Case Report

Dapsone-induced methemoglobinemia: "Saturation gap"—The key to diagnosis

Shivinder Singh, Navdeep Sethi, Sushmitha Pandith, Gouri Shankar Ramesh

Department of Anesthesiology and Critical Care, Armed Forces Medical College, Pune, Maharashtra, India

Abstract

Two cases of Acquired Methemoglobinemia are presented. The significance of a high index of suspicion for diagnosisis emphasized, especially in the presence of a "saturation gap". The various causes of acquired methemoglobinemia are enumerated and the management reviewed.

Key words: Acquired methemoglobinemia, dapsone, saturation gap

Introduction

Dapsone is a drug that is used in the treatment of leprosy and acne vulgaris owing to its immunosuppressive effects. Long-term administration of dapsone at standard doses (100 mg/day) results in methemoglobinemia in about 15% of patients.[1] Classically, low pulse oximeter readings are associated with hypoxia, however methemoglobinemia is an important albeit uncommon cause.[2] We report two cases of dapsone-induced methemoglobinemia with evident cyanosis, one in the emergency department and the other in a patient undergoing elective splenectomy.

Case Report

Case 1

A 36-year-old woman was diagnosed with immune thrombocytopenic purpura in July 2012 and started on oral prednisolone and dapsone 100 mg/day. About 3 months later, she was admitted to the hospital with fatigue, headache, arthralgia, and severe dyspnea. Physical examination was normal except for peripheral cyanosis. She had a platelet count of 1,000/cmm, hemoglobin of 7.9 gm%. SpO_2 on room air was 84%, respiratory rate was 52/min. Owing to intolerance for non-invasive ventilation (NIV) and low saturation, the patient was intubated and ventilated.

Arterial blood gas (ABG) analysis revealed a pH of 7.43, PaO_2-180 mmHg, $PaCO_2$-32 mmHg, SaO_2-99.1% on oxygen by facemask. In view of history of dapsone intake, cyanosis, low SpO_2 with normal PaO_2 and SaO_2 (on ABG) a diagnosis of methemoglobinemia was considered and dapsone was stopped, however, the facility for methemoglobin (methHb) estimation was not available. After 48 hrs of mechanical ventilation, she improved symptomatically and was extubated following a weaning trial. She was shifted to high dependency unit with oxygen 5l/min. The SpO_2 continued to remain low ranging from 88-92% over the next 3 days though the SaO_2 was normal. As the patient remained clinically stable, no further intervention was carried out and she made an uneventful recovery.

Case 2

An 8-year-old girl, a known case of immune thrombocytopenic purpura, with treatment history of oral prednisolone 20 mg/day and dapsone 50 mg/day since 1 year, was planned for laparoscopic splenectomy.

Pre-operative assessment revealed cushingoid features, skin discoloration all over the body and splenomegaly [Figure 1].

She had a platelet count of 20,000/cmm but the other hematological variables were normal. Oxygen saturation on

Address for correspondence: Dr. Col. Shivinder Singh, Department of Anesthesiology and Critical Care, Armed Forces Medical College, Solapur Road, Pune - 410040, Maharashtra, India. E-mail: sshivinder@hotmail.com

Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/0970-9185.125710

room air was 88%. During maintenance of general anesthesia with a 60:40 (nitrous oxide:oxygen) gas oxygen ratio, the SpO_2 rose to 92%. Vital signs, physical examination including bilateral air entry was normal, end tidal carbon dioxide and airway pressures were unremarkable. Intraoperative ABG analysis revealed a PaO_2 of 260 mmHg, pH 7.40, $PaCO_2$ 38 mmHg, HCO_3 22.4 meq.l-1 and SaO_2 of 99%. Filter paper test done on the patient's blood comparing it with blood from a normal patient [Figure 2] which showed that the patient's blood remained dark even after exposure to atmospheric oxygen.

Deoxyhemoglobin can be distinguished from methHb by this simple bedside test. By placing 1 or 2 drops of the patient's blood on a white filter paper: Deoxyhemoglobin brightens after exposure to atmospheric oxygen, but methHb does not change color.[2]

She was transferred to the pediatric intensive care unit (ICU) with oxygen therapy by polymask at 5 l/min, as SpO_2 remained 86% on room air. Blood analysis showed methHb levels of 28.6%. Dapsone was stopped and the patient remained asymptomatic with supplemental oxygen by facemask. As the methHb levels were less than 30% and the patient was stable, therapy with methylene blue was not considered.

