Transient Psychosis in an Immune-Competent Patient After Oral Trimethoprim-Sulfamethoxazole Administration

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ABSTRACT. We describe a rare adverse reaction to trimethoprim-sulfamethoxazole (TMP-SMX; Septra, Bactrim) in an immune-competent female adolescent. She was prescribed TMP-SMX for a urinary tract infection, which she had developed while being treated in the hospital for an extensive leg cellulitis. Shortly after receiving her third dose of TMP-SMX, she developed an acute altered mental status with agitation as well as vivid visual and auditory hallucinations. After prompt discontinuation of TMP-SMX, the patient slowly began to improve and was able to return to her baseline mental status within 10 days. No residual mental status changes were present. Despite the recent emergence of multidrug-resistant bacterial pathogens, TMP-SMX, one of the first-generation broad-spectrum antibiotics, continues to be widely prescribed, in part because of its low cost and its easy availability. It is generally well tolerated and is associated with relatively few adverse effects. More common toxicities associated with TMP-SMX include hypersensitivity reactions, bone marrow suppression, and gastrointestinal side effects. Central nervous system toxicity is very rare; when reported, it has been in an immune-compromised or an elderly patient. Pediatrics 2005; 115:e739–e741. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1352

CASE REPORTS

A 19-year-old female adolescent who had a history of spina bifida and paraplegia and had been on no chronic medications other than occasional ibuprofen for analgesia presented to the emergency department with an extensive cellulitis of her left foot. She was admitted to the hospital for intravenous antibiotic management with oxacillin. The patient also had a history of urinary retention, which required intermittent bladder catheterization, and several previous urinary tract infections (UTIs), for which she had always been treated successfully with amoxicillin. More recently, ciprofloxacin was used to treat her UTI. On her first hospital day, a catheterized urine specimen was obtained from the patient and was noted to be cloudy. A urinalysis confirmed the presence of a UTI. Antibiotic therapy was initiated with twice-daily TMP-SMX (160 mg of TMP and 800 mg of SMX per double-strength tablet). This was the first occasion when TMP-SMX was used to treat her UTI.

On the second hospital day, shortly after receiving her third dose of TMP-SMX, the patient suddenly became confused and agitated. She was found staring at the wall of her hospital room and shouting inappropriate words while seeming to follow imaginary objects on the wall with her eyes. Administration of lorazepam (2 mg) seemed to improve the patient’s agitation; however, she did not regain lucidity after the episode. She remained awake but continued to be confused and could not follow verbal commands. A computed tomography scan of her head did not reveal any acute bleed or mass. An evaluation of her electrolytes revealed mild hyponatremia (Na = 131 mEq/L) and hypophosphatemia (phosphorus = 1.9 mg/dL) but was otherwise unremarkable. Her glucose was also normal. A lumbar puncture revealed a slight protein elevation (protein = 52 mg/dL), but the reminder of her cerebrospinal fluid analysis was normal. A comprehensive toxicology screen was negative as was a qualitative HIV testing. Finally, all bacterial and fungal cultures were negative.

Because of the acute nature of the patient’s mental status changes, a review of her medications was conducted and TMP-SMX was suspected as the agent responsible for the abrupt change in the patient’s mental status. Her other medications, which were oxacillin and multivitamins, did not seem to have a side effect profile that would produce such central nervous system (CNS) disturbances. On additional questioning of her family regarding any other medications, the patient’s parents did not report any antispasmodics or other chronic medications. A detailed family history revealed mood disorders in 2 distant cousins on the maternal side of the family and also a second cousin on the maternal side of the family with schizoaffective disorder. No other psychiatric illnesses were reported in the family.

At this time, TMP-SMX was discontinued and intravenous ceftriaxone was initiated for the continued management of the patient’s UTI. Over the following 24 hours, the patient had sustained intermittent hallucinations, although they seemed to change from visual to predominantly auditory ones in nature. She was able to communicate to the hospital staff that she was hearing voices and that these voices were angry with her. She was evaluated by the neurology and psychiatry services, and on hospital day 3, olanzapine (Zyprexa) therapy was initiated.

On hospital day 4, the patient was transferred to the psychiatric ward of a tertiary care hospital for additional evaluation. Her serum chemistries at this time all were within the normal range.
Psychiatric evaluation of the patient did not reveal any findings consistent with the Diagnostic and Statistical Manual of Mental Disorders IV, Revised, diagnosis for a primary psychiatric disorder. She remained on olanzapine, oxacillin, and ceftriaxone. On hospital day 6, the patient was able to communicate with the hospital staff that she felt exhausted and that the voices and the images had stopped. She continued to improve and was released on the hospital day 8 with the psychotic episode entirely resolved. The patient stated that she was eager to return to school. A follow-up visit 2 days later with her pediatrician revealed no residual altered mental status.

