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CASE REPORT

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Dapsone-induced methemoglobinemia—A case report

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Abstract

Dapsone therapy is associated with methemoglobinemia. Pulse oximetry is used to indicate adequate oxygen saturations, and co-oximetry is needed to diagnose low arterial oxygen saturations. Clinicians should aware while prescribing dapsone.

KEYWORDS

dapsone, methemoglobinemia, methylene blue, oxygen saturation, saturation gap, vitamin C

1 | CASE REPORT

A 23-year-old female initially presented to the hospital with a 1-week history of worsening blurry vision and mild headache that had progressed to ataxia and difficult ambulation. On examination, she was found to have nystagmus, left eye ophthalmoplegia, and diplopia with otherwise normal neurological examination and CT (computed tomography) brain. She was admitted under neurology for further workup with a view to exclude multiple sclerosis (MS) among other differentials.

Her medical history was significant for fibromyalgia and Mucha-Habermann disease or pityriasis lichenoides et varioliformis acuta (PLEVA) for which she has been on prednisone 30 mg-50 mg/day for 2 years and more recently dapsone 150 mg daily.

Three days into her hospital admission, a medical emergency team (MET) call was activated for ongoing hypoxia with pulse oximetry saturation (SpO_2) ranging from 88% to 92% despite being on 8 L of oxygen on the Hudson mask. Upon arrival of the MET team, patient complained of dyspnea and appeared tachypneic but denied cough, hemoptysis, chest pain, or previous history of deep vein thrombosis (DVT), pulmonary embolism (PE), or acute asthma attacks. On examination, her lips and fingertips appeared mildly blue; chest sounds were clear and heart sounds dual without any additional murmurs on auscultation, and no lower limb tenderness or swelling was present. Her blood pressure was 103/66 mm Hg and noted to be sinus tachycardia ranging from 90 to 105 beats per minute (bpm). A point-of-care (iStat) arterial blood gas analysis (ABG) was performed while the patient was on 8 L/min of oxygen with SpO_2 90%, which showed a PaO_2 of 178 mm Hg, SaO2 98%, PCO_2 20 mm Hg, pH 7.56, bicarbonate 18 mmol/L, lactate 2.9 mmol/L, and Hb 98 g/L. Inspecting her medication chart, she had not received DVT prophylaxis for 3 days, so a CT pulmonary angiogram (CTPA) was performed due to her high risk of thromboembolism. Both PE and pneumonia were excluded on review. The patient was brought to intensive care unit (ICU) due to ongoing hypoxia and placed on high flow nasal prongs (HFNP). Her ABG in ICU (which includes co-oximetry analysis) showed a methemoglobin (MetHb) level of 17.7%, which then led to a diagnosis of dapsone-induced methemoglobinemia. She was administered vitamin C intravenously 10 g every 6 hours for 4 days prior to being switched to oral vitamin C with MetHb, returning to 1.3% after 5 days of treatment with SpO2 98%-99% on room-air oxygen.

2 | DISCUSSION

Dapsone Indications and Metabolism: Dapsone is a sulfone antibiotic and anti-inflammatory agent that inhibits folate synthesis.[1] It has traditionally been used against leprosy, but in the modern era, it has been prescribed for dermatological conditions including pyoderma gangrenosum, dermatitis herpetiformis, and several infectious organisms like *Pneumocystis jerovici* (*PJP*) and toxoplasmosis.[1-3]

The metabolism of dapsone includes two routes: nitrogen (N)-acetylation and N-hydroxylation. The former is considered the major route of dapsone metabolism, forming mono-acetyl dapsone and di-acetyl dapsone where the NAT (N-acetyl transferase) enzyme is responsible for the formation of these derivatives. The N-hydroxylation is mediated by hepatic cytochrome P450 isoforms such as CYP3A4, forming N-hydroxylated metabolites such as dapsone hydroxylamine (DDS-NHOH) and mono-acetyl dapsone hydroxylamine (MADDS-NHOH).[8] These metabolites oxidize the Fe^{2+} to Fe^{3+} of hemoglobin forming methemoglobin. It is these latter metabolites that cause methemoglobinemia and hemolytic anemia from oxidative stress.[2,4,5] Dosages above 200 mg/day are usually most frequently associated with methemoglobinemia.[4]

2.1 | Mechanism for methemoglobinemia

A single hemoglobin (Hb) molecule normally has four heme-iron complexes imbedded in the globin chains where the iron is in the ferrous (Fe2+) state.[6] When one oxygen reversibly binds to one heme-iron (Fe^{2+}) complex, it makes it easier for oxygen to attach to the remaining heme-iron (Fe^{2+}) complexes due to the allosteric quaternary structure of hemoglobin.[6] Methemoglobin (MetHb) is an aberrant form of hemoglobin, which occurs when the iron in the heme-iron complex changes from a ferrous (Fe^{2+}) to a ferric (Fe^{3+}) state by undergoing oxidation.[2] The ferric state is unable to bind to oxygen, and the oxygen affinity of any remaining heme-iron complex in the globin protein is increased which shifts the oxygen dissociation curve to the left.[5,7] Normally, auto-oxidation of Hb to MetHb occurs spontaneously, which is paralleled by continuous reduction back to Hb via one dominant physiological pathway to maintain an equilibrium MetHb level of 1%-2%[2,5,7]; a second pathway does exist but remains mostly inactive unless an extrinsic electron carrier like methylene blue becomes available.

