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Early-Onset Methemoglobinemia in an HIV Patient Receiving Dapsone for PCP Prophylaxis Without G6PD Deficiency: A Case Report

G6PD Eksikliği Olmayan ve PCP Profilaksisi İçin Dapson Alan Bir HIV Hastasında Erken Başlangıçlı Methemoglobinemi: Bir Vaka Raporu

Özden et al. Early-Onset Methemoglobinemia in an HIV Patient Receiving Dapsone for PCP Prophylaxis Without G6PD Deficiency

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Abstract
Dapsone is used for *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis in patients with human immunodeficiency virus (HIV) infection who cannot tolerate trimethoprim–sulfamethoxazole (TMP-SMX), the first-line agent. Methemoglobinemia is a known adverse effect of dapsone, usually associated with glucose-6-phosphate dehydrogenase (G6PD) deficiency, but it may also occur in patients with normal enzyme activity. We report a case of early-onset methemoglobinemia in a newly diagnosed HIV-infected patient without G6PD deficiency receiving dapsone for PCP prophylaxis. A 24-year-old male with a CD4 T-cell count of 32/mm^3 developed decreased oxygen saturation approximately 72 hours after starting dapsone. Despite minimal symptoms, methemoglobin levels increased up to 11.5%. Dapsone was discontinued, and the patient was treated with methylene blue with rapid improvement. Although dapsone-induced methemoglobinemia is well described, reports in HIV-infected patients receiving dapsone for PCP prophylaxis are limited. This case highlights that methemoglobinemia may occur without G6PD deficiency and emphasizes early recognition.
Keywords: Dapsone, methemoglobinemia, HIV, PCP prophylaxis, G6PD

Özet
Dapson, trimetoprim–sülfametoksazol (TMP-SMX)'i tolere edemeyen HIV enfeksiyonu olan hastalarda, birinci basamak ajan olan TMP-SMX'e alternatif olarak Pneumocystis jirovecii pnömonisi (PCP) profilaksisinde kullanılmaktadır. Methemoglobinemi, dapsonun bilinen bir yan etkisi olup genellikle glukoz-6-fosfat dehidrogenaz (G6PD) eksikliği ile ilişkilidir; ancak normal enzim aktivitesine sahip hastalarda da görülebilir. Bu çalışmada, PCP profilaksisi amacıyla dapson kullanan ve G6PD eksikliği olmayan yeni tanı almış HIV enfekte bir hastada gelişen erken başlangıçlı methemoglobinemi olgusu sunulmuştur. CD4 T hücre sayısı 32/mm³ olan 24 yaşındaki erkek hastada, dapson başlanmasından yaklaşık 72 saat sonra oksijen satürasyonunda düşüş gelişti. Minimal semptomlara rağmen, methemoglobin düzeylerinin %11,5'e kadar arttığı saptandı.
Dapson tedavisi kesildi ve hasta metilen mavisi ile tedavi edilerek hızlı düzelme sağlandı. Dapsona bağlı methemoglobinemi iyi tanımlanmış olmakla birlikte, PCP profilaksisi amacıyla dapson kullanan HIV enfekte hastalarda bildirilen olgular sınırlıdır. Bu olgu, methemoglobineminin G6PD eksikliği olmaksızın da gelişebileceğini ve erken tanının önemini vurgulamaktadır.
Anahtar Kelimeler: Dapson, methemoglobinemi, HIV, PCP profilaksisi, G6PD

Introduction
Dapsone is a sulfone antibiotic widely used in the prophylaxis of *Pneumocystis jirovecii* pneumonia (PCP), particularly in patients intolerant to tolerate trimethoprim–sulfamethoxazole (TMP-SMX)[1]. One of its well-recognized adverse effects is methemoglobinemia, which results from oxidative stress on erythrocytes[2]. Although the risk is increased in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, it may also occur in individuals with normal enzyme activity[3].

Methemoglobinemia can present with non-specific symptoms and may be overlooked, particularly in patients without overt cyanosis or respiratory distress. Early identification is crucial, as delayed diagnosis may lead to unnecessary investigations and potential clinical deterioration[4].

Here, we present a case of early-onset, mild methemoglobinemia in a patient with human immunodeficiency virus (HIV) infection receiving dapsone for PCP prophylaxis, emphasizing the importance of clinical suspicion even in low-risk individuals.

