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증 례

# Exchange Transfusion Treatment for Dapsone-induced Methemoglobinemia

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Methemoglobinemia can be caused by dapsone toxicity. We report a case dapsone induced methemoglobinemia unresponsive to methylene blue successfully treated by exchange transfusion. A 52-year-old male ingested a handful of dapsone. He presented with severe peripheral cyanosis in lips and fingertips and his methemoglobin level was found to be 21.9%. After admission, methylene blue (1%) at 1 mg/kg was injected each time peripheral cyanosis and rising serum methemoglobin occurred. Despite methylene blue therapy, the patient' s methemoglobin level continued to fluctuate. Five days after the injections of methylene blue, many Heinz bodies were visualized in the peripheral blood, suggestive of hemolytic anemia occurrence. By hospital day 6, serum methemoglobine levels were elevated and not measurable (> 50%) and the patient was constantly in a semi-comatose mental state. An exchange transfusion carried out by utilizing 6 units of packed red blood cells and 4 units of fresh frozen plasma was performed. The patient' s methemoglobin levels were subsequently kept up below 20% and his peripheral cyanosis receded. Physicians should recognize the important role of exchange transfusion in refractory dapsone-induced methemoglobinemia.

**Key Words:** Exchange Transfusion, Whole Blood, Methemoglobinemia, Dapsone

## INTRODUCTION

Poisoning with a number of oxidizing drugs and chemicals may be complicated by methemoglobinemia[1-3]. Two important chemical groups in this regard are organic nitrites (e.g. amyl and isobutyl nitrite) and amino- or nitro-derivatives of benzene (e.g aniline, dapsone and lidocaine)[4]. Dapsone, a sulfone antibiotic, is one of the most important and main drug available for the treatment of leprosy. It is also used in the treatment of malarial diseases and as an anti-inflammatory remedy in acute ileitis. It is also used for prophylaxis against pneumocystic carinii pneumonia (PCP) in immunosuppressed population. Methylene blue is the drug of choice for treatment of dapsone induced methemoglobinemia[4]. But In cases of treatment failure with methylene blue, exchange transfusions can be considered[5]. We report a case of successful exchange transfusion treatment for dapsone-induced methemoglobinemia, which was unresponsive to intravenous injection of methylene blue given in excess of 12 mg/kg.

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## CASE REPORT

A 52-year-old, 70 kg male who had been previously treated for dapsone intoxication had ingested about a handful of dapsone with alcohol in an attempt to kill himself two hours ago. His wife said

that he had treated with methylene blue for dapsone intoxication years ago. Other past medical history was not remarkable. Family history was nonspecific. He was transferred to an Emergency department (ED) after undergoing gastric lavage in another hospital. On arrival at the ED, he complained of nausea and vomiting: although mentally alert, he showed severe peripheral cyanosis in lips and fingertips, and his pulse oximetry read 92% in room air. His initial vital signs included a blood pressure of 130/90 mm Hg, heart rate of 90/min, respiratory rate of 20/min and body temperature of 36°C. Laboratory studies revealed a white blood count of 7,900/$mm^3$, hemoglobin of 15.7g/dl, platelets of 280,000/$mm^3$, normal electrolytes and serum methemoglobin of 7.2%. His arterial blood gas analysis was as follows: pH 7.428, $PaO_2$ 86 mm Hg, $PaCO_2$ 35 mm Hg, $HCO_3^-$ 22.9 mmol/L, BE -1.4 mmol/L, $SaO_2$ 96.8%. After activated charcoal (70 g) was administered, the patient was injected with 70 mg of methylene blue intravenously (IV) because of peripheral cyanosis and methemoglobinemia. Another dose of ranitidine (50 mg every 12 h) and metoclopromide hydrochloride (10 mg every 12 h) and ascorbic acid (1,000 mg every 12 h) were administered intravenously. Peripheral cyanosis improved immediately after injection of methylene blue. However, within 6 hours of the injection, his oxygen saturation went down 85%; he fell into semicomatose mental state and presented peripheral cyanosis again. We tried intubation and supplied oxygen (3 L/min). His arterial blood gas analysis was as follows: pH 7.377, $PaO_2$ 85.5 mm Hg, $PaCO_2$ 35.8 mm Hg, $HCO_3^-$ 20.6 mmol/L, BE -4.6 mmol/L, $SaO_2$ 96.4% and serum methemoglobine level was 21.9%.

