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DAPSONE INDUCED METHEMOGLOBINIMEA: A DIAGNOSTIC DILEMMA

Pediatrics

Dr. Vinita Dch in Paedtrics, Aadhar Hospital, Hisar.

Dr. Arun Aggarwal Consultant Head of Department, MD Radiotherapy, Aadhar Hospital, Hisar.

Dr. Deepak Tayal MD Respiratory Medicine, Aadhar Hospital, Hisar.

Dr. Neeraj Nagar* MD Anaesthesia, Aadhar Hospital, Hisar.*Corresponding Author

ABSTRACT

Methemoglobinemia is a condition of elevated methemoglobin in the blood.[1] Methemoglobinemia is a life-threatening condition that can be difficult to diagnose.Methemoglobinemia can result from either congenital or acquired processes. Congenital forms of methemoglobinemia are due to autosomal recessive defects in the enzyme cytochrome b5 reductase (CYB5R) or due to autosomal dominant mutations in the genes that code for globin proteins collectively known as hemoglobins M.[2] Acquired methemoglobinemia, which is much more common, is the result of exposure to substances that cause oxidation of the hemoglobin either directly or indirectly. This exposure results in the production of methemoglobin that exceeds the body's capacity to convert the iron within the hemoglobin back to its ferrous state.[3] It can be due to certain chemicals and medications for example fewantibiotics (trimethoprim, sulfonamides,and dapsone[4]), localanesthetics (especially articaine, benzocaine, prilocaine,[5] and lidocaine[6]),and aniline dyes, metoclopramide, rasburicase, chlorates, bromates, nitrates and nitrites[7,8]. Physicians and other health care providers should routinely consider the relationship between medications and atypical clinical symptoms.[9] We describe the diagnosis and management of a patient with acquired methemoglobinemia as a result of dapsone use for certain skin condition.

KEYWORDS

CASE:

13 year old malepresented to our emergency ward with the history of fever since 10 days, rashes all over extremities since 8 days.

Before presenting to our hospital,he was admitted at another hospital for 7 days, where he was worked up for fever and rashes and treated with antibiotics and Dapsone was given considering autoimmune etiology.

On general physical examination, patient was afebrile, alert and comfortable. There was no dyspnea/distress, heart rate was 100/min, and spo2 was 80% on room air. Further examination revealed rashes all over extremities. He was shifted to Intensive care because of low oxygen saturation for further investigation. Patient was investigated thoroughly with the differential diagnosis of:sepsis, mycoplasma infection, tuberculosis, typhoid, autoimmune disease, Anemia, Asthma and Congestive heart failure. Cardiac workup was normal and in view of saturation gap of spo2 and arterial po2,methmoglobinimea levels were also ordered and were found to be 23.9% as shown in Fig 1. The blood was chocolate-brown coloured.Thus, the diagnosis of dapsone induced methemoglobinaemia was made.

Dapsone was discontinued with immediate effect. He was given infusion of vitamin-C(2 gm infusion over 24 hours for 48 hours) and other conservative measures, under intensive care. As blood levels of methemoglobin were below 30%, Methylene blue was not indicated. High flow oxygen delivered by non-rebreather mask increases oxygen delivery to tissues and enhances the natural degradation of methemoglobin. Patient improved gradually and methemoglobin concentration dropped to 3%.He was discharged in stable condition after about a week of hospitalization.

DISCUSSION:

Methaemoglobinemia is more often an adverse medication effect, most commonly related to dapsone use.[10] Dapsone (4, 4′-diaminodiphenyl sulfone) is a sulfone antibiotic and potent anti-inflammatory that inhibits folate synthesis,[11-13] 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.14 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.[10,13,15–17] This left shift in the oxygen saturation curve results in functional anemia.[10]

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.[15] Methemoglobinemia secondary to toxic exposures occurs when cytochrome-b5 reductase's ability to reduce ferric hemoglobin, or methemoglobin, is overwhelmed by the induced oxidant stress. The result is increasing concentrations of methemoglobin leading to methemoglobinemia[3].

