Delayed Diagnosis in Army Ranger

Postdeployment Primaquine-Induced Methemoglobinemia

Robyn Essendrop, MD1*; Nathan Friedline, MD2; John Cruz, DO3

ABSTRACT

Presumptive antirelapse therapy (PART) with primaquine for Plasmodium vivax malaria postdeployment is an important component of the US military Force Health Protection plan. While primaquine is well tolerated in the majority of cases, we present a unique case of an active duty Army Ranger without glucose-6-phosphatase dehydrogenase or cytochrome b5 reductase (b5R) deficiencies who developed symptomatic methemoglobinemia while taking PART following a deployment to Afghanistan.

Keywords: presumptive antirelapse therapy; Plasmodium vivax; primaquine; methemoglobinemia

Introduction

Prevention of plasmodial infection remains an important concern among deployed US Servicemembers and encompasses both primary prophylaxis and PART.1 Both Plasmodium vivax and Plasmodium ovale can cause delayed infection due to activation of dormant hypnozoites in the liver. The primary goal of PART is the eradication of intrahepatic P vivax hypnozoites. First licensed in 1952, primaquine (PQ) was the only US Food and Drug Administration (FDA)-approved medication for this purpose until the recent FDA approval of tafenoquine in 2018.2 The Centers for Disease Control and Prevention (CDC) recommends that providers consider prescribing PQ to travelers with prolonged exposure to endemic areas where P vivax accounts for >80% of malaria cases.3 Afghanistan, North Korea, and Iran are among the countries with highest risk of P vivax exposure; the Armed Forces Health Surveillance Center has identified PART as a key component in the US military Force Health Protection plan.4

Prescribing considerations for PQ include ruling out an underlying glucose-6-phosphatase dehydrogenase (G6PD) deficiency, the screening for which is now mandated for all military personnel. PQ can precipitate both severe hemolysis and methemoglobinemia in individuals with G6PD deficiency. Reports of symptomatic methemoglobinemia related to malaria prophylaxis with PQ are particularly rare in the absence of G6PD deficiency, with the last cases published during the Vietnam Conflict among a group of soldiers heterozygous for b5R deficiency.4 Our review of current English-language literature identified fewer than 10 published cases of symptomatic PQ-induced methemoglobinemia, which were all described in HIV-positive patients treated for Pneumocystis jiroveci pneumonia. Additionally, only two of these cases required treatment with methylene blue.6–8 We present a unique case of a PQ-induced methemoglobinemia diagnosed in an otherwise healthy, postdeployment, active duty Army Ranger without G6PD deficiency.

Case Presentation

A 22-year-old white Army Ranger presented to our emergency department (ED) with concern for contrast-induced allergic reaction following computed tomography pulmonary angiography (CTPA). On arrival, we noted both labial cyanosis (Figure 1) and an initial oxygen saturation (SpO2) of 90% without any evidence of anaphylaxis or other allergic reaction. Our patient reported persistent shortness of breath, dry cough, and “blue lips” for the past 2 weeks, which originally began 1 week after returning from a several-month-long deployment to Afghanistan. He reported dyspnea at home after climbing a single flight of stairs and had been unable to resume any of his typical work-out routines. He was otherwise healthy and denied any chest pain, palpitations, leg swelling, hemoptysis, fever, or history of clotting disorder. Medical workup 6 days earlier was inconclusive with a normal electrocardiogram, chest radiography, venous blood gas, complete blood count, and basic metabolic panel. CTPA at that time was negative for large

*Correspondence to ressendrop@gmail.com
1CPT Essendrop, 2LTC Friedline, and 3CPT Cruz are affiliated with the Madigan Army Medical Center, Tacoma, WA.
and may not be reproduced, distributed, transmitted, displayed, or otherwise published without the prior written permission of Breakaway Media, LLC. Contact publisher@breakawaymedia.org.

Methemoglobinemia occurs when >1% of red blood cells contain iron in the ferric (Fe³⁺) form, causing a leftward shift of the oxygen–hemoglobin dissociation curve. In the ferric form, hemoglobin affinity for oxygen increases, preventing oxygen delivery to tissues regardless of the concentration of oxygen inhaled. This diagnosis should be considered in patients with dyspnea or cyanosis when relatively low Spo₂ levels fail to respond to oxygen supplementation. Venous blood samples may exhibit a chocolate-colored appearance, and a thorough history may reveal exposure to one of several medications known to increased MetHb levels. Although asymptomatic elevations of MetHb levels have been measured in patients in South America receiving 2 to 5 times the recommended treatment dose of PQ for P vivax, none of these patients reported symptoms typically associated with methemoglobinemia.

TABLE 1 Sample Differential Diagnosis for Life-Threatening Causes of Dyspnea

| Cardiogenic Pulmonary Edema | Cough, dyspnea, children, fever
| Pulmonary Contusion | Hemoptysis, chest wall trauma
| Valvular Disease | Cyanosis, tachycardia
| Right Ventricular Failure | Sudden death, arrhythmias
| Pulmonary Arterial Hypertension | Syncope, dizziness

Discussion

The differential diagnosis for dyspnea in a Soldier returning from deployment is broad (Table 1) and distinct from the most common diagnoses encountered in civilian EDs, such as cardiogenic pulmonary edema, community-acquired pneumonia, and acute exacerbation of chronic respiratory disease. Specifically, postdeployment considerations should be tailored to include pathogenes more common to the region where the Soldier was recently deployed (e.g., tuberculosis, Avian influenza), job-related exposures, animal contacts, side effects of any new medications, and increased risk of venous thromboembolism secondary to venous stasis during prolonged travel.