The patient was transferred to an emergency intensive care unit (ICU). At this time, his blood pressure was 90/60 mm Hg and his heart and respiratory rates were 110/min and 28/min, respectively. His $O_2$ saturation showed 84% in spite of mechanical ventilation and serum methemoglobin was 32.3%. After admission to the ICU, methylene blue (1%) at 1 mg/kg was injected each time peripheral cyanosis and rising serum methemoglobin occurred. Serial activated charcoal (25 g every 4 hours) was also started. A total dose of methylene blue, which we administered for seven days, was 955 mg. Despite methylene blue therapy, the patient' s methemoglobin levels continued to fluctuate and his mental state and $O_2$ saturation didn' t return to normal. Five days after the injections of methylene blue, Heinz bodies were visual-

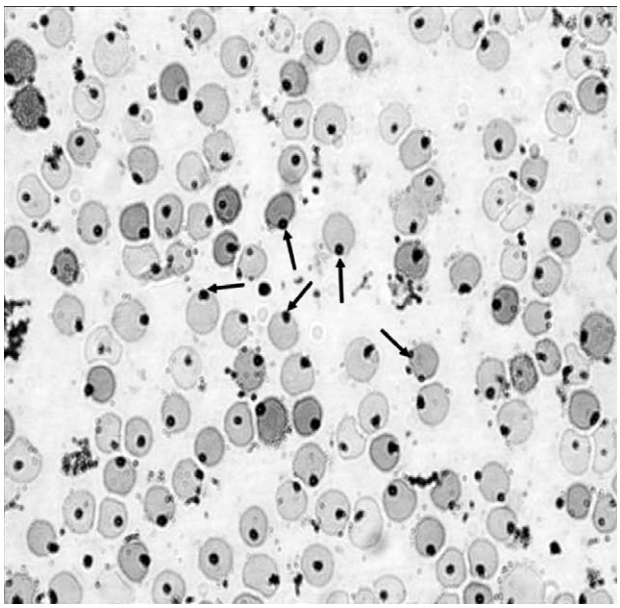

**Fig. 1.** Peripheral blood morphology at 5 days after methylene blue injection. There are many Heinz bodies (black arrows) suggesting of hemolytic anemia (crystal violet stain, × 1,000).

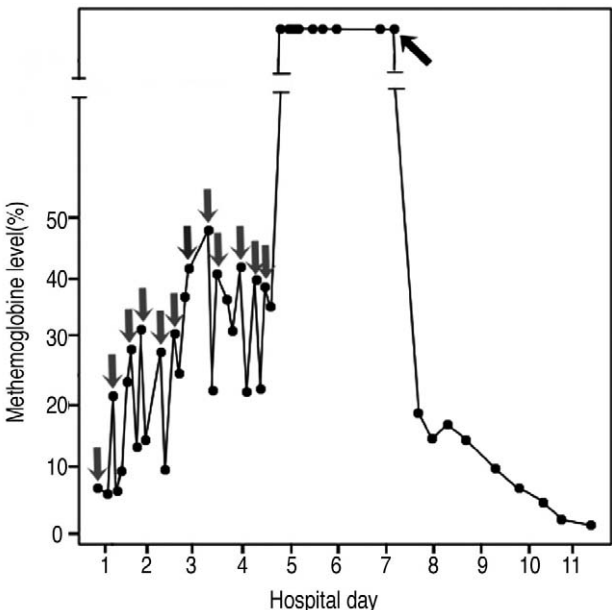


**Fig. 2.** Methaemoglobin fluctuation after methylene blue injections (gray arrows) and exchange transfusion (black arrow).

ized in the peripheral blood, suggestive of hemolytic anemia occurrence and serum methemoglobine level was 40.2% (Fig. 1).

By hospital day 6, serum methemoglobine levels were elevated and not measurable (〉 50%) and the patient was constantly semi-comatose mental state. His blood pressure and heart rate were 170/100 mm Hg and 113/min. Homoglobin and hematocrit were 12.6 g/dL and 33.6%. There were 30 nucleated red blood cells per 100 white blood cells. Reticulocyte was 44.22%. By hospital day 7, Methylene blue injections were stopped and an exchange transfusion carried out by utilizing 6 units of packed red blood cells and 4 units of fresh frozen plasma, simultaneously letting 2000ml of blood. Following the exchange transfusion, the patient' s methemoglobin levels were kept below 20% and his peripheral cyanosis receded (Fig. 2). By hospital day 8, his mental state became drowsy.

Magnetic resonance imaging scan of the brain performed following the recovery of methemoglobinemia, showed the possibility of metabolic toxin-induced Wernicke encephalopathy, so we injected thiamine to him. He was treated with aspiration pneumonia using antibiotics because of long-term hospitalization in the ICU. He was discharged 51 days post-ingestion, with indications of normal methemoglobin levels and alert mental state.

