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CASE REPORT

Dapsone-induced methemoglobinemia in immune thrombocytopenia: A case report

Chanshi Chandran[1], Anju A Mathew[1], Ranjini Pillai[2], Roshni P R[1]

[1]Department of Pharmacy Practice, Amrita School of Pharmacy, Kochi, Kerala, India, [2]Department of Medical Oncology and Hematology, Amrita Institute of Medical Sciences, Kochi, Kerala, India

Correspondence to: Roshni P R, E-mail: roshnipr@aims.amrita.edu

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ABSTRACT

ITP is a bleeding disorder which is not associated by a systemic disease caused by low platelet count or thrombocytes. However, use of dapsone is limited by adverse effects such as methemoglobinemia, reticulocyte increase, hemolysis, hemoglobin decrease, red cell life span shortened, agranulocytosis, anemia, leukopenia, and pure red cell aplasia. This report relates to an incident to methemoglobinemia after administration of dapsone as the second line agent for treatment of ITP in a tertiary care hospital. A 46-year-old male, with a case of immune thrombocytopenia and a family history of aplastic anemia in mother. Now presented with high grade fever associated with generalized weakness, cough with expectoration and shortness of breath and decreased urine output. He was admitted for further management. Initial laboratory investigations were done. Blood and urine cultures were sent. His arterial blood gas showed elevated methemoglobin (18.2). Peripheral smear revealed microcytic hypochromic anemia with polychromatophils, microspherocytes, and relative neutrophilia. Urine culture showed *Escherichia coli* and blood culture was sterile. Serum electrolytes were sent. He had elevated international normalized ratio (INR) value (5.93). Warfarin and dapsone were withheld.

KEY WORDS: Dapsone; Immune thrombocytopenia; Methemoglobinemia

INTRODUCTION

Dapsone (4,4'-diaminodiphenylsulfone) is a synthetic sulfone[1] used as second-line therapy in patients with immune thrombocytopenic purpura (ITP). ITP is an immune-mediated acquired disease. It is characterized by temporary or constant decrease in platelet count. IT patients are treated with dapsone as a second-line agent which has an anti-inflammatory and antibacterial property which shows advanced therapeutic activity. The risk of the disease is determined depending on the degree of thrombocytopenia and the number of platelet count.[2] Dapsone was found to cause significant rise in platelet count in some patients with chronic ITP. Dapsone can be used as an alternative to other second-line drugs in chronic ITP.[3] Methemoglobinemia is a condition which occurs when iron in the hemoglobin gets trapped in the ferric state. If not treated, accordingly decreased oxygen carrying capacity would lead to severe hypoxia and cyanosis[4] Dapsone is known to be the potent cause for methemoglobinemia. This report relates an incident of methemoglobinemia after administration of dapsone as the second-line agent for treatment of ITP.

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CASE REPORT

A 46-year-old male, a case of ITP was brought to the Department of Oncology and Hematology in a tertiary care

hospital, presented with complaints of petechial patches all over the body and ecchymosis in the right side of abdomen. He had a history of bleeding from gum. He was evaluated at a local hospital. On evaluation, he was found to have marked thrombocytopenia. Laboratory investigations showed platelet count of 42,000.

Patient was started on pulse dose of injection dexamethasone for 4 days, followed by oral steroids. Patient was found to be not responsive to steroids and is on tablet wysolone (tapering dose) and tablet dapsone 100 mg 1-0-0. Patient had a history of acute left middle cerebral artery infarct with dural venous sinus thrombosis and is on oral anticoagulation with tablet Warf.

Now, the patient is presented with fever which was high-grade associated with generalized weakness, cough with expectoration, shortness of breath, and decreased urine output. He was admitted for further management. The patient was presented to casualty with above-mentioned complaints. Initial laboratory investigations were done. Blood and urine cultures were sent. His arterial blood gas showed elevated methemoglobin (metHb) (18.2). Peripheral smear revealed microcytic hypochromic anemia with polychromatophils, microspherocytes, and relative neutrophilia. Urine culture showed *Escherichia coli* and blood culture was sterile. Serum electrolytes were sent. He had elevated INR value (5.93). Warfarin and dapsone were withheld. He was started on empirical IV antibiotics and other supportive measures. He had low Hb levels for which blood transfusion was given.

DISCUSSION

In 1943, dapsone was innovated as an effective chemotherapeutic agent. Dapsone poisoning is usually unintended. The major cause of drug-induced methemoglobinemia was found to be dapsone according to recent research conducted at several tertiary hospitals.[5] It not only results in methemoglobinemia but also includes other conditions such as hemolysis, hepatitis, coma, seizures, and metabolic acidosis. Ferrous iron is in reduced form in normal Hb, it when oxidized in the sixth coordination position to ferric iron to form metHb. This oxidized ferric iron bounds to hydroxyl group of water molecule in which this complex has a shift toward the left in oxygen dissociation curve and is incapable to transport oxygen which leads to an ablated oxygenation in tissue with consequent hypoxic features. Methemoglobinemia is an uncommon condition caused by induction of several toxic compounds including chlorates, inorganic, and organic nitrates or with drugs such as local anesthetics and sulfa drugs including dapsone or it can be congenital due to of red cell nicotinamide adenine dinucleotide reductase deficiency.[5] When more than 30% of normal Hb is converted to metHb, methemoglobinemia becomes fatal. The modular management of ingested drug-induced methemoglobinemia includes methylene blue and ascorbic acid, gastric lavage, and administration of charcoal. Methylene blue is the first-line drug of choice in the management of methemoglobinemia. Methylene blue reduces the metHb back to hemoglobin using the enzyme nicotinamide adenine dinucleotide phosphate-metHb reductase by reducing to leucomethylene blue by a cyclic reaction given intravenously. The expeditious treatment with frequent methylene blue doses engendered the reversal of metHb. The currently approved methylene blue regimen is often meager due to longer half-life of dapsone which contributes to the recurrence of clinically significant methemoglobinemia due to enduring oxidative stress[5] In both therapeutic use and overdose, methemoglobinemia is caused when hydroxylamine metabolite is formed from N-hydroxylation of dapsone. As an outcome of persistent absorption of dapsone from the gastrointestinal tract and by forming toxic metabolites, the recurrence has been reported. Simultaneous use of other insipid reducing agents such as ascorbic acid provides a reducing environment in blood and allows the dye to act more readily by competing directly with the chemical cause. The earlier reports suggests that exchange transfusion is the effective management of methemoglobinemia but which was later found with least benefit, probably due to large volume of distribution of dapsone.[5]

CONCLUSION

Based on our clinical experience including the present case report, we consider that physicians need to be alert in the possible association between dapsone use and methemoglobinemia.[6] A high degree of intuition for the association of dapsone administration and methemoglobinemia should be kept in mind while treating patients. For patients who do not successfully respond to supportive therapy or who have substantially higher than normal levels of metHb, methylene blue with adjuvant activated charcoal can be considered as a legitimate and intact treatment option. Early recognition of dapsone toxicity will allow for appropriate treatment of patients with dapsone-induced methemoglobinemia, thereby preventing further metHb production,[6] the disease is often less recognized and diagnosis is delayed, and hence, health-care professionals need to provide sufficient care[7] and thereby improve quality of life of the patients.

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