Identifying the Cause of the “Saturation Gap”: Two Cases of Dapsone-induced Methemoglobinemia

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Abstract

Diaphenylsulfone (DDS: Dapsone) is used for Pneumocystis pneumonia (PCP) prophylaxis, and methemoglobinemia has rarely been reported as a side effect of DDS. We herein report two cases of DDS-related methemoglobinemia in an 81-year-old man with organizing pneumonia and an 84-year-old woman with eosinophilic pneumonia under treatment with prednisolone. Both patients initially received trimethoprim/sulfamethoxazole for PCP prophylaxis and were switched to DDS due to side effects and subsequently exhibited a clinically unexplainable decrease in SpO2. Methemoglobinemia was diagnosed based on the findings of arterial blood gas analyses. In both cases, the methemoglobinemia improved after discontinuing DDS.

Key words: methemoglobinemia, dapsone, diaphenylsulfone, saturation gap


Introduction

Trimethoprim/sulfamethoxazole (TMP/SMX) is recommended for Pneumocystis pneumonia (PCP) prophylaxis in patients with risk factors for PCP, such as a history of steroid therapy. However, TMP/SMX may induce various side effects, including skin rashes, electrolyte abnormalities and hematological toxicities, in which case, the drug should be discontinued. In such patients, diaphenylsulfone (DDS: Dapsone) is often used, although it may also cause side effects, such as DDS syndrome and methemoglobinemia. We herein report two cases of methemoglobinemia following DDS administration.

Case Reports

Case 1

An 81-year-old man with effort dyspnea and a cough was referred to our department for an assessment of an abnormal lung shadow. Following bronchofiberscopy, he was diagnosed with organizing pneumonia, and treatment with oral prednisolone (PSL; 30 mg/day=0.6 mg/kg body weight/day) was started, which resulted in a trend toward improvement in the shadow. In addition, TMP/SMX was administered simultaneously with prednisolone for PCP prophylaxis. However, the dose of TMP/SMX was discontinued due to the onset of hyperkalemia, and DDS therapy (100 mg bid) was initiated after obtaining the patient’s informed consent because DDS is not approved for use in Japan. The dose of PSL was slowly decreased; however, after three months, at which time the dose of PSL was 8 mg/day, the pulmonary shadow worsened and he was admitted to our hospital. After admission, we increased the PSL dose to 30 mg/day; however, no improvements were noted on a chest X-ray. Following the addition of cyclosporine A, the patient’s disease condition became stable and he underwent rehabilitation.

During rehabilitation, the SpO2 level did not increase with the administration of an adequate dose of oxygen. Therefore, an arterial blood gas analysis (ABGA) was performed, which revealed a difference between the SpO2 (91%; O2 at 2 L/min via nasal cannula) and SaO2 (96.9%, and PaO2, 123 torr) with 10.5% methemoglobinemia. We then suspected a
diagnosis of DDS-induced methemoglobinemia and discontinued the dose of DDS. Two days later, we again performed an ABGA, the results of which showed an SpO₂ of 90% (ambient air) and SaO₂ of 94.2% (PaO₂ 92.3 torr). Furthermore, the level of methemoglobin (MHB) decreased to 4.9%. DDS was discontinued and treatment with TMP/SMX was started again, in addition to the administration of calcium polystyrene sulfonate for hyperkalemia.

**Case 2**

An 84-year-old woman visited her family doctor with a complaint of general fatigue, and hypoxemia and an abnormal lung shadow were detected. She was referred to our department and was diagnosed with eosinophilic pneumonia on bronchofiberscopy. Because she was in respiratory failure, we administered oral PSL (40 mg/day=1.0 mg/kg body weight/day) followed by pulse steroid therapy. At the same time, treatment with TMP/SMX was started for PCP prophylaxis. The dose of PSL was subsequently tapered in association with an improvement in the lung shadow; however, two months after starting this treatment, she developed a skin rash and TMP/SMX was discontinued. Although the rash was ameliorated, we decided not to reapply TMP/SMX and instead administered DDS at a dose of 100 mg bid for PCP prophylaxis after obtaining the patient’s informed consent.

During the patient’s regular visit to the outpatient department one month after the start of DDS therapy, a low SpO₂ (90%; ambient air) was noted. However, the PaO₂ (84.9 torr) was within the normal range, we gradually tapered the dose of PSL. However, the SpO₂ remained low and we performed another ABGA five months after starting treatment with DDS. The analysis revealed a difference between the SpO₂ (90%; ambient air) and SaO₂ (92.4%, and PaO₂ 79.9 torr) with 9.1% methemoglobinemia, which was much higher than the value of 0.6% noted before PSL treatment. We suspected a diagnosis of DDS-induced methemoglobinemia and subsequently discontinued DDS. One month later, we performed another ABGA, and the results showed an SpO₂ of 97% (ambient air) and SaO₂ of 94.2% (PaO₂ 77.9 torr). In addition, the level of MHB decreased to 1.0%. We alternatively started therapy with aerosolized pentamidine for PCP prophylaxis.

**Discussion**

PCP can sometimes be fatal in immunocompromised hosts, making prophylaxis important for those at high risk. There are guidelines for PCP prophylaxis in cancer patients and hematopoietic cell transplantation recipients (1, 2). Furthermore, in a meta-analysis of adults without HIV infection, PCP prophylaxis was found to be necessary when the risk of PCP was ≥3.5% (3). On the other hand, PCP prophylaxis is often performed in compliance with these guidelines in patients treated with long-term steroid or immunosuppressive therapy for collagen diseases or respiratory diseases, such as interstitial pneumonia.

