American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2016; 17: 499-502
DOI: 10.12659/AJCR.897820

Received: 2016.01.28
Accepted: 2016.04.27
Published: 2016.07.18

Methemoglobinemia in a Pediatric Oncology Patient Receiving Sulfamethoxazole/Trimethoprim Prophylaxis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Timothy G. Carroll
ABCDEF 2 Megan G. Carroll

1 Department of Pediatrics, Section of Critical Care, University of Oklahoma Health Science Center, Oklahoma City, OK, U.S.A.
2 Independent Researcher, Oklahoma City, OK, U.S.A.

Corresponding Author: Timothy G. Carroll, e-mail: tcarrollmd@me.com
Conflict of interest: None declared

Patient: Male, 6-month
Final Diagnosis: Methemoglobinemia
Symptoms: —
Medication: Sulfamethoxazole/trimethoprim
Clinical Procedure: Methylene blue administration
Specialty: Pediatrics and Neonatology

Objective: Unusual or unexpected effect of treatment

Background: Methemoglobinemia due to the administration of sulfamethoxazole/trimethoprim has been documented in a series of case reports. However, all of these reports are on adult patients, and all patients received at least daily administration of sulfamethoxazole/trimethoprim for the treatment of active or suspected infection.

Case Report: Herein we report the development of methemoglobinemia in a pediatric patient receiving sulfamethoxazole/trimethoprim three times weekly for the prophylaxis of opportunistic infections.

Conclusions: The clinician should always consider sulfamethoxazole/trimethoprim, even when administered for opportunistic infection prophylaxis at reduced doses and intervals, as a possible cause of methemoglobinemia.

MeSH Keywords: Antibiotic Prophylaxis • Methemoglobin • Methemoglobinemia • Pediatrics • Trimethoprim-Sulfamethoxazole Combination

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/897820

Background

Sulfamethoxazole/trimethoprim (SMX/TMP) is a common first-line treatment for many types of infections. An important indication of SMX/TMP is prophylaxis against the immunosuppression-induced pneumonia caused by *Pneumocystis jiroveci*.

Methemoglobinemia is a potentially life-threatening disorder that requires prompt identification and treatment to prevent serious sequelae. There are several reports of the development of methemoglobinemia with traditional dosing of SMX/TMP used for treatment of various infections when administered several times daily [1–7]. However, upon a thorough literature review, no articles were found describing the development of this serious adverse effect in children or when SMX/TMP was given only three times weekly, which is the standard dosing frequency for the prophylaxis of opportunistic infections. This is an important consideration because SMX/TMP given only three times weekly may be overlooked when evaluating possible causes of methemoglobinemia. Herein we report a case of a pediatric patient who developed SMX/TMP-induced methemoglobinemia while receiving the medication at significantly reduced doses and intervals compared with those in previous reports of this adverse effect.

Case Report

A 6-month-old male with no previous medical history or history of methemoglobinemia was admitted to the pediatric hematology/oncology service for workup and treatment of an abdominal mass, lethargy, and poor feeding. Prior to this encounter, he had no significant past medical history. After a thorough workup, he was diagnosed with juvenile myelomonocytic leukemia (JMML). JMML is a rare and aggressive myeloid neoplasm that requires aggressive treatment with chemotherapy known to cause immunosuppression. While on chemotherapy, the patient was maintained on SMX/TMP for prophylaxis of opportunistic infections. During the course of therapy, the patient developed respiratory failure requiring intubation and mechanical ventilation, which required admission to the pediatric intensive care unit (PICU) on hospital day 9.

Upon admission to the PICU, the patient's oxygen saturation (SpO_2) was 99–100%, and his arterial blood gas (pO_2) levels were within the normal range. On hospital day 23 (16 days after initiation of SMX/TMP therapy) while in the PICU, the patient's SpO_2 levels became abnormally low despite escalating fraction of inspired oxygen (FiO_2) delivery (85–93% over the 24-hour period immediately preceding methylene blue administration), while conversely the pO_2 levels were normal to slightly increased (93–162 mm Hg).

Table 1. Medications administered <7 days prior to desaturations and symptoms.

Cefepime
Amphotericin B liposomal
Sulfamethoxazole/trimethoprim
Fentanyl
Docusate
Ursodiol
Midazolam
Dexmedetomidine
Famotidine
Mephyton

Methemoglobinemia is strongly suggested when there is clinical cyanosis or hypoxia by pulse oximeter in the presence of a calculated normal arterial pO_2 (PaO_2) as obtained by arterial blood gases, as documented in this patient. Other manifestations that may suggest methemoglobinemia include symptoms of hypoxia and/or clinical symptoms of reduced oxygen availability after administration or ingestion of an agent with oxidative potential (of which SMX/TMP is a known cause), hypoxia that does not improve with an increased FiO_2, or abnormal coloration of the blood observed during phlebotomy (dark red, chocolate, or brownish to blue). A methemoglobin level was checked on hospital day 23 (day 16 of SMX/TMP prophylactic therapy) and was found to be 7.2% (normal range: 0–3%). When an elevated level of methemoglobinemia was found in our patient, an investigation of the cause of his methemoglobinemia ensued.

