

Dapsone-induced methemoglobinemia

Case of the blue lady

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Methemoglobinemia is a life-threatening condition that can be difficult to diagnose. While methemoglobinemia can be congenital and should be considered in cyanotic infants,¹ it is more often an adverse medication effect, most commonly related to dapsone use.² As up to 1 in 9 emergency department visits in Canada might be owing to adverse medication effects, physicians and other health care providers should routinely consider the relationship between medications and atypical clinical symptoms.³ We describe the diagnosis and management of a patient with acquired methemoglobinemia as a result of dapsone use.

Case

A 46-year-old woman presented to a rural emergency department with a 4-day history of progressive weakness, blue discoloration of her lips and nails, and a 1-day history of shortness of breath.

Her medical history was relevant for biopsy-proven pyoderma gangrenosum. Her regular medications included zopiclone. Two weeks before presentation she started 40 mg of prednisone once daily and 200 mg of dapsone once daily for a pyoderma gangrenosum flare.

On examination, the patient was alert and appeared comfortable. She was afebrile, but her heart rate was tachycardic at 130 beats/min, her respiratory rate was 24 breaths/min, and her blood pressure was 160/96 mm Hg. She was not in respiratory distress but had marked peripheral and central cyanosis. Digital pulse oximetry showed an oxygen saturation of 85% on room air. Results of a physical examination of her cardiovascular and respiratory systems were unremarkable. Oxygen (4 L/min by nasal prongs) was started but her oxygen saturation did not rise above 87%.

Two arterial blood samples taken on room air appeared chocolate brown. Analysis of arterial blood gas from both samples revealed a P_{O_2} of 99 mm Hg, a P_{CO_2} of 17 mm Hg, a pH of 7.7, a bicarbonate level of 20.8 mmol/L, and an oxygen saturation of 99%. Additional laboratory and chest x-ray scan findings were not outside the reference ranges (Table 1).

Methemoglobinemia secondary to dapsone use was suspected and methemoglobin level tests were ordered. A medical toxicologist recommended treatment with 2 mg/kg of intravenous methylene blue. Within 15 minutes of methylene blue therapy, the central and peripheral cyanosis started to resolve. The patient was admitted to our rural hospital, dapsone was stopped, and no further treatment was required. Her methemoglobin level improved from 18.3% to 8.6% the

EDITOR'S KEY POINTS

- Diagnosis of methemoglobinemia is normally based on clinical symptoms and an elevated serum methemoglobin level. However, serum methemoglobin levels are not always immediately available. Therefore, the typical oxygen "saturation gap" observed between arterial blood gas analysis and pulse oximetry readings is helpful for making the diagnosis.
- Initial management of patients with methemoglobinemia is supportive care with discontinuation of the causative medication. For patients with signs of hypoxia or methemoglobin levels exceeding 30%, intravenous methylene blue should be administered.
- Physicians and other health care workers should always consider adverse medication reactions in the differential diagnosis of atypical or unusual clinical presentations.

POINTS DE REPÈRE DU RÉDACTEUR

- Le diagnostic de la méthémoglobinémie se fonde normalement sur les symptômes cliniques et sur un taux de méthémoglobine sérique élevé. Par ailleurs, les concentrations sériques de méthémoglobine ne sont pas toujours disponibles immédiatement. Par conséquent, « l'écart de saturation » en oxygène typique observé entre l'analyse des gaz du sang artériel et les lectures de l'oxymétrie pulsée est utile pour poser le diagnostic.
- La prise en charge initiale des patients atteints de méthémoglobinémie repose sur des soins de soutien et la discontinuation du médicament responsable. Pour les patients présentant des signes d'hypoxie ou des niveaux de méthémoglobine supérieurs à 30%, il faudrait administrer du bleu de méthylène par voie intraveineuse.
- Les médecins et les autres professionnels de la santé devraient toujours envisager des réactions médicamenteuses indésirables comme diagnostic différentiel des présentations cliniques atypiques ou inhabituelles.

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following day. Two days later, as she was clinically well with an oxygen saturation of 95% measured by pulse oximetry, she was discharged from hospital.

Literature search

A literature search using the terms *dapsone* and *methemoglobinemia* was performed in the EMBASE and MEDLINE databases. Potentially relevant studies published in English were reviewed and considered for inclusion. References from selected articles were also searched.

Discussion

Dapsone (4,4'-diaminodiphenyl sulfone) is a sulfone antibiotic and potent anti-inflammatory that inhibits folate synthesis.⁴⁻⁶ Although it is traditionally an antileprosy drug, the use of dapsone has expanded into the treatment of dermatologic conditions, including pyoderma gangrenosum and dermatitis herpetiformis. Dapsone has several off-label uses—namely, treatment of *Pneumocystis jiroveci* pneumonia, bullous systemic lupus erythematosus, and severe aphthous ulcers.⁷ Dapsone is metabolized in the liver via the cytochrome P450 pathway to potent oxidants that are responsible for

its adverse hematologic effects—namely, hemolytic anemia and methemoglobinemia.

