medical attention. There is also considerable overlap between these neurologic symptoms and antibiomania (ie, mania associated with starting an antibiotic), however, the mechanisms of antibiomania are distinct and not antibiotic-class specific.[5] Many antibiotics, including metronidazole,[6] can cause antibiomania, however, fluoroquinolones and clarithromycin are the most common offenders.[7] Overall, there is considerable overlap and inconsistent nomenclature for these neuropsychiatric reactions. Since both conditions resolve in most cases when the antibiotic is discontinued, clinically differentiating the 2 is less material than identifying that the antibiotic is the likely culprit.

Whereas antibiomania is a clinical diagnosis, direct CNS tissue injury can occur with metronidazole, which creates characteristic findings on brain magnetic resonance imaging (MRI).[8] The patient in the case presented did not undergo brain imaging, however, his akathisia was more suggestive of metronidazole-related CNS toxicity than antibiomania, which tends to have more manic or psychotic features.[7] Metronidazole-related neurotoxicity most commonly affects the CNS causing cerebellar symptoms (eg, dyscoordination, dysarthria, gait disturbance) but can also cause akathisia, encephalopathy, and even seizures.[9] While less common, metronidazole-related PNS toxicity has also been a long recognized, rare complication.[10] The most common PNS disorder associated with metronidazole therapy is peripheral neuropathy, however, autonomic neuropathy has also been reported. Metronidazole related PNS disorders almost always involve treatment courses exceeding 4 weeks and cumulative doses over 42 grams.[11] Compared with CNS injury, metronidazole-related PNS toxicity has a more favorable prognosis, with nearly all patients experiencing full recovery after discontinuing metronidazole.[11] Manifestations of peripheral neuropathies include paresthesia and numbness with characteristic findings evident in patients who have nerve conduction studies.[12]

While the most important facet of treatment of metronidazole-related neuropsychiatric symptoms is prompt discontinuation of the medication, there are reports in the literature of corticosteroid treatment and supplementation with thiamin (Vitamin B1) and cyanocobalamin (Vitamin B12) perhaps hastening recovery in patients with CNS symptoms and lesions visible on brain MRI.[13,14] While B vitamin supplementation is typically safe, given the doses and

duration of corticosteroid use described in the literature, it is recommended that this decision be deferred to a neurologist or other appropriate specialist at follow-up. Neuropsychiatric symptoms, such as agitation and anxiety, can be treated symptomatically and limited courses of benzodiazepines are a reasonable option. Unlike generalized anxiety disorder, in which SSRIs are recommended as a first-line therapy, there are no reports of SSRIs reducing metronidazole-related neuropsychiatric symptoms.

"For metronidazole-related neurologic symptoms, if the diagnosis is correctly made, the prognosis for affected patients is generally favorable."

Because metronidazole relies on both renal and hepatic clearance, patients with more advanced liver or kidney disease are at greater risk of neurotoxicity.[15] Low body mass index (BMI) is also a risk factor for neurologic toxicity.[15] As such, patients with end-stage renal disease (ESRD) and/or severe hepatic impairment (Child-Pugh Class C) require dose adjustment if metronidazole therapy is prescribed.[1] The patient in this case had both low BMI and some degree of liver disease. In patients with either liver or kidney disease and low BMI, it is useful to consider alternative therapies. While there are no studies that specifically address the likelihood of neurologic symptoms recurring with repeat exposure to the drug (as was seen with the patient in the case presented), if neurologic symptoms arise in a patient exposed to metronidazole, it is prudent to consider alternative agents—as would be the case after any adverse drug reaction.