Investigations to rule out congenital causes of methemoglobinemia were performed to rule out hemolysis (complete blood count [CBC], reticulocyte count, peripheral smear review, lactate dehydrogenase, bilirubin, haptoglobin, and Heinz body preparation) and end-organ dysfunction or failure (liver function tests, electrolytes, renal function tests). There were no signs of acute liver or kidney injury, and CBC and peripheral smear showed no signs of hemolysis in this patient. Although these tests did not completely exclude the possibility of congenital methemoglobinemia, it made the likelihood very low.

After a thorough workup and medication review, the most probable etiology of methemoglobinemia was found to be SMX/TMP administration. A list of the patient's medications in the seven days preceding his diagnosis with methemoglobinemia can be found in Table 1. After his diagnosis of methemoglobinemia, all of these medications were continued with the exception of SMX/TMP. The patient's SMX/TMP therapy was immediately discontinued in favor of pentamidine for opportunistic infection

prophylaxis, and he was given methylene blue 2 mg/kg intravenously for treatment of methemoglobinemia. This was repeated two hours after the first dose was administered for a total of two doses administered to the patient.

After these two doses of methylene blue (hospital day 25), his methemoglobin level was 1.4% and his SpO_2 had normalized, indicating that the methemoglobinemia had resolved. Pentamidine was continued for opportunistic infection prophylaxis in this patient, and subsequent methemoglobin levels remained normal, confirming that SMX/TMP was the cause of this patient's methemoglobinemia.

Discussion

Methemoglobin is a form of the oxygen-carrying metalloprotein hemoglobin, in which the iron in the heme group is in the Fe^{3+} (ferric) state, not the Fe^{2+} (ferrous) state of normal hemoglobin [8]. Reduced ferrohemoglobin (Fe^{2+}) binds oxygen reversibly, but methemoglobin cannot bind oxygen [9]. Normally 1–2% of a person's hemoglobin is methemoglobin; a higher level of methemoglobin will tend to cause a pulse oximeter to read closer to 85% regardless of the true level of oxygen saturation [1]. Signs and symptoms of methemoglobinemia can vary drastically from patient to patient. Some healthy individuals may not experience symptoms with a methemoglobin level of 15%, but this level could be deadly in a patient with comorbidities that affect oxygenation [10]. Methemoglobinemia carries serious implications for patients, including cyanosis, arrhythmias, and possible death. Severity of symptoms is dependent on the percentage of methemoglobin that is present [11]. Patients with lung disease, anemia, sepsis, or sickle cell disease, infants younger than age 6 months, and any patient with a comorbidity that affects oxygenation are at the greatest risk for developing methemoglobinemia [10].

Because of the patient's chemotherapy regimen and risk for opportunistic infections, specifically *Pneumocystis jiroveci* pneumonia, he was initiated on SMX/TMP via nasogastric tube at a dose of 24 mg daily (~5 mg of TMP/kg/day) given three times weekly. The recommended treatment dose for pediatric patients with active *Pneumocystis jiroveci* pneumonia is 15–20 mg of TMP/kg/day, which in this patient would have been a total dose of 75–100 mg of TMP/day. This comparison highlights the significantly decreased daily dose (24 mg/day *vs.* 75–100 mg/day) administered as well as the reduced prophylactic dosing interval of three times weekly versus daily in patients with active infection.

Methemoglobinemia can be either congenital or acquired [12]. Acquired forms of the disease are far more common and are usually induced by medications such as SMX/TMP, dapsone, lidocaine, benzocaine, acetaminophen, and nitroprusside [9]. These medications speed the production of methemoglobin to levels that overwhelm the reduction enzymes within red blood cells [13]. Our patient had received no other medications that are known to cause methemoglobinemia (Table 1). Of the drugs known to cause methemoglobinemia, SMX/TMP is one of the most commonly used and is prescribed for many indications and types of infections. In our patient, because of his immunocompromised status, SMX/TMP was indicated for prophylaxis of a common opportunistic infection, *Pneumocysitis jiroveci*, which is a known cause of morbidity and mortality in patients with malignancies. When given for an active infection, SMX/TMP is a known cause of methemoglobinemia, as described in many previous case reports [1–7,12]. All of these case reports were of adult patients, and all patients were receiving SMX/TMP at treatment doses, with one exception. Kawasumi et al. reported the case of an adult systemic lupus erythematosus patient who received the appropriate adult prophylactic dosing for opportunistic infections (400/80 mg), but received only one dose before developing methemoglobinemia [12]. To our knowledge, our case is the first report of the development of methemoglobinemia in a pediatric patient receiving prophylactic dosing given three times weekly, which represents a markedly reduced dose when compared with treatment for active infection (24 mg/day given three times weekly *vs.* 75–100 mg in daily divided doses, respectively).