What is methemoglobinemia? Methemoglobin is an aberrant form of hemoglobin arising from oxidation of iron in the normal heme molecule from the ferrous form (Fe^{2+}) to the ferric (Fe^{3+}) form. The presence of ferric heme molecules causes a structural change in the hemoglobin molecule, resulting in reduced oxygen-carrying capacity and impaired unloading of oxygen at the tissue.^{2,6,8-10} This left shift in the oxygen saturation curve results in functional anemia.²

Typically, red blood cells maintain a steady-state methemoglobin level of less than 1% via 2 main enzymatic pathways. Elevation in methemoglobin levels can be caused by congenital enzyme deficiencies or exposure to exogenous oxidizing agents that disrupt the equilibrium established by these pathways. Several exogenous oxidizing agents are known to cause acquired methemoglobinemia. Dapsone is the medication that most commonly causes methemoglobin, but other offending drugs include the local anesthetics benzocaine and lidocaine.⁸ There is a paucity of literature regarding the incidence of dapsone-induced

Table 1. Laboratory findings at presentation: Findings of the chest x-ray scan showed both lungs were well inflated and clear; the pleural spaces were normal; and the heart and mediastinum were unremarkable in appearance.

COMPONENT	FINDING
White blood cells, $\times 10^9/L$	8.9
Red blood cells, $\times 10^{12}/L$	3.9
Hemoglobin level, g/L	139
Hematocrit	0.4
Mean cell volume, fL	104
Platelets, $\times 10^9/L$	459
Chemistry panels, mmol/L	
• Sodium level	135
• Potassium level	3.5
• Chloride level	98
• Carbon dioxide level	20.7
Creatinine level, $\mu\text{mol}/L$	92
D-dimer level, nmol/L	1.1
Erythrocyte sedimentation rate, mm/h	38
Arterial blood gas	
• P_{O_2} , mm Hg	99
• P_{CO_2} , mm Hg	17
• pH	7.7
• Oxygen saturation, %	99
• Bicarbonate level, mmol/L	20.8
• Base excess level, mmol/L	1

methemoglobinemia. However, in hematopoietic stem cell transplant recipients receiving dapsone for *P jiroveci* pneumonia prophylaxis, the incidence is approximately 3%.¹¹

Signs and symptoms. Clinical symptoms of methemoglobinemia depend on the serum concentration of methemoglobin. Peripheral and central cyanosis are usually seen at a serum methemoglobin level of 15%. Methemoglobin levels of 30% to 45% result in headache, fatigue, tachycardia, weakness, and dizziness, while levels above 60% result in cardiac arrhythmia, dyspnea, seizures, and coma. Death typically occurs at methemoglobin levels greater than 70%.⁴


Diagnosis. Diagnosis of methemoglobinemia is normally based on clinical symptoms and an elevated serum methemoglobin level. However, serum methemoglobin levels are not always immediately available. Therefore, the typical oxygen “saturation gap” observed

between arterial blood gas analysis and pulse oximetry readings is helpful for making the diagnosis of methemoglobinemia.²

The saturation gap arises owing to the limitations of pulse oximetry. Pulse oximetry can only measure 2 hemoglobin species—oxyhemoglobin and reduced hemoglobin.⁵ As other hemoglobins such as methemoglobin rise, the oxygen saturation on pulse oximetry falls and plateaus at 85%.⁵ This saturation gap, where oxygen saturation levels measured with pulse oximetry are substantially lower than arterial blood gas oxygen saturation levels, should alert the practitioner that an alternative, nonfunctional species of hemoglobin is present. Also, in cases of methemoglobinemia, arterial blood samples will be a characteristic chocolate-brown colour.¹²

Management. Initial management of patients with methemoglobinemia is supportive care with discontinuation of the offending agent. For patients with signs of hypoxia or methemoglobin levels exceeding 30%, administration of intravenous methylene blue at 1 to 2 mg/kg is required.⁴ In vivo, methylene blue is reduced by NADPH (reduced form of nicotinamide adenine dinucleotide phosphate)–methemoglobin reductase to leukomethylene blue. Leukomethylene blue subsequently acts as an artificial electron donor to methemoglobin, thereby enhancing the erythrocyte’s ability to reduce methemoglobin. If symptoms persist after 1 hour, repeat doses are given with caution, as accumulation of the drug can result in increased production of methemoglobin.¹³ Studies support the use of activated charcoal to improve clearance rates of methemoglobin at lower concentrations of methylene blue, particularly in cases of accidental or intentional dapsone overdose.¹⁴ If symptoms persist despite the above-outlined therapy, hemodialysis might be required.

Conclusion

The nonspecific presentation of methemoglobinemia can make it difficult to recognize in clinical practice. However, clinical symptoms, the characteristic saturation gap between oxygen saturation on pulse oximetry and on arterial blood gas analysis, and serum methemoglobin levels aid in making the diagnosis. Favourable outcomes are usually seen with prompt diagnosis and treatment. Physicians and other health care workers should always consider adverse medication reactions in the differential diagnosis of atypical or unusual clinical presentations. 

At the time of the case, **Dr Burke** was a family medicine resident at the University of Alberta in Red Deer. **Dr Jahangir** was Assistant Clinical Professor in the Department of Family Medicine at the University of Alberta and a rural family physician in Peace River, Alta. **Dr Kolber** was Associate Professor in the Department of Family Medicine at the University of Alberta and a rural family physician in Peace River.

Competing interests

None declared

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