Case Report

Dapsone-Induced Methemoglobinemia: Blue Cures Blue

Basil Jose, Josephine Valsa Jose, Mobin Paul[1]

Departments of Clinical Pharmacology and [1]Clinical Haematology and Haemato-oncology, Rajagiri Hospital, Aluva, Kerala, India

Abstract

Dapsone, a sulfone group antibiotic, was traditionally used for the treatment of leprosy. It has potent anti-inflammatory and immunosuppressive properties. Hence later, its use has been expanded to conditions such as acne vulgaris, dermatitis herpetiformis, chronic immune thrombocytopenia, pemphigoid, malaria, and cutaneous leishmaniasis. Dapsone is less expensive and effective second-line treatment used in chronic immune thrombocytopenia (c ITP). It is metabolized in the liver by cytochrome P-450 enzymes to potent oxidants that are responsible for the adverse hematological complications like methemoglobinemia. We hereby report a case of dapsone-induced methemoglobinemia in an adult female patient used for the treatment of c ITP. She presented with hypoxia, fatigability, and improved subsequently on low-dose intravenous methylene blue. The patient was discharged without any complications. Initial assessment at Emergency services was suggestive of probable adverse drug reaction according to the WHO causality assessment scale and Naranjo algorithm. The preventability assessment was unpreventable according to Schumock and Thornton preventability assessment scale. A key to the diagnosis of methemoglobinemia is cyanosis with low-oxygen saturation and normal partial pressure of oxygen on arterial blood gas analysis. Treatment should be initiated immediately with IV methylene blue which acts by converting methemoglobin to normal hemoglobin, and thus, increasing the oxygen-carrying capacity of the red blood corpuscles. Dapsone-induced methemoglobinemia is rare but a life-threatening complication. Be cautious, when dapsone is used for the long-term treatment such as c ITP. Relevant pathophysiology and treatment principles are summarized in this case report to enhance awareness among physicians about this life-threatening adverse reaction to dapsone.

Keywords: Adverse drug reaction, chronic immune thrombocytopenia, methemoglobinemia, methylene blue

Introduction

Dapsone is an antibiotic belonging to sulfone group with potent anti-inflammatory and immunosuppressive properties.[1] Dapsone was traditionally used as an anti-leprosy drug and later, its use has been expanded to conditions such as acne vulgaris, dermatitis herpetiformis, thrombocytopenic purpura, and pemphigoid.[2] Dapsone is metabolized in the liver through cytochrome P-450 pathway to metabolites which are potent oxidants, responsible for the adverse hematological effects such as methemoglobinemia. Here, we report a case of methemoglobinemia secondary to use of dapsone for the treatment of chronic immune thrombocytopenia (c ITP) and also discuss the relevant pathophysiology, clinical presentation, and management. Since the incidence of dapsone-induced methemoglobinemia is rare, our aim here is to enhance awareness about this life-threatening adverse event. Few studies (six case reports) were identified from India using the MeSH terms (Dapsone, Methemoglobinemia) in Pubmed from 2008 to 2018 to the best of our knowledge.[3]

Access this article online

Quick Response Code:

Website: www.jpharmacol.com

DOI: 10.4103/jpp.JPP_16_18

Case Report

A 53-year-old female belonging to the middle class socioeconomic strata, residing in the rural area in Kerala with no habits, was diagnosed with immune thrombocytopenia in 2009. She was treated with steroids and later was put on a second line agent azathioprine which was stopped subsequently. In 2017, she presented to us with a relapse and was given dapsone at a dose of 3 mg /kg/day [150 mg/day] with folic acid 2.5 mg/day. Two weeks later, she had presented to the emergency department with complaints of fatigability and excessive tiredness. Her past medical history included hypertension and type II diabetes mellitus. She is not glucose-6-phosphate dehydrogenase (G6PD) deficient. There is no significant family history.

Address for correspondence: Mobin Paul,
Department of Clinical Haematology and Haemato-oncology,
Rajagiri Hospital, Aluva - 683 112, Kerala, India.
E-mail: mobinpaul99@yahoo.co.in

How to cite this article: Jose B, Jose JV, Paul M. Dapsone-Induced methemoglobinemia: Blue cures blue. J Pharmacol Pharmacother 2018;9:117-20.

