**Methemoglobinemia from dapsone therapy for suspected dermatitis herpetiformis.**

Sophia Delicou¹, Anastasios Andreopoulos²

¹Thalassemia Unit, Ippokrateion Hospital Of Athens
²First Departement of Internal Medicine, National Kapodistrian University of Athens, Laikon Hospital

**ABSTRACT:** Dapsone, for many years restricted to use in cases of leprosy and rare dermatologic disorders, has significant side effects that must be recognized. A case of methemoglobinemia is reported in one such patient treated with dapsone.

**Key Words:** Methemoglobinemia, Dapsone, Dermatitis herpetiformis.

**INTRODUCTION**

Dapsone is a leprostatic agent commonly prescribed for the treatment of patients with leprosy, malaria, and a variety of blistering skin diseases, including dermatitis herpetiformis. Methemoglobinemia, a potentially life-threatening condition in which the oxygen-carrying capacity of blood in body tissues is reduced, is a known adverse effect of dapsone use.

We report a case of dapsone-induced methemoglobinemia in a 64 year old woman whose condition was misdiagnosed by dermatologists as a flare of dermatitis herpetiformis. This, in turn, caused them to prescribe the wrong medication which led to acute dapsone-induced methemoglobinemia. This is a teaching case report as the doctor does not only need to make an initial diagnosis but also provide medical treatment appropriate to the histological anatomy diagnosis.

**CASE REPORT**

A 64-year old woman who was taking 100mg dapsone daily for dermatitis herpetiformis presented with a several-day history of weakness, and shortness of breath.

She was noticeably cyanosed peripherally and centrally. Her vital signs included a blood pressure of 130/70 mm Hg; a body temperature of 36.7°C; a pulse of 90 beats per minute; a respiratory rate of 20 breaths per minute; and an oxygen saturation of 89% with ambient air. The patient’s lungs were clear to auscultation. Skin examination revealed multiple areas of excoriation and swelling of the bilateral lower extremities. Central and peripheral cyanosis was noted. Abdominal, cardiac, and neurologic examinations were unremarkable.

Initial investigations included a blood gas on ambient air: pH 7.36, PCO₂: 30.9, PO₂: 96, HCO₃⁻: 17, methemoglobin (metHb) level 14.7%. Complete blood count showed a hemoglobin level of 12.8g/dl, leucocyte count of 5.8 with a normal differential count, and platelets of 185. Blood glucose, electrolytes, troponin, creatinine, alkaline phosphatase, transaminases, bilirubin, lipase, INR and PTT were normal. The patient was treated with discontinuation of dapsone, and use of diphenhydramine for the rash. During the 3 days after dapsone discontinuation the patient’s methemoglobin level decreased to 1.8%, trending toward the normal range, and her oxygen saturation also improved. Direct immunofluorescence microscopy did not show granular IgA deposits which is often found continuously along the dermal-epidermal junction rather than focally in the tips of the dermal papillae.

Corresponding author: Sophia Delicou, Thalassemia Unit, Ippokrateion Hospital Of Athens, Vassilisis Sophias 114, 115 27, Athens, Tel. +30 2132 088000, 6940 636397, email: sophiadelicou@myopera.com
Met-Hb is an oxidation product of Hb in which there is an oxidized ferric iron in the sixth co-ordination position instead of reduced ferrous iron in normal Hb. This oxidized ferric iron containing site is then bound to a water molecule or to a hydroxyl group. This complex is dark brown and unable to transport oxygen with a leftward shift in oxygen dissociation curve, thus leading to a decreased tissue oxygenation with subsequent hypoxic features.

