JPPT | Case Report

Occult Methemoglobinemia in a Medically-Complex 7-Year-Old Child and the Opportunity for Pharmacist Intervention in Pediatric Emergency Medicine

Kendra L. Walsh, PharmD; Christian R. Silva, PharmD; and Patrick H. Lee, PharmD

Methemoglobinemia is a rare, yet life-threatening disorder that occurs due to an accumulation of methemoglobin in the blood. The clinical presentation often includes dyspnea, cyanosis, and hypoxemia that shows little improvement with the administration of supplemental oxygen. The US Food and Drug Administration (FDA) warns against the administration of benzocaine to those younger than 2 years of age and urges manufacturers to add a statement regarding the possible development of methemoglobinemia to the packaging of any products containing this ingredient. However, providers caring for pediatric patients should recognize that methemoglobinemia may occur in toddlers and children outside of the FDA's specific age warning window and must keep a broad differential for patients presenting with respiratory distress. The objective of this article is to highlight a case of a child subsequently found to have benzocaine-induced methemoglobinemia and emphasize the importance of pharmacists in an emergency medicine setting, particularly in the care of patients with uncommon acute conditions requiring lesser-known pharmacologic treatments.

ABBREVIATIONS Cyb5R, cytochrome-b5 reductase; FDA, US Food and Drug Administration; FiO_2, fraction of inspired oxygen; G6P, glucose-6-phosphate; G6PD, glucose-6-phosphate dehydrogenase; ISMP, Institute for Safe Medication Practices; IV, intravenous; MAP, mean arterial pressure; NADPH, nicotinamide adenine dinucleotide phosphate; OTC, over-the-counter; PICU, pediatric intensive care unit; SIRS, systemic inflammatory response syndrome; SpO_2, oxygen saturation

KEYWORDS multidisciplinary care team; pediatric emergency medicine; pediatric pharmacy; toxicology

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Introduction

Methemoglobinemia is a rare disorder that occurs due to an accumulation of methemoglobin in the blood.[1] Methemoglobin is an abnormal form of the hemoglobin molecule that is created when at least 1 of the 4 iron atoms in a single hemoglobin unit is oxidized from the ferrous (Fe^{+2}) to the ferric state (Fe^{+3}).[2] An iron atom that has transitioned to the ferric state can no longer form a bond with oxygen and will also influence the remaining heme groups in the molecule to bind oxygen tighter (left shift on oxyhemoglobin dissociation curve), impairing tissue oxygen delivery.[2]

The clinical presentation of methemoglobinemia often includes dyspnea, cyanosis, and hypoxemia that shows little improvement with the administration of supplemental oxygen.[3] Other signs include tachycardia, tachypnea, and varying degrees of lethargy; if untreated, cardiac arrythmia, seizures, coma, or death may ensue.[3,4] The standard of care for the treatment of methemoglobinemia in pediatric and adult patients is intravenous (IV) methylene blue dosed at 1 to 2 mg/kg using actual body weight, with a maximum single dose of 100 mg.[3] Ascorbic acid is an alternative for those with glucose-6-phosphate dehydrogenase (G6PD) deficiency or when methylene blue is unavailable.[4]

Most cases of methemoglobinemia are acquired and occur due to the ingestion of exogenous substances that can act as oxidants; examples include benzocaine, lidocaine, chloroquine, dapsone, and well water contaminated with nitrites.[5–8] Due to this risk, the US Food and Drug Administration (FDA) has issued a warning against administration of benzocaine to those younger than 2 years old and urged manufacturers to add a statement regarding the possible development of methemoglobinemia to the packaging of products containing this ingredient.[9,10]

The objective of this article is to summarize the unique constellation of signs and symptoms observed in a child subsequently found to have benzocaine-induced methemoglobinemia and highlight the role of pharmacists in a pediatric emergency department setting.

Case Presentation

A 7-year-old female weighing 27 kg presented to the pediatric emergency department via ambulance

at 1655 for urgent treatment of status epilepticus persisting for approximately 30 minutes. The patient's past medical history included anoxic brain injury with associated epilepsy from placental abruption at birth, spastic quadriplegia cerebral palsy, multicystic leukomalacia with global developmental delay, and asthma. Home medications consisted of baclofen, diazepam, levetiracetam, montelukast, and inhaled albuterol. The patient had no known drug, food, or environmental allergies. Over the past 2 weeks, she had been experiencing upper respiratory tract infection symptoms and completed a course of prednisolone therapy for associated wheezing.

