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Dapsone Induced Methemoglobinemia in an Adolescent Girl: The Treatment Challenge

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Abstract

Dapsone is a sulfone group of antibiotics that works as anti-inflammatory and immunosuppressive agents. It is widely used in many diseases like Acne vulgaris, leprosy, dermatitis herpetiformis, thrombocytopenic purpura, and pemphigoid. Though it is a very cheap drug it has life-threatening side effects like Methemoglobinemia. We hereby report a case of dapsone-induced Methemoglobinemia in an adolescent girl who used dapsone for the treatment of acne vulgaris. She presented with hypoxia, cyanosis, and fatigability. Treatment should be initiated as early as possible otherwise it could be fatal. Here, in this case, immediate treatment was started with vitamin C and N Acytyle cystine as the most effective antidote Methylene blue was not available. As the patient's condition did not improve with pharmacological treatment so exchange transfusion was done from 2nd day. This case report aims to enhance awareness among physicians about the life-threatening adverse reaction to Dapsone and also the importance of prompt management.

Keywords: *Dapsone, Methemoglobin, Methemoglobinemia*

Introduction

Dapsone (Diamino diphenyl sulfone) is a sulfone group of antibiotics which works as an anti inflammatory and immunosuppressive agents.[1] It is a cheap drug which widely used in many diseases such as Leprosy, acne vulgaris, dermatitis herpetiformis, thrombocytopenic purpura, and pemphigoid.[2] Dapson can rarely cause dose independent Methemoglobinemia(meth Hb). This drug metabolized in the liver through cytochrome P-450 pathway to metabolites which are potent oxidants, responsible for some adverse hematological effects such as Methemoglobinemia. Here, we report a case of Methemoglobinemia secondary to use of Dapsone for the treatment of Acne vulgaris and also discuss the relevant pathophysiology, clinical presentation, and management of drug induced Methemoglobinemia. Since the incidence of dapsone-induced Methemoglobinemia is rare, our aim here is to enhance awareness about this life-threatening adverse event. The key of managing such cases is strongly on clinical suspicion and prompt discontinuation of the agent. Methilin blue is the most effective antidote and other options are high dose vitamin C, N – acytyle cystine and exchange transfusion has life saving role when indicated.

An abnormal increase of methemoglobin will increase the oxygen binding affinity of normal hemoglobin, resulting in a decreased unloading of oxygen to the tissues causing the oxyhemoglobin curve to shift to the left.[3] In normal person methemoglobin concentration is usually less than 2%. Once the methemoglobin concentration rises above 20% (levels range from 19%-75% in various case reports), it can potentially be harmful or even fatal. A higher level of methemoglobin will tend to cause a pulse oxymeter to read closer to 85% regardless of the true level of oxygen saturation.

There are two types of methemoglobinemia: acquired and congenital. At least two forms of congenital cytochrome b5 reductase deficiency exist, in an autosomal recessive pattern. Cyanosis is usually the first presenting symptom and appears since birth but

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usually is otherwise asymptomatic.[4,5] Congenital conditions include glucose-6-phosphodiesterase deficiency, nicotinamide adenine dinucleotide phosphate (NADPH) dependent methemoglobin reductase deficiency, and NADH-dependent methemoglobin reductase deficiency are quite rare. Majority of reported cases are acquired Methemoglobinemia and involves excessive production of methemoglobin. Often, it is associated with the use of or exposure to oxidant drugs, chemicals, or toxins, including dapsone, local anesthetic agents.[6] Certain foods or food additives, which contain nitrates such as silver beets and incorrectly stored homemade purees, toxins like aniline possess similar action on hemoglobin.[7]

Drugs causing methemoglobinemia are nitrite derivatives (nitroprusside, amyl nitrite, and nitric oxide), nitrates salt and nitroglycerin, sulfonamides, dapsone, phenazopyridine, anesthetics such as prilocaine, benzocaine, and bupivacaine, antimalarials (chloroquine and primaquine).[8]

Dapsone, is a sulfone group of antibiotic should be used with great caution in patients with known G6PD deficiency, methemoglobin reductase deficiency, or Hb M.[9,10] Dapsone is particularly potent because of its pro oxidant metabolite hydroxylamine which has a very long half life and catalyzed by a variety of hepatic enzymes or by myeloperoxidase present in white blood cell. About 20% of patients treated with dapsone suffer hemolysis.[11] Hydroxylamine derivatives of dapsone is responsible for a severe oxidative stress to Hb inside the erythrocytes causes hemolysis which may lead to hemolytic anemia and methemoglobinemia.[12] This side-effect is more common and severe in those with glucose-6-phosphate dehydrogenase deficiency, leading to the dapsone-containing antimalarial combination Lapdap being withdrawn from clinical use.[13]

Case reports

A 14 years old girl came to emergency department from a rural area with the history of respiratory difficulty for last 3 days; she also had history of excessive tiredness and fatigability for last 2 weeks. On examination she has tachypnea, tachycardia, on pulse oxymetry O2 saturation was 82% in room air. She was also pale and had marked peripheral and central cyanosis (figure-1, figure-2)

Chest examination revealed vesicular breath sound with no added sound, heart sounds were normal. After giving high flow oxygen her saturation was still 86%. Her others systemic examinations revealed no abnormality. The patient was subsequently admitted to the intensive care unit for close monitoring with continuous pulse oximetry.