Discussion

The majority of cases of acquired methemoglobinemia described in literature have resulted from exposure to exogenous oxidizing agents like nitrites used as preservatives in food or as a deliberate poison,[3,4] amyl nitrate used as a recreational agent,[5,6] abuse of paint thinner by addicts,[7] intake of nitrate containing vegetables[8] use of EMLA cream,[9,10] and Dapsone intake.[11,12]

The peak plasma concentrations of Dapsone are reached within 2-8 hours after ingestion. The mean elimination half-life varies from 10 to up to 80 hours in overdose situations. In healthy erythrocytes, cellular enzymes rapidly reduce any naturally occurring methHb. An exposure to oxidative medications can overcome these reducing enzymes thus causing an accumulation of methHb.[2] The role of nitric oxide (NO) in the pathophysiology of methemoglobinemia is also being studied.[13] The presence of methHb in the erythrocyte prevents the binding of oxygen as also increases the affinity of normal hemoglobin molecules for oxygen, shifting the oxygen dissociation curve to the left, thus further decreasing oxygen delivery to the tissues.[2,14]

The symptoms and signs are proportional to the level of methemoglobin. Asymptomatic, if less than 15%; cyanosis in levels above15%; headache, dyspnea, nausea, tachycardia, and weakness in levels above 20%; coma sets in above 45%, and a high mortality rate is associated with levels above 70%.[15]

While cyanosis is a pointer to the diagnosis, varying oxygen saturation seen with pulse oximetry often confuses the issue. Standard colorimetric pulse oximeters show falsely low readings in mild toxicity and falsely high readings in severe toxicity by giving a constant reading in the low 80s in the presence of methHb.[2] On the other hand, most arterial blood gas analyzers calculate the oxygen saturation based on the PaO_2 (which is a measure of the dissolved oxygen in plasma) and so give false high values. Therefore, a "saturation gap" between the recorded saturation from the pulse oximeter as compared to the reported saturation in the arterial blood gas may be detected[16] and in the presence of a high index of suspicion, may be the key to diagnosis, especially in the resource limited setting.[3]

A pulse oximeter is now available that uses eight wavelengths of light and can accurately measure both methHb and carboxyhemoglobin (the Rainbow-SET Rad-57 Pulse CO-Oximeter, Masimo, Inc., Irvine, CA). It is capable of giving continuous readings of methHb level at the bedside.[17]

Management consists of removing the offending agent, high-dose oxygen, and intravenous methylene blue. Methylene blue

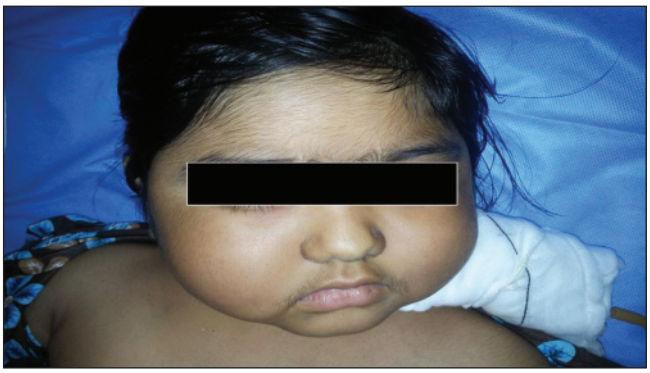

Figure 1: Cushingoid features with cyanosis

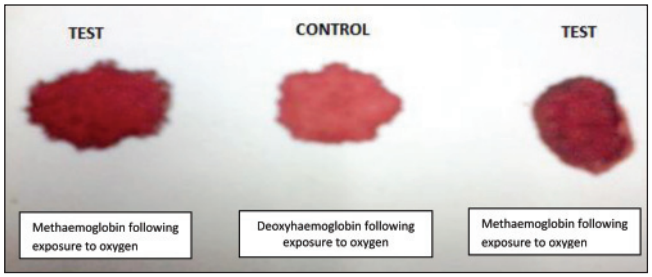

Figure 2: Filter paper test

(1-2 mg.kg^{-1}) administered intravenously over a period of 3-5 minutes (contraindicated in G6PD deficiency) produces a rapid conversion of meth Hb to hemoglobin. Its use is recommended in all patients with meth Hb levels greater than 30% or in symptomatic patients at lower levels. Exchange transfusion and hyperbaric oxygen may also be considered for severe or refractory cases.[18]

These two cases emphasize the importance of good history taking, knowledge of drugs likely to cause methemoglobinemia and a high index of suspicion especially in the presence of a "saturation gap".