Causes of Methemoglobinemia can be congenital or acquired with dapsone (including topical) being the most common but other offending agents include local anesthetic benzocaine (especially spray 20%), and lignocaine.[1,2,7,8]

2.2 | Clinical presentation and diagnosis of methemoglobinemia

Clinically, the symptoms depend on MetHb blood levels with peripheral and central cyanosis seen at 15%, which was evident in our patient; headache, fatigue, tachycardia, weakness, and dizziness at 30% to 45%; respiratory depression, paralysis, arrhythmia, convulsions and coma manifest at 60%, and death at concentrations of 70% to 80%.[1,2,4]

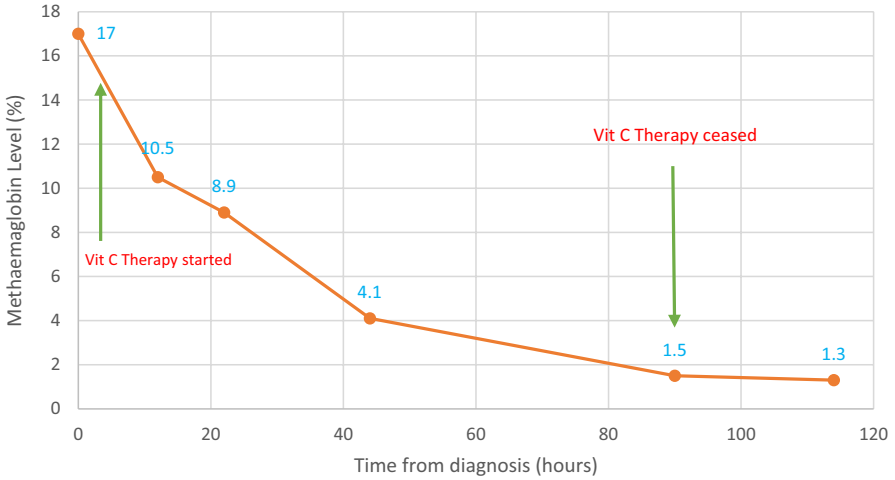
The ideal way to diagnose methemoglobinemia is to detect elevated blood levels of MetHb with a blood gas machine that has co-oximetry. But not all machines are equipped with co-oximeter, so clinicians need to be aware of the phenomenon known as the "saturation gap" that arises in these cases.[4,9] In our patient, even though her dyspnea and tachypnea had resolved, her saturation remained 88%-90% despite being placed on to HFNP with FiO_2 0.4 in the ICU that contrasted with her ABG analysis, which showed a SaO2 of 98% with a PaO_2 of 178 mm Hg. The reason behind this is twofold: the pulse oximeter measures SpO_2 through absorption at two wavelengths (hemoglobin at 660 nm and oxyhemoglobin 940 nm), which drops as MetHb starts to rise and plateaus at around 85%[4,5]; the ABG machine measures arterial oxygen partial pressure that remains normal in methemoglobinemia and estimates oxygen saturation by using the standard oxyhemoglobin dissociation curve (ODC).[7] Due to these factors, a so-called "saturation gap" arises that should alert clinicians to the presence of an alternate non-functional Hb species. Our ICU ABG machine showed the oxyhemoglobin level to be at 81%, demonstrating that the pulse oximeter overestimates the SpO2 in these scenarios and cannot be a reliable marker of arterial oxygen saturation.[1,4,5,10] Clinically, the blood from this condition is described as "chocolate brown".[1,7]

2.3 | Management of methemoglobinemia

In most cases, methylene blue (MB) is the first choice of treatment, but high-dose vitamin C (VC) provides an alternative and effective management strategy.[7,11] Vitamin C was chosen for our patient because she had an unknown glucose-6-phosphate dehydrogenase (G6PD) status and had become reasonably stable without any further respiratory distress (most likely caused by anxiety). 10 g of vitamin C was administered every 6 hours that led to the decline of MetHb to 1.3% in 4 days (Figure 1). Park et al also used this regime for a patient that had MetHb level of 64.4%, continued until MetHb fell below 10% at 54 hours post-presentation. Further MetHb measurements showed ongoing decline despite cessation of VC therapy.[11] The mechanism of VC therapy is not well understood but postulated that it removes oxidative stress, the main causative factor for methemoglobinemia.[11] High-dose VC also avoids rebound methemoglobinemia seen when repeated doses of MB are needed and hypoxia from hemolysis in those deficient of G6PD.[1,2,7] Vitamin C can increase the urinary excretion of oxalate which in the context of renal disease can lead to renal failure due to hyperoxaluria.[11]