Case Report

A 24-year-old male patient, with no known history of chronic disease, was under follow-up for newly diagnosed acquired immunodeficiency syndrome (AIDS), with a CD4 T lymphocyte count of 32/mm^3. As the patient had no clinical signs of pneumonia, PCP prophylaxis was initiated according to the European AIDS Clinical Society guideline version 12.1 with TMP-SMX 960 mg once daily orally [5]. However, the patient developed severe dyspnea on the second day of TMP-SMX prophylaxis, and TMP-SMX prophylaxis was discontinued, considering the drug side effect. Current guidelines recommend agents such as dapsone, atovaquone, and pentamidine as alternatives to TMP-SMX for the primary prophylaxis of opportunistic infections[5]. Since G6PD deficiency was not detected in the patient, dapsone prophylaxis was initiated at a dose of 100 mg per day.

Approximately 72 hours after initiation of dapsone therapy, oxygen saturation decreased to 87% on room air. The patient did not exhibit cyanosis and reported no significant dyspnea. Physical examination was otherwise unremarkable. Electrocardiography revealed sinus tachycardia, and chest radiography was normal.

Arterial blood gas analysis demonstrated methemoglobin levels of 5.3%, 7.3%, 9.8% and 11.5% over serial measurements. The hemoglobin level was 7.7 g/dL. Given the progressive increase in methemoglobin levels and the associated decrease in oxygen saturation, dapsone-induced methemoglobinemia was suspected. Dapsone was discontinued immediately. The patient received supplemental oxygen and a single dose of methylene blue (1 mg/kg). He was monitored in the intensive care unit.

At approximately 52 hours after initiation of methylene blue therapy, oxygen saturation was 98% on room air, with normalization of methemoglobin levels on arterial blood gas analysis (Figure 1). The patient's clinical condition remained stable. After ruling out opportunistic infections, antiretroviral therapy was initiated with a regimen of tenofovir disoproxil fumarate, emtricitabine, and dolutegravir. After discontinuation of dapsone treatment, primary prophylaxis was continued with 960 mg TMP-SMX three times a week, and no new side effects were observed in the patient.

Discussion

Dapsone-induced methemoglobinemia is a well-documented adverse effect mediated by its hydroxylamine metabolite, which oxidizes hemoglobin[2]. While G6PD deficiency is a known risk factor, cases in patients with normal enzyme activity have also been reported[3,4].

This case is notable for the early onset and relatively mild presentation of methemoglobinemia, which occurred within days of initiating standard-dose dapsone. Despite relatively low methemoglobin levels, the patient exhibited decreased oxygen saturation, illustrating that even mild elevations may have clinical relevance.

A key diagnostic feature is the discrepancy between pulse oximetry and arterial oxygen measurements (the so-called "saturation gap") and clinical presentation [1]. In such cases, co-oximetry or blood gas analysis is essential for accurate diagnosis. Recognizing this pattern can prevent unnecessary investigations for pulmonary or cardiac causes of hypoxia[4,6].

Although dapsone-induced methemoglobinemia is well described, a focused literature search was performed in PubMed and Google Scholar using the terms "dapsone", "methemoglobinemia", "HIV", and "PCP prophylaxis". This search identified only a limited number of reports specifically describing this complication in HIV-infected patients receiving dapsone for PCP prophylaxis. In contrast, most published cases, including recent reports such as those summarized in Table 1, describe dapsone-induced methemoglobinemia in patients without G6PD deficiency but in non-HIV clinical settings, rather than in the context of HIV infection. In clinical practice, hypoxemia in people living with HIV (PLWH) is often primarily attributed to opportunistic infections such as PCP, bacterial pneumonia, or other pulmonary complications. This diagnostic bias may delay consideration of drug-related causes such as methemoglobinemia.

Our case highlights the importance of maintaining a high index of suspicion for methemoglobinemia in PLWH receiving dapsone, even in the absence of G6PD deficiency and in the presence of mild or non-specific symptoms. Early recognition in this population is particularly important to avoid unnecessary diagnostic procedures and delays in appropriate management.

Management involves prompt discontinuation of the offending agent. Methylene blue is indicated in symptomatic patients or those with higher methemoglobin levels and typically results in rapid clinical improvement, as observed in our case[1]. Compared to previously reported cases, our patient presented with lower methemoglobin levels but clinically relevant hypoxemia, highlighting the importance of early recognition even in mild cases.

