

CASE REPORTS

Trimethoprim-Sulfamethoxazole–Induced Hepatotoxicity in a Pediatric Patient

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Due to the escalating rates of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infection, trimethoprim-sulfamethoxazole (TMP-SMX) is being used increasingly in the pediatric population for skin and soft tissue infections. Although this combination agent has been associated with a hypersensitivity syndrome involving cutaneous skin eruptions, pediatric cases of TMP-SMX-induced hepatotoxicity are rare. We describe a relatively healthy, 9-year-old boy who developed a CA-MRSA skin and soft tissue infection and was treated with TMP-SMX. After 14 days of therapy, he was taken to the emergency department with a 3-day history of fever, headache, and neck pain. He was diagnosed with a viral syndrome, acetaminophen was prescribed, and he was sent home. Three days later, the patient returned to the emergency department with fever, vomiting, decreased energy and appetite, and suprapubic abdominal pain, and he was hospitalized. Laboratory test results revealed elevated liver function test values. After other potential causes of liver toxicity were excluded, TMP-SMX was determined to be the cause of his acute liver toxicity. The drug was discontinued, his symptoms resolved, and his liver function tests returned to normal. Use of the Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 5) between the patient's development of hepatotoxicity and the TMP-SMX therapy. This rare adverse reaction to TMP-SMX has been reported in adults; however, to our knowledge, it has been reported in only five other children. Due to the increasing use of TMP-SMX in children, clinicians should be aware of this potentially life-threatening, immune-mediated hypersensitivity reaction. Fortunately, however, the hepatotoxicity appears to resolve after discontinuation of the TMP-SMX therapy in most reported cases. This case report illustrates the importance of early detection of drug-induced hepatotoxicity and timely drug discontinuation to prevent the need for liver transplantation.

Key Words: trimethoprim-sulfamethoxazole, TMP-SMX, hepatotoxicity, hypersensitivity reaction, pediatric.

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Trimethoprim-sulfamethoxazole (TMP-SMX) has been available in the United States since 1973. This drug combination inhibits bacterial growth by preventing the breakdown of folic acid to its active form, tetrahydrofolic acid.¹ It has been used in the pediatric population for various indications, such as prophylaxis and treatment of urinary tract infections and *Pneumocystis jiroveci*

pneumonia in immunocompromised children.^{1,2} Trimethoprim-sulfamethoxazole is being prescribed more frequently for skin and soft tissue infections caused by community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA), due to the increasing rates of these infections in pediatric patients.³

Adverse reactions to TMP-SMX usually involve

the skin (rash) and the gastrointestinal tract (nausea, vomiting, diarrhea) in children.¹ Severe systemic hypersensitivity reactions to TMP-SMX, such as hepatotoxicity, are infrequent but have been documented in case reports. Patients with a drug hypersensitivity syndrome can experience a variety of symptoms such as fever, rash, internal organ damage, and eosinophilia.⁴ We describe a pediatric patient who developed hepatotoxicity as part of an immune-mediated hypersensitivity reaction induced by TMP-SMX.

Case Report

A 9-year-old, previously healthy, 37.5-kg African-American boy was taken to the emergency department with a fever of 102.6° F (axillary) after he had been on a family vacation at a water park. The family reported that he had a 3-day history of fever, headache, and some neck pain, but no photophobia or back pain. The patient had been taking TMP 160 mg–SMX 800 mg twice/day (8.2 mg/kg/day of TMP) for a 21-day course of therapy for a CA-MRSA skin infection on his buttocks and lower back (he was on day 14 of therapy during this visit). He was sent home with a diagnosis of viral syndrome and prescribed acetaminophen as needed for fever.

Three days later, the patient returned to the emergency department with a fever of 102.8°F (oral) and a 24-hour history of nausea and vomiting (not bloody or bilious). He also complained of suprapubic abdominal pain, which was described as sharp and constant, and decreased energy and appetite. He had not experienced diarrhea, rash, jaundice, or painful urination. The patient's family was questioned about possible etiologies for the fever. They stated that they had eaten home-cooked meals while on vacation and were not in known contact with any sick individuals. The patient denied any tick exposure, and his mother stated that his vaccinations were up to date.

