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Dapsone Induced Methemoglobinemia: The Importance of Early Diagnosis

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ABSTRACT

Dapsone, a commonly used medication for various dermatologic and infectious diseases, is associated with the rare but potentially serious side effect of methemoglobinemia. Methemoglobinemia, a condition characterized by elevated levels of methemoglobin (MetHb), is an uncommon but critical cause of cyanosis. It is often ignored in differential diagnoses of the same. MetHb is an abnormal form of hemoglobin resulting from the physiological process of auto-oxidation. Disruption of this process, either through genetic anomalies or exposure to certain drugs or toxins, leads to increased MetHb levels. Once MetHb surpasses 3%, tissue hypoxia can develop [1].

We present a case of a 65-year-old male with lower respiratory tract infection who developed methemoglobinemia after starting dapsone therapy. The patient presented with cyanosis and dyspnea, and arterial blood gas analysis revealed a methemoglobin level of **14%**. Dapsone was discontinued, and the patient was treated with methylene blue and Vitamin C IV infusion, which resulted in rapid improvement of symptoms and normalisation of methemoglobin levels. This case highlights the importance of recognizing dapsone-induced methemoglobinemia early and promptly initiating appropriate treatment to prevent complications.

KEYWORDS: Methemoglobinemia, Cyanosis, Dapsone, Arterial Blood Gases.

INTRODUCTION

Methemoglobinemia is a rare and potentially life-threatening condition characterized by a reduced ability of hemoglobin to carry oxygen. This occurs due to the conversion of iron in hemoglobin from the ferrous (Fe2+) to the ferric (Fe3+) state, rendering it unable to bind oxygen molecules. Cyanosis occurs when 10-25% of hemoglobin is converted to methemoglobin. While congenital forms exist, acquired methemoglobinemia is more common and typically results from exposure to certain chemicals or topical agents. In our case discussed here, Dapsone was the causative agent [2].

Dapsone-induced methemoglobinemia is comparatively a rare but potentially life-threatening condition that can occur as a side effect of dapsone therapy. Dapsone, a sulfone antibiotic, is widely used in the treatment of various dermatologic conditions such as leprosy, dermatitis herpetiformis, and some types of vasculitis, as well as in the prophylaxis and treatment of Pneumocystis jirovecii pneumonia (PJP) in patients with HIV/AIDS.

Dapsone-induced methemoglobinemia can occur via several mechanisms. Dapsone is metabolized in the liver to its hydroxylamine metabolite, which can oxidize hemoglobin to methemoglobin. Additionally, dapsone can inhibit the activity of cytochrome b5 reductase, an enzyme responsible for reducing methemoglobin back to hemoglobin. As a result, methemoglobin accumulates, leading to methemoglobinemia.

The clinical presentation of dapsone-induced methemoglobinemia can vary depending on the severity of methemoglobinemia. Mild cases may be asymptomatic or present with nonspecific symptoms such as fatigue and headache. In more severe cases, patients may develop cyanosis, shortness of breath, dizziness, and altered mental status. Severe methemoglobinemia can progress rapidly and lead to respiratory distress, organ failure, and death if not promptly recognized and treated.

Management of dapsone-induced methemoglobinemia involves discontinuation of dapsone therapy and administration of methylene blue. Methylene blue is typically the first-line management for methemoglobinemia, but high-dose vitamin C can be an effective alternative. Administering 10g every 6 hours reduced methemoglobin levels to 1.3% in 4 days. The mechanism of vitamin C's effectiveness is not fully understood but is thought to reduce oxidative stress, a key factor in methemoglobinemia. High-dose vitamin C also avoids rebound methemoglobinemia and hypoxia seen with repeated doses of methylene blue, particularly in G6PD-deficient individuals. However, caution is advised in patients with renal disease due to the potential for hyperoxaluria-induced renal failure [3].

CASE REPORT

A 64-year old gentleman presented with complaints of cough since 7 days with mucoid expectoration. He then developed dyspnea which was gradual in onset, persistent and mild not associated with orthopnea or palpitation. He had a history of bullous lichen planus for which he was started on T. Dapsone 100mg daily. On routine investigation his ABG report showed elevated methemoglobin (MetHb) levels and blood reports showed reticulocytosis with macrocytosis. On examination, his lips and fingertips appeared mildly blue; chest was clear and heart sounds normal. His blood pressure was 130/90 mm Hg. Sinus tachycardia was noted, (Heart rate ranging from 90 to 105 beats per minute). His ABG showed a methemoglobin (MetHb) level of 14 %, which then led to a diagnosis of dapsone-induced methemoglobinemia. The offending agent, Dapsone was discontinued. He was treated with methylene blue 1 mg/kg intravenously daily and high-dose vitamin C 5 g intravenously every six hours. ABGs were monitored every 12 hours. He continued to show signs of improvement with progressively decreasing oxygen requirements.

