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## **The role of arterial blood gas in distinction of intravascular hemolysis in a patient with lupus nephritis**

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## Abstract

Dapsone is a leprostatic agent routinely used for malaria and leprosy. It is also used as a prophylaxis for pneumocystis jiroveci pneumonia (PCP), as well as for toxoplasma gondii in immunocompromised patients. Methemoglobinemia is an adverse effect of dapsone and can be life-threatening. Detailed is a case of dapsone-induced methemoglobinemia in a young woman with lupus nephritis who was treated with chronic immunosuppressant medications.

## Keywords

Dapsone, Methemoglobinemia, Intravascular Hemolysis

## Introduction

Dapsone is a synthetic sulfone that inhibits folate synthesis. The adverse effects of dapsone may occur after few days of drug consumption. Acute adverse effects include nausea, vomiting, abdominal pain, methemoglobinemia, seizure, and coma; chronic adverse effects include eosinophilic pneumonia, aplastic anemia, hemolysis, neuropathy, hepatitis and agranulocytosis. Methemoglobinemia may be acute or chronic, while hemolytic anemia occurs after chronic consumption of dapsone. In this article, we report a rare combination of Dapsone-induced methemoglobinemia and hemolytic anemia in a patient with lupus nephritis and normal G6PD level.<sup>1</sup>

## Case Presentation

### Initial Presentation and history

A 22-year-old woman with an 8-year history of stage IV lupus nephritis presented to the emergency department with hypertensive emergency. Upon admission, blood pressure was recorded as 220/116 mmHg and anasarca was documented. Review of systems was remarkable for arthralgia. Current home medications included hydroxychloroquine 200 mg daily, lisinopril 2.5 mg daily, aspirin 81 mg daily, mycophenolate mofetil 1000 mg twice a day and methylprednisolone 4 mg daily. She was compliant with all of her medications except for mycophenolate mofetil. Allergy to sulfa antibiotics was reported. Physical examination revealed blood pressure of 220/116 mmHg and heart rate of 119 bpm. Integumentary exam noted malar rash, conjunctival injection, pitting edema and petechiae on lower extremities. Abdominal exam noted tenderness in right upper quadrant without rebound or guarding. Clinically significant laboratory tests are shown in Table 1.

### Hospital Course

The patient was admitted for hypertensive emergency. Blood pressure was controlled with intravenous nicardipine and lisinopril. Nephrology was consulted for blood pressure control and management of possible exacerbation of lupus nephritis. The clinical presentation along with active urinary sediment in addition to recent interruption of immunosuppressive therapy suggested relapse of lupus nephritis. Documentation of marked hypocomplementemia and high titer Anti-DS-DNA as shown in Table 1 also supported exacerbation of lupus nephritis.

Treatment initially consisted of pulse dose methylprednisolone (500 mg IV day 1-3), dapsone 100 mg daily for PCP prophylaxis, in addition to mycophenolate mofetil 1000 mg twice daily. Acute anemia was noted on hospital day six with a symptomatic drop in hemoglobin from 12.4

g/dl on the day of admission down to 6.9 g/dl. Thrombocytopenia and acute renal insufficiency were noted with platelet count of 75 and an elevation in creatinine as respectively noted in Table 1. Physical exam noted a pulse oximetry of 80% but was otherwise unremarkable. Chest radiograph did not show evidence of pulmonary vascular congestion.

Hemolysis work up showed significantly elevated lactate dehydrogenase (LDH) level, low haptoglobin and high reticulocyte count. Peripheral blood smear showed slight anisocytosis, occasional ovalocytes, macrocytes, and schistocytes.

In the setting of immunologically active SLE and lupus nephritis, the intravascular hemolysis along with thrombocytopenia and acute kidney injury suggested the presence of microangiopathic hemolytic anemia (MAHA) particularly, antiphospholipid syndrome (APS) or thrombotic thrombocytopenic purpura (TTP). On the other hand, the low level of oxygen saturation at rest in spite of oxygen supplementation along with the absence of clinical and radiological evidence of pulmonary edema suggested an oxygen dissociation curve disorder. This was further confirmed by arterial blood gas (ABG) analysis showing oxygen saturation gap (pH, 7.41;  $P_{aCO_2}$ , 29 mm Hg;  $P_{aO_2}$  156 mmHg; bicarbonate, 18.7mEq/L; base excess 5.4mEq/L. and Oxygen saturation, 80% on 4L/min by nasal cannula).

Considering the ABG results, the clinical condition and recent dapsone therapy, methemoglobinemia was confirmed by plasma methemoglobin level of 17.9%. Proceeding confirmation of methemoglobinemia, treatment commenced with intravenous methylene blue.