Despite use of a non-rebreathing face mask, the patient remained hypoxic, with oxygen saturations of around 88%. A portable chest x-ray scan taken immediately showed no relevant findings, an electrocardiogram had normal findings, and both blood pressure and heart rate remained within normal limits. Arterial blood gas was measured expeditiously; the blood was noted to be chocolate brown in colour, with a pH of 7.48, a Pco_2 of 34 mm Hg, a bicarbonate level of 24 mmol/L, and a Po_2 of 128 mm Hg. On query parents gave history of taking oral Dapsone 100mg /day for last 1 month for acne vulgaris. Immediately bed side filter paper test was done which showed positive result for methemoglobin (figure-3).

Serial methemoglobin levels were checked. Which is shown on graph-1. Her others investigations reports were mentioned on table -1.

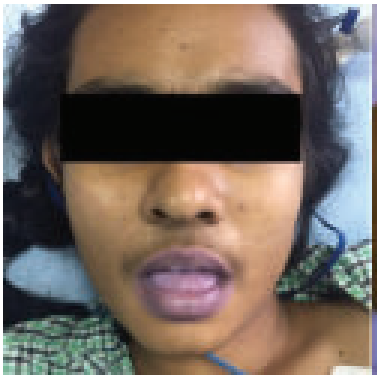

Fig.-1

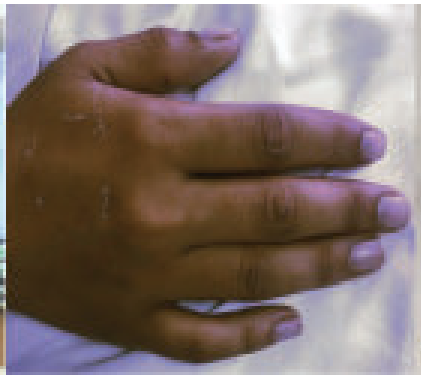

Fig-2

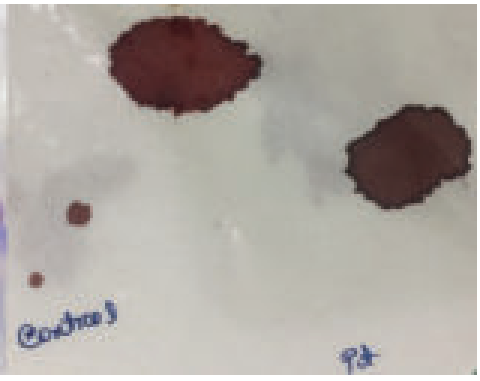

Fig-3

Table-I

Laboratory parameters of patients

Hemogram	Hb-9.6gm/dl, TLC 12500/cu mm, Plts 280000/cu mm
Peripheral smear	Neutrophilic leucocytosis, with hypersegmented neutrophil
Liver function	normal
Renal function	normal
Pulse oxymetry	82%
ABG	Ph -7.48, p O2-128 mm of Hg, pCO2 -34mm of Hg, HCO3-24mmol/L.
D –dimer	0.42
electrolytes	Na-141,K-4.1,CL-103, TCO2-22
Chest X-ray	normal
Echocardiography	normal
CT pulmonary angiography	normal

Portable co-oximetry was then performed, which identified a methemoglobin level of 35.3 gm%. Although methylin blue is a effective antidote for methemoglobinemia but as it was not available, immediately high dose vitamin C-1000 mg I/V 6 hourly and N-acetyl cysteine (NAC) 600 mg I/V 6 hourly started. Repeat co-oximetry showed a methemoglobin level of 25 %, as significant clinical improvement was not there, single volume exchange transfusion was started for 3 consecutive days. Then methemoglobin level gradually declined and the level was reduced to 12 g% on the 3rd day of exchange transfusion and came to normal level on day 5 of admission. The patient's lips and nail beds color had returned to normal and her oxygen saturation was 100% on room air. She was improved clinically and symptomatically. So she was discharged on Day 7 with oral vitamin C and N-acytyle cystine and also with advice of avoiding offending drugs in future.

Post discharge the patients is in regular follow up. Her last follow up was 6 months back . She has no respiratory difficulty afterwards and in her last follow up she is vitally stable, no features of cyanosis and methemogloin level was normal.