A 2011 systematic review of case reports found that the average duration of therapy with metronidazole before onset of neurologic symptoms was 54 days. However, importantly 26% of cases occurred within the first week of therapy, and 11% occurred within the first 3 days.[2] Given that neuronal, especially CNS, toxicity can occur with even short courses of metronidazole, consideration for similarly efficacious and safer therapeutic alternatives to metronidazole is advisable in the setting of low-risk infections. For example, bacterial vaginosis (BV) is the most common indication for metronidazole prescribing in outpatient settings.[16] However, there are many alternative treatment options for BV, including intravaginal metronidazole, which does not carry the same risk of systemic side effects.[17] As BV frequently recurs even after treatment with oral metronidazole, shared decision-making and counseling about the risks of repeat oral metronidazole exposure is worthwhile, especially as intravaginal therapy is safer, equally efficacious, and also associated with fewer minor side effects (eg, nausea, metallic taste) as well.[18,19]

Failing to identify a temporally associated change in medications that corresponds to the onset of symptoms can lead to both delays in stopping the offending medication and in unnecessary testing and referrals.[20] For metronidazole-related neurologic symptoms, if the diagnosis is correctly made, the prognosis for affected patients is generally favorable. With cessation of metronidazole, 65% of patients have complete resolution of symptoms and 29% experience significant improvement with recovery generally occurring over days-to-weeks.[2,21]

Takeaways For Urgent Care Providers

Metronidazole, even during short courses of therapy, can result in disabling neuropsychiatric symptoms. It is important for UC clinicians to be knowledgeable of serious adverse medication reactions, even if relatively uncommon, especially those related to the medications they commonly prescribe. In patients with new neuropsychiatric symptoms, a thorough review of all prescription and over-the-counter medications is essential. When metronidazole is implicated as a cause of neurologic toxicity, recognition and prompt discontinuation are imperative to allow for the highest likelihood of rapid and complete recovery. Finally, it is critical to avoid premature closure. Acute neuropsychiatric symptoms have a broad differential diagnosis, and in patients with severe symptoms (eg, inability to walk, seizures), ED referral is recommended, even if an adverse medication reaction is suspected.

Ethics Statement and Patient Perspective

Verbal informed consent for publication was obtained from the patient to share his story. He was hopeful that clinicians might learn from his experience about this relatively uncommon but severe and life altering side effect of metronidazole.