The patient was admitted to the hospital. His

Table 1. Laboratory Results

Laboratory Test	Hospital Day			
	Day 1	Day 2	Day 3	Day 4
Liver function tests				
Total bilirubin (mg/dl)	0.6	0.8	0.5	0.5
Albumin (mg/dl)	3.3	2.8	3.1	3.1
Alkaline phosphatase (U/L)	153	125	127	116
AST (U/L)	947	555	306	153
ALT (U/L)	624	467	457	322
White blood cell count (x 10 ³ /mm ³)				
	2.8	3.8	4.0	4.3
Differential (%)				
Neutrophils	28	3	13	11
Lymphocytes	31	75	58	65
Eosinophils	9	17	16	12

AST = aspartate aminotransferase; ALT = alanine aminotransferase.

laboratory values were significant for a decreased white blood cell count of 2.8 x 10³/mm³ (normal range 3.8–12.7 x 10³/mm³); a differential of 28% neutrophils (39–65%), 27% bands (0–6%), and 9% eosinophils (0–9%); aspartate aminotransferase 947 U/L (15–41 U/L); alanine aminotransferase 624 U/L (8–40 U/L); and a prothrombin ratio 1.6 seconds (0.9–1.1 sec). Other laboratory values were total bilirubin 0.6 mg/dl (< 1.5 mg/dl), alkaline phosphatase 153 U/L (24–280 U/L), and albumin 3.3 g/dl (3.3–5.2 g/dl). Serologic studies for hepatitis A, hepatitis B, and hepatitis C were nonreactive. Cytomegalovirus, human immunodeficiency virus, and Epstein Barr virus antibodies were negative. Appendicitis, pancreatitis, and pyelonephritis were ruled out. Testing was negative for *Shigella*, *Salmonella*, and Rocky Mountain spotted fever. Blood, urine and cerebral spinal fluid cultures were also negative.

The patient's acetaminophen serum concentration was 14.9 µg/ml (therapeutic range 10–25 µg/ml). In addition, amylase, lipase, and γ-glutamyl transferase levels were all within normal limits. Computed tomography of the abdomen and pelvis was also normal. The patient had no known drug allergies, and his only drug exposures were to acetaminophen and TMP-SMX. Therefore, it was concluded that TMP-SMX was potentially the etiology of his liver dysfunction; the drug was discontinued.

The patient's liver function test results and white blood cell count and differential returned to normal after the TMP-SMX had been discontinued for 1 week (Table 1). By hospital day 4, the patient's symptoms had resolved, and he was discharged home. On follow-up, the patient continued to be asymptomatic, and his liver function test results remained within normal limits.

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Table 2: Summary of Five Pediatric Case Reports of a Trimethoprim-Sulfamethoxazole–Induced Hepatotoxic Hypersensitivity Reaction

Sex, Age	Time Between Exposure and Symptom Onset (days)	Previous Exposure	Positive Effect with Rechallenge	Fever	Rash	Eosinophilia	Liver Biopsy	Outcome
M, 16 yrs ⁹	41	No	Not done	Yes	Yes	Yes	Yes	Recovered
F, 16 mo ¹⁰	7	Yes	Yes	Yes	Yes	Yes	No	Recovered
F, 5 yrs ¹¹	1 (12 days until jaundice)	No	Not done	Yes	Yes	No	Yes	Recovered
M, 10 yrs ¹²	3 (14 days until jaundice)	No	Yes, but with trimethoprim only	Yes	Yes	UNK	Yes	Recovered
F, 5 yrs ¹³	28 (patient received drug for 7 days)	Yes, twice in past 4 yrs	Not done	UNK	UNK	Yes	Yes	Liver transplantation

UNK = unknown.