TMP/SMX is recommended as a first-line agent for PCP prophylaxis, although it is sometimes withdrawn due to side effects, such as skin rashes, electrolyte abnormalities and hematological toxicities. According to the guidelines for HIV-infected patients issued by the US Centers for Disease Control and Prevention (4), recommended alternative regimens include decreased doses of TMP/SMX, DDS, DDS+pyrimethamine+leucovorin, aerosolized pentamidine, atovaquone and atovaquone+pyrimethamine+leucovorin. In the two patients discussed in this report, TMP/SMX was discontinued due to the onset of hyperkalemia in one patient and a skin rash in the other; both patients received 100 mg/day of DDS instead.

DDS was developed for the treatment of leprosy. However, it is also widely known to have a prophylactic effect on PCP. In a report comparing TMP/SMX, aerosolized pentamidine and DDS in HIV-infected patients (5), DDS was as effective as the two other drugs for PCP prophylaxis and had a stronger prophylactic effect than aerosolized pentamidine in patients with <100/mm³ CD4-positive cells in particular. Moreover, Beumont et al. reported that DDS can be used relatively safely in patients who exhibit TMP/SMX intolerance (6) and El-Sadr et al. reported that DDS and atovaquone are similarly effective for preventing PCP in patients who cannot tolerate TMP/SMX (7). However, as this report also found that the relative risk of discontinuation with respect to adverse events is significantly higher among patients who receive DDS than those who receive atovaquone, side effects may be induced by DDS, including DDS syndrome which is characterized by dose-independent hypersensitivity reactions such as skin rashes, fever, eosinophilia and liver dysfunction; hematological toxicities, namely hemolytic anemia and agranulocytosis; and methemoglobinemia.

MHB is a ferrihemoglobin containing oxidized heme iron (Fe³⁺). Reduced (Fe²⁺) ferrohemoglobin binds O₂ reversibly between heme iron and distal histidine, whereas MHB cannot bind O₂. MHB is only produced in trace amounts in normal red blood cells and is immediately reduced to ferrohemoglobin (Fig. 1) (8). As a result, the formation and reduc-
Hb + DDS-NOH + O₂ \rightarrow MHb + DDS-NO + H₂O

Figure 2. This figure shows the production of methemoglobin by DDS. DDS-NOH and oxygen convert Hb to MHb.

The concentration of MHb is normally balanced, and MHb is stable when it accounts for approximately 1% of total hemoglobin. The cause of an increased MHb level may be congenital or acquired. Congenital causes include deficiencies in NADH (reduced nicotinamide adenine dinucleotide) cytochrome b5 and NADH cytochrome b5 reductase, which account for the majority of the MHb reduction system, and hemoglobin M disease. Most cases of methemoglobinemia are acquired and are caused by increased MHb production due to various exogenous agents. Acquired methemoglobinemia may be asymptomatic if the MHb level is <20%, although it can also cause headaches, fatigue, dyspnea and lethargy. At an MHb level of >40%, respiratory depression, altered consciousness, shock, seizures and death can occur. The ratio of oxyhemoglobin to total hemoglobin is measured using a standard pulse oximeter; therefore, when MHb or other hemoglobin derivatives are present, the oxygen saturation measured on pulse oximetry may be lower than the oxygen saturation calculated based on an arterial blood gas analysis; this is referred to as the “saturation gap.”

DDS has two metabolic pathways: one in which amino groups are oxidized to become hydroxylamine (\(-\text{NH}_2\rightarrow\text{NOH}\)) and another in which amino groups directly undergo N-acetylation (\(-\text{NH}_2\rightarrow\text{NHCOCCH}_3\)). As shown in Fig. 2, methemoglobinemia is caused by the conversion of Hb to MHb in the presence of DDS-NOH and oxygen. MHb is said to reach a concentration of approximately 10% in blood sampled six hours after the oral administration of a single 200 mg DDS dose. Methemoglobinemia is known to occur more frequently with a DDS dose of >200 mg/day, and MHb production is considered to be a dose-dependent side effect of DDS treatment (9). In a retrospective study (10) including 167 pediatric patients with hematologic malignancies or aplastic anemia who received DDS for PCP prophylaxis, methemoglobinemia was observed in 32 (19.8%) cases. In addition, in a retrospective study of 138 patients with acquired methemoglobinemia, DDS was found to be the cause of symptoms in 42% of the patients (11).

The first step in the treatment of acquired methemoglobinemia is to discontinue the causative drug; however, treatment with intravenous methylene blue is also effective. Methylene blue is reduced to leucumethylene blue by NADPH (reduced nicotinamide adenine dinucleotide phosphate) within the body which thus affects methemoglobinemia by reducing MHb to hemoglobin. In conclusion, DDS may be just as effective as TMP/SMX for PCP prophylaxis. However, it can also induce side effects, including methemoglobinemia. When PCP prophylaxis is necessary, desensitization therapy for TMP/SMX should be performed if possible, and efforts should be made to continue the administration of this drug. On the other hand, in cases in which DDS must be used, methemoglobinemia should be suspected and physicians should investigate when a clinically inexplicable decreases in SpO₂ (saturation gap) is seen that do not conform with the pathology.

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References