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Case Report

Cyanosis and Hypoxemia Caused by Acquired Methaemoglobinemia

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Abstract

Methaemoglobinemia can occur due to a congenital enzyme defect or can be secondary to medication or drugs. Symptoms depend on the concentration of methaemoglobin in the blood and the existence of additional risk factors. Methaemoglobinemia can cause significant tissue hypoxia, with no reaction on oxygen therapy, leading to severe, potentially life-threatening clinical features and/or death. A discrepancy between the oxygen saturation, as measured by pulse oximeter and the arterial oxygen saturation can be indicative of methaemoglobinemia. The diagnosis is made by blood gas analysis. Here, we describe the clinical course of two male patients. One patient, aged 53, develops methaemoglobinemia after the ingestion of poppers (nitrite-containing recreational drugs). A 3-year old boy with a glucose-6-phosphate-dehydrogenase-deficiency develops methaemoglobinemia after treatment with rasburicase. The first patient was treated with methylene blue. In the second patient methylene blue was contra-indicated due to the glucose-6-phosphate-dehydrogenase-deficiency. He was treated with red blood cell transfusions. Both patients recovered without sequelae.

ABBREVIATIONS

SpO_2: Saturation in Pulse Oximetry; G6PD: Glucose-6-phosphate Dehydrogenase; SaO_2: Arterial Oxygen Saturation; NADPH: Nicotinamide-Adenine Dinucleotide Phosphate;

INTRODUCTION

Cyanosis and low saturation in pulse oximetry (SpO_2) are mostly caused by hypoxemia due to cardiopulmonary causes. However, methaemoglobinemia should always be considered as a differential diagnosis. Especially when there is a discrepancy between the oxygen saturation, as measured by pulse oximeter and the arterial oxygen saturation (SaO2), and no reaction on oxygen therapy.

Methaemoglobinemia can be due to an inborn error of metabolism or it can be acquired. Acquired methaemoglobinemia as a side effect to several oxidizing drugs, chemicals and food items, and occasionally are secondary to pathologic conditions, such as sepsis, sickle cell crisis, and gastrointestinal infections in children. If unrecognized it can cause tissue hypoxia, and it can even lead to death in severe cases. Effective treatment is available in the form of methylene blue. This treatment however isn't possible for every individual patient with methaemoglobinemia. Below we will demonstrate the different considerations in diagnosis and treatment in two cases with both acquired methaemoglobinemia.

CASE PRESENTATION

Patient A, a 53-year-old Dutch man, with no documented medical history, is brought into the emergency ward with a low oxygen saturation and hypotension. He was in a bar, when he became dyspnoeic and cyanotic. He is somnolent and barely reacts to speech. The SpO_2 is 84%, and increases to 88% with 15L/minute oxygen. His respiratory rate is 18/minute; examination of the lungs shows no abnormalities. His blood pressure is 86/60mmHg with a pulse of 80 beats per minute. The Glasgow Coma Score is Eye (3), Motor (6) and Verbal (4), otherwise no abnormalities. An EKG and chest X-ray provide no explanation for his condition. An arterial blood gas shows: pH 7.36, pO_2 10.7kPa, bicarbonate 20.5mmol/l, SaO_2 95%, oxygen

fraction 67% and methaemoglobin 29%, which is routinely codetermined in our hospital. On inquiry, the patient admits to have ingested 'poppers' (nitrite containing recreational drugs). After administration of methylene blue (1mg/kg) the patient's clinical condition and consciousness improve rapidly. After 1.5 hours a methaemoglobinemia level of 0.4% is measured. By the next day the patient is totally recovered.

