CASE REPORT

Hepatotoxicity Induced by Trimethoprim-Sulfamethoxazole in a Child with Cystic Fibrosis

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Patients with cystic fibrosis (CF) have chronic and progressive lung infections with various bacterial organisms that require treatment with oral and intravenous antibiotics on a regular basis. Trimethoprim-sulfamethoxazole (TMP-SMX) is one of the medications used to treat acute pulmonary infectious exacerbations in patients with CF. Hepatic toxicity secondary to TMP-SMX was previously described in normal subjects but has not been reported in children with CF. Here we describe a 14-year-old female child with CF who was given oral TMP-SMX for an acute pulmonary infectious exacerbation. She developed a rash, severe constitutional symptoms, and significant elevation of liver enzyme concentrations secondary to immunity-mediated reaction to TMP-SMX. Discontinuation of TMP-SMX and supportive treatment led to resolution of her symptoms and normalization of liver enzyme concentrations.

INDEX TERMS: cystic fibrosis, hepatotoxicity, liver enzymes, trimethoprim-sulfamethoxazole

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INTRODUCTION

Patients with cystic fibrosis (CF) have chronic lung infections, bronchiectasis, and progressive obstructive lung disease. They require frequent prolonged courses of treatment with oral and parenteral antibiotics for recurrent infectious pulmonary exacerbation. These patients are more susceptible to various adverse drug hypersensitivity reactions secondary to repeated drug exposure, intense systemic inflammation, and elevated concentrations of inflammatory mediators.^{1–3} Trimethoprim-sulfamethoxazole (TMP-SMX) is regularly prescribed to children with CF for treatment of infection by various Gram-negative and Gram-positive bacteria colonizing their airways. Common reactions to TMP-SMX affect the skin and the gastrointestinal tract in children.⁴ Manifestations of delayed SMX-TMP adverse drug reactions (ADRs) can occur up to 41 days after the exposure. As a result, delayed ADR symptoms may be attributed to primary disease, comorbid conditions, or other medications.⁵ Hepatic hypersensitivity secondary to TMP-SMX is

relatively rare and, to our knowledge, was previously described only in children without CF.^{5,6} TMP-SMX-associated liver hepatotoxicity has not been reported in children with CF. We describe a 14-year-old female child with CF who was given oral TMP-SMX for an acute pulmonary infectious exacerbation. She developed an erythematous macular rash, constitutional symptoms, abdominal pain, and significant elevation of liver enzyme concentrations believed to be secondary to ADR to TMP-SMX and its induced hepatotoxicity. She was admitted to hospital where TMP-SMX was discontinued, which resulted in significant improvement of clinical symptoms and normalization of liver enzyme serum concentrations.

CASE REPORT

This report describes the case of a 14-year-old Caucasian female with CF who was admitted with abdominal pain, rash, fatigue, headaches, and swelling of the lips and eyelids. Approximately 4 weeks prior to this admission, she received a 14-day course of oral ciprofloxacin, us-

ing an appropriate dose twice daily for increased coughing, sputum production, and reduction of her lung function. Her symptoms did not completely resolve, and she was advised to be admitted for intravenous antimicrobial therapy, but she declined. She was then started on an appropriate dose of oral TMP-SMX twice a day. After starting TMP-SMX, she had mild upper abdominal pain that worsened after eating. She did not experience changes in bowel movements. On day 3 of TMP-SMX therapy, she reported throbbing headache, fatigue, dizziness, and decreased oral intake. On day 5 of TMP-SMX administration, she developed swelling of the lips and eyelids and a generalized maculoerythematous rash. She also had pancreatic insufficiency, chronic eczema, asthma, and obstructive lung disease. Her home medications included fluticasone-salmeterol inhalation, dornase alpha aerosol, oral montelukast, pancrelipase, and multivitamins. The patient had previous sputum cultures that grew *Pseudomonas aeruginosa* and *Staphylococcus aureus*. She had repeated normal serum chemical profiles and liver enzyme concentrations in the past, except for an elevated immunoglobulin E (IgE) serum concentration believed to be due to her chronic atopic eczema. One month before this admission, she had normal liver enzyme concentrations as follows: ALT of 26, AST of 31, and GGT of 10 units/L (Figure). Her last IgE concentration was 3772 IU/mL, approximately 18 months prior to this admission. The patient was admitted this time for further evaluation of a possible drug reaction and was started on intravenous tobramycin and meropenem every 8 hours for treatment of *P aeruginosa* and *S aureus* lung infections.