There are two types of methemoglobinemia congenital and acquired:

Congenital methemoglobinemia is characterized by diminished enzymatic reduction of methemoglobin back to functional hemoglobin. Affected patients appear cyanotic but are generally asymptomatic. Most cases of the less common hereditary methemoglobinemias are due to homozygous or compound heterozygous deficiency (autosomal recessive) or in compound heterozygous cytochrome b5 reductase deficiency, which is primarily seen in sporadic cases. Another congenital cause of methemoglobinemia is hemoglobin M disease, which is due to mutations in a single globin gene (autosomal dominant) of either the alpha, beta, or rarely gamma globin gene. Deficiency of cytochrome b5 is the rarest form of congenital methemoglobinemia, and has been described in only one or two families.

Acquired methemoglobinemia typically results from ingestion of specific drugs or agents that cause an increase in the production of methemoglobin. It can be a fatal disease.

Dapsone (4,4’-diaminodiphenyl sulfone) is the parent compound of many sulfone medications, and has two primary toxicities: methemoglobinemia and hemolytic anemia.

It is absorbed from the gastrointestinal tract and undergoes enterohepatic circulation. Peak plasma concentrations are reached within 2 to 8 hours after ingestion. Mean half-life of plasma elimination varies from 10 to up to 80 hours in overdose situations. Cyanosis is evident with only 1.5g/dL of metHb, in contrast to the 5g/dL of deoxygenated hemoglobin required to see hypoxia-related cyanosis. Levels between 20-45% are associated with dyspnea, lethargy, dizziness, lightheadedness, weakness and headaches. MetHb levels above 45% are usually associated with impaired consciousness, and levels above 55% can cause seizures, coma and cardiac arrhythmias. The diagnosis of methemoglobinemia is based on clinical symptoms and laboratory testing. Arterial blood gas analysis paired with oxygen saturation analysis by pulse oximetry are now considered the definitive measures for making a correct diagnosis of methemoglobinemia. Further evaluation of our patient’s medical history revealed that she had been medicating with dapsone in an effort to manage the rash on her lower extremities, which was believed to be dermatitis herpetiformis. Dermatitis herpetiformis (DH) is a chronic pruritic cutaneous eruption associated with gluten-sensitive enteropathy (celiac disease [CD]) and immunoglobulin A (IgA) deposition in the skin. In our case direct immunofluorescence examinations, granular IgA deposition at the dermoepidermal junction with stippling in the dermal papillae, which is pathognomonic of the condition, was negative.

Treatment consists of removing the inducing agent, administration of high-flow O2, observation, and evolutive co-oximetric assessment. After discontinuation of the causative agent, fMetHb returns to baseline levels within 36 hours. The use of supplementary O2 increases plasma levels of dissolved O2 and oxygen consumption during tissue hypoxia. Methylene blue is indicated as the first-line antidotal therapy for patients with severe methemoglobinemia. Although successful treatment with plasma exchange therapy, hyperbaric oxygen therapy and ascorbic acid has also been reported, these therapies should be considered as second-line treatments for patients unresponsive to methylene blue.
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Σοφία Ντελίκου, Αναστάσιος Ανδρέοπουλος

1 Μονάδα Μεσογειακής Αναιμίας, Νοσοκομείο Ιπποκράτειο, Αθήνα
2 Α’ Παθολογική Κλινική, Εθνικό Καποδιστριακό Πανεπιστήμιο, Νοσοκομείο Λαϊκό, Αθήνα

ΠΕΡΙΛΗΨΗ: Η Δαψόνη για πολλά χρόνια χρησιμοποιήθηκε ως θεραπεία εκλογής για την λέπρα αλλά και για πιο σπάνια δερματολογικά νοσήματα, ενώ σήμαντικές παρενέργειες του φαρμάκου έχουν αναγνωριστεί. Η μεθαιμοσφαιριναιμία είναι μια σήμαντική παρενέργεια της δαψόνης και περιγράφεται σε μια ασθενή που έλαβε το σκεύασμα αυτό.

Αξίως Κλειδιά: Μεθαιμοσφαιριναιμία, Δαψόνη, Ερπητοειδής δερματίτις.

REFERENCES