ISSN: 2583-5386
DOI: doi.org/10.51219/JIH/farzana-hoque/33

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Journal of Integrated Health

https://urfpublishers.com/journal/integrated-health

Vol: 3 & Iss: 1

Case Report

Neurotoxicity: A Rare Complication of Trimethoprim-Sulfamethoxazole

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Citation: Blackburn D, Hoque F. Neurotoxicity: A Rare Complication of Trimethoprim-Sulfamethoxazole. *J Integrated Health* 2024;3(1):188-187. DOI: doi.org/10.51219/JIH/farzana-hoque/33

Received: 03 March, 2024; **Accepted:** 20 March, 2024; **Published:** 26 March, 2024

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A B S T R A C T

Trimethoprim-sulfamethoxazole (TMP/SMX) is widely used for various infections, yet its potential to cause neurotoxicity is underreported, typically emerging from case reports and predominantly involving immunocompromised patients. Here, we document a rare instance of TMP/SMX-induced neurotoxicity in a 61-year-old male who developed encephalopathy with myoclonus, without any prior immune compromise or relevant underlying diseases. Clinical evaluation, including laboratory tests and imaging, excluded metabolic and seizure-related origins. Remarkably, the patient's neurological condition improved rapidly following the cessation of TMP/SMX and the initiation of supportive care, with symptoms resolving within a few days. Recognizing the signs of drug-induced neurotoxicity early can prevent unnecessary diagnostic procedures, reduce the risk of complications, and ensure a swift recovery, with most cases resolving within 3-11 days after discontinuation. This case highlights the critical need for awareness among clinicians regarding the potential neurotoxic effects of TMP/SMX, even in patients without typical risk factors.

Keywords: Neurotoxicity, Trimethoprim-Sulfamethoxazole, Encephalopathy.

1. Introduction

Neurological effects and tremors are uncommon adverse effects of trimethoprim-sulfamethoxazole (TMP/SMX or Bactrim) that are not well understood in the literature. TMP/SMX has also reportedly been associated with encephalopathy, transient psychosis, and aseptic meningitis, especially with high doses[1]. Patients with TMP/SMX-induced aseptic meningitis often started showing symptoms a few hours after ingestion with a seemingly direct relationship between symptoms and the total amount of drug consumed or the number of times they've been exposed[2]. In other cases, symptoms are often associated with underlying disease processes predominantly in immunocompromised patients, and often resolve within a few days after discontinuing the drug[3]. Some of these reports hypothesize that the cause is an immunologic process[4]. Differentiating the cause of neurotoxicity, especially in acutely ill patients, can be very difficult and found only after ruling out other more common causes. This unique case report illustrates the development of acute encephalopathy and myoclonus due to the use of TMP/SMX in an immunocompetent patient.

2. Case Report

A 61-year-old white male with a past medical history of hypertension, hyperthyroidism, and spinal subdural hematoma presented to the emergency department with complaints of whole-body spasms and confusion. He had been previously hospitalized a month prior for lower extremity weakness, back pain, and urinary retention. He underwent a T11-L5 laminectomy and drainage of an intradural hematoma, after which he was discharged to a rehabilitation facility. The patient was readmitted