On admission, she was afebrile but her oral temperature increased to 39.6°C the following day. Her home medications were continued. However, TMP-SMX was discontinued upon admission for suspected ADR and hepatotoxicity. Her weight and height were 45.2 kg and height 151.2 cm, respectively. Initial laboratory work-up revealed elevated AST and ALT concentrations at 828 units/L and 567 units/L, respectively. Repeated measurements of liver enzymes revealed the highest ALT recorded was 1519 units/L (normal: 0-65 units/L), the highest AST was 1347 units/L (normal: 0-75 units/L), and the highest GGT recorded was 136 units/L (normal GGT: 8-78 units/L) (Figure). Her prothrombin time and international normalized ratio were slightly elevat-

ed on admission and normalized 2 days later. She had normal antibody profiles against Epstein-Barr virus and cytomegalovirus infection and hepatitis A, B, and C. She also had normal bilirubin, glucose, electrolytes, lactate dehydrogenase, lipids, amylase, lipase, total protein, albumin, alkaline phosphatase, iron, copper, ceruloplasmin, α 1 antitrypsin, smooth muscle antibody, and liver kidney microsomal antibody concentrations. Abdominal ultrasonography showed normal liver and gall bladder anatomy. Liver biopsy was not performed. Her IgE serum concentration was 9965 IU/mL, but her *Aspergillus* IgG and IgE antibodies were normal. Although TMP-SMX serum concentration test was not performed, the drug was discontinued upon admission for suspected drug reaction and hepatotoxicity. Shortly after admission and discontinuation of TMP-SMX, her rash started fading, and her gastrointestinal symptoms decreased significantly. Her liver enzyme concentrations decreased gradually and eventually normalized 6 weeks after admission, with an ALT of 75 units/L, AST of 35 units/L, and GGT of 58 units/L (Figure).

DISCUSSION

Various types of oral and intravenous antibiotics are frequently administered to patients with CF to treat their chronic lung infections and acute pulmonary exacerbations. Hypersensitivity and ADRs, especially to beta-lactam antibiotics, were reported to be 3 times more common in patients with CF than in the general population, with piperacillin being the most common offending agent.^{2,7} Intravenous antibiotics cause more ADRs than oral dosage forms. The incidence rate of immediate allergic reactions ranged from 1.9% to 4.5% in 1 adult series.⁸ Other small series have reported total allergic reaction rates of 9.5% in children and up to 25% in adult subjects with CF.^{2,7} Patients with CF are more likely to develop delayed or late reactions affecting multiple organ systems. These delayed reactions are not usually IgE-mediated and may not be readily diagnosed by skin testing.²

Sulfonamide agents such as TMP-SMX are frequently used in patients with CF, especially in patients who are infected by TMP-SMX-sensitive organisms such as *S aureus* and *Stenotrophomonas maltophilia*. However, little is known about toxic or adverse effects of TMP-SMX in this patient popu-

Figure. Serum concentrations of liver enzymes during and after admission to the hospital.

■ GGT; ▲ ALT (SGPT); ● AST (SOGT)

lation. Elsheikh et al.³ showed that T cells from patients with CF and SMX hypersensitivity are primarily stimulated with oxidative metabolites of SMX, most likely due to recurrent infections that promote SMX metabolism. These T cells were also found to secrete higher levels of proinflammatory cytokines, such as interferon-gamma, than T cells from patients without CF. This may be one of the mechanisms of enhanced delayed hypersensitivity ADRs in patients with CF.

Only 6 previously healthy pediatric patients were reported in the literature with TMP-SMX-induced hepatic toxicity.^{5,6} Their ages ranged from 16 months to 16 years, and their symptoms occurred from 1 to 41 days after exposure to TMP-SMX. All of these patients recovered well, except for a 5-year-old female who needed a liver transplant afterward. We believe our patient is the first reported case of a child with CF who developed this severe type of delayed reaction and liver toxicity.

Over the past 30 years, several causality assessment methods, including a Bayesian approach, have attempted to improve ADR diagnosis in adults and children.^{9–20} Naranjo's algorithm is the most widely used ADR assessment algorithm

because it is simple and brief.¹⁷ Validity and reliability of Naranjo's algorithm have been demonstrated in adults and in 3 studies examining ADRs in a pediatric setting.^{21–23} An analysis by Avner et al.²⁴ demonstrated the effectiveness of Naranjo's algorithm for assessment of ADRs in children. Objective causality assessment using Naranjo's algorithm in our patient revealed that it is highly probable (score of 8, 5–8 probable) that TMP-SMX caused this adverse reaction and her liver toxicity. Although a liver biopsy was not performed for our patient, clinical and laboratory data provide a clear diagnosis of hepatocellular injury. The child's personal and medical histories and extensive laboratory investigations did not reveal any underlying cause or risk factors for liver disease. Albeit no rechallenge was attempted, the improvement in the patient's symptoms and liver enzyme concentrations after discontinuation of the drug suggests a strong association between TMP-SMX and hepatic injury in this patient. The continued improvement in our patient's status despite use of other medications strengthens the association between the ADRs and TMP-SMX.

In summary, we report a child with CF who developed a significant clinical adverse reaction and hepatotoxicity related to TMP-SMX which resolved with discontinuation of the medication. Due to the lack of clear criteria to predict the risk of developing hypersensitivity delayed reaction, maintaining a high index of suspicion, monitoring of symptoms, and discontinuation of hepatotoxic agents are essential for hepatic preservation and reversal of acute hepatic injury. Increased effort is needed to better understand the incidence of ADR and its associated risk factors in the pediatric population, especially in those with chronic diseases and use of polypharmacy.

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Abbreviations ADRs, adverse drug reactions; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CF, cystic fibrosis; GGT, gamma-glutamyl transferase; IgE, immunoglobulin E; IgG, immunoglobulin G; IU, international units; TMP-SMX, trimethoprim-sulfamethoxazole

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