Two cases of acquired methemoglobinemia

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Abstract: Methemoglobinemia is a rare pathology that results from the oxidation of iron in the hemoglobin molecule. Oxidation of iron switches it from the ferrous to the ferric state, and impedes the ability of hemoglobin to carry oxygen. Hence, methemoglobinemia often results in hypoxemia. The disease can be hereditary or acquired, and its diagnosis can be challenging. This rare condition may often be missed by clinicians, since information on oxygen saturation provided by standard pulse oximeters is unreliable. We here present two cases of acquired methemoglobinemia. The first one is a 24-year-old woman, who received dapsone as an alternative antibiotic therapy because of known allergies to a series of other antibiotics and who could not get weaned from mechanical ventilation support. The second case describes a 49-year-old man who developed respiratory insufficiency following the use of 'poppers' containing alkyl nitrites. Following treatment of both patients using the antidote methylene blue, they could be successfully weaned from mechanical ventilation.

Key words: Methemoglobinemia; methylene blue; dapsone; poppers.

INTRODUCTION

Methemoglobinemia is a rare disorder, where the iron molecule contained in hemoglobin is oxidized from the ferrous state to its ferric state. The ferric hemoglobin cannot carry oxygen. Methylene blue is the antidote for methemoglobinemia (1). This report describes 2 cases of methemoglobinemia that were successfully treated.

CASE 1

A 24-year-old female was referred to the intensive care unit with respiratory insufficiency. Several years before, she had suffered from a Caisson disease, which resulted in central paresis and muscle weakness of her right leg, as well as in urine incontinence. She had been recently diagnosed with HIV-1 but did not take any antiretroviral medication yet. She had known allergies to trimethoprim, sulfamethoxazole, paracetamol and quinolones. She was admitted to the hospital because of fever and cough. She rapidly developed respiratory insufficiency and was transferred to the Intensive Care Unit (ICU). There, her trachea was intubated and her lungs were mechanically ventilated. She received treatment for a suspicion of pneumonia that consisted in amoxicillin/clavulanate and erythromycin. Due to her low CD 4+ count (193·106/L), a prophylaxis against Pneumocystis jiroveci was started. Because of her known allergies to sulfamethoxazole and trimethoprim, prophylaxis was performed using dapsone. Although she recovered from her infection, weaning from mechanical ventilation revealed impossible. Indeed, despite minimal mechanical support of her ventilation, her hemoglobin saturation was stagnating at 85%. In front of such clinical picture, methemoglobinemia was suspected. A 14.1% level of methemoglobin was finally discovered. Efficient treatment consisted in the intravenous administration of methylene blue, as illustrated in Figure 1. Shortly after starting methylene blue administration, namely within two hours, the tube was successfully removed from the patient’s trachea.

CASE 2

A 49-year-old male with a history of hepatitis B was urgently transferred to the emergency department because of respiratory failure. Shortly before, he had used alcohol, marihuana and a so called ‘poppers’. Poppers is a popular word for alkyl nitrites, which are inhaled by people with the goal of enhancing sexual pleasure. They are often used among the homosexual community to relax smooth muscles, including the sphincter muscles of the anus. In the Netherlands, ‘poppers’ have been illegal since 2003, but they are still sold behind the
counter in sex shops. Shortly after using the ‘poppers’, the patient became dyspnoeic and collapsed. Upon arrival of the ambulance, he was tachypnoeic and had a Glasgow Coma scale score of 8/15 (1/4 for eye opening, 5/6 for motor response, and 2/5 for verbal response). He was transferred to the Emergency Department of our Institution, where his trachea was immediately intubated because of a clear condition of respiratory insufficiency, with explicit cyanosis and ongoing gastric secretion aspiration. Noteworthy, his hemoglobin saturation in oxygen, as measured by pulse oximetry, was higher than expected. At that time, it was 85%. The information on previous use of ‘poppers’ by the patient led to the assessment of methemoglobin concentration in his blood. It was found to be as high as 31%. Intravenous methylene blue was immediately administered at the dose of 1 mg/kg. Immediately after, oxygen saturation as measured by our standard oximeter dropped as low as 51%, revealing the hypoxia. Twenty minutes later and under an 100% inspired fraction in oxygen, saturation improved to 97%. A chest x-ray revealed patchy bilateral consolidations, with a perihilar and basal distribution, more pronounced in the right lung. The patient was then transferred to our ICU, and could be successfully weaned from mechanical ventilation the day after. Four hours after administering methylene blue, methemoglobin concentration decreased to 0.8% (see figure 2).

