High-dose Vitamin C therapy in Methemoglobinemia

Department of Emergency Medicine, Catholic University of Daegu School of Medicine, Daegu, Republic of Korea, Department of Emergency Medicine, College of Medicine, Yeungnam University, Daegu, Republic of Korea

Kyung-Woo Lee, M.D., Ph.D., Tae-Sin Kang, M.D., Sin-Youl Park, M.D., Ph.D.¹

Methylene blue is the first choice antidote for management of methemoglobinemia, however, some patients are refractory to methylene blue and in most cases, methylene blue cannot be available instantly in Korean emergency departments because of import suspension. A 69-year-old woman visited our emergency department for tachypnea and cyanosis after ingesting 30 tablets of dapsone. Because methylene blue was not available, we intravenously administered 10 g of vitamin C for symptomatic methemoglobinemia. Repeated i.v. administrations of 10 g of vitamin C in patient without preexisting renal insufficiency successfully treated dapsone-induced methemoglobinemia without causing renal complications. Thus, we recommend that if methylene blue is unavailable or methemoglobinemia is refractory to methylene blue, repeated administrations of 10 g of vitamin C may be considered for the treatment of methemoglobinemia in patients without renal insufficiency.

Key Words: Methemoglobinemia, Vitamin C, Dapsone, Methylene blue

Case Report

A 69-year-old woman visited the emergency department (ED) after intentionally ingesting 30 tablets of dapsone. She did not complain of dyspnea, but tachypnea and cyanosis were evident. She had been taking medication for depression for several years and was taking dapsone to treat intractable pemphigus. At presentation, her vital signs were: blood pressure, 206/107 mmHg; body temperature, 36.3°C; pulse rate, 136 beats/min; respiratory rate, 30 breaths/min, with an oxygen saturation of 94% on room air. Additional nasally administered oxygen (3 L/min) was provided. The patient’s lung sounds were clear, without rales. Arterial blood test revealed the following: pH, 7.38; PaCO₂, 27.0 mmHg; PaO₂, 113 mmHg; HCO₃⁻, 16 mmol/L; oxygen saturation, 98.1%; and her methemoglobin concentration was 39.7%. In other laboratory test results, definite abnormal findings were not observed (Table 1). The administration of...
methylene blue was required for symptomatic methemoglobinemia, but methylene blue was not available in our ED. We advised her family to go regional emergency medical center for patient’s intensive care, but they refused to transfer to other hospital in consideration of patient’s age, economic situation, and the convenience of nursing.

Her methemoglobin concentration rose to 40.2% at approximately 2 h after first laboratory examination (Fig. 1). We unavoidably recommended high dose vitamin C therapy to her family. After receiving content, high dose vitamin C therapy started. A vitamin C solution was prepared by mixing 10 g of vitamin C (Merit C®, Huons, Seoul, Korea) in 100 mL of normal saline; the solution was administered intravenously over 30 minutes. After administration of 10 g of vitamin C, methemoglobin concentration declined to 15.2% and her tachypnea and cyanosis improved gradually. However, considering the prolonged effect of dapsone on the methemoglobinemia, we decided to additionally administer 10 g of vitamin C until the methemoglobin concentration fell below 10%. Methemoglobin concentration measured after a second administration was 7.4%, and then we stopped the administration of vitamin C. However, 18 h later, methemoglobin concentration measured rebounded to 9.3%. Although it did not exceed 10%, we administered 10 g of vitamin C again in considering recurrence of dapsone-induced methemoglobinemia. Methemoglobin concentration steadily reduced after the i.v. implementation of 10 g of vitamin C every 8 hours (Fig. 1). The patient occasionally complained of epigastric discomfort and nausea during vitamin C therapy, but her serum creatinine concentration had remained below 1 mg/dl during and after vitamin C therapy. The patient was discharged from the hospital at 10th day after presentation without any complaint.

**Table 1.** Laboratory test results for patient in case at presentation.

<table>
<thead>
<tr>
<th>Laboratory findings at present</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells</td>
<td>16060 cells/μL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>14.8 mg/dL</td>
</tr>
<tr>
<td>Platelets</td>
<td>352000 cells/μL</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.8 mEq/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>145 mEq/L</td>
</tr>
<tr>
<td>BUN</td>
<td>15.9 mg/dL</td>
</tr>
<tr>
<td>Cr</td>
<td>0.89 mg/dL</td>
</tr>
<tr>
<td>AST</td>
<td>69 mg/dL</td>
</tr>
<tr>
<td>ALT</td>
<td>78 mg/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.1 mg/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>147 mg/dL</td>
</tr>
</tbody>
</table>

BUN: blood urea nitrogen, Cr: creatinine, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

**Discussion**

Dapsone was widely used as a treatment for leprosy,
but its use for that indication is declining. However, among the elderly in rural Korea, the drug remains popular for the treatment of intractable dermatitis and arthritis. Therefore, the drug is frequently kept in homes, which contributes to the number of intentional overdoses. Dapsone, potent oxidant, is metabolized by the liver through the oxidative reactions involving N-acetylation and N-hydroxylation. Hydroxylated amine metabolites are produced during this process and are assumed to be responsible for the induction of methemoglobinemia. The pharmacological half-life of dapsone is about 30 h, but because its overdose can prolong this period to about 80 h, dapsone overdose-induced methemoglobinemia can persist for a long time through ongoing oxidative stress.

Traditionally, methylene blue has been the first choice antidote for methemoglobinemia. However, current most Korean EDs do not possess methylene blue because of import suspension. Therefore, an effective replacement treatment for methemoglobinemia is required. Vitamin C, a common antioxidant, can theoretically transform methemoglobin back to normal hemoglobin, but it has been thought to be inappropriate for the management of methemoglobinemia because of its slow reduction time. However, recent several studies showed that methemoglobinemia can be treated successfully by vitamin C of high dose.

The current tolerable upper intake dose in adult of vitamin C is known to be 2000 mg/day. Although little is known about the optimal pharmacologic plasma concentration of vitamin C for treatment of methemoglobinemia, there was a report that vitamin C therapy with plasma concentrations above 10 mM reduced methemoglobinemia, whereas that at a concentration of ≤1 mM failed to do so. However, above 30 g of vitamin C may be required to achieve a plasma concentration of 10 mM according to distribution of plasma vitamin concentration related to dose. Higher dose vitamin C may reduce methemoglobin concentrations more easily, whereas they can increase the possibility of adverse events related to overdose of vitamin C.

Vitamin C administered in doses exceeding 1 g can cause nausea, vomiting, and increase the urinary excretion of oxalate. In particular, in the presence of previous renal insufficiency, high dose vitamin C can cause renal failure related to hyperoxaluria. However, in various studies, 10 g of vitamin C probably do not cause adverse renal complications in absence of preexisting renal insufficiency.

Recent Korean studies showed that 10 g of vitamin C was used safely and effectively as antioxidant for general population or terminal cancer patients. In consistent with these studies, this case showed that in spite of repeated administration, 10 g of vitamin C did not cause any adverse events including renal complication except intermittent epigastric discomfort and nausea.

Relations between vitamin C dosage and side effects are not well understood, and interactions with other drugs are possible. In addition, no optimal vitamin C plasma concentration has been determined for the treatment of methemoglobinemia. Nevertheless, we found that repeated administrations of 10 g of vitamin C successfully treated dapsone-induced methemoglobinemia without causing renal complications. Thus, we recommend that if methylene blue is unavailable, repeated administrations of 10 g of vitamin C may be considered for the treatment of dapsone-induced methemoglobinemia in patients without renal insufficiency.

REFERENCES