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Case Report

Dapsone induced methemoglobinemia

Shubhank Narula[1]*, Pooja Khosla[2], Vinus Taneja[2]

[1]Department of Family Medicine, Sir Ganga Ram Hospital, New Delhi, India
[2]Department of Internal Medicine, Sir Ganga Ram Hospital, New Delhi, India

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***Correspondence:**
Dr. Shubhank Narula,
E-mail: narulashubhank@gmail.com

ABSTRACT

Increase in levels of methemoglobin is termed as methemoglobinemia which leads to organ level hypoxia. It can be congenital or acquired. In this case report we present a case of a middle-aged female with methemoglobinemia due to dapsone overdose and how immediate introduction of ascorbic acid, oxygen therapy and dapsone discontinuation cured the patient.

Keywords: Dapsone, Methemoglobinemia, Overdose, Hypoxia, Toxic hemoglobin

INTRODUCTION

Methemoglobinemia is a rarely found disorder affecting the oxygen carrying of haemoglobin. It is a toxic haemoglobin compound which leads to tissue hypoxia when levels are more than 3 percent.[1] We report a case of 53-year-old patient of immune mediated thrombocytopenia on dapsone, who presented with complaints of fever, cough and dyspnea and how a timely intervention and stoppage of dapsone helped to salvage the life of the patient.

CASE REPORT

A 53-year-old female known case of immune mediated thrombocytopenia on dapsone, hypothyroidism and hypertension, presented with complaints of fever with chills for 5 days, cough with scanty whitish sputum for 5 days, dyspnea on exertion since 5 days, progressive in nature not associated with orthopnea or platypnea. On examination patient had pallor, peri oral cyanosis. Blood pressure of 110/70 mmHg, pulse rate-113/min, oxygen saturation of 93 percent on room air. On systemic examination patient had bilateral basal crepitations. Other systems had no significant abnormal findings. Blood gas analysis revealed fractional methemoglobin as 9.1 percent. Initial workup revealed anemia (hemoglobin-10.4 g/dl), total leucocyte count-10.2 thous/cubic mm and thrombocytopenia (platelets-55 thousand/cubic mm). Renal function test was within normal limits. Liver function test showed elevated liver enzymes alanine and aspartate aminotransferase 88.4 IU/l and 88.6 IU/l.

Infective and inflammatory workup was sent in view of history of fever which revealed serum procalcitonin-0.11 ng/ml. C-reactive protein-21.3 mg/dl. D- dimer test revealed a value of 0.30 mg/l. Blood and urine cultures came out to be sterile. Her influenza RT PCR and covid RT PCR was negative. Ultrasound whole abdomen showed grade 2 fatty liver. Patient was started on intravenous antibiotics ceftriaxone 2gm intravenously twice daily along with oxygen supplementation of 5L/ min. Vitamin C 1000mg once daily dosage and vitamin E 400 mg twice daily were initiated. Patient was started on injection hydrocortisone and dapsone was stopped.

To look for other causes of breathlessness a 2D echocardiography was done which revealed trace mitral regurgitation, trace tricuspid regurgitation with a LV ejection fraction of 65 percent. Her computed tomography pulmonary angiogram was done which was normal. Due to persistence of oxygen requirement High

resolution computed tomography of the chest was done which revealed linear atelectatic bands in bilateral lower lobes, right middle lobes and lingular segment with mild surrounding ground glass haziness, small nodular densities in the anterior segment of the right upper lobe with subcentimetric mediastinal lymph nodes. Gradually methemoglobin levels began to decrease and oxygen requirement reduced. Patient eventually became better and was discharged in a hemodynamically stable condition after 10 days.

