Trimethoprim-Sulfamethoxazole–Induced Exacerbation of Anxiety and Depression

To the Editor: Trimethoprim-sulfamethoxazole is a broad-spectrum antibiotic prescribed for the treatment of uncomplicated infections.[1] It is an irreversible inhibitor of dihydrofolate reductase, leading to a reduction in the production of folic acid.[1] The combination of trimethoprim and sulfamethoxazole works as a bactericidal antibiotic due to its synergistic effect.[1] It is metabolized by the liver and eliminated primarily by the kidney.[1] The serum concentration and half-life of trimethoprim-sulfamethoxazole increase in patients with impaired renal clearance, requiring dose adjustments.[1,2] Adverse effects of trimethoprim-sulfamethoxazole are related to the gastrointestinal tract and include anorexia, nausea, vomiting, and diarrhea. Neuropsychiatric side effects are rare but are more common in elderly and immunocompromised patients.

Case report. A 72-year-old immunocompetent woman presented to the outpatient clinic with symptoms of urgency, dysuria, lower back discomfort, fever, chills, nausea, and vomiting for 1 week. The physical examination was unremarkable with the exception of an abnormal urine dipstick result. Her past medical history was significant for urinary tract infection about 3 years ago, which was treated with ciprofloxacin with no complications. She was previously diagnosed with major depressive disorder and was stable on sertraline 75 mg for the last 4 years.

The patient was prescribed trimethoprim-sulfamethoxazole 160 mg/800 mg twice daily for 5 days to treat the urinary tract infection. She reported extreme anxiety with excessive worries, racing thoughts, excessive clinginess to her husband, and insomnia with sleep duration of 3–4 hours at night and required frequent reassurance. These symptoms emerged 2 days after starting trimethoprim-sulfamethoxazole. She also reported depressed mood, anhedonia, crying spells, fatigue, and decreased appetite. She was admitted to the inpatient psychiatric hospital. Her dose of sertraline was increased from 75 mg to 100 mg, trimethoprim-sulfamethoxazole was discontinued, and ceftriaxone was started. Her anxiety and depression improved immediately after the discontinuation of trimethoprim-sulfamethoxazole.

The patient was seen in the outpatient clinic 12 days after discharge from the inpatient psychiatric hospital. However, 3 days after the follow-up visit she was admitted to the emergency department with fatigue, nausea, vomiting, dry heaves, urinary incontinence, increased urinary frequency, fever, and chills. Her workup was positive for neutrophilic leukocytosis. The urinalysis result was consistent with urinary tract infection, blood urea nitrogen was 29 mg/dL, serum creatinine was 1.30 mg/dL, and modification of diet in renal disease glomerular filtration rate (MDRD GFR) was 40.3 mL/min/1.73 m2. Her MDRD GFR improved to 54.5 mL/min/1.73 m2 before discharge from the hospital. During this hospital stay, the patient was anxious about being discharged. She also reported being more on edge but denied any other symptoms of anxiety. The patient also denied any symptoms of depressed mood, anhedonia, or suicidal ideations during this hospital stay. She was prescribed clonazepam 0.25 mg twice a day, resulting in an improvement in her anxiety.

There are a few case reports[3–5] of trimethoprim-sulfamethoxazole–induced neuropsychiatric adverse effects like insomnia, tremors, depression, panic attacks, and hallucinations, but the worsening of generalized anxiety disorder has not been reported. These neuropsychiatric adverse reactions were most commonly reported among HIV-infected persons.[3,4] Trimethoprim can inhibit renal creatinine secretion, leading to high serum creatinine levels. It also inhibits dihydrofolate reductase, causing decreased dopamine production, which may lead to parkinsonian symptoms.[3] The relationship between the worsening of symptoms and trimethoprim-sulfamethoxazole in this case suggests a causal effect. The exact mechanism for the central nervous system (CNS) toxicity of trimethoprim-sulfamethoxazole is unknown, but it can be attributed to impaired renal clearance and excellent CNS penetration, resulting in the accumulation of toxic drug levels. The toxic drug levels of trimethoprim-sulfamethoxazole can result in the exacerbation of depression and anxiety. Clinicians should be aware of the potential worsening of anxiety and depression with trimethoprim-sulfamethoxazole, and a low index of suspicion should be kept to monitor the neuropsychiatric symptoms, especially in elderly patients.

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