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References

1. U.S. Food and Drug Administration. *Label: Inderal (propranolol hydrochloride)*. Published 2018. Accessed February 17, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/018890s052lbl.pdf
2. Kuriyama A, Jackson JL, Doi A, Kamiya T. Metronidazole-induced central nervous system toxicity: a systematic review. *Clin Neuropharmacol*. 2011;34(6):241-247. doi:10.1097/WNF.0b013e3182334b35
3. Daneman N, Cheng Y, Gomes T, et al. Metronidazole-associated Neurologic Events: A Nested Case-control Study. *Clin Infect Dis*. 2021;72(12):2095-2100. doi:10.1093/cid/ciaa395
4. Lee SJ, Kim J, Lee KH, et al. Frequency and Risk Factor Analysis for Metronidazole-Associated Neurologic Adverse Events. *J Gen Intern Med*. 2024;39(6):912-920. doi:10.1007/s11606-023-08566-w
5. Abouesh A, Stone C, Hobbs WR. Antimicrobial-induced mania (antibiomania): a review of spontaneous reports. *J Clin Psychopharmacol*. 2002;22(1):71-81. doi:10.1097/00004714-200202000-00012
6. Puri P, Parnami P, Chitkara A, Athwal PSS, Khetrapal S. Antibiomania: A Rare Case of Metronidazole-Induced Mania. *Cureus*. 2021;13(1):e12414. Published 2021 Jan 1. doi:10.7759/cureus.12414
7. Lambrichts S, Van Oudenhove L, Sienaert P. Antibiotics and mania: A systematic review. *J Affect Disord*. 2017;219:149-156. doi:10.1016/j.jad.2017.05.029
8. Miki Y, Takeuchi Y, Murasawa S, et al. Correlation of magnetic resonance images with neuropathology of irreversible metronidazole-induced encephalopathy: an autopsy case report. *BMC Neurol*. 2022;22(1):485. Published 2022 Dec 15. doi:10.1186/s12883-022-03006-4
9. Sørensen CG, Karlsson WK, Amin FM, Lindelof M. Metronidazole-induced encephalopathy: a systemic review. *J Neurol*. 2020;267:1–13. doi: 10.1007/s00415-018-9147-6
10. Bradley WG, Karlsson IJ, Rassol CG. Metronidazole neuropathy. *Br Med J*. 1977;2:10–1. doi: 10.1136/bmj.2.6087.610.
11. Goolsby TA, Jakeman B, Gaynes RP. Clinical relevance of metronidazole and peripheral neuropathy: a systematic review of the literature. *Int J Antimicrob Agents*. 2018 Mar;51(3):319-325. doi: 10.1016/j.ijantimicag.2017.08.033. Epub 2017 Sep 5. PMID: 28887203.
12. Hobson-Webb LD, Roach ES, Donofrio PD. Metronidazole: newly recognized cause of autonomic neuropathy. *J Child Neurol*. 2006 May;21(5):429-31. doi: 10.1177/08830738060210051201. PMID: 16901452.
13. Peng Q, You Q, Zhang J, Liu S. Isolated involvement of corpus callosum in metronidazole-induced encephalopathy with concomitant peripheral neuropathy: A case report. *Medicine* (Baltimore). 2020 May;99(20):e20198. doi: 10.1097/MD.0000000000020198. PMID: 32443341; PMCID: PMC7253656.
14. Li L, Tang X, Li W, Liang S, Zhu Q, Wu M. A case of methylprednisolone treatment for metronidazole-induced encephalopathy. *BMC Neurol*. 2019 Mar 30;19(1):49. doi: 10.1186/s12883-019-1278-6. PMID: 30927916; PMCID: PMC6441175.
15. Sonthalia N, Pawar SV, Mohite AR, et al. Metronidazole-Induced Encephalopathy in Alcoholic Liver Disease: A Diagnostic and Therapeutic Challenge. *J Emerg Med*. 2016;51(4):e79-e83. doi:10.1016/j.jemermed.2016.05.038
16. Sobel R, Sobel JD. Metronidazole for the treatment of vaginal infections. *Expert Opin Pharmacother*. 2015 May;16(7):1109-15. doi: 10.1517/14656566.2015.1035255. PMID: 25887246.
17. Tomás M, Palmeira-de-Oliveira A, Simões S, Martinez-de-Oliveira J, Palmeira-de-Oliveira R. Bacterial vaginosis: Standard treatments and alternative strategies. *Int J Pharm*. 2020;587:119659. doi:10.1016/j.ijpharm.2020.119659
18. Bradshaw CS, Morton AN, Hocking J, Garland SM, Morris MB, Moss LM, Horvath LB, Kuzevska I, Fairley CK. High recurrence rates of bacterial vaginosis over the course of 12 months after oral metronidazole therapy and factors associated with recurrence. *J Infect Dis*. 2006 Jun 1;193(11):1478-86. doi: 10.1086/503780. Epub 2006 Apr 26. PMID: 16652274.
19. Brandt M, Abels C, May T, Lohmann K, Schmidts-Winkler I, Hoyme UB. Intravaginally applied metronidazole is as effective as orally applied in the treatment of bacterial vaginosis, but exhibits significantly less side effects. *Eur J Obstet Gynecol Reprod Biol*. 2008 Dec;141(2):158-62. doi: 10.1016/j.ejogrb.2008.07.022. Epub 2008 Sep 4. PMID: 18775597.
20. Casagrande Tango R. Psychiatric side effects of medications prescribed in internal medicine. *Dialogues Clin Neurosci*. 2003;5(2):155-165. doi:10.31887/DCNS.2003.5.2/rcasagrandetango
21. Mizuta K, Sonohata M, Nozaki O, Kobatake T, Nakayama D, Morimoto T, Mawatari M. Metronidazole-induced encephalopathy in a patient with pyogenic spondylitis: a case report. *BMC Musculoskelet Disord*. 2018 Sep 18;19(1):336. doi: 10.1186/s12891-018-2255-8. PMID: 30223809; PMCID: PMC6142345.