Patient B, a 3-year-old boy of Dutch-Thai origin with recently diagnosed acute lymphatic leukaemia develops a decreasing SpO_2 several hours after the first administration of rasburicase (0.2mg/kg). No other medication was started yet. On physical examination, cyanosis is difficult to assess due to the tinted skin. We see a tired, but responsive boy with a free airway, no signs of increased work of breathing, normal breath sounds, SpO_2 86% without oxygen administration increasing to 88% with oxygen 15L/minute through a non-rebreathing mask, heart frequency 120 beats per minute, blood pressure 115/60mmHg. A chest X-ray shows no abnormalities. A capillary blood gas shows: pH 7.41, pO_2 34.8kPa, bicarbonate 24.3mmol/l, oxygen saturation 99%, oxygen fraction 85% and methaemoglobin 12.8%. Methaemoglobinemia as a side effect of rasburicase was considered, possibly with an underlying glucose-6-phosphate dehydrogenase (G6PD) deficiency, which increases the risk for the development of methaemoglobinemia. Methylene blue was not given, partly due to the good clinical condition and low methaemoglobin percentage, and partly because methylene blue is contraindicated in G6PD patients. Twelve, 24 and 48 hours after administration of rasburicase, methaemoglobin percentages were 7.6%, 2.2% and 1.0%, respectively. Red blood cell transfusions were necessary due to anaemia caused by a combination of existing anaemia combined with haemolysis. Haemolysis was due to a G6PD deficiency, which was confirmed later on with enzyme diagnostics.

DISCUSSION

Both patients presented with a low SpO_2 that was unresponsive to oxygen administration. In addition there was a discrepancy between measured SpO_2 and oxygen saturation in blood gas analysis. This fits the clinical picture of acquired methaemoglobinemia.

Normally, the concentration of methaemoglobin is <2%. This is due to the continuous balance between formation and reduction of methaemoglobin (Figure 1). Methaemoglobin is formed by auto-oxidation of haemoglobin, where the iron molecule ferro (Fe2+) is transformed into ferri (Fe3+) within the haem. Agents that increase oxidative stress, such as nitrites (poppers) and rasburicase, amplify the oxidation. In humans, there are three mechanisms by which erythrocytes reverse the effects of oxidation and the formation of methaemoglobin. The physiological main pathway is the formation of nicotinamide dinucleotide (NAD+), which is dependent of cytochrome b5 methaemoglobin reductase, and accounts for more than 95% methaemoglobin reduction to haemoglobin. The second mechanism is the formation of methylene blue. This mechanism is dependent on nicotinamide-adenine dinucleotide phosphate (NADPH) as electron donor, with the enzyme NADPH-Met-Hb reductase as catalyst. NADPH production is dependant of G6PD. After reduction of methaemoglobin, methylene blue is converted back into leuco-methylene blue. This system can drastically increase in capacity under the influence of exogenous co-factors, like administering methylene blue. More slowly and less important mechanisms, like intracellular glutathione and ascorbic acid, are known non-enzymatic antioxidants with methaemoglobin reducing ability [1,2,3].

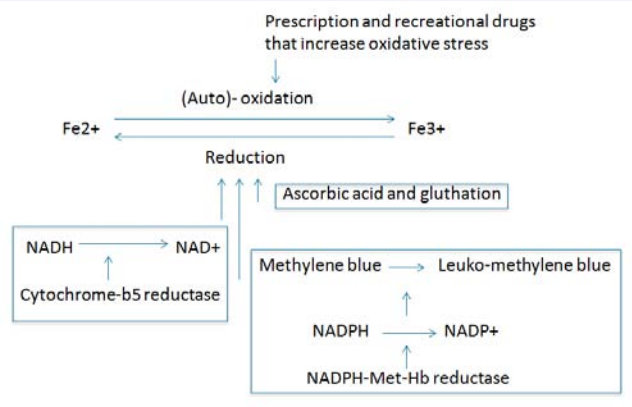

Figure 1 Schematic representation of the balance between haemoglobin and methaemoglobin, the (auto) oxidation and reduction of ferro (Fe2+) and ferri (Fe3+). At the top the (auto)-oxidation and at the bottom of the figure three mechanisms that cause reduction of methaemoglobin.

Methaemoglobinemia causes tissue hypoxia by way of two different mechanisms: firstly, oxygen cannot bind to methaemoglobin. Secondly, the different molecule structure of methaemoglobin makes the release of oxygen to the tissues more difficult [1].