## DISCUSSION

On exposure to a non-oxygen oxidizing agent, iron donates an electron and transforms the oxidation states from $Fe^{2+}$ to $Fe^{3+}$, which is unreactive, and the hemoglobin that contains this unreactive $Fe^{3+}$ is termed methemoglobin. Methemoglobin, therefore, is unable to bind oxygen. A small amount of methemoglobin naturally exists in the blood (〈1 percent), but when the blood level of methemoglobin rises than 1 percent, it is defined as methemoglobinemia[6]. Clinical features of methemoglobinemia depend on the level of methemoglobin in the blood. Headache, weakness and fatigue predominate at methemoglobin concentrations up to 30%, whereas nausea, dizziness, anxiety, chest pain and dyspnea may be observed at methemoglobin concentrations of 30~50%[7]. Impaired consciousness, cardiac arrythmia and seizures are likely when methemoglobin concentrations exceed 60% and concentrations approaching 80% are life-threatening[8,9]. Methemoglobinemia can be caused either by genetic defect or a variety of drugs and toxins. Currently, most cases of drug-induced methemoglobinemia are caused by phenazopyridine, benzocaine, and dapsone[6]. Nitrate and nitrite salts are the chemicals most often responsible for epidemic methemoglobinemia. Studies of genetic defect were excluded from this case, because past medical history was not remarkable except dapsone intoxication and family history was nonspecific.

In the case of dapsone poisoning, clinical symptoms are presented according to the blood level of methemoglobin. Two clinical observations may be of help. First, the victim is often less unwell than one would expect from the severity of the cyanosis present. Second, the cyanosis is unresponsive to oxygen therapy. The arterial blood gas analysis shows normal partial pressures of oxygen and carbon dioxide even in the presence of high methemoglobin concentrations; this is because these parameters reflect dissolved gas in the sample and are not affected by methemoglobinemia. If there is significant tissue hypoxia, a metabolic acidosis may be present. An analysis incorporating a co-oximeter would measure methemoglobin concentrations directly to confirm the diagnosis[8].

Methylene blue is the drug of choice for the treatment of methemoglobinemia. Methylene blue indirectly accelerates the enzymatic reduction of methemoglobin by NDAPH-methemoglobin reductase, a normally minor enzymatic pathway. In this capacity, methylene blue is reduced to leucomethylene blue, which is capable of directly reducing the oxidized iron back to its oxygen carrying form. The initial dose of methylene blue is 1 to 2 mg/kg IV over 5 minutes and symptomatic improvement usually occurs within 30 minutes[4]. Continuous infusion of methylene blue (0.1 mg/kg/hr) with keeping 5~10% of serum metehemoglobin is also recommended to minimize adverse effect that can happen according to

administration of a large dose of methylene blue[10,11].

But we didn't try this method because his methemoglobin concentration fell and the most severe signs and symptoms resolved immediately after injection of methylene blue. Resolution of the cyanosis is a late finding, occurring only after the concentration of methemoglobin falls below 1.5 g/dl (1.5%).

Repeated doses of methylene blue may be acceptable, if needed, but high doses of it (〉20 mg/kg) can induce severe intravascular hemolytic anemia or may exacerbate the hemolytic effect of oxidizing chemicals[4]. Methylene blue therapy may paradoxically result in both hemolysis and worsening methemoglobinemia in Glucose-6-phosphate dehydrogenase (G6PD)-deficient patients[12,13].

But it was thought that worsening methemoglobinemia in our case is induced by dapsone intoxication itself because level of methemoglobin decreased dramatically just after injection of methylene blue. The half life of dapsone after ingestion of large quantities also can be extended to about four days[11]. And because this patient had experience of dapsone intoxication treated by methylene blue, it was getting increasing difficult to say that he has deficiency of G6PD. Severe renal impairment is an absolute contraindication to methylene blue administration since it is eliminated predominantly renally. Patients who do not respond to methylene blue should be treated supportively. If clinically unstable, the use of blood transfusion or exchange transfusion is indicated, especially in patients who cannot receive methylene blue[4,5,14]. If newly administered red blood cell hemoglobin undergoes oxidation, it will respond to methylene blue.

Methemoglobinemia induced by dapsone overdose is not uncommon in Korea. Most of patients recovered completely with methylen blue injection and conservative treatment[11,15]. But in the case of our patient, he didn't respond to methylene blue and elevated methemoglobine level. So we tried exchange transfusion to treat methemoglobinemia and intravascular hemolytic anemia induced by dapsone toxicity. It worked as expected and the patient had no further complications and his methemoglobin was completely resolved.

We should therefore consider the option of exchange transfusion treatment for dapsone induced methemoglobinemia unresponsive to injection of methylene blue.

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