Received: 21-02-2018 **Revised:** 11-04-2018 **Accepted:** 05-06-2018

On examination, she was hypoxic and cyanotic. She was afebrile, and her vital signs include blood pressure: 160/70 mmHg and pulse rate: 119 beats/min. Oxygen saturation (SpO2) was 85% on 2 L oxygen. Arterial blood gas analysis revealed partial pressure of oxygen (pO2) of 81 mm Hg, pCO2 of 31 mm Hg, pH is 7.48, $HCO3^-$ of 24.5 mmol/L, and lactate: 9.4 mmol/L. Detailed laboratory findings are given in Table 1.

Methemoglobinemia secondary to use of dapsone was suspected, and the patient was immediately shifted to Intensive Care Unit for further management. The patient's blood sample was sent for methemoglobin (MetHb) concentration analysis. MetHb level came out to be 35.2 gm%. She was administered with one dose of methylene blue 1 mg/kg intravenously, followed by 0.5 mg/kg after 50 min. Subsequently, her hypoxia got better. She also received N-acetyl cysteine (NAC) 600 mg thrice daily, Vitamin C 1000 mg thrice daily. Serial monitoring of MetHb level was done, and the level was reduced to 9.5 g% on the 3rd day [Figure 1].

She has improved clinically and symptomatically. She also received dexamethasone pulse to keep her platelet count optimal. She was discharged on day 9 with tablet eltrombopag 50 mg once daily, along with Vitamin C, pantoprazole, and folic acid. The reaction was reported to VigiFlow database with unique Id: 2017–51402.

Table 1: Laboratory findings

Laboratory test	Day 1	Day 2	Day 3
Platelet count (×10³/ul)	50	30	10.0
Lymphocyte (%)	18	18	12.0
Hb (g/dl)	12	11.0	9.9
LDH (U/L)	-	547	474
RBC count (×10⁶/ul)	4.4	3.9	3.8
Hematocrit (%)	40	35	34.0
Chemistry panel (mEq/L)			
Sodium level	129	138	134
Potassium level	3.9	3.5	3.0
Arterial blood gas			
pH	7.45	7.314	7.527
Oxygen saturation (%)	85	85	88
Bicarbonate level (mmol/L)	24.5	24.1	28.3
PO_2 (mmHg)	81	221	275
PCO_2 (mHg)	31	48.9	34.3
Base excess level (mmol/L)	0.2	−0.2	5.7
Lactate level (mmol/L)	9.4	4.9	2.0

RBC=Red blood corpuscles, Hb=Hemoglobin, LDH=Lactic dehydrogenase

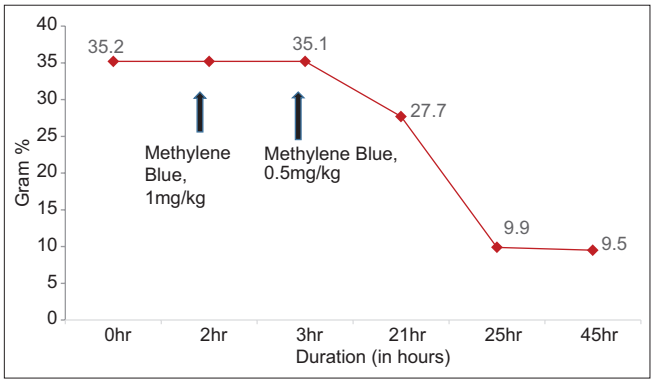

Figure 1: Serial methemoglobin level during the course of treatment

Discussion

ITP is an autoimmune disorder characterized by a persistent reduction in platelet count with or without bleeding. Corticosteroids and intravenous (IV) immunoglobulin G are given as first-line treatment. Other treatment options are splenectomy, immunosuppressants, rituximab, and thrombopoeitin-receptor agonist, but are costly with side effects. Dapsone is less expensive, effective, and safer alternative for chronic ITP, used as second-line therapeutic agent if first-line treatment fails.[4] The mechanism of action of dapsone in ITP is not well-known. Theories suggest that dapsone-induced hemolysis lead to erythrophagocytosis by the reticuloendothelial system and prevent sequestration and destruction of platelets.[5]