2 weeks later due to a pseudomeningocele and CSF leak and was discharged 5 days later after his Foley catheter was replaced. TMP/SMX was started for a possible urinary tract infection (UTI) at the rehab facility. He began experiencing headaches and tremors in his hands and whole body 2 days later. Upon arrival at the emergency department, he exhibited jerk-like movements in his upper and lower extremities. He denied dizziness, chest pain, shortness of breath, fever, chills, cough, numbness, tingling, or decreased range of motion. His family noted episodes of confusion and instances when the patient was talking aloud to no one. On presentation, his vital signs were blood pressure 119/84 mm Hg, pulse 92/min, temperature 98.2°F, respiratory rate 12/min, and SpO2 94% on room air. Upon examination, he was tremulous, exhibiting motor weakness with abnormal coordination and gait. He was alert and oriented to person, place, time, and situation. Hyperkinetic tremors were observed during the finger-nose-finger test and reflex exam, with whole-body jerks also present. The labs were unremarkable, and urinalysis was normal. Computed tomography (CT) of the head without contrast showed trace volume residual subarachnoid hemorrhage along the frontal sulci, which had decreased from the previous examination, and no new acute intracranial hemorrhage, vascular infarct, or mass effect. MRI with and without contrast showed no acute infarction. CT angiography of the brain and neck showed no acute hemorrhage or occlusion. A continuous EEG showed abnormal results consistent with encephalopathy but no specific etiology. Given the onset of myoclonus symptoms with the initiation of TMP-SMX treatment, along with an unremarkable workup (Table 1), we conducted a literature review and discovered a previous case of reversible TMP-SMX-induced myoclonus in the setting of spinal trauma. We recommended the patient to discontinue TMP-SMX. His tremors and myoclonus dramatically improved over the next few days, and he was advised to follow up with neurology in an outpatient setting.

CMP	Day 1	Day 3	Reference Range
Creatinine	1.33 (H)	0.87	0.71 - 1.16 mg/dL
BUN	32 (H)	28 (H)	7 – 26 mg/dL
Sodium	137	141	136 – 145 mmol/L
Potassium	4.5	4.1	3.5 – 4.5 mmol/L
Chloride	108 (H)	105	98 – 107 mmol/L
CO2	20 (L)	23	22 – 29 mmol/L
Glucose	110	101	70 – 115 mg/dL
Calcium	9	9.2	8.4 – 10.2 mg/dL
Bilirubin	0.5	0.9	0.2 – 1.2 mg/dL
Lactic acid	1.1	1.1	<=2.0 mmol/L
Magnesium	1.9	1.8	1.6 – 2.6 mg/dL
Phosphorus	3.8	3.7	2.8 - 4.5 mg/dL
Ammonia	39	30	<= 72 umol/L

Table 1: Laboratory results on Day 1 and Day 3 of hospital stay.

5. Discussion

The patient's myoclonus and tremors were not associated with a seizure disorder, as evidenced by the continuous EEG (cEEG), indicating that these episodes were spontaneous and occurred while the patient remained conscious. MRI and CT imaging of the head also did not reveal any acute changes that could have led to the tremors, and metabolic causes of movement disorders were ruled out as well. The symptoms resolved only upon discontinuing TMP/SMX, with no other etiology identified. The prevalence of adverse drug reactions (ADRs) related to TMP/SMX use varies, with studies reporting that 40-80% of HIV patients and 3-5% of the general population experience an ADR of any kind while on this medication[5-8]. Case reports have described similar symptoms in patients taking TMP/SMX in the context of immune compromise, particularly those being treated for Pneumocystis jirovecii pneumonia (PJP), showing a similar pattern of symptom onset within 3-5 days of starting therapy and resolution 2-4 days after its discontinuation[3,4,9]. Our patient, having no history of immunocompromising diseases, does not fit into this category. Although the exact mechanism of encephalopathy related to Bactrim remains unclear, its ability to cross the blood-brain barrier may play a role in causing this adverse effect[10]. A literature review on similar cases suggests that neurologic symptoms generally resolve within 3-11 days after the drug is withdrawn, with no lasting effects reported.

3. Conclusion

Trimethoprim-sulfamethoxazole (TMP-SMX), though widely regarded as safe, can cause reversible myoclonus that ceases with the drug's discontinuation, even in patients without known sulfa drug allergies. Early detection of adverse effects through thorough history-taking and physical examination is vital for myoclonus reversibility, underscoring the need for more research. Moreover, evaluating the timing of symptoms to medication changes is crucial for diagnosing acute neurological issues, particularly when neurological evaluations show no notable abnormalities.

4. Financial Support and Sponsorship

None

5. Conflicts of Interest

None

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