On 27/02/2024, His ABG showed:

Sample Type	Arterial		
FO2(I)	21.0	%	(-)
Blood Gas Values			
pH	**7.456**		(7.35 - 7.45)
pCO2	**33.6**	mmHg	(35 - 48)
pO2	**55.3**	mmHg	(83 - 108)
Oximetry Values			
ctHb	**12.9**	g/dL	(13.5 - 17.5)
sO2	**88.3**	%	(95 - 99)
FO2Hb	**75.8**	%	(94 - 98)
FCOHb	**0.1**	%	(0.5 - 1.5)

FHHb	10.1	%	(-)
FMetHb	**14.0**	%	(0 - 1.5)
Hct(c)	**39.7**	%	(40.5 - 52.5)

After stopping Dapsone, an ABG analysis done on the following day showed a reducing MetHb levels:

Sample Type	Arterial		
FO2(I)	21.0	%	(-)
Blood Gas Values			
pH	**7.494**		(7.35 - 7.45)
pCO2	**28.3**	mmHg	(35 - 48)
pO2	**165.0**	mmHg	(83 - 108)
Oximetry Values			
sO2	97.7	%	(95 - 99)
FO2Hb	**93.4**	%	(94 - 98)
FCOHb	**0.1**	%	(0.5 - 1.5)
FHHb	2.2	%	(-)
FMetHb	**4.3**	%	(0 - 1.5)
FShunt(e)	0.1	%	(-)

DISCUSSION

Methemoglobin (MetHb) is the oxidized form of hemoglobin (Hb) that does not bind oxygen but enhances oxygen affinity for partially oxidized Hb. Elevated MetHb levels in circulating red blood cells characterize methemoglobinemia, which can be either congenital, caused by reductase enzyme deficiency, or acquired, often triggered by drugs, chemicals, or food. These include nitrite and nitrate derivatives, sulfonamides, dapsone, anesthetics, and antimalarials. Hydroxylamine derivatives found in dapsone induce significant oxidative stress in red blood cells, leading to the formation of MetHb. The presence of MetHb indicates that heme iron is in the ferric (Fe^{3+}) state rather than the normal ferrous (Fe^{2+}) state, resulting in a shift to the left of the Hb-Oxygen dissociation curve. This shift leads to inadequate delivery of oxygen to tissues, causing cellular hypoxia [4].

In 42% of instances, dapsone was the cause, benzocaine was less prevalent but resulted in elevated amounts of methemoglobin. In 4%–13% of dapsone patients, hemolytic anemia manifests. After initiation of dapsone therapy, usually methemoglobin levels are not regularly monitored. Nonetheless, after two weeks of therapy, all patients in one series showed high levels. After starting dapsone, methemoglobinemia can manifest itself in a variety of ways; a research found that it typically takes 48 days. Refractory hypoxemia, cyanosis with low SpO2 measurements, and normal PaO2 are the hallmarks of methemoglobinemia. Blood gas analysis is used to confirm the diagnosis, and symptoms usually start to show at levels greater than 20% [5].

Clinical symptoms and serum methemoglobin (MetHb) levels are crucial for diagnosing methemoglobinemia. Suspect methemoglobinemia in a patient if he/she has hypoxia or cyanosis after dapsone ingestion, which doesn't improve with increased oxygen. Patients may have normal arterial pO2 with cyanosis or a saturation gap. Central and peripheral cyanosis are typically seen at MetHb levels of 15%. Levels of 30–45% result in headache, nausea, and weakness, while 60% lead to arrhythmia, dyspnea,

and seizures. Death usually occurs at levels above 70%. Initial treatment involves discontinuing the offending drug. For symptomatic or severe cases (>20% MetHb), intravenous methylene blue 1–2 mg/kg is recommended, with a repeat dose if MetHb remains high. Ascorbic acid is an effective alternative [6].

CONCLUSION

In conclusion, Dapsone-induced methemoglobinemia is a rare but serious complication. It is characterized by the presence of elevated Methemoglobin levels in the blood, which impairs the ability of hemoglobin to effectively bind and deliver oxygen to tissues. Prompt recognition and management of this condition are crucial to prevent serious complications and ensure optimal patient outcomes.Patients receiving Dapsone therapy should be monitored closely for signs and symptoms of methemoglobinemia, such as cyanosis, shortness of breath, and fatigue. If methemoglobinemia is suspected, treatment should be promptly initiated, including discontinuation of dapsone therapy and administration of methylene blue or, if unavailable, alternative agents such as high-dose vitamin C. Healthcare providers should be aware of the risk factors and potential complications associated with Dapsone-induced Methemoglobinemia, and should consider this diagnosis in patients presenting with unexplained cyanosis or hypoxia. By maintaining a high index of suspicion and implementing appropriate management strategies, healthcare providers can effectively diagnose and treat Dapsone-induced Methemoglobinemia, ultimately improving patient outcomes.

REFERENCE

1. Mahmood, N., Khan, M.U., Haq, I.U.L. *et al.* A case of DAPSONE INDUCED METHEMOGLOBINEMIA. *J of Pharm Policy and Pract* **12**, 22 (2019).
2. Shenouda M, Padilla M, Silva J, et al. (February 21, 2022) Dapsone-Induced Methemoglobinemia: A Case Report. Cureus 14(2): e22466. doi:10.7759/cureus.22466
3. Kabir H, Lakshmanan R, Gopinath S, Bhonagiri D. Dapsone-induced methemoglobinemia-A case report. Clin Case Rep. 2021 May 5;9(5):e04054. doi: 10.1002/ccr3.4054. PMID: 34084488; PMCID: PMC8142417.
4. Jose, Basil & Jose, JosephineValsa & Paul, Mobin. (2018). Dapsone-Induced Methemoglobinemia: Blue Cures Blue. Journal of Pharmacology and Pharmacotherapeutics. 9. 117. 10.4103/jpp.JPP_16_18.
5. Jacob G, Schorr M, Moist LM. Methemoglobinemia in a 28-year-old woman treated with dapsone. CMAJ. 2022 Aug 8;194(30):E1062-E1065. doi: 10.1503/cmaj.212015. PMID: 35940623; PMCID: PMC9365429.
6. Tan YA, Ng KC, Cheo SW, Khoo TT, Low QJ. A case of dapsone-induced methaemoglobinaemia. Clin Med (Lond). 2020 Sep;20(5):519-521. doi: 10.7861/clinmed.2020-0364. PMID: 32934050; PMCID: PMC7539702.