**DISCUSSION**

Methemoglobin contains ferric iron (Fe3+) instead of ferrous iron (Fe2+). This form of hemoglobin is not able to bind oxygen. This results in functional anemia. The ferric form interferes with oxygen unloading, and causes a switch of the hemoglobin dissociation curve to the left, increasing the risk of tissue hypoxia. Under physiological circumstances, oxidants are present in the body, and convert a small part of hemoglobin to methemoglobin. The ferric (Fe3+) form changes the absorption spectrum of hemoglobin, resulting in inaccurate oxygen saturation measurements by conventional pulse oximeters, which are based on the above-mentioned absorption spectrum. Methemoglobin levels are normally below 2%. Enzyme systems, such as cytochrome-b5 reductase and NADPH methemoglobin reductase, counteract the endogenous formation of methemoglobin. Under normal circumstances NADPH methemoglobin reductase does not play an important role in this conversion, but this enzyme has high affinity for methylene blue (2, 4).

Methemoglobinemia can be caused by genetic or congenital disorders (see table 1). In hereditary methemoglobinemia, there is an alteration or deficiency in enzyme function for reducing endogenous methemoglobin. Another cause of congenital methemoglobinemia is seen in patients with abnormal hemoglobin variants, which are not amenable to reduction despite intact enzyme systems. The most frequent cause of methemoglobinemia is exposure to drugs or toxins. More than 100 medications are known to potentially cause this disorder. The administration of dapsone, which was the cause of methemoglobinemia in our first case, is the most common etiology of acquired methemoglobinemia, accounting for 42% cases (3). In the liver, dapsone undergoes N-hydroxylation through the action of several cytochrome P-450 enzymes. The metabolite N-hydroxy dapsone, rather than the drug itself, causes methemoglobinemia in a dose-dependent manner (4).

Diagnosing methemoglobinemia can be challenging. A discrepancy between saturation numbers provided by the pulse oximeter and the arterial oxygen partial pressure must incite to suspect it. This condition is known as the “saturation gap”. In
that case, blood gas analysis reveals normal to slightly decreased arterial oxygen partial pressures. In most laboratories, oxygen saturation of hemoglobin is calculated from the arterial oxygen partial pressure, and not directly measured. If one looks at those calculated values only, methemoglobinemia may not be detected. Pulse oximeters are only based on the absorption at two distinct light wavelengths, namely 940 nm for the assessment of oxyhemoglobin and 660 nm for the assessment of deoxyhemoglobin. Oxygen saturation then corresponds to the ratio between absorbance at those two wavelengths. The ratio is compared with a reference table obtained in volunteers exposed to hypoxemia until an oxygen saturation of 80%. For that reason, reliability of pulse oximeters is only valid above an oxygen saturation of 80%. Methemoglobin has similar absorption at 660 nm and 940 nm, which leads to erroneous absorption ratio (2, 4). In 1989, Barker et al. showed that the peripheral saturation in oxygen as estimated by conventional two-wavelength pulse oximeters is forced toward 85% in the presence of high methemoglobin levels. At a level of 35%, the pulse oximeter saturation estimate reaches a plateau of 84 to 86%. The estimate will not decrease further with higher methemoglobin levels. Therefore, until methemoglobin levels reach 35%, pulse oximeters usually underestimate functional hemoglobin saturation to an extent that is proportional to methemoglobin concentration. In other words, the conventional two-wavelength pulse oximeters will underestimate the saturation of functional hemoglobin at true values above 85%. In contrast, true hypoxic patients with a low value their functional hemoglobin saturation (as in our second case) will exhibit an overestimation of that parameter (4, 2009).