There is a paucity of literature regarding the incidence of dapsone-induced methemoglobinemia. However, in hematopoietic stem cell transplant recipients receiving dapsone for *P jiroveci* pneumonia prophylaxis, the incidence is approximately 3%.[18]

SIGNS AND SYMPTOMS

Methemoglobinemia should be considered in the setting of dyspnoea or cyanosis and hypoxemia that is refractory to supplemental oxygen, especially in the setting of exposure to a known oxidative agent. However, the presentation may vary in severity from minimally symptomatic to severe. The clinical presentation of methemoglobinemia is based on a spectrum illness that is associated with cyanosis, pallor, fatigue, weakness, headache, central nervous system depression, metabolic acidosis, seizures, dysrhythmias, coma, and death. The degree of symptom severity is multifactorial and depends on the patient's percentage of methemoglobin, the rate at which methemoglobin was accumulated, the individual's ability to intrinsically clear it, and the underlying health status of the patient. Duration and magnitude of exposure to an oxidizing agent may also play a role.[3]

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%.[11]

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.[10]

The saturation gap arises owing to the limitations of pulse oximetry. Pulse oximetry can only measure 2 hemoglobin species—oxyhemoglobin and reduced hemoglobin.[12] As other hemoglobins such as methemoglobin rise, the oxygen saturation on pulse oximetry falls and plateaus at 85%.[12] 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.[19]

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.[11] 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.[20] 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.[21] When treatment with methylene blue is ineffective or not recommended, additional options may include ascorbic acid, exchange transfusion, hyperbaric oxygen therapy.[22, 23] High-dose ascorbic acid (vitamin C), up to 10 g/dose intravenously, can be considered to treat methemoglobin. However, it is generally ineffective and not considered standard of care. High dose ascorbic acid administration is associated with increased urinary excretion of oxalate. In the presence of renal insufficiency, high dose ascorbic acid may be predisposed to renal failure due to hyperoxaluria.[24] If symptoms persist despite the above-outlined therapy, haemodialysis might be required.

CONCLUSION

Most patients with methemoglobinemia respond well to treatment and can be discharged after brief period of observation and symptomatic management. Anyone with persistent symptoms after initial treatment or exacerbated underlying medical conditions should be considered for admission. If symptoms persist haemodialysis, exchange transfusion, hyperbaric oxygen therapy might be required.

15/06/2020 Patient Id 10205171 Collection Date 15/06/2020 15:55:03
Mr. KRISH AGGARWAL Lab No. M-86 Received Date 15/06/2020 15:55:05
13 Yrs / Male Ref Dr Aadhar Hosp. Report Date 15/06/2020 16:07:15
Sample Heparin Printing Date 15/06/2020 16:13:36

Test Name	Value	Unit	Biological Ref. Range
Complete Arterial Blood Gases (ABG)			
Blood Gas			
pH	7.41		7.35 - 7.45
pCO2	**45.1**	mmhg	35.0 - 45.0
PO2	**23.1**	mmhg	83.0 - 108.0
Electrolytes Values			
Na+	138.0	mmol/L	135.0 - 145.0
K+	4.1	mmol/L	3.5 - 4.5
Cl-	100.0	mmol/L	98.0 - 106.0
Ca++	1.16	mmol/L	1.15 - 1.29
Mg++	0.49	mmol/L	0.45 - 0.60
Oximetry Values			
Hb	**9.4**	gm/dl	12.0 - 16.0
SO2	**46.9**	%	94.0 - 99.0
FCOHb	0.2	%	
FHHb	38.5	%	
FMetHb	27.3	%	
FO2Hb	34.0	%	
Metabolite Values			
Glu	100.00	mg/dl	70.00 - 105.00
Lac	1.6	mmol/L	0.5 - 1.6
Crea	0.60	mg/dl	0.60 - 1.30
BUN	11.0	mg/dl	7.0 - 18.0
Acid Base Status			
HCO3-(P, st)e	26.6	mmol/L	
CO2(P)e	65.7	Vol%	
Base(B,ox)e	2.4	mmol/L	
ABEe	3.4	mmol/L	
SBEe	3.6	mmol/L	
Calculated Values			
Ca++(7.4)e	1.16	mmol/L	
Hctc	29.1	%	
p50c	24.2	mmhg	
p02(A)e	23.1	mmhg	

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