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Methemoglobinemia induced by automobile exhaust fumes

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Abstract
Although methemoglobinemia is an uncommon disorder, it should always be considered in the differential diagnosis of cyanosis. Major causes of acquired methemoglobinemia are nitrates, aniline, and analgesics, though rare cases have been reported to have been caused by automobile exhaust fumes. A 24-year-old man had inhaled a large amount of automobile exhaust fumes, intending to commit suicide. He had become unconscious, with dilated pupils and symptoms of cyanosis. Arterial hemoglobin oxygen saturation (Sp_{O_2}) was 86%, with a methemoglobin level of 44.3% and a carboxyhemoglobin level of 0%, while electrolytes, blood urea nitrogen, creatine, and glucose measurement results were normal. He was treated with methylene blue 250 mg (approximately 4 mg/kg) through a nasogastric tube. Four hours after the treatment, because the methemoglobin level was slightly above normal (2.2%), we added 180 mg of methylene blue. The results of final arterial blood gas analysis were a methemoglobin level of 0.4% and a carboxyhemoglobin level of 0.8%. He recovered uneventfully and returned home by himself the next day. To summarize, we successfully treated, with methylene blue given through a nasogastric tube, a young man who had developed severe methemoglobinemia from inhaling automobile exhaust fumes.

Key words Methemoglobinemia · Automobile exhaust fumes · Oral methylene blue

Case report

A 24-year-old man was brought to our emergency department by ambulance with a chief complaint of consciousness disturbance. After drinking alcohol, the man had drawn automobile exhaust fumes into his car (1992 Honda Civic), using a water hose, with the intention of committing suicide. He had been in the car with the engine running for at least 1 h before he felt dizzy and got out of the car; 3 h later, his brother found him in a disoriented state. By the time the emergency crew arrived, he had become unconscious (Japan Coma Scale: [JCS] 300), with dilated pupils and symptoms of cyanosis.

Upon admission to our hospital, his consciousness improved (JCS 10). Arterial blood gas was evaluated with 10 l/min oxygen. The results were: pH, 7.366; Pa_{CO_2}, 37.4 mmHg; and Pa_{O_2}, 349.3 mmHg. Arterial hemoglobin oxygen saturation (Sp_{O_2}) was 86%, with a methemoglobin level of 44.3% and a carboxyhemoglobin level of 0%, while electrolytes, blood urea nitrogen, creatine, and glucose measurement results were normal. Despite 100% oxygen therapy, the patient remained pale and cyanotic and did not receive any drugs.

The patient was treated with 250 mg of methylene blue (approximately 4 mg/kg) administered through a nasogastric tube, and symptoms were resolved except for a slight headache. Four hours after the administration of methylene blue, the results of arterial blood gas analysis were: pH, 7.431; Pa_{CO_2}, 39.5 mmHg; Pa_{O_2}, 236.2 mmHg; and Sp_{O_2}, 98%, with a methemoglobin level of 2.2%. Because the methemoglobin level was slightly above normal, we added 180 mg of methylene blue (approximately 3 mg/kg). In the final analysis, arterial blood gas with room air was pH 7.424; Pa_{CO_2}, 41.8 mmHg; and Pa_{O_2}, 71.2 mmHg, with a methemoglobin level of 0.4% and a carboxyhemoglobin level of 0.8%. He recovered uneventfully and returned home by himself the next day.

Discussion

Cyanosis is a commonly encountered symptom in the clinical setting, and central cyanosis indicates impaired pulmonary function, an anatomic shunt, decreased inspired oxygen, or dyshemoglobinemia. Although meth-

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emoglobinemia is an uncommon disorder, it should always be considered in the differential diagnosis of cyanosis.

Methemoglobin is produced when ferrous iron is oxidized to ferric iron within a hemoglobin molecule. This process inhibits the binding and delivery of oxygen and it also shifts the oxygen/hemoglobin dissociation curve to the left, further impairing oxygen delivery to tissues [1]. Methemoglobinemia can be divided into three basic categories, which are the hereditary presence of abnormal levels of hemoglobin, various methemoglobin hereditary enzyme deficiencies, and acquired methemoglobinemia (exposure to drugs or chemicals) [2]. We considered that hereditary factors were not associated with our patient's methemoglobinemia, on two grounds. One was that this event was the first occasion for him, and the other was that he had no relatives with methemoglobinemia. A large number of drugs (nitrites, nitrates, bromates, chlorates, aniline, antimalarials, antimicrobials, and analgesics, and others) are known to be associated with acquired methemoglobinemia [3], though there are only a few reports of methemoglobinemia caused by the inhalation of automobile exhaust fumes [4].

Normal physiologic levels of methemoglobin range from 0% to 2%, while a level of up to 20% is usually well tolerated in healthy adults. As the level approaches 20% to 30%, patients experience the onset of headache, dizziness, fatigue, and shortness of breath. When the methemoglobin level reaches 50% to 70%, it may be associated with lethargy, stupor, coma, and death [3].

In the patient we have reported here, when the emergency services arrived at the scene, he had fallen into coma (JCS 300), but his consciousness improved (JCS 10) after arrival at our hospital, and the methemoglobin level at that time was 44.3%. Thus, we considered that the methemoglobin level had been above 50% when the ambulance first arrived, because shortness of breath, headache, nausea, and blurred vision have been seen with a methemoglobin level of 24.8%.

As reported by Katsumata et al. [5], victims of city gas poisoning showed high carboxyhemoglobin levels, with only a negligible change in the methemoglobin level, whereas in victims of fire and exhaust fume poisoning, both carboxyhemoglobin and methemoglobin levels were high, though the former exceeded that of the latter in those who had died. Laney and Hoffman [4] reported a patient who had methemoglobinemia induced by automobile exhaust fumes while driving a sports car. In the present patient, as in the patient reported by Laney and Hoffman [4], methemoglobin increased without an accompanying elevation of the carboxyhemoglobin level, which we considered to be an interesting pathognomonic phenomenon. Katsumata et al. [5] performed their measurements in corpses, while our measurements and those of Laney and Hoffman [4] were in living patients. Therefore, in the case of exposure to automobile exhaust fumes, mortality may be related to the carboxyhemoglobin level and not the level of methemoglobin.

It has been reported that nitric oxide-induced methemoglobinemia can be reduced effectively by a medium to high concentration of methylene blue, or by a high dose of riboflavin in vitro, but not by *N*-acetylcysteine [6]. Methylene blue acts as a cofactor for nicotinamide adenine dinucleotide phosphate, reduced (NADPH) methemoglobin reductase, an alternative hemoglobin reduction pathway, and greatly increases the enzymatic reduction of methemoglobin through this pathway [7]. Methylene blue is commonly administered intravenously at a dose of 1 to 2 mg/kg, as a 1% solution, over 5 to 10 min [8], and sometimes via the oral route [9]; further, an intraosseous infusion has been reported for infant methemoglobinemia [10]. However, repeated doses (cumulative dose greater than 7 $mg \cdot kg^{-1}$) can cause dyspnea, chest pain, tremors, cyanosis, and even hemolytic anemia [8]. Those patients with very high levels of methemoglobin may require respiratory and cardiovascular support in an intensive care unit. In our patient, methylene blue was administered via a nasogastric tube, because it takes a significant amount of time to obtain an injectable preparation in Japan, and a dose of approximately 4 $mg \cdot kg^{-1}$ was found to be effective for treating methemoglobinemia induced by automobile exhaust fumes. Even though the patient received a high dose of methylene blue (approximately 7 $mg \cdot kg^{-1}$ in total) with a repeat administration, he was able to be discharged the next day without any side effects.

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