Upon arrival, the patient's status epilepticus was treated with a single intramuscular midazolam injection dosed at 2.7 mg (0.1 mg/kg) while IV access was being obtained, then IV lorazepam 2.7 mg (0.1 mg/kg) once with clinical resolution of seizure activity. A loading dose of IV levetiracetam 1620 mg (60 mg/kg) was ordered but discontinued given the cessation of seizures with benzodiazepine therapy. She did not receive any additional anticonvulsant medications in this acute period, but her home levetiracetam was continued in the hospital intravenously as 1000 mg (37 mg/kg) in the morning and 750 mg (28 mg/kg) in the evening.

During her initial presentation, the patient's vital signs revealed a heart rate of 50 beats/min, blood pressure of 60/40 mm Hg, respiratory rate of 26 breaths/min, and temperature of 30°C. For her hemodynamic instability she was started on an IV epinephrine infusion at 0.1 mcg/kg/min to attain a mean arterial pressure (MAP) goal of 60 mm Hg and she was provided with a forced-air warming blanket for her hypothermia. Notably, the patient's oxygen saturation (SpO_2) was 85% and she appeared cyanotic, having a blue-like discoloration to the lips and skin. Other pertinent labs included an arterial pH of 7.56, arterial pCO_2 of 26 mm Hg, glucose of 148 mg/dL, and lactate of 3.3 mEq/L. A complete blood count yielded no abnormalities in white or red cell count, and hemoglobin was 11.7 g/dL. At this time, the differential diagnosis focused on sepsis with acute respiratory distress syndrome, which led to initiation of broad-spectrum antibiotics for a 24-hour infection rule-out. The patient was started on ceftriaxone 1 g IV (rounded down from 50 mg/kg) once, vancomycin 500 mg IV (rounded up from 15 mg/kg) every 6 hours, and piperacillin/tazobactam 3 g piperacillin/kg IV (rounded up from 100 mg piperacillin/kg) every 8 hours.

After intubation and administration of 100% oxygen at approximately 1730, SpO_2 failed to elevate beyond 85% despite correct placement of the endotracheal tube. This prompted the team to consider a possible right-to-left shunt, which would explain the patient's cyanosis. Although the patient was severely ill, pulses were never lost, and she did not deteriorate to the point of a code blue activation. During this initial stabilization in the emergency department, history obtained from the patient's parents revealed that the child had been given an over-the-counter (OTC) sore throat spray for the past several days. This product was determined to contain 7% benzocaine by volume, which ultimately shifted the differential diagnosis to methemoglobinemia. A stat methemoglobin serum concentration was ordered at 1846, yielding a >30% concentration in the blood (normal range, 0%–1.8%). After consulting with Poison Control and the evening clinical pharmacist team, 27 mg (1 mg/kg) of IV methylene blue via peripheral veinous administration was ordered with recommendations to redose at 27 mg (1 mg/kg) IV if unable to decrease her fraction of inspired oxygen (FiO_2) or if worsening hypoxia ensued. Further questions regarding administration and fluid compatibility were answered by the pharmacists who recommended diluting the methylene blue 27 mg (1 mg/kg) in 100 mL of 5% dextrose in water and infusing over 30 minutes. Additionally, they answered questions from nursing regarding the medication's pharmacology and monitoring criteria given the relative infrequent use of methylene blue in routine clinical practice. Given the proximity of the pharmacy to the pediatric emergency department, a pharmacist stat-prepared and hand-delivered the methylene blue to the team and remained bedside during and after the infusion to answer nursing and provider questions. The methylene blue infusion was started at 1954 and the SpO_2 rose to 95% by 2040.

The patient was subsequently transferred to the pediatric intensive care unit (PICU) where she remained for 3 days. She was sedated and paralyzed with continuous IV infusions of fentanyl 0.8 to 1 mcg/kg/hr and vecuronium 0.1 mg/kg/hr. By 2309, her FiO_2 concentration was successfully decreased from 100% to 45%. Lactate concentration gradually normalized and vasoactive agents (epinephrine 0.1 mcg/kg/min, norepinephrine 0.05 mcg/kg/min, milrinone 0.25 mcg/kg/min) were weaned once blood pressures remained stable and at or above the MAP goal of 60 mm Hg. A follow-up methemoglobin concentration an hour after methylene blue administration was 2.9%, which further decreased to 0.6% 8 hours later. Sedation was gradually lightened, and the patient was extubated on the second day of her PICU admission. By day 3, vasopressors and inotropic support were no longer needed, and she was transferred to a general pediatric medical floor for continued observation. After a total of 4 days in the hospital, the patient returned to her baseline status and was discharged home. The root cause was suspected to be unintentional overdosage of a benzocaine-containing OTC sore throat spray, so the pediatric emergency medicine pharmacist specialist recommended editing the patient's electronic medical record to include an intolerance to benzocaine. Furthermore, although this patient was born full-term at 39 weeks, underlying enzymatic deficiencies could not be ruled out and may represent an area of further investigation.