Previous reports have described dapsone-induced methemoglobinemia in various clinical contexts, including patients with G6PD deficiency, malignancy, renal disease, or overdose[2,7,8]. Compared to these cases, our patient had no significant comorbidities, highlighting that this adverse effect can occur even in relatively uncomplicated clinical scenarios (Table 1).

Conclusion

It is known that the number of PLWH is increasing. Although we are in the antiretroviral era, it is anticipated that the need for TMP-SMX use for PCP prophylaxis in PLWH may increase secondary to the increase in the number of patients. However, TMP-SMX treatment or prophylaxis is associated with serious adverse effects that may necessitate discontinuation of the drug. In this context, the use of dapsone, recommended as an alternative to TMP-SMX, may become more common.

With this case report, we aim to emphasize that patients receiving dapsone should be closely monitored for adverse effects even if asymptomatic, that screening for G6PD deficiency should be performed prior to initiation, and that methemoglobinemia may develop even in the absence of G6PD deficiency. Furthermore, we highlight that this condition can range from an asymptomatic course to severe respiratory failure. Early recognition and treatment are essential to prevent complications and avoid unnecessary diagnostic procedures.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Concept: D.K.Ö., F.P., Design: D.K.Ö., F.P., Data Collection or Processing: D.K.Ö., C.C., Analysis or Interpretation: D.K.Ö., E.Ö.Ç., Literature Search: D.K.Ö., Writing: D.K.Ö.

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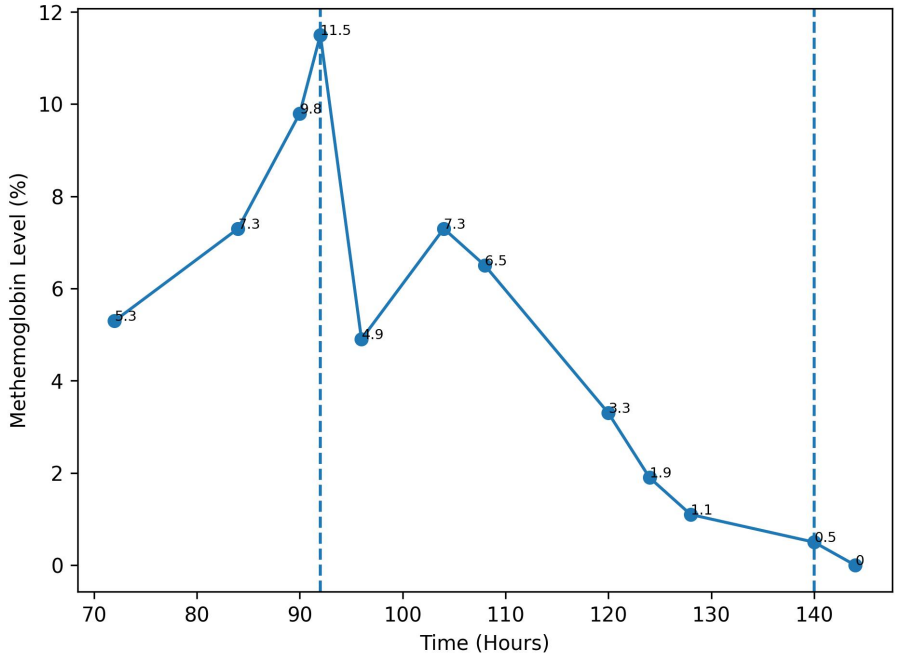

Figure 1. Serial measurements of methemoglobin levels following dapsone exposure. Methemoglobinemia developed after 72 hours of therapy, with levels increasing progressively and reaching a peak of 11.5% at 92 hours, when methylene blue (MB) was initiated. MB therapy was discontinued at 140 hours, with normalization by 144 hours.

Table 1. Reported cases of dapsone-induced methemoglobinemia without G6PD deficiency.

Study	Patient characteristics	Indication	Dapsone dose	MetHb (%)	Outcome
Bai et al.[3]	49F, multiple myeloma, CKD	PCP prophylaxis	100 mg/day	~20%	Recovered
Shenouda et al.[4]	64M, Behçet's syndrome	Behçet's syndrome	100 mg/day	15–25%	Recovered
Present case	24M, HIV (CD4: 32)	PCP prophylaxis	100 mg/day	11.5%	Recovered

G6PD, glucose-6-phosphate dehydrogenase; CKD, chronic kidney disease; HIV, human immunodeficiency virus; PCP, *Pneumocystis jirovecii* pneumonia; MetHb, methemoglobin.