MetHb being the oxidized form of hemoglobin (Hb) does not bind to oxygen, but increases the affinity of oxygen for the partially oxidized portion of Hb. Methemoglobinemia is characterized by an elevated amount of MetHb within the erythrocytes in circulating blood. Methemoglobinemia is of two types: congenital and acquired. The congenital form is due to the absence of reductase enzyme. Acquired methemoglobinemia is the more common form and can occur secondary to drugs, chemicals, and food. Drugs causing methemoglobinemia are nitrite derivatives (nitroprusside, amyl nitrite, and nitric oxide), nitrate derivatives (nitrates salt and nitroglycerin), sulfonamides, dapsone, phenazopyridine, anesthetics such as prilocaine, benzocaine, and bupivacaine antimalarials (chloroquine and primaquine).[6]

Hydroxylamine derivatives of dapsone deliver a severe oxidative stress to Hb inside the erythrocytes superseding the compensatory physiologic reductive capacity. MetHb occurs when heme iron is in the ferric state (Fe^{3+}) rather than the normal ferrous state (Fe^{2+}). A single ferric (Fe^{3+}) ion in Hb tetramer makes remaining ferrous (Fe^{2+}) ion to bind to oxygen and cause a leftward shift of Hb-Oxygen dissociation curve leading to poor oxygen delivery at tissue level resulting in hypoxia at cellular level.[7]

Diagnosis

Clinical symptoms and serum MetHb level guide the diagnosis in methemoglobinemia. However, MetHb level monitoring may not be feasible in all scenarios. Cyanosis out of proportion to respiratory distress is the key to diagnosis in methemoglobinemia. The characteristic finding in methemoglobinemia is cyanosis with low SpO2 and normal pO2 on arterial blood gas analysis. pO2 in blood is the function of small amount of oxygen dissolved in the plasma and not bound to Hb. A simple bedside test – filter paper test can be done to distinguish between metHb and deoxyhemoglobin. Place, 1 or 2 drops of the patient's blood on a white filter

paper. Deoxyhemoglobin gets brightened after exposure to atmospheric oxygen, while metHb does not change color. Blowing oxygen on to the filter paper speeds up the reaction.[8] This method can be tried in resource-poor settings. MetHb does not impair delivery of oxygen to blood plasma in the alveoli, and thus, pO2 remains unaffected. SpO_2 reflects the oxygen bound to Hb in erythrocytes and will be reduced as MetHb has poor affinity to oxygen. In addition, chocolate brown color of the arterial blood samples is highly suggestive.[7]

The clinical manifestations of methemoglobinemia based on MetHb concentration in the blood are given in Table 2.

Management

Initial management of methemoglobinemia involves respiratory support with discontinuation of the offending drug. Patient with hypoxia and MetHb level (30% or above) should be treated with IV methylene blue 1–2 mg/kg over 5 min. The next dose of methylene blue is given after 30 min of first dose if cyanosis does not improve. Methylene blue is converted to leukomethylene blue which is a reducing agent that reduces ferric ion (Fe^{3+}) to oxygen-carrying ferrous form (Fe^{2+}). This reaction requires adequate G6PD and nicotinamide adenine dinucleotide phosphate (NADP) levels. The maximum dose of methylene blue is 5–7 mg/kg/day.[9]

The reduction of MetHb by methylene blue is dependent upon NADPH generated by G6PD. G6PD converts glucose-6-phosphate to 6-phosphogluconate, generating 1 mole of NADPH, as the initial step in the hexose monophosphate shunt. The failure of this reaction to occur would be rate limiting in the production of NADPH and in the reduction of methylene blue. G6PD-deficient individuals do not generate enough NADPH to efficiently reduce methylene blue to leukomethylene blue, which is needed for activation of the NADPH-dependent MetHb reductase system. As a result, methylene blue may not only be ineffective but also potentially dangerous since it has got oxidant potential that induces hemolysis in G6PD deficient patients. Therefore, methylene blue is not the ideal mode of treatment of methemoglobinemia in G6PD-deficiency as it can worsen the condition of the patient by increasing hemolysis.[10]

Methylene blue acts as a cofactor for NADPH to reduce MetHb levels; however, at high doses, it can act as an oxidizing agent, and thus, oxidizes the ferrous iron of the reduced hemoglobin to ferric state converting Hb to MetHb inducing methemoglobinemia. Leukomethylene blue, the metabolite of methylene blue, reduces oxygen to hydrogen peroxide, some of which is detoxified through the hexose monophosphate shunt. However, when this mechanism is overwhelmed, reduced glutathione is depleted. The remaining hydrogen peroxide can oxidize Hb to MetHb again inducing methemoglobinemia known as rebound methemoglobinemia.[11]

Ascorbic acid is an effective alternative for treatment, if methylene blue is not available. It is a strong reducing agent that takes part in various oxidative–reductive reactions. It is proved to be effective in treating MetHb when given at the dose of 300 mg/kg IV. In our case, ascorbic acid is given as 1000 mg thrice daily from day 2.

