

# Methemoglobinemia - Two Uncommon Presentations

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## ABSTRACT

Two rather different cases of methemoglobinemia are presented. The first case is an infant who had a circumcision procedure with prilocaine. The second case involves a 14-year-old girl who attempted suicide with an overdose of metoclopramide and butamirate citrate. The attention is drawn to differences in hospital admission and management especially with respect to methemoglobin level and age. If methemoglobin levels reach  $\geq 10\%$ , cyanosis would appear first. Symptoms of hypoxemia and diminished oxygen transport do not develop until levels reach 30 to 40%. Not only early intervention is crucial but also patients should not be discharged from the hospital too soon. Doctors should be able to identify high risk patients, paying a special attention to infants younger than three months old who might be at an increased risk of methemoglobinemia which is a potentially lethal complication of prilocaine. As for our second case, methemoglobin level has not increased, despite an overdose of metoclopramide. This may be due to age or timely elimination of toxic agents by gastric lavage, catharsis and administration of procyclidine.

**Keywords:** Methemoglobinemia, metoclopramide, butamirate citrate, circumcision, prilocaine

## INTRODUCTION

Methemoglobin describes the oxidized form of the iron moiety ( $\text{Fe}^{3+}$ ) within the hemoglobin molecule. It is formed in the presence of an oxidizing substrate and is useless for oxygen carrying. In addition, methemoglobin shifts the oxygen-hemoglobin dissociation curve to the left and changes the sigmoid shape of the curve into a more hyperbolic one, thus hindering unloading of oxygen to tissues.<sup>1</sup> In healthy normal children, the ferric iron is reduced to ferrous state by the aid of cytochrome b5 oxidase (methemoglobin reductase) along with other systems such as NADH reductase, glutathione reductase and glucose-6-phosphate dehydrogenase (G-6-PD). Normal concentration of methemoglobin is maintained below 1% in healthy individuals by these enzyme systems.<sup>2</sup> Infants are particularly vulnerable to hemoglobin oxidation because their cytochrome

b5 reductase level is approximately 50% of the adult value.<sup>3</sup>

We report two methemoglobinemia cases where we would like to draw attention to differences in hospital admission and management.

**CASE 1:** A 74-day-old boy weighing 7500 gr, admitted to the paediatric intensive care unit with cyanosis.

On September 13, 2012, a previously healthy 74 day-old boy was admitted to the paediatric intensive care unit with cyanosis. On admission, no abnormality was detected other than central and peripheral cyanosis. His medical history was unremarkable and he was born full term with no perinatal problems. The history obtained from his parents revealed that he had undergone a circumcision procedure with prilocaine, and an hour later he had been discharged from the hospital. Three hours after the procedure parents realized cyanosis on the infant's fingers and toes at home while he was asleep. Parents brought him to the paediatrics emergency clinic of our university hospital within approximately an hour. When he was examined in the emergency clinic, there was a marked cyanosis and he was admitted into paediatric intensive care unit (PICU) within ten minutes where his treatment was started. His haemoglobin level was 11.3 g/dl with normal white cell and platelet count. Arterial blood gas was done while the patient was breathing from an oxygen mask. Values of  $\text{PaO}_2$ ,  $\text{PaCO}_2$  and pH were 118 mmHg, 41 mmHg and 7.38 mmHg, respectively. His oxygen saturation was 82% when measured with a pulse

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oximetry. MetHb was suspected on the basis of the fact that despite breathing through an oxygen mask no improvement was observed in cyanosis and circumcission with prilocaine supported by laboratory results where methemoglobin level was found to be as high as 26.5% (normal range: <1%). These findings prompted an immediate initiation of treatment with intravenous (IV) methylene blue. 1.0 mg/kg IV from 1% methylene blue solution was administered for 5 minutes. When there was no improvement in cyanosis; the dose was repeated for the second time an hour later. There was a marked clinical improvement within a few hours. Oxygen saturation increased to 98% and blood methemoglobin level decreased to 1.3% after 12 hours. The patient was discharged from the paediatric intensive care unit within 24 hours of admission.

**CASE 2:** 14 year-old girl brought into the paediatric intensive care with an attempted suicide.

On December 01, 2012, a previously healthy a 14-year-old girl attempted suicide with approximately 8 or 9 tablets of METPAMID® 10mg containing metoclopramide and butamirate citrate overdose. She was taken into another hospital where she had initial gut decontamination. She was transferred into our university hospital three hours later where she was admitted into the paediatric intensive care unit. Her medical history was unremarkable; she was born full term and had no known diseases as revealed from history obtained from her parents. When she was brought into the clinic, her oxygen saturation was 89% on room air, haemoglobin level was 12.4 g/dl and her white blood cell count was 10,400/mm<sup>3</sup>. Arterial blood gas done while the patient was breathing oxygen from an oxygen mask showed a PaO<sub>2</sub> as 124 mmHg, PaCO<sub>2</sub> as 35 mmHg, and pH as 7.42 mmHg. MetHb was suspected on the basis of the clinical signs and subsequently confirmed by laboratory results which reported methemoglobin levels of 2.2% (normal range: <1%).