### Table 1

Etiologies of methemoglobinemia

<table>
<thead>
<tr>
<th>Hereditary</th>
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<tr>
<td>Hemoglobin M</td>
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<td>Cytochrome-B5 deficiency</td>
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<th>Acquired</th>
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<td>Nitrates in water or diet</td>
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<td>Aniline</td>
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<tr>
<td>Meditations:</td>
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<tr>
<td>benzoic cocaine, cetacaine, chloroquine, dapsone, flutamine, lidocaine, metoclopromide, nitrates, nitric oxide, nitrocellor, ni tropeptide, prilocaine, primaquine, rifaxim, silver nitrate, sulfonamides, …</td>
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![Fig. 2. — Same as in figure 1 for case 2](image-url)
In our second case, the oxygen saturation measured by the pulse oximeter decreased from 85% to 51% after administering methylene blue, revealing a true hypoxemic state. In this example, hypoxemia was most likely caused by a massive aspiration when the patient collapsed.

Co-oximeters measure the light absorption more than two wavelengths. Therefore, they are able to determine percentages of oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin and methemoglobin. Conventional pulse oximeters continuously and non-invasively monitor oxygen saturation. In contrast, co-oximeters require blood sampling (2). In 2005, an non-invasive co-oximeter, the Masimo Rainbow® SET Pulse CO-Oximetry, was developed. This non-invasive pulse-oximeter can be a useful tool for the diagnosis of methemoglobinemia, and can be used for following up its treatment.

Due to the difficulty in diagnosing methemoglobinemia, physicians should be aware of typical clinical findings. A clue towards recognizing methemoglobinemia is the observation of a characteristic chocolate-brown color of blood. Most symptoms can be explained by tissue hypoxia and will become more pronounced as the levels of circulating methemoglobin increase. Cyanosis occurs when levels reach 15-20%. These levels are usually well tolerated. Levels of 25-40% are associated with headache, fatigue, dyspnoea and dizziness. Levels above 45% will result in consciousness alteration and coma. Levels above 70% are usually lethal (5).

Symptomatic methemoglobinemia should be treated using methylene blue. Methylene blue acts as a cofactor for NADPH methemoglobin reductase and thereby increases the enzymatic reduction of methemoglobin. Methylene blue is dependent on NADPH. Therefore, treatment will be ineffective if NADPH levels are too low, such as in patients with glucose-6-phosphate dehydrogenase deficiency, or if a NADPH-methemoglobin reductase deficiency is present. Noteworthy, high concentrations of methylene blue can be deleterious. In that case, it acts as an oxidant, worsens iron oxidation, and can cause hemolysis. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis can be severe (1, 8).

Methylene blue should be administered intravenously at an initial dose of 1 to 2 mg/kg over 3 to 5 minutes, and followed by a 15 to 30 ml fluid flush. Within 20 minutes, resolution of cyanosis usually occurs. If no response is obtained, the administration methylene blue should be repeated to a maximum of 7 mg/kg. Adverse effects include gastrointestinal complaints, bladder irritation, bluish discoloration of the skin, which complicates the assessment of cyanosis, and methemoglobinemia (6).

When methylene blue treatment fails, particularly in acquired methemoglobinemia, exchange transfusion has been used successfully in adults and children. Exchange transfusion can also be used in addition to methylene blue in patients where the clinical condition is severe, or where the maximum dose of methylene blue has been reached (9). In NADH-cytochrome-b5 reductase deficiency, ascorbic acid and riboflavin may be considered to gradually reduce methemoglobin levels. In life-threatening cases, hyperbaric oxygen can be considered (8).

CONCLUSION

Our reported cases are typical drug-induced methemoglobinemia cases, one secondary to the administration of dapsone, and one secondary to the use of "poppers". Both cases resulted in respiratory insufficiency and severe hypoxemia. Our patients were successfully treated with the antidote, namely methylene blue.

References