A discrepancy between a measured low SpO_2 and a high-normal SaO_2 may be indicative of a methaemoglobinemia. A pulse oximeter measures the light absorption of oxyhaemoglobin and deoxyhaemoglobin at two different wavelengths. The amount of light absorption has a known relation with the arterial oxygen saturation. Methaemoglobin disrupts the measurement of the pulse oximeter. Therefore the measured SpO_2 will never reach values above 85% with high methaemoglobin concentrations. Because a CO-oximeter measures at more than two different wavelengths, it is able to correctly measure the oxygen saturation [1,4].

A chocolate brown discolouration of the blood, which can be noticed during blood collection, may be indicative of the presence of the dark pigment of methaemoglobin. Methaemoglobinemia is diagnosed by measuring an elevated concentration of methaemoglobin in the blood. It is important that the blood sample is analyzed quickly, as the methaemoglobin concentration in the sample will decrease in time due to natural defence mechanisms (Figure 1) [1].

The symptoms associated with methaemoglobinemia depend on its concentration (Table 1) [5]. Children, elderly patients and patients with known cardiopulmonary co-morbidities can experience symptoms at lower methaemoglobin concentrations (8-15%) [6]. Additionally, neonates and small children are at higher risk for developing methaemoglobinemia, because haemoglobin-F is more easily oxidized than haemoglobin -A in

Table 1: Symptoms in relation to the severity of methaemoglobinemia.

Percentage methaemoglobinemia	Symptoms
<3%	Physiological
3-15%	Asymptomatic, gray skin colour
15%	Cyanosis, chocolate coloured blood
30%	Headache, fatigue, dyspnoea, lethargy
60%	Respiratory depression, altered consciousness, shock, convulsions, death

adults and because there is a relative deficiency of endogenous reducing enzyme systems at young age [7,8].

In the first patient methaemoglobinemia was caused by ingestion of poppers, a nitrite-containing recreational drug. Methaemoglobinemia has also been described with the use of prescribed drugs, such as dapsone, sulphanomides, lidocaine/prilocaine (Eutectic mixture of local anesthetics (EMLA) ointment) [4]. For an overview of drugs that may cause methaemoglobinemia [1,9]

The second patient, who was later found to have a G6PD deficiency, was unable to produce sufficient amounts of NADPH (Figure 1). This causes an excess of peroxides, which can cause cell damage and haemolysis. Food, like broad beans, or drugs that cause oxidative stress, like rasburicase, can be a trigger [10].

As for every acute intoxication, initial stabilisation should be according to the ABCDE-system and symptomatic treatment should be started when necessary. The treatment of symptomatically acquired methaemoglobinemia consists of methylene blue (methylthionine chloride) 1%, dosed 1-2 mg/kg I.V. This shortens the half-life of methaemoglobin from 15-20 hours to 40-90 minutes. In case of insufficient effect after one hour, this gift can be repeated till a maximum dosage of 7 mg/kg [1,6,11].

Methylene blue is reduced to leuco-methylene blue, which spontaneously reacts with methaemoglobin and converts it back to haemoglobin. If the given concentrations of methylene blue are too high, ferro (Fe2+) is converted to ferri (Fe3+) and methaemoglobin is formed, inducing haemolytic anaemia. It is recommended to test the blood for haemolysis after administering methylene blue [1]. Methylene blue is contraindicated in patients with a G6PD deficiency due to a shortage of NADPH, as it may cause severe haemolytic reactions. In case of a (high suspicion of a) deficiency or in case methylene blue treatment is ineffective, exchange transfusions or red blood cell transfusions may be considered. Intravenous ascorbic acid (vitamin C) twice daily in a dose of 100-1000mg could be considered, but its effect on acquired methaemoglobin, in contrast to congenital methaemoglobinemia, is probably small [3,4].

Cyanosis itself is not an indication for (renewed) methylene blue administration; methylene blue itself can cause bluish discolouration of the skin, similar to cyanosis. As methylene blue causes a disruption of a regular pulse oximeter similar to methaemoglobin, the traditional pulse oximeter cannot be used for therapy evaluation [1].

CONCLUSION

Acquired methaemoglobinemia is a treatable cause of hypoxemia, but can be lethal without proper treatment. It is important that methaemoglobinemia is considered in case of a low SpO_2 that is unresponsive to oxygen administration. A blood gas should be done to confirm the diagnosis.

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