Discussion

The risk of developing methemoglobinemia with benzocaine use is well-established in the medical literature.[2–8] Specific predisposing factors for this condition include G6PD deficiency as well as low cytochrome-b5 reductase (Cyb5R) activity, which is common in infants, especially those born premature, and heterozygotes for pathogenic variants of this enzyme.[11] Under normal conditions, the Cyb5R pathway is the main appreciable mechanism in the body for elimination of methemoglobin. This enzyme utilizes an endogenous electron donor to reduce Fe^{+3} to Fe^{+2}, meaning those with an abnormal allele have reduced ability to mitigate methemoglobinemia.[11] A less major pathway is the reduction of glucose-6-phosphate (G6P) by G6PD which creates the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH).[12] Molecules of NADPH have reduction potential as well, but only a truly meaningful impact when in the presence of an intermediary electron-acceptor.[12] Methylene blue is one such molecule, and its mechanism of action in treating methemoglobinemia is to serve as a reducing agent for the iron in hemoglobin, returning it to the Fe^{+2} state.[12] The patient in this case report did not have lab studies performed for low Cyb5R activity or G6PD deficiency while admitted in the hospital but the team had noted these tests could be performed in the outpatient setting.

However, it is important to note that most cases of methemoglobinemia are acquired and occur due to excessive methemoglobin formation induced by exogenous substances such as anesthetics, antimalarials, antibiotics, nitrogenous compounds, and aniline dyes.[13] Due to ease-of-access in the form of OTC sore throat products, unintentional benzocaine overdose should always be considered in the setting of self-treated upper respiratory infections. Since 2002, the Institute for Safe Medication Practices (ISMP) and FDA have warned against the use of benzocaine-containing OTC products in children less than 2 years old.[14] This case emphasizes the risk of methemoglobinemia indeed prevails outside of this small age range; in fact, data from a 10-year retrospective case-control study estimated an incidence of 0.035% of adults that developed this condition in the setting of topical anesthetic use.[15] Correspondingly, clinicians and families alike should be aware of the dangers of these products and limit use to the lowest dosage necessary to achieve analgesia for the shortest time.

During the treatment of this child, the quick response from pharmacists in providing medication information on methylene blue was paramount in ensuring an optimal outcome. Specifically, we emphasize the emerging role of pharmacists embedded within a pediatric emergency department.[16–19] Interprofessional teams are embedded in most US hospitals and have been shown to immensely improve the quality and safety of health care interventions.[20,21] During the evening when this case occurred, pharmacists provided direct patient care with medication information, including dosing and administration considerations for methylene blue, coordination of critical medication availability, as well as medication monitoring considerations such as FiO_2 requirements and methemoglobin concentrations that may determine whether a repeat dose is needed. Furthermore, a pediatric emergency medicine pharmacist later collaborated with the medication safety team to document patient intolerance, educate staff on methemoglobinemia risk, and remove benzocaine products stocked for inpatient use. A joint pharmacy-nursing communication was disseminated to the hospital regarding the risks of benzocaine in children; furthermore, within Pharmacy Services, one of our pharmacy practice residents created a case presentation to educate members of the department.

This case report is intended to highlight the importance of pharmacists in an emergency medicine setting, particularly in the care of patients with uncommon acute conditions requiring lesser-known pharmacologic treatments. For the patient described in our report, the correct diagnosis of methemoglobinemia was not readily apparent at that time due to her complex past medical history, especially with her initial presentation of status epilepticus. The differential diagnosis progressed from a systemic inflammatory response syndrome (SIRS) or sepsis presentation versus pulmonary pathologies like pulmonary embolism, pneumothorax, and mucus plugging when it was determined that the patient's profound hypoxemia was not correcting with respiratory support from endotracheal intubation. Testing for methemoglobinemia was only considered after obtaining a detailed history from the parents. The diagnosis was then confirmed when the blood methemoglobin concentration returned at over 30%.

All clinicians practicing in a pediatric emergency department should be aware of the inherent risks of benzocaine-containing products, especially those marketed as OTC cough and cold remedies. Methemoglobinemia has classic signs and symptoms, but due to its rarity, a thorough history and physical examination must be conducted to rule out more common pathologies that may mimic this condition. Furthermore, utilizing the help of pharmacists with identifying and mitigating the effects of harmful medications can only serve to improve patient outcomes.

Article Information

Affiliations. The Warren Alpert Medical School of Brown University (KLW), Providence, RI; Pharmacy Services, Hasbro Children's Hospital, Lifespan (KLW, CRS, PHL), Providence, RI.

Correspondence. Patrick H. Lee, PharmD; plee3@lifespan.org

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