DISCUSSION

Dapsone is an antibiotic of sulphur base holding anti-inflammatory properties that are helpful in inhibiting folate synthesis.[2] Dapsone has multiple usage, probably as an anti-leprosy agent, and in treatment of multiple skin conditions like pyoderma gangrenous and dermatitis herpetiformis.[3] Dapsone metabolises by two pathways one being acetylation and the other being hydroxylation of the nitrogen base. Acetylation leads to formation of mono-acetyl dapsone and di-acetyl dapsone which is a major pathway. Hydroxylation is mediated by cytochrome P450 leading to formation of dapsone hydroxyl amine. These metabolites oxidise the lower valent iron states to ferric ions of haemoglobin forming methemoglobin. The oxidised haemoglobin is not able to complex with oxygen, and the oxygen affinity of the left heme-iron complex gets enhanced causing shifting of oxygen dissociation curve to the left.[4] Generally, a dose of 200mg/day is considered to be associated with methemoglobinemia.[5]

Methemoglobinemia is a diagnosis based on clinical symptomatology of hypoxemia which does not respond to oxygen support. It can although be confirmed by blood gas analysis by calculating the "saturation gap" which is the difference between saturation recorded by the pulse oximeter and that recorded by the arterial sample.[4] Etiology of methemoglobinemia can be genetic or acquired. Methemoglobinemia if present on birth can be an autosomal recessive condition due to mutants of an enzyme cytochrome b5 reductase (CYB5R) or haemoglobin beta chain genes forming hemoglobin M.[6] Hemoglobin M is a term used to describe all the pathologic abnormal mutants of the haemoglobin alpha or beta chains.[7] Acquired toxicities of methemoglobin can be attributed to exposure to oxidising agents or drugs like aniline and dapsone. The diagnostic technique that helps in differentiating between congenital and acquired forms is by measurement of the CYB5R (cytochrome b5 reductase) activity.[8]

The clinical spectrum of methemoglobinemia usually leads to bluish discoloration of extremities, paleness, acidosis, breathlessness and headache. Severe patients can end up in coma. Methemoglobin percentage in blood indicates severity of the toxin. Conditions aggravating the toxicity include anemia, heart failure and pulmonary disease like obstructive airway disease, these conditions disrupt the oxygen carrying capacity of the blood. Generally, treatment of methemoglobinemia, is started at levels of more than 20 percent and 30 percent in people with symptoms and without symptoms respectively.[9] Treatment of the condition includes methylene blue where it is reduced to leukomethylene blue. This leukomethylene moiety changes methemoglobin to haemoglobin. The dose of the antidote is 1-2mg/kg intravenously over 5 minutes. Doses can be given again or infusion can be started if patient shows no clinical improvement or if blood stream levels of the toxic haemoglobin complex of methemoglobin are above 20%. Other treatment measures include usage of vitamin C, oxygen therapy and hemodialysis. The most common adverse drug reaction of methylene blue encountered is bluish-greenish coloured urine. Other side effects include injection site related pain. Caution needs to be taken when it is administered with other antihypertensives, as it might trigger serotonin syndrome due to it's monoamine oxidase inhibitory actions. Serotonin syndrome is a sympathetic drive cascade that can lead to clonus and tremors. In rare instances methylene blue can also involve the nervous system, presenting as headache, seizures and feeling of giddiness. The catastrophic affects can also produce toxic effects in neonates when used and can lead to jaundice, depression of the respiratory drive, fluid-filled alveoli causing pulmonary oedema and hemolysis of red blood cells. It should be cautiously used in patients of renal failure as it might trigger systemic and pulmonary hypertension. However, these toxic affects usually get manifested at an amount of over 7 mg/kg or more. In cases when patient defoliates even after methylene blue, urgent exchange transfusion is warranted.[10-12]

In a case report involving a 34 year old male patient, presenting with complaints of vomiting and diarrhoea and an oxygen saturation of 84%, and gave an history of dapsone overdose was managed with methylene blue, vitamin C and high pressure oxygen.[13] A middle aged female patient was given dapsone due to pyoderma gangreosum, presented with cyanosis and breathlessness and treatment with methylene blue, led to improvement in symptoms of patients.[14] Serial monitoring of methemoglobin levels is essential to ensure the effectiveness of treatment and to detect any potential rebound increases in methemoglobin level. Methemoglobinemia cases due to drugs that undergo enterohepatic circulation such as dapsone can be detrimental but proper interventions like methylene blue and in severe cases, hemodialysis can prove beneficial for the patient.

CONCLUSION

Methemoglobinemia is a life-threatening condition that is a challenge to diagnose as in patients with hypoxia the primary focus is usually shifted to either infective or embolic. It is more often an adverse effect due to drugs like dapsone. It is important to be considered as a

differential diagnosis of central cyanosis in cases of normal ventilation and circulation. The outcomes can be favourable by prompt diagnosis and treatment.

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