Methemoglobinemia occurs when >1% of red blood cells contain iron in the ferric (Fe³⁺) form, causing a leftward shift of the oxygen–hemoglobin dissociation curve. In the ferric form, hemoglobin affinity for oxygen increases, preventing oxygen delivery to tissues regardless of the concentration of oxygen inhaled. This diagnosis should be considered in patients with dyspnea or cyanosis when relatively low Spo₂ levels fail to respond to oxygen supplementation. Venous blood samples may exhibit a chocolate-colored appearance, and a thorough history may reveal exposure to one of several medications known to increased MetHb levels. Although asymptomatic elevations of MetHb levels have been measured in patients in South America receiving 2 to 5 times the recommended treatment dose of PQ for P vivax, none of these patients reported symptoms typically associated with methemoglobinemia.

Risk of clinically significant methemoglobinemia increases significantly with G6PD or b5R deficiency. Treatment with methylene blue in these patients can lead to hemolytic anemia.

Our patient did not have either of these deficiencies, and we did not identify any additional factors apart from his recent PQ course which would have otherwise increased his risk for elevated MetHb levels.

The 2017 World Malaria Report specifically identifies Afghanistan as an area of increasing P vivax infection. PART with PQ remains an important intervention to reduce delayed malarial infections following deployment. Soldiers returning from deployment to endemic areas may have received PQ, and providers should be alert to the development of adverse effects including both hemolytic anemia and methemoglobinemia. Although only recently approved and not yet widely used, tafenoquine has also been shown to increased MetHb levels. Treatment thresholds should be tailored individually and may be considerably lower in Soldiers requiring rapid return to high performance levels compared to the chronically ill patients described in most published cases.

Conclusion

This case emphasizes the importance of considering a broad differential particularly in patients with repeated health care visits. Specifically, when evaluating shortness of breath in a patient who has recently travelled internationally, careful history regarding potential infectious exposures and new medications must be considered. Our case also suggests that, although symptomatic methemoglobinemia following PART is rare, PQ alone can induce symptomatic methemoglobinemia, even among soldiers previously screened negative for G6PD deficiency.

Disclosure

The authors have no conflicts of interest to report.
Co-oximetry. Blood test that reports percentages of various forms of hemoglobin including hemoglobin bound to carbon monoxide (carboxyhemoglobin) and hemoglobin containing ferric iron (methemoglobin).

Cytochrome b5 reductase. Also known as NADH-cytochrome b5 reductase 3, a soluble enzyme found in red blood cells that protects the cell from oxidative stress by reducing methemoglobin (containing ferric iron) to normal hemoglobin (containing ferrous iron).

Force Health Protection Plan. “All measures taken by commanders, supervisors, individual Servicemembers, and the MHS to promote, protect, improve, conserve, and restore the mental and physical well-being of Servicemembers across the full range of military activities and operations.”

Glucose-6-phosphatase dehydrogenase. An enzyme found in red blood cells essential to protecting against oxidation and hemolysis through the regeneration of the molecule NADPH and reduction of glutathione stores.

Hemolytic anemia. An abnormally low hemoglobin levels and thus oxygen carrying capacity due to destruction of red blood cells.

Hemoglobin electrophoresis. Blood test that can identify variations of the hemoglobin protein including normal variants and abnormal types such as those found in sickle cell disease or thalassemia.

Hemolysis. The destruction (rupture) of red blood cells.

Heterozygous. An individual with two distinct alleles for a given gene.

Hypnozoite. A dormant form in a parasitic life cycle that can persist in human liver and cause delayed infection.

Presumptive antirelapse therapy (PART). Medication taken following prolonged exposure in malaria-endemic areas to prevent delayed-onset infection caused by the dormant liver stage of specific malaria strains (Plasmodium vivax, Plasmodium ovale).

Primaquine. An antimalarial medication used to eliminate dormant hypnozoites of Plasmodium vivax and Plasmodium ovale.
Inside this Issue:

- CASE REPORT: Postdeployment Primaquine-Induced Methemoglobinemia
- TCCC Critical Decision Case Studies
- IN BRIEF: Red Light Illumination in Helicopter Air Ambulances
- Risk Associated With Autologous FWB Training
- SPECIAL ARTICLE: NATO Special Operations Course
- FEATURE ARTICLES: iTClamp Mechanical Wound Closure Device
- Tourniquet Placement ➔ Getting Tourniquets Right
- Airway Management for Army Reserve Combat Medics
- Laryngeal Handshake vs Index Finger Palpation
- Enteral Resuscitation in Resource-Poor Environments
- Tranexamic Acid in the Prehospital Setting
- Survival for Prehospital SGA Placement vs Cricothyrotomy
- Military Working Dogs in the Prehospital Combat Setting ➔ SOMSA Research Abstracts
- ONGOING SERIES: Human Performance Optimization, Infectious Diseases, Injury Prevention, Prolonged Field Care, SOFsono Ultrasound, Unconventional Medicine, Book Reviews, TCCC Updates, and more!

Dedicated to the Indomitable Spirit and Sacrifices of the SOF Medic

A Peer-Reviewed Journal That Brings Together the Global Interests of Special Operations’ First Responders