## DISCUSSION

### Dapsone and Methemoglobinemia

Dapsone is a sulfone antibiotic and potent anti-inflammatory that inhibits folate synthesis. Although an antileprosy drug, its use has expanded into the treatment of dermatologic conditions, including pyoderma gangrenosum, bullous systemic lupus erythematosus, and dermatitis herpetiformis and also as prophylaxis for pneumocystis jiroveci pneumonia.<sup>1</sup> Dapsone is metabolized in the liver via the cytochrome P450 pathway to potent oxidants that are responsible for its adverse effects; hemolytic anemia and 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 form ( $Fe^{3+}$ ). 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. This results in functional anemia.<sup>2</sup>

Normally, red blood cells maintain a steady-state methemoglobin level of less than 1%. Elevation in methemoglobin levels can be caused by congenital enzyme deficiencies or exposure to exogenous oxidizing agents. Several exogenous oxidizing agents are known to cause acquired methemoglobinemia. Dapsone is the medication that most commonly causes methemoglobinemia, but other offending drugs include the local anesthetics benzocaine and lidocaine. There is a paucity of literature regarding the incidence of dapsone-induced methemoglobinemia for *P jiroveci* pneumonia prophylaxis.<sup>3</sup>

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%.<sup>1</sup>

Definitive diagnosis of methemoglobinemia is based on an elevated serum methemoglobin level. However, serum methemoglobin levels are not always immediately available. Therefore, clinical suspicion in presence of the oxygen “saturation gap” between arterial blood gas analysis and pulse oximetry readings is helpful in making clinical diagnosis of methemoglobinemia.<sup>4</sup> Pulse oximetry can only measure oxyhemoglobin and reduced hemoglobin.<sup>5</sup> As other hemoglobins such as methemoglobin rise, the oxygen saturation on pulse oximetry falls and plateaus at 85%.<sup>5</sup> 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 to presence of methemoglobinemia. Also, in cases of methemoglobinemia, arterial blood samples will be a characteristic chocolate-brown colour.<sup>6</sup>

In addition to oxidation of heme iron, dapsone’s metabolites induce erythrocyte destruction by the formation of reactive oxygen species. The primary defense against oxidative injury in erythrocytes is the glucose-6-phosphate dehydrogenase (G6PD)–NADPH–glutathione pathway, which neutralizes free radicals. In patients with G6PD deficiency, dapsone causes severe hemolysis, since less reduced glutathione is available to handle the oxidative injury.<sup>7</sup> Unlike substances that cause hemolysis only in persons with G6PD deficiency, dapsone can cause hemolysis in patients with normal G6PD levels. This patient had elevated hemolysis markers, including unconjugated hyperbilirubinemia, an elevated lactate dehydrogenase level, low haptoglobin level, and reticulocytosis despite of normal G6PD level.

Initial management of patients with methemoglobinemia is immediate 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 indicated.<sup>1</sup> Methylene blue is reduced by NADPH (reduced form of nicotinamide adenine dinucleotide phosphate) to act as an artificial electron donor to methemoglobin, thereby enhancing the erythrocyte’s ability to reduce methemoglobin. If symptoms persist, repeat doses of methylene blue can be given with caution, as accumulation of the drug can result in increased production of methemoglobin.<sup>8</sup> If symptoms persist despite adequate therapy, hemodialysis might be required.

In our patient, the presence of MAHA in the setting of immunologically active lupus nephritis initially suggested the existence of APL or TTP, two life threatening and well known conditions to develop in active lupus patients. High index of suspicion and rapid diagnosis was necessary in order to plan active therapy that can include plasma exchange. On the other hand, the oxygen saturation gap prompted the consideration and diagnosis of methemoglobinemia. Arterial blood gas analysis in this case was essential in differentiating between the causes of MAHA.

## CONCLUSION

Patients receiving dapsone are at risk of developing methemoglobinemia. Methemoglobinemia is a medical emergency that may result in death if not detected and promptly treated. Successful diagnosis and treatment require high index of suspicion. Occurrence of cyanosis or unexplained

decrease in oxygen saturation should alert the medical team to the possibility of methemoglobinemia. An ABG should be performed when methemoglobinemia is suspected and the offending agent should be discontinued.<sup>9</sup>

**Table 1: Laboratory Results**

<b>Event</b>	<b>Day 1</b>	<b>Day 6</b>	<b>Day 7</b>	<b>Ref. Range</b>
<b>WBC</b>	6.4	12.3	14	4.5-10
<b>Hgb</b>	12.4	6.9	10.0	12.0-16.0
<b>Platelet</b>	145	75	95	150-440
<b>Potassium</b>	4.5	5.0	5.1	3.5-5.0
<b>Sodium</b>	152	142	136	135-145
<b>Creatinine</b>	0.97	2.13	2.16	0.6-1.10
<b>BUN</b>	23	89	91	7-21
<b>Reticulocytes count</b>		3.7		0.7-3.1
<b>LDH</b>		752	652	100-190
<b>Haptoglobin</b>		<7		32-145
<b>Complement C3, Serum</b>		28		90-180 mg/dL
<b>Complement C4, Serum</b>		8		9-36 mg/dL
<b>Anti-DNA (DS) Ab</b>		>300		<5 IU/mL
<b>Methemoglobin</b>		17.9, 4.7, 4.5	3.6	

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