Drug-Induced Methemoglobinemia After Recent High-Altitude Travel: Case Report

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INTRODUCTION

Methemoglobin is an oxidized form of hemoglobin in which the iron atom, normally in ferrous state (Fe^{2+}) becomes oxidized into the ferric state (Fe^{3+}). Methemoglobinemia can be congenital, but it is also a known adverse reaction to several medications and toxins.

While it occurs most famously from local anesthetics and dapsone, it can also occur from a much wider array of medications with high variability from patient to patient. Both celecoxib, frequently used for multimodal pain control, and the analgesic phenazopyridine, frequently used in gynecologic and urologic procedures, have been reported to induce methemoglobin formation. [1]

In this case report we describe a patient who developed sudden onset hypoxemia and methemoglobinemia following administration of phenazopyridine and celecoxib despite prior uneventful exposure to both medications during surgery three years prior.

CASE PRESENTATION

- Patient is a 77-year-old Caucasian female, ASA Physical Status 2, presenting for Robotic Sacrocolpopexy and cystoscopy for pelvic organ prolapse/vaginal enterocele.
- Past medical history includes mitral valve prolapse, hypothyroidism, coronary artery disease, hypertension, hypercholesterolemia and pseudogout.
- Past surgical history includes a hysterectomy 45 years ago, cataract surgery 2 years ago and urogynecologic surgery for incontinence 3 years ago.
- Family history was noncontributory with no history of adverse anesthesia reactions.
- Her social history was largely negative except for a two-week vacation with hiking at high altitude two weeks prior to surgery.

The patient was asymptomatic at time of initial evaluation on the day of her scheduled operation. She received Midazolam 0.5 mg IV for anxiolysis and phenazopyridine 200 mg PO to reduce irritation of the urinary tract mucosa from surgery. She also received Celecoxib 400 mg PO as part of a preoperative multimodal pain regimen.

After administration of these mediations, pulse oximetry began showing desaturation down to 95%. The patient remained asymptomatic and vital signs were stable and within normal limits. 100% FiO2 was administered via nonrebreather mask. Bedside chest X-ray revealed no acute cardiopulmonary findings. Saturations continued to worsen to ~88%, when arterial blood gas studies with co-oximetry returned showing a methemoglobin level of 9.1%. The patient remained asymptomatic, showing no symptoms of cyanosis, shortness of breath, or lethargy.

Methylene blue 50 mg IV was administered, and the patient showed improvement in oxygen saturation to ~92%, upon which an additional 50 mg of intravenous methylene blue was given. Several minutes later, pulse oximetry showed 100% saturation and repeat ABG showed reduction of methemoglobin to 1.3%. The surgery was cancelled, and the patient was monitored overnight. No further hypoxemia was noted, and the patient was discharged the next day. She returned one month later for the procedure. She did not receive phenazopyridine or celecoxib in the preoperative area, and the procedure was completed successfully without incident.

68-year-old Caucasian female presents for urologic surgery, past medical, surgical and family history largely noncontributory

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Phenazopyridine 200 mg PO, Celecoxib 400 mg PO, Gabapentin 300 mg PO, and Midazolam 0.5 mg IV administered in preoperative holding area

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Rapid desaturation on pulse oximetry to ~88% with no response to supplemental oxygen; otherwise asymptomatic in no apparent distress

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ABG showed 9.1% methemoglobin

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Methylene Blue 1 mg/kg administered intravenously

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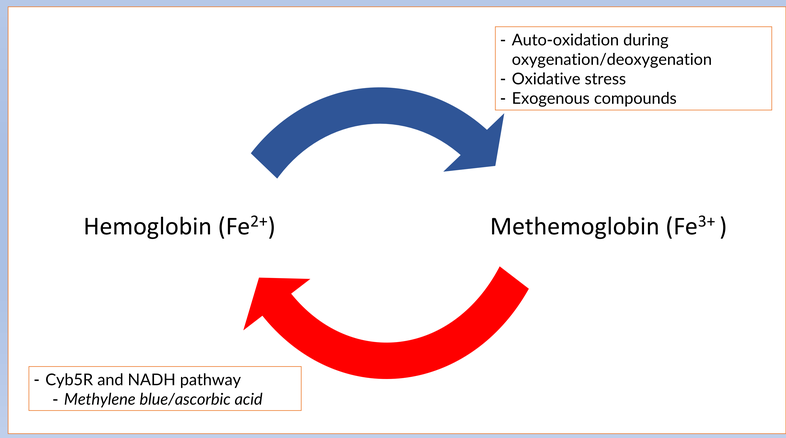
Rapid recovery to 100% SaO2



DISCUSSION

Treatment of methemoglobinemia initially involves discontinuation any suspected offending agents and supportive measures for IV access/hydration, ventilatory support, or seizure termination. Clinical improvement and reduction of methemoglobinemia on co-oximetry are the most significant markers of improvement, as MB has a similar absorbance spectrum to methemoglobin. For refractory cases, blood transfusion is a consideration.[6]

While rare, there are several case reports of acquired methemoglobinemia from administration of phenazopyridine and celecoxib, with symptoms ranging from lethargy to acute hypoxemia unresponsive to supplemental oxygen.[9,10]

A proposed explanation attributes the methemoglobinemia to the formation of aniline, a metabolite of phenazopyridine that is known to cause methemoglobinemia. In cases of aniline-induced methemoglobinemia, however, the response to MB is less robust than observed in this case study.

Given the patient's history of receiving these medications before without issue, a possible explanation in this case study includes the patient's recent high-altitude travel. Oxygen pressure and availability is lower at high altitude, causing well-known adaptive changes in hemoglobin activity though 2,3-bisphoshoglycerate formation, and a right-shift in the hemoglobin dissociation curve. This adaptation normally favors the release of oxygen and stabilization of deoxygenated hemoglobin. [7]

Despite the positive adaptive changes that favor the stability of normal functioning hemoglobin, high altitude exposure can also cause significant oxidative stress or the formation of reactive oxygen and nitrogen species.[11] These radicals would favor the formation of methemoglobin in its normal equilibrium with hemoglobin. Red Blood Cells, where this reaction occurs, have a 3-month lifespan, leading credence to the possibility that this state of oxidative stress may have persisted in this patient upon her return from high altitude. It is thus possible that either the exposure to hypoxic atmospheric conditions, or the process of recovery from such conditions, was responsible for predisposing this patient to development of methemoglobinemia after the medications were administered. Further correlation of high-altitude exposure, oxidative stress, and the presence of methemoglobinemia would be beneficial in guiding treatment plans for patients with any of these characteristics.

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