References

1. Coleman MD, Rhodes LE, Scott AK, Verbov JL, Friedmann PS, Breckenridge AM, *et al*. The use of cimetidine to reduce dapsone-dependent methaemoglobinaemia in dermatitis herpetiformis patients. Br J Clin Pharmacol 1992;34:244-9.
2. Steiner IP, Nichols DN. A case of dapsone-induced cyanosis in the emergency department. Isr J Emerg Med 2006;6:10-3.
3. Nabukeera-Barungi N, Mworozi E. Sudden onset methaemoglobinaemia in a previously well Ugandan child: A case report and literature review. Pan Afr Med J 2012;11:49.
4. Su YF, Lu LH, Hsu TH, Chang SL, Lin RT. Successful treatment of methemoglobinemia in an elderly couple with severe cyanosis: Two case reports J Med Case Rep 2012;6:290.
5. Sheena Y, Baston EL, Downs A, Chester DL. A sticky situation: Methaemaglobinaemia in a hand trauma patient. BMJ Case Rep 20121;2012.
6. Hall A, Stessel B, Bergmans D, Schnabel R. Two cases of acquired methemoglobinemia. Acta Anaesthesiol Belg 2012;63:97-100.
7. Singh R, VinayagamS, Vajifdar H. Methemoglobinemia as a result of accidental lacquer thinner poisoning. Indian J Crit Care Med 2012;16:44-7.
8. Martinez A, Sanchez-Valverde F, Gil F, Clerigué N, Aznal E, Etayo V, *et al*. Methemoglobinemia induced by vegetable intake in infants in north Spain. J Pediatr Gastroenterol Nutr 2013;56:573-7.
9. Schmitt C, Matulic M, Kervégant M, Tichadou L, Boutin A, Glaizal M, *et al*. Methaemoglobinaemia in a child treated with Emla(®) cream: Circumstances and consequences of overdose. Ann Dermatol Venereol 2012;139:824-7.
10. García-Saura PL, Serrano Álvarez C. Methaemoglobinaemia in a healthy patient after using topical anaesthetic cream, for laser depilation. Rev Esp Anestesiol Reanim 2012.
11. Ash-Bernal R, Wise R, Wright SM. Acquired methemoglobinemia: A retrospective series of 138 cases at 2 teaching hospitals. Medicine (Baltimore) 2004;83:265-73.
12. Stichtenoth D. Lip cyanosis in dapsone therapy: Should the dosage be reduced? MMW Fortschr Med 2012;154:32.
13. Sanyal T, Chakraborty S. Multiscale analysis of hypoxemia in methemoglobin anemia. Math Biosci 2013;241:167-80.
14. Burke MD, DelGiacco E, Curran AL, Savior DC. Methhemoglobinemia in Besa EC eds. Emedicine Available from: http: //www. emedicine. com /Emerg/topic313. htm Updated: Jun 3, 2013 Accessed on 13 Dec 2013.
15. Curry S. Methemoglobinemia. Ann Emerg Med 1982;11:214-21.
16. Barker SJ, Tremper KK, Hyatt J. Effects of methemoglobinemia on pulse oximetry and mixed venous oximetry. Anesthesiology 1989;70:112-7.
17. Annabi EH, Barker SJ. Severe methemoglobinemia detected by pulse oximetry. Anesth Analg 2009;108:898-9.
18. Mycyk MB. Poisoning and drug overdosage. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, Eds. Harrison's Online. 18th ed. New York: McGraw-Hill; 2012.

How to cite this article: Singh S, Sethi N, Pandith S, Ramesh GS. Dapsone-induced methemoglobinemia: "Saturation gap"-The key to diagnosis. J Anaesthesiol Clin Pharmacol 2014;30:86-8.
Source of Support: Nil, **Conflict of Interest:** None declared.