

Perioperative Hypoxia Secondary to Phenazopyridine-induced Methemoglobinemia in an Adolescent Patient Without Renal Insufficiency or Overdose: An Unusual Case



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Phenazopyridine is a common, well-tolerated medication with minimal side effects. Severe side effects are rare and include methemoglobinemia in setting of overdose, elderly patients, renal insufficiency, and chronic use. Here, we report a case of methemoglobinemia-induced perioperative hypoxia in an adolescent patient without renal insufficiency or overdose which has not been reported previously. This case underscores the importance of judicious use of this medication in all patients but notably in pediatric patients and those with chronic lung disease. *UROLOGY* 130: 142–143, 2019. © 2019 Elsevier Inc.

Phenazopyridine (Azo, Pyridium) is routinely prescribed by physicians for treatment of lower urinary tract symptoms. It is also available over the counter and marketed directly to consumers. The medication is well tolerated with minimal side effects with the most notable being orange staining of urine. Severe side effects such as hemolytic anemia, renal toxicity, hepatic toxicity, sulfhemoglobinemia, and methemoglobinemia have been reported but are rare.¹⁻³ These typically occur in the setting of drug overdose, in the elderly, or with extended use.⁴⁻⁷ There is 1 case report of phenazopyridine-induced methemoglobinemia in an adult with normal renal function,⁸ yet there is a dearth of literature involving this side effect in the adolescent population with normal renal function. Here, we report a case of a 17-year-old male with no prior exposure to phenazopyridine or history of renal insufficiency who developed phenazopyridine-induced methemoglobinemia and hypoxia after a total of 6 as needed doses.

CASE PRESENTATION

The patient is a 17-year-old male with history of morbid obesity, cerebral palsy, Duchenne muscular dystrophy with associated dilated cardiomyopathy and obstructive sleep apnea on bilevel positive airway pressure therapy who was referred to urology for further evaluation of

bilateral nephrolithiasis. His case was reviewed at multidisciplinary conference and given his significant bilateral stone burden, symptoms as well as goal of limiting anesthetic exposure, he was offered bilateral percutaneous nephrolithotomy.

The patient underwent surgery without intraoperative complication. Both sides were treated through a single, lower pole puncture. At the end of the case, there was no residual stone burden. Bilateral 7 French nephrostomy tubes and externalized ureteral catheters were placed. Estimated blood loss was 75 mL. Given his comorbidities, he was admitted to the pediatric intensive care unit for planned postoperative care and extubation.

On postoperative day (POD) 1, he was started on phenazopyridine 200 mg 3 times a day as needed. Baseline arterial blood gas (ABG) demonstrated methemoglobin level of 0.7%. He received a total of 6 doses. On POD 3, he was noted to have increasing fraction of inspired oxygen (FiO₂) and positive end expiratory pressure to maintain saturations. Pulse oximetry demonstrated oxygen saturation of 88% while on 100% FiO₂. ABG was obtained which demonstrated O₂ level of 84%, pO₂ 354 mmHg, and methemoglobin level of 15.8% (normal 0%-1.5%). Phenazopyridine was immediately stopped and serial ABGs were obtained which demonstrated decreasing levels of methemoglobin. Glucose-6-phosphate dehydrogenase levels were normal. His renal function remained normal throughout the hospitalization. By POD 4, his methemoglobinemia had resolved and his respiratory status improved. His remainder of hospital course was complicated by ventilator associated pneumonia and he was ultimately extubated on POD 11.

Declaration of Interest: None.

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DISCUSSION

Phenazopyridine was originally compounded in the 1930s and has become a mainstay of treatment of lower urinary tract symptoms. It is renally metabolized and 60% is excreted within 6 hours of administration. Most common adverse effects have been well described previously.⁷ More atypical side effects including hemolytic anemia, renal toxicity, hepatic toxicity, sulfhemoglobinemia, and methemoglobinemia have been reported but in the setting of overdose, in the elderly, or with extended use. Here, we describe phenazopyridine-induced methemoglobinemia in a 17-year-old male taking therapeutic doses with no prior exposure or acute renal insufficiency, which is a previously undescribed circumstance.

Methemoglobin is the oxidized form of hemoglobin which is unable to efficiently transport oxygen leading to tissue hypoxia. There are 2 main enzymatic mechanisms in place to maintain low methemoglobin levels and; in the absence of rare congenital defects impacting the activity of these 2 enzymes, methemoglobinemia is most commonly an acquired phenomenon from exposure to toxins, chemicals, and oxidant drugs.⁶ Anesthetic agents associated with methemoglobinemia include prilocaine, benzocaine, lidocaine, nitrous oxide, phenacetin, metoclopramide, nitroglycerine, sodium nitroprusside.⁹ Case reports of fentanyl-induced methemoglobinemia have also been reported.¹⁰

Clinically, methemoglobinemia is defined as methemoglobin levels greater than 1% of total hemoglobin on ABG. Increasing methemoglobin levels correlate to increasing symptoms. Methemoglobin level >15% is known to cause cyanosis; >20% is associated with headache, weakness, lightheadedness; 30%-50% is associated with tachypnea, lethargy, and confusion; >50% is typically lethal.⁷

Treatment includes stopping the offending agent, oxygen administration, and administering methylene blue if methemoglobin levels are >30% or if patient is symptomatic with levels >20%. Methylene blue must be avoided in patients with G6PD deficiency as it will be ineffective and may cause hemolytic anemia or in patients with renal insufficiency to prevent toxicity from overdose. Typical dosing is 1-2 mg/kg which can be repeated if needed within 1 hour.^{11,12}

In our case, the patient was administered fentanyl intraoperatively; however, given that the methemoglobin levels were normal on initial ABG, make this an unlikely etiology of methemoglobinemia especially considering the temporal relationship of methemoglobin levels with initiation and cessation of phenazopyridine. In this case, the patient's symptomology was likely exacerbated by his

history of restrictive lung disease secondary to obstructive sleep apnea and obesity, which likely did not allow him to compensate a methemoglobin level of 15.8%, a level which in standard patients typically would not experience severe symptoms. There is no literature suggesting that patients with Duchenne muscular dystrophy are more prone to developing methemoglobinemia.

Phenazopyridine is an easily accessible medication whose toxicity has been well described in patients who overdose, are elderly, are in renal failure, or are exposed to chronic therapy. Keeping this patient in mind as well as a prior case report of a patient with history of chronic obstructive pulmonary disease who similarly developed severe respiratory symptoms at methemoglobin level of 18.8%,⁷ clinicians should be more judicious of their use of this seemingly inert medication in patients with chronic respiratory issues. Furthermore, patients with chronic lung disease should be counseled on the potential side effects of this medication, given the ease of access of this medication without a physician's prescription.

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