N-Acetyl Cysteine (NAC) is an experimental therapy for the treatment of methemoglobinemia.[7] NAC can reduce MetHb through glutathione production. NAC reacts with glutamate and glycine in the presence of ATP to form glutathione. The glutathione could then detoxify oxidative agents or directly reduce MetHb. These reactions are not dependent on NADPH; thus, NAC may be an effective antidote for G6PD-deficient individuals with methemoglobinemia.[12]

Causality assessment of the reaction was done. Dapsone is the "probable" cause for methemoglobinemia according to the WHO causality assessment as dechallenge was positive, and rechallenge was not done. According to Naranjo algorithm also, the causality is "probable" with a score of 8.[13] The adverse drug reaction (ADR) is not preventable according to Schumock and Thornton preventability scale.[14] Based on Hartwig and Siegel severity assessment, the reaction is placed at Level 5 severity which involves withholding of the suspected drug and ADR was the reason for admission to Intensive Care Unit.[13]

Table 2: Clinical manifestations of methemoglobinemia*

MetHb level (%)	Signs and symptoms
<3	None
3-15	Pale, gray or blue color of the skin
15-30	Cyanosis, chocolate-brown color
30-50	Breathlessness, headache, dizziness, syncopal attacks
50-70	Tachypnea, lactic acidosis, arrhythmias, seizures, CNS depression, coma
>70	Death

*Adapted from Goldfrank's Toxicologic Emergencies.
MetHb=Methemoglobin, CNS=Central nervous system

Conclusion

Dapsone-induced methemoglobinemia is a rare, but life-threatening adverse event. Be cautious, when dapsone is used for long-term treatment such as c ITP. A key to the diagnosis of methemoglobinemia is cyanosis with low SpO2 and normal pO2 on arterial blood gas analysis. Treatment should be initiated immediately with IV methylene blue that converts MetHb to normal hemoglobin, thus increasing the oxygen-carrying capacity of erythrocytes. Prompt diagnosis and treatment will be lifesaving.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Ashurst JV, Wasson MN, Hauger W, Fritz WT. Pathophysiologic mechanisms, diagnosis, and management of dapsone-induced methemoglobinemia. J Am Osteopath Assoc 2010;110:16-20.
2. Rodrigo C, Gooneratne L. Dapsone for primary immune thrombocytopenia in adults and children: An evidence-based review. J Thromb Haemost 2013;11:1946-53.
3. 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.
4. Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr., Crowther MA, *et al*. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117:4190-207.
5. Hill QA. How does dapsone work in immune thrombocytopenia? Implications for dosing. Blood 2015;125:3666-8.
6. Alanazi MQ. Drugs may be induced methemoglobinemia. J Hematol Thromb Dis 2017;5:3.
7. Madke B, Kumar P, Kabra P, Singh AL. How to manage a side effect: Dapsone-induced methemoglobinemia. Indian J Drugs Dermatol 2016;2:117-20.
8. Steiner IP, Nichols DN. A case of dapsone – Induced cyanosis in the emergency department. Isr J Emerg Med 2006;6:10-3.
9. Sweetman SC. Methylthionium chloride. In: Martindale: The Complete Drug Reference. 36th ed. London: Pharmaceutical Press; 2009. p. 1450-1.
10. Rosen PJ, Johnson C, McGehee WG, Beutler E. Failure of methylene blue treatment in toxic methemoglobinemia. Association with glucose-6-phosphate dehydrogenase deficiency. Ann Intern Med 1971;75:83-6.
11. Fitzsimons MG, Gaudette RR, Hurford WE. Critical rebound methemoglobinemia after methylene blue treatment: Case report. Pharmacotherapy 2004;24:538-40.
12. Wright RO, Magnani B, Shannon MW, Woolf AD. N-acetylcysteine reduces methemoglobin *in vitro*. Ann Emerg Med 1996;28:499-503.
13. Srinivasan R, Ramya G. Adverse drug reaction-causality assessment. IJRPC 2011;1:606-12.
14. Gholami K, Shalviri G. Factors associated with preventability, predictability, and severity of adverse drug reactions. Ann Pharmacother 1999;33:236-40.