When caught early, methemoglobinemia can be effectively treated by removal of the offending agent and administration of oxygen, which can accelerate the conversion of methemoglobin to hemoglobin. Patients with symptomatic methemoglobinemia, patients with comorbidities and a methemoglobin level of >10%, and asymptomatic patients with a methemoglobin level of >30% require treatment [13]. The treatment of choice for methemoglobinemia is methylene blue [14]. Methylene blue works as a cofactor for NADPH-methemoglobin reductase, which is the major pathway for reduction of methemoglobin in the red blood cell. Increased levels of this cofactor can speed the reduction of methemoglobin to hemoglobin [1]. For the treatment of methemoglobinemia, methylene blue is given intravenously at a dose of 1–2 mg/kg over 5 minutes. This dose can be repeated in 30 minutes if needed [10]. Although there are currently no other approved therapies for methylene blue–resistant methemoglobinemia, exchange transfusions and hyperbaric oxygen therapy have been used, but the efficacy of these methods have not been validated [15].

Conclusions

To our knowledge, this is the first report of methemoglobinemia occurring after the use of three times weekly dosing of SMX/TMP in a pediatric patient. Because of the serious adverse

effects of methemoglobinemia, early detection and appropriate treatment are essential. The clinician should always consider SMX/TMP, even when given at reduced frequencies as prophylaxis, as a possible cause of methemoglobinemia and adjust therapy accordingly.

References:

1. Turner MD, Karlis V, Glickman RS: The recognition, physiology, and treatment of medication-induced methemoglobinemia: A case report. Anesth Prog, 2007; 54(3): 115–17
2. Kohl BA, Domski A, Pavan K, Fortino M: Use of telemedicine for the identification and treatment of sulfamethoxazole-induced methaemoglobinemia. J Telemed Telecare, 2012; 18(6): 362–64
3. Koirala J. Trimethoprim-sulfamethoxazole – induced methemoglobinemia in an HIV-infected patient. Mayo Clin Proc, 2004; 79(6): 829–30
4. Lopez A, Bernardo B, Lopez-Herce J et al: Methaemoglobinaemia secondary to treatment with trimethoprim and sulphamethoxazole associated with inhaled nitric oxide. Acta Paediatr, 1999; 88(8): 915–16
5. Medina I, Mills J, Leoung G et al: Oral therapy for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. A controlled trial of trimethoprim-sulfamethoxazole versus trimethoprim-dapsone. N Engl J Med, 1990; 323(12): 776–82
6. Jakobson B, Nilsson A: Methemoglobinemia associated with a prilocaine-lidocaine cream and trimetoprim-sulphamethoxazole. A case report. Acta Anaesthesiol Scand, 1985; 29(4): 453–55
7. Damergis JA, Stoker JM, Abadie JL: Methemoglobinemia after sulfametoxazole and trimethoprim. JAMA, 1983; 249(5): 590–91
8. Ash-Bernal R, Wise R, Wright SM: Acquired methemoglobinemia: A retrospective series of 138 cases at 2 teaching hospitals. Medicine, 2004; 83(5): 265–73
9. Furuta K, Ikeo S, Takaiwa T et al: Identifying the cause of the "Saturation Gap": Two cases of dapsone-induced methemoglobinemia. Inter Med, 2015; 54(13): 1639–41
10. Umbreit J: Methemoglobin – it's not just blue: a concise review. Am J Hematol, 2007; 82(2): 134–44
11. Curry S: Methemoglobinemia. Ann Emerg Med, 1982; 11(4): 214–21
12. Kawasumi H, Tanaka E, Hoshi D et al: Methemoglobinemia induced by trimethoprim-sulfamethoxazole in a patient with systemic lupus erythematosus. Intern Med, 2013; 52(15): 1741–43
13. Shamriz O, Cohen-Glickman I, Reif S, Shteyer E: Methemoglobinemia induced by lidocaine-prilocaine cream. Isr Med Assoc J, 2014; 16(4): 250–54
14. Haymond S, Cariappa R, Eby CS, Scott MG: Laboratory assessment of oxygenation in methemoglobinemia. Clin Chem, 2005; 51(2): 434–44
15. Ward KE, McCarthy MW: Dapsone-induced methemoglobinemia. Ann Pharmacother, 1998; 32(5): 549–53

Conflicts of interest

The authors declare that there are no conflicts of interest.