Methylene blue is the first choice of treatment especially in the acutely unwell patient where a standard dose of 1-2 mg/kg over 5 minutes can lead to a rapid decline in MetHb levels with a second dose rarely being needed.[7] Moulis et al showed that in their patient MetHb level fell from 17% to 4% in

FIGURE 1 Decrease In Methemoglobin Levels over time



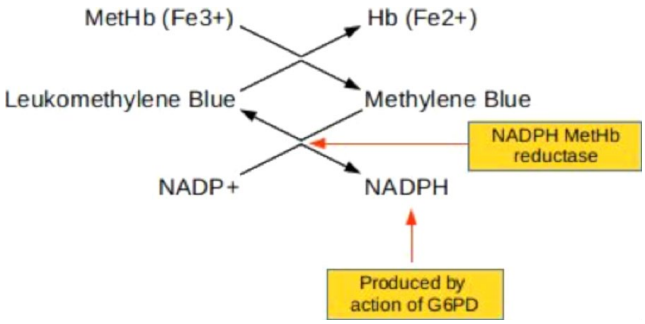


FIGURE 2 Mechanism of Action of Methylene blue in Methemoglobinemia

20 minutes after a 2 mg/kg dose of MB, but 10 days later, the patient had rebound methemoglobinemia at 14%, which was attributed to the long half-life of dapsone; MetHb eventually declined to 5% the next day without intervention.[12] Methylene blue works by utilizing the normally dormant G6PD pathway to act as an electron transporter to ultimately reduce MetHb back to Hb (Figure 2).[4,7]

3 | CONCLUSION

Methemoglobinemia is a rare cause for hypoxia and tachypnea. Methemoglobin levels can be elevated in patients on dapsone and should be considered as a cause for hypoxia and tachypnea in patients on dapsone. Methemoglobin levels are available on most modern blood gas analyzers to aid diagnosis. Vitamin C and methylene blue are recommended treatments for methemoglobinemia.

4 | GLOSSARY

- Arterial blood gas (ABG): a commonly used diagnostic tool to evaluate the partial pressures of gas in arterial blood as well as acid-base content. (https://www.ncbi.nlm.nih.gov/books/NBK536919)
- Computed tomography (CT): a medical imaging technique that takes multiple X-rays from different angles to render a cross-sectional image through a computational algorithm.
- Computed tomography pulmonary angiogram (CTPA) is a diagnostic test that uses computed tomography to visualize the pulmonary arteries. Its main use is to diagnose PE (see below).
- Deep vein thrombosis (DVT): The formation of a blood clot known as a thrombus in one or more of the body's large veins (https://www.ncbi.nlm.nih.gov/books/NBK44184/)
- Fibromyalgia: a chronic widespread musculoskeletal, often accompanied by fatigue, cognitive disturbance, psychiatric symptoms, and multiple somatic symptoms (Up to date)
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency: an inherited condition that leads to a deficiency in the enzyme G6PD, which leads to early breakdown of red blood cells in a process known as hemolysis (https://www.hopkinsmedicine.org/health/conditions-and-diseases/g6pd-glucose6phosphate-dehydrogenase-deficiency)
- High flow nasal prongs (HFNP): a system capable of delivering concentrated, humidified, and warmed oxygen at high flow rates beyond that which is available for standard nasal prongs (https://www.ncbi.nlm.nih.gov/books/NBK526071/)
- Medical emergency team (MET): an emergency response team for the hospital
- Mucha-Habermann disease: a febrile subtype of PLEVA (https://dermnetnz.org/topics/pityriasis-lichenoides/)
- Pityriasis lichenoides et varioliformis acuta (PLEVA): an acute form of pityriasis lichenoides that is characterized by sudden eruption of small scaling papules that develop into blisters and crusted red spots (https://dermnetnz.org/topics/pityriasis-lichenoides/)
- Pneumocystis jerovici: a fungus that can cause Pneumocystis pneumonia in those whose immune system is compromised (https://www.cdc.gov/fungal/diseases/pneumocystis-pneumonia/index.html)

- Pulmonary embolism (PE): blood clot in the lung that occurs when a clot in another part of the body (often the leg or arm) moves through the bloodstream and becomes lodged in the blood vessels of the lung (https://my.clevelandclinic.org/health/diseases/17400-pulmonary-embolism)
- Toxoplasmosis: a disease caused by the protozoan parasite Toxoplasma gondii in those whose immune system is compromised (https://www.cdc.gov/parasites/toxoplasmosis/epi.html)

CONFLICT OF INTEREST

None of the authors have any conflict of interest.

AUTHOR CONTRIBUTIONS

HK: Principal author. RL: supervisor and author. SG: author and supervisor. DB: Chief Investigator and author.

ETHICAL APPROVAL

Consent obtained from patient's representative.

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