Methylene blue was not given immediately and she was followed up by clinic and laboratory examinations for 24 hours. She was given oxygen and IV procyclidine which is a non-specific antidote of metoclopramide. Blood methemoglobin levels were tested at 2, 7, and 19 hrs after admission and decreased gradually to 1.7%, 1.2%, and 1%, respectively.

## DISCUSSION

The clinical presentation of acquired methemoglobinemia may be confusing, particularly without obvious history of exposure to oxidizing agents.<sup>4</sup> In many cases, there are no clinical features other than cyanosis, but when the concentration of methemoglobin reaches 30-45%, anoxic symptoms commonly develop. These include headache, dizziness, tachycardia, dyspnea on exertion, muscle cramps and weakness.<sup>5</sup>

Cyanosis is the first clinical sign when methemoglobin levels reach  $\geq 10\%$ , but symptoms of hypoxemia and diminished oxygen transport do not appear until levels increase to 30 to 40%. Usually when the methemoglobin levels reach more than 70%, death may ensue.<sup>3</sup> Life threatening symptoms such as seizures, cardiovascular collapse and coma are seen with higher methemoglobin fractions.<sup>3</sup> Methemoglobinemia should be considered in differential diagnosis of a child with cyanosis.<sup>3</sup>

Co-oximetry should be done, if available, since it measures methemoglobin accurately and is the key in diagnosing methemoglobinemia. Low oxygen saturation by pulse oximetry in patients with normal arterial blood gases can be an indication of methemoglobinemia. The presence of "saturation gap" can be a possible clue to the diagnosis when there is a difference between the oxygen saturation measured by pulse oximetry and the oxygen saturation calculated on the basis of ABG results. When methemoglobin levels reach 30-35%, the pulse oximeter reading becomes stable in the 82-86% range independent of actual methemoglobin levels. However, significant desaturation may not be solely attributed to the methemoglobinemia and may have been caused by reduced oxygenation during the period of unconsciousness.<sup>4,5</sup>

Local anaesthetic-related methemoglobinemia is not very rare in infants as in our first case. Guay<sup>1</sup> summarized all episodes of local anaesthetic related to methemoglobinemia found in the medical literature. He found 242 episodes (40.1% published in the year 2000 or after) concerning local anaesthetics and methemoglobinemia.<sup>3</sup> It is reported that plain prilocaine may induce clinically symptomatic methemoglobinemia in children older than 6 months at doses exceeding 2.5 mg/kg.<sup>1,3</sup> Prilocaine treatment at recommended dose might cause methemoglobinemia especially in children under the age of 6 months as shown in our first case.

Metoclopramide-induced MetHb is rare in routine clinical practice especially if given at treatment doses. Metoclopramide is known to cause methemoglobinemia in newborns and premature babies.<sup>6-8</sup> Merieau *et al.* (2005)<sup>9</sup> reported methemoglobinemia in a 5 day-old newborn who was agitated and restless from the first hours of life with difficulty of breast feeding. Treatment with metoclopramide (Primperan) and sodium alginate and bicarbonate (Gaviscon) for suspected gastroesophageal reflux was initiated. On the fifth day, there were ventilatory disorders with periods of agitated hyperventilation. It was associated with a generalized cyanosis and abdominal meteorism. A venous approach was taken and oral treatment was discontinued 24 hours before transfer. Transaminases and abdominal ultrasound were normal. ECBU and coproculture were sterile. The child was referred to the neonatal resuscitation

unit. Since cyanosis was not explained by cardiopathy, pulmonary pathology or polyglobulia, methemoglobinemia was suspected before the association of low SaO<sub>2</sub> and PaO<sub>2</sub>. This diagnosis was confirmed by the methemoglobin assay, which showed a high rate of 18.6%. Methylene blue was administered at a dose of 1mg/kg intravenously and subsequent assays of methemoglobin on the fifth day after injection of methylene blue were normal, less than 1%.

Kearns and Fiser (1988)<sup>10</sup> reported another case in a 3 week-old infant boy who has received iatrogenic overdose of metoclopramide (1.0 mg/kg every six hours) throughout a 36-hour period for treatment of suspected gastroesophageal reflux. He became cyanotic, lethargic, irritable, diarrhoea and respiratory distress. Newborns and premature babies