CLINICAL VIGNETTE

Methemoglobinemia Following Acute Overdose on Chronic Use of Phenazopyridine

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Background

Phenazopyridine has been used as a urinary tract analgesic since the early 1900's. The precise mechanism for analgesic properties of phenazopyridine is still unknown. Although it has no FDA-approved indications due to availability prior to 1938, it is sold over the counter for management of dysuria. A rare but potentially life-threatening adverse effect associated with phenazopyridine is methemoglobinemia. There are case reports of methemoglobinemia with both chronic use and acute overdose.[1,2] We present a unique case of phenazopyridine associated methemoglobinemia in the setting of acute overdose in a 23-year-old female patient on chronic phenazopyridine.

Case Description

A 23-year-old female with a past medical history of bladder neck obstruction presented to the emergency department for evaluation of acute onset of palpitations, dizziness, shortness of breath, and cyanosis of her lips. The patient had a chronic burning sensation with urination over the previous six months, for which she was prescribed multiple courses of antibiotics as well as daily phenazopyridine. She reported taking 2 to 4 tablets of the over the counter phenazopyridine (200 to 400 mg) per day. However, due to increased urinary discomfort during the 24-hour period prior to admission, she ingested 10 tablets of phenazopyridine (1000 mg) in one day. The patient's concurrent medications included levofloxacin, terazosin, and valacyclovir. The patient is followed by urology for bladder neck obstruction on terazosin.

On arrival at the Emergency Department, the patient was tachycardic with a heart rate of 130/bpm and in mild respiratory distress with an oxygen saturation of 88% on room air. Physical examination revealed cyanotic lips with otherwise clear heart and lung examination. Chest X-ray indicated normal cardiomediastinal contours, clear lungs, normal pleural surfaces, and no visible chest wall abnormalities. Basic metabolic panel and complete blood count were unremarkable. Patient was placed on a non-rebreather mask at 15 L/min without significant improvement in oxygen saturation. While on a non-rebreather mask, arterial blood gas demonstrated pH of 7.44, pCO2 of 36 mmHg, pO2 329 mmHg, and bicarbonate of 24.3 mmol/L. CO-oximetry study was significant for methemoglobin of 11.1%. Given symptomatic presentation concerning for methemoglobinemia, she was administered intravenous (IV) methylene blue (1 mg/kg). Within an hour, symptoms were remarkably diminished with oxygen saturation improving to 96%. No further episodes of tachycardia or increased work of breathing were noted.

Other laboratory findings included urinalysis significant for white blood count of 239 cells/microliter, leukocyte esterase 3+, and nitrite 1+. The patient was treated empirically for urinary tract infection with intravenous ceftriaxone. Using the Naranjo Adverse Drug Reaction Probability Scale a score of 5 was calculated, indicating probable adverse drug reaction to phenazopyridine.

Discussion

Methemoglobinemia is a potentially life-threatening condition caused by the oxidation of iron from ferrous (Fe^{+2}) to ferric (Fe^{+3}) state within hemoglobin which prevents its ability to bind oxygen. Furthermore, a conformational change occurs to the hemoglobin tetramer that greatly increases the affinity of ferrous ions (Fe^{+2}) for oxygen, resulting in decreased unloading of oxygen to tissues and cellular hypoxia.[1]

The symptoms of methemoglobinemia are dependent on methemoglobin level. The initial symptoms of methemoglobinemia are typically vague including fatigue, headaches, low saturations on pulse oximeter, gray skin and dyspnea. However, symptoms can progress to severe respiratory depression, dysrhythmias, shock, seizures, coma and even death with escalating methemoglobin levels.[1,3]

Methemoglobinemia may be congenital or more commonly acquired. Multiple medications have been linked to acquired methemoglobinemia, most notably dapsone, local anesthetics (e.g lidocaine, benzocaine) and nitrate-based medications.[1,4] Case reports link phenazopyridine to methemoglobinemia due to both chronic use as well as acute overdose.[1,2,5] Our case of methemoglobinemia was due to acute overdose overlying chronic use of phenazopyridine emphasizing the dose-dependent toxicity.

Phenazopyridine is available as an over the counter medication for treatment of urinary tract discomfort. Although its precise mechanism of action is unknown, it appears to have local analgesic properties on the urinary tract. The labeling for phenazopyridine recommends a dose of 200 mg three times daily with a two-day duration of therapy when used concomitantly with antibiotics. There are no current recommendations regarding maximum daily dose of phenazopyridine or appropriate duration when used for non-infectious etiologies. A recent retrospective trial showed low incidence of adverse effects when patients with radiation cystitis on 14+ days of phenazopyridine were compared to a matched group without phenazopyridine.[6] Our patient tolerated six months of therapy with phenazopyridine for primary bladder neck obstruction without any noted toxicity. The patient presented with signs and symptoms of methemoglobinemia only after an acute overdose.

Reversal of methemoglobinemia requires reduction of iron from ferric (Fe^{+3}) to ferrous (Fe^{+2}) state within the hemoglobin molecule. Primary intrinsic mechanism is via NADH-dependent reduction catalyzed by cytochrome b5 reductase.[7] When intrinsic mechanisms are overwhelmed, an alternate pathway that utilizes nicotinamide adenine dinucleotide phosphate (NADPH) is capable of reducing ferric to ferrous hemoglobin with the assistance of extrinsic electron acceptors such as methylene blue. Phenazopyridine labeling recommends 1 to 2 mg/kg of methylene blue for suspected methemoglobinemia. Administration of 1 mg/kg methylene blue resulted in rapid resolution of symptoms and marked improvement in oxygenation for this patient.

Conclusion

There is a paucity of evidence for safety and efficacy of phenazopyridine, especially when used chronically. Our patient tolerated doses up to 400 mg daily for nearly six months. Presentation with methemoglobinemia happened shortly after ingesting a larger dose of approximately 1000 mg. To our knowledge this case report is the first phenazopyridine-associated methemoglobinemia after acute overdose despite long-term lower dose use of phenazopyridine. This emphasizes the dose-dependent methemoglobinemia toxicity. In addition, chronic use does not appear to have induced resistance to toxicity due to acute overdose. It is crucial for healthcare providers to educate patients regarding safe use of phenazopyridine. Meanwhile, further studies are required to establish a safe maximum daily dose of phenazopyridine.

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