**DISCUSSION**

TMP-SMX, a widely prescribed first-generation, broad-spectrum antibiotic medication, is composed of a sulfonamide with TMP. The sulfonamides have been used clinically since 1935 as the first antibiotic agents directed against a wide variety of bacterial pathogens. In 1968, the combination of sulfonamides and TMP was first registered for clinical use.

TMP-SMX acts by producing a sequential blockade of folic acid synthesis. The sulfonamides are competitive inhibitors of para-amino-benzoic acid, an intermediate compound in the synthesis of folic acid. TMP binds and irreversibly inhibits the enzyme dihydrofolate reductase, preventing the reduction of dihydrofolic acid to tetrafolic acid. Subsequently, a decrease in the production of folic acid itself is observed. Combining TMP and SMX provides a synergistic effect, making this a bactericidal antibiotic, whereas, individually, sulfonamides and TMP are bacteriostatic.

TMP-SMX is absorbed rapidly from the gastrointestinal tract and reaches therapeutic concentrations in all body fluids, including expressed breast milk. For this reason, it is contraindicated for breastfeeding preterm infants. It is also not indicated in individuals with glucose 6-phosphate dehydrogenase deficiency. Metabolism of TMP-SMX is primarily through hepatic conversion to inactive metabolites by means of cytochrome P450 enzyme CYP2C9. This enzyme is genetically polymorphic, occurring in various mutant allelic variations. The most common of the mutant forms are CYP2C9*2 and CYP2C9*3. Compared with the wild-type form of the enzyme, CYP2C9*1, the mutant forms have markedly diminished enzymatic activity and result in higher serum concentrations of TMP-SMX after the administration of a single dose. They differ from the wild type by only 1 allele. Identification of these polymorphic enzyme variants can be accomplished by polymerase chain reaction, which can also identify homozygosity or heterozygosity of each of these polymorphisms.

Drug elimination is through renal excretion, with a smaller proportion of the drug being excreted unchanged in the stool. Individuals with deficiencies in either renal or hepatic function, such as the elderly or patients with chronic renal or hepatic failure, are at a greater risk for developing complications related to impaired drug elimination. The elderly are also at an increased risk as a result of their relative folate deficiency state.

After oral administration of TMP-SMX, peak blood levels for the 2 individual drug components occur between 1 and 4 hours. The mean serum half-lives of both TMP and SMX are ~8 to 10 hours. Patients with renal failure require dosage adjustment as a result of prolongation of drug half-life. Detectable amounts of TMP-SMX are present in the blood within 24 hours after drug administration. Steady-state levels of the drug can be achieved after 3 days of drug administration; this timeline seems to be consistent with the onset of mental status changes in the patient described in this case report.

TMP-SMX is generally well tolerated by most immune-competent patients and is a cost-efficient therapy directed toward specific pathogens. Recent emergence of bacterial resistance to TMP-SMX has resulted in a slight decrease in the prescription rate of this medication for Pneumocystis carinii pneumonia prophylaxis, as well as for several other clinical indications. Overall, TMP-SMX continues to be prescribed widely, in part as a result of its cost-effectiveness.

Several adverse reactions have been associated with the ingestion of TMP-SMX. The most commonly reported adverse effects of TMP-SMX are gastrointestinal in nature, including nausea, anorexia, vomiting, and diarrhea. Hypersensitivity reactions also occur frequently with the longer acting sulfonamides. Drug fevers have been seen in immune-compromised patients, particularly those with HIV. Other adverse events reported in the literature include electrolyte abnormalities such as hyperkalemia and hyponatremia. Rare toxicities associated with TMP-SMX include hematologic abnormalities, such as severe thrombocytopenia, hepatitis, and pancreatitis.

CNS adverse reactions associated with TMP-SMX are very rare and, when reported, have occurred in immune-compromised patients or the elderly. The exact mechanism for the CNS toxicity of TMP-SMX in these patients is not known, but it is thought that impaired metabolism and clearance of the drug may result in accumulation of toxic drug levels. This fact, combined with the excellent CNS penetration of TMP-SMX, may contribute to CNS complications. In addition, frequent infections and prolonged therapy with TMP-SMX in the immune-compromised patient may result in sustained higher drug levels. Cases of aseptic meningitis or delirium in immune-compromised and elderly patients have been reported. In contrast, cases involving immune-competent patients with CNS adverse events are rarely reported. One recent case in the literature described an immune-competent patient who developed transient tremors while taking TMP-SMX, which resolved in 2 days after discontinuation of the medication.

**SUMMARY**

CNS adverse reactions after TMP-SMX administration are very rare and, when present, occur in the elderly and the immune compromised. The finding of acute transient psychosis in a young, immune-competent patient after the administration of TMP-SMX is extremely rare and has not been reported previously in the pediatric literature. In light of this report, health care providers may consider a discus-
sion of this very rare adverse affect when prescribing TMP-SMX.

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