Discussion

Most adverse reactions reported with TMP-SMX are due to the SMX component.¹ In children, cutaneous drug eruptions are well known adverse reactions due to TMP-SMX therapy. In general, drug eruptions are short in duration and show complete resolution once the drug is discontinued. The most dangerous drug eruptions, which occur rarely with TMP-SMX, are Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme.¹

Hypersensitivity syndrome associated with TMP-SMX can affect various internal organs and also manifest with blood dyscrasias such as hemolytic anemia, eosinophilia, and atypical lymphocytosis.⁵ Other hematologic reactions associated with TMP-SMX include thrombocytopenia and neutropenia.⁶ In a study of 50 children who received TMP-SMX for either otitis media or uncomplicated urinary tract infection, the frequency of neutropenia and thrombocytopenia was 34% and 12%, respectively.⁷ Although our patient did not have neutropenia, he did have decreased white blood cell counts and increased eosinophil counts, which returned to normal after cessation of TMP-SMX.

The SMX component of TMP-SMX is mainly responsible for the known cases of hepatotoxicity.¹ Trimethoprim is excreted mostly in the urine unchanged, whereas SMX undergoes a considerable amount of conjugation in the liver.¹ The aromatic amines in sulfonamide antibiotics are oxidized to hydroxylamines, then to nitroso derivatives in the liver.¹ These two oxidized components subsequently go through an oxidation-reduction reaction. This reaction can

cause oxidative stress, which may lead to the nitroso derivatives reacting with and binding to proteins covalently. These proteins, considered foreign by the body, may induce an immunologic response, which is known as the hapten hypothesis.^{4, 8} This response results in the damage seen with idiosyncratic drug reactions and may be responsible for TMP-SMX–induced hepatotoxicity.

The incidence of TMP-SMX–induced adverse reactions involving the liver is 1/11,000–45,000 adults; however, after we performed a search of PubMed, OVID, MEDLINE, and Google, we found only five published case reports in children (Table 2).^{1, 9–15} Common symptoms accompanying hepatotoxicity in these patients suggest a hyper-sensitivity reaction with fever, rash, and eosinophilia in a majority of the cases. The time between exposure to TMP-SMX and onset of symptoms varied and was as sudden as 1 day after exposure to 41 days after exposure. Four of the five patients had hepatic recovery once TMP-SMX was discontinued. Based on these few pediatric cases reported in the literature, we speculate that hepatotoxicity to TMP-SMX is underreported because most patients likely present with an initial rash and the drug is discontinued before further testing is conducted.

The diagnosis of TMP-SMX–induced hypersensitivity reaction, which manifest as hepatotoxicity, in our patient is supported by the normalization of both the liver function tests and white blood cell count after discontinuation of the drug. Furthermore, viral and serologic markers were negative, and computed tomography

of the abdomen and pelvis was normal. The only other drug that the patient was taking, acetaminophen, can cause hepatic injury; however, acetaminophen is unlikely the cause of hepatotoxicity in this patient because his acetaminophen serum concentration was within the therapeutic range. The patient's parents also verified that they had administered the correct acetaminophen dosage regimen to their son.

Trimethoprim-sulfamethoxazole has been associated with a hypersensitivity syndrome. This syndrome can be defined as a systemic disease that involves fever, skin eruption, and one or more internal organs.⁴ Our patient's condition can be classified as drug hypersensitivity syndrome, as he presented with a high fever (102.9°F), elevated liver enzyme levels, and eosinophilia. Although skin eruptions occur in 85% of cases of drug hypersensitivity syndrome, our patient did not experience this symptom.⁴

Finally, use of the Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 5) between the patient's development of hepatotoxicity and the TMP-SMX therapy.¹⁶

Conclusion

Due to the increasing use of TMP-SMX in the pediatric population for treatment of CA-MRSA infections, it is important for clinicians to be able to recognize the signs and symptoms of an immune-mediated hypersensitivity reaction to TMP-SMX therapy. Our patient's hepatotoxicity, was probably induced by TMP-SMX, and his condition resolved after the drug was discontinued. This case illustrates the importance of early detection of drug-induced hepatotoxicity and timely drug discontinuation to prevent the need for liver transplantation.

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