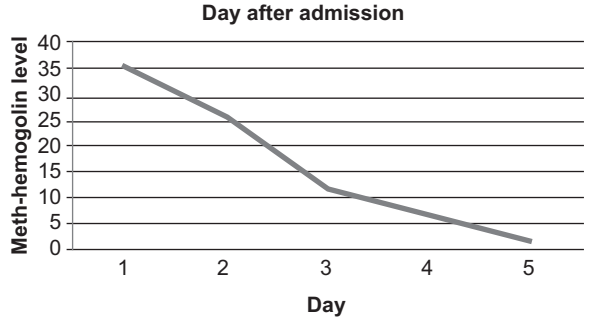

Fig.-1: *Graphical representation of meth- hemoglobin levels and effect of exchange transfusion.*

Discussion

Dapsone can induce significant methemoglobinemia after using it in standard doses of 100 mg/day. In this case report the girl was on oral dapson for more than 3 weeks with a dose of 100 mg/day, for the treatment of her Acne vulgaris. Dapson can induce significant methemoglobinemia in normal person but anemia, fever; any infection can accelerate the situation due to increase oxidative stress. For many years scientists attempted to develop a topical formulation of dapsone that would be as effective against acne as oral dapsone without any hemolysis side effect.[14] Aczone, a 5% dapsone gel is an emulsion and is constituted into an aqueous gel base that was shown to be effective against acne without causing clinically significant declines in hemoglobin levels, even in subjects with G6PD deficiency.[15] Topical dapsone results in a 100-fold lower plasma concentration than oral dapsone and has a limited adverse event making it a favorable formulation for the treatment of acne vulgaris in both adults and adolescents.[15]

In congenital methemoglobinemia, characteristic diffuse persistent slate-gray cyanosis, often present from birth; patients are often asymptomatic despite the presence of cyanosis. In acute methemoglobinemia, which is usually acquired, a history of exposure to methemoglobinemia-inducing substances (not always available), family history of methemoglobinemia or glucose-6-phosphate dehydrogenase (G6PD) deficiency. Cyanosis out of proportion to respiratory distress is the key indicator to diagnosis in Methemoglobinemia.[15] Symptoms are proportional to the fraction of methemoglobin. Skin color changes and blood color changes occur at

levels up to 15% in venous blood samples and death occurs at levels higher than 70%, although survival has been reported with much higher levels.[16] The characteristic finding in methemoglobinemia is cyanosis with low SpO2 and normal pO2 on arterial blood gas analysis. A simple bedside test – filter paper test can be done to distinguish between MetHb and deoxyhemoglobin. One or two drops of the patient's blood place on a white filter paper and observe. Deoxyhemoglobin gets brightened after exposure to atmospheric oxygen, while metHb does not change colour. Blowing oxygen on to the filter paper speeds up the reaction.[17] MetHb does not impair delivery of oxygen to plasma in the alveoli, and thus, pO2 remains unaffected but chocolate brown color of the arterial blood samples is highly suggestive of methhemoglobinemia.[18] If Methemoglobinemia is suspected, it is much more prudent to look at the saturation gap instead of the oxygen saturation on the pulse oximeter.

Primary treatment of methemoglobinemia involves discontinuation of the inciting agent whenever possible. The first-line treatment of moderate to severe cases is Methylene blue and should be infused in asymptomatic patients with methemoglobin levels greater than 30% and in symptomatic patients with levels greater than 20%. Methylene blue 1-2 mg/kg is administered intravenously; may repeat 1 mg/kg × 1 if symptoms persist after 20 minutes. Observation with serial monitoring of methemoglobin levels might be done in asymptomatic patients with methemoglobin levels less than 20%.[19] Ascorbic acid (vitamin C) is an effective alternative if methylene blue is not available, it acts as a strong reducing agent in various oxidative reductive reactions. It requires in a very high dose like 300 mg /kg, in this case as methylene blue was not available. We have given vitamin C 1000 mg every 6 hourly from the beginning. The effective antidote N-Acetyl Cysteine (NAC) is an experimental therapy for the treatment of Methemoglobinemia. It can reduce MetHb through glutathione production. NAC reacts with glutamate and glycine in the presence of ATP to form glutathione. The glutathione 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.[20]

If symptoms of methemoglobinemia do not resolve after this primary treatment with oxygen and the antidote, then a prompts decision should be taken for secondary options like exchange transfusion, plasma exchange and or dialysis as our patient was improved after exchange transfusion.

Conclusion

Dapsone induced methhemoglobinemia, though it is not so common but it has life threatening adverse effect. So safe alternative drugs or formulations should be use for the treatment of various disease. Also prompt diagnosis and treatment should be initiated as delay in management could be fatal.

Declaration of patients consent: The authors obtained patients parents consent to publish the clinical information and images in the journal.

Conflicts of interest: There were no conflicts of interest

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