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Case Report
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Methemoglobinemia from Prolonged Therapeutic Use of Phenazopyridine

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Abstract

Background: Phenazopyridine is often prescribed for patients suffering from urinary tract infections as its local analgesic properties can provide immediate symptomatic improvement. It is classically taken for two days while awaiting antibiotic effect. It is available without a prescription in the United States under the trade names: Azo Urinary Pain Relief, Uricalm, and Uristat. Common adverse reactions include urine discoloration, rash, pruritus, nausea, dyspepsia, and headache. Phenazopyridine has been reported to cause methemoglobinemia in overdose, though rarely with therapeutic doses.

Case Report: We report a case of an 82-year-old woman who had been taking phenazopyridine at a therapeutic dose for three months when she presented to emergency department with hypoxia. Arterial blood gas revealed a methemoglobinemia level of 15%. Patient's hypoxia corrected with administration of methylene blue. Why should an emergency physician be aware of this?: Phenazopyridine toxicity, most commonly reported with acute overdose, can lead to methemoglobinemia by converting the iron molecule in hemoglobin to methemoglobin. Administration of methylene blue is typically curative. This case highlights the importance of considering methemoglobinemia in patients who present with hypoxia while taking phenazopyridine.

Keywords: Methemoglobinemia; Phenazopyridine; Hypoxia; Methylene blue

Introduction

Methemoglobinemia refers to a disorder characterized by abnormal levels of methemoglobin in the blood resulting from the oxidation of iron in hemoglobin from the ferrous (Fe^{2+}) to ferric (Fe^{3+}) form. The oxidized ferric group has an impaired ability to bind oxygen; in addition, oxygen affinity for any remaining ferrous hemoglobin is increased, thereby shifting the oxygen dissociation curve to the left. As a result, oxygen cannot be appropriately released, leading to tissue hypoxia [1].

While there are several congenital causes, methemoglobinemia is most commonly caused by medications that contain oxidizing chemicals such as nitrites, nitroglycerin, nitroprusside, trimethoprim/ sulfamethoxazole, inhaled nitrous oxide, and aniline derivatives [1].

Phenazopyridine has been described in the literature as an agent causing methemoglobinemia, hemolytic anemia and renal failure in the adult and pediatric overdose situation [2-8], and in the therapeutic usage in patients with renal impairment [9]. Few case reports describe the development of methemoglobinemia at therapeutic doses in patients with normal renal function [10-12], though no similar cases have been reported in the emergency medicine literature.

Since phenazopyridine is available without a prescription, it is essential that emergency physicians appropriately recognize the adverse reaction of methemoglobinemia in patients taking urinary anesthetics. A case of an 82-year-old woman with a methemoglobinemia level of 15% from prolonged use of phenazopyridine is reported.

Case Presentation

An 82-year-old woman presented to the emergency department by ambulance for hypoxia. Patient had no known pre-existing cardiac or pulmonary conditions. During routine vitals assessment at her assisted living facility, the patient's pulse oximeter was noted to be 83%. She received albuterol without improvement in the pulse oximeter reading, and transferred to the emergency department for further evaluation. Paramedics put the patient on 15 liters of oxygen via a non-rebreather for transport.

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On arrival to emergency department, the patient denied chest pain or shortness of breath. Past medical history was significant for multiple sclerosis and deep vein thrombosis; patient also had a chronic indwelling Foley catheter. Medications included warfarin 4.5mg once a day, baclofen 10mg as needed and phenazopyridine 200mg three times a day. Patient began taking phenazopyridine three months prior to presentation for urinary irritation secondary to the indwelling Foley catheter.

On general examination, the patient was well appearing. The vital signs were: temperature 36.7'C, blood pressure 146/62 mmHg, pulse 77bpm, respiratory rate 18/min, and oxygen saturation of 92% on 15L oxygen via a non-rebreather. The patient appeared mildly cyanotic. Cardiovascular and pulmonary examinations are unremarkable. The urinary catheter was in place with orange colored urine in the bag. The remainder of the physical examination was unremarkable.

Arterial blood gas with co-oximeter was obtained with the following results: pH 7.44, pCO_2 44, pO_2 461, HCO_3 28, O_2 sat 98, Carbon monoxide 3.1, O_2 content arterial 10, OxyHemoglobin 80.8%, Methemoglobin 14.9 %on15L oxygen via non-rebreather.

On further laboratory testing, electrolytes and kidney function were unremarkable, as were the troponin and B-type natriuretic peptide. Complete blood count results were WBC 8.4 with normal differential, Hemoglobin 8.5, Hematocrit 27.9, MCV 99, MCH 30.4, MCHC 30.5, RDW 18.7, and Platelet 269.The INR was 2.2.

The patient received IV methylene blue 1mg/kg for a total dose of 80mg and within minutes her pulse oximeter improved to 98% on room air. The patient was observed in the hospital for 24 hours and had no further episodes of hypoxia. She was then discharged back to her assisted living facility.

Discussion

Phenazopyridine is utilized for its local anesthetic properties in patients suffering from urinary tract infection, though its use should be limited to 48 hours and discontinued after appropriate antibiotics have lessened symptoms. In the case presented, a patient developed toxicity from a therapeutic dose of phenazopyridine for a prolonged duration.

Methemoglobinemia can develop from medications that lead to the oxidation of the iron molecule in hemoglobin. In healthy individuals, a reducing enzyme cascade converts methemoglobin back to hemoglobin. In the case of phenazopyridine toxicity, the reduction cascade is overwhelmed, leading to the accumulation of methemoglobin [4].

Patients with methemoglobinemia can present with hypoxia or cyanosis, though the PaO2 on arterial blood gas is normal. Patients may be asymptomatic at low levels, but may experience fatigue, headache, dizziness, tachycardia, weakness, dyspnea, bradycardia, seizures, coma, and death at progressively higher levels [1]. Treatment is determined by associated symptoms and may range from discontinuing the offending medication in a minimally symptomatic patient with a low methemoglobin level to administration of intravenous methylene blue at a dose of 1-2mg/kg over 5 minutes with a repeated dose in 1 hour if the level remains high. If a patient presents in shock, then blood transfusion or exchange transfusion may be initiated. Additional therapies have included hyperbaric oxygen administration with anecdotal success [4] and N-acetyl cysteine, though a randomized controlled trial demonstrated no reduction in methemoglobin levels [13,14].

In the case described above, the patient was on prolonged use of phenazopyridine and presented with hypoxia on pulse oximeter but a normal oxygen level on ABG; the methemoglobin level was 15% on co-oximeter. This patient received intravenous methylene blue and achieved normalization of the level within minutes.

Conclusion

The diagnosis of methemoglobinemia is a time-sensitive emergency. As therapeutic use of over-the-counter phenazopyridine may result in methemoglobinemia, emergency physicians must consider this adverse reaction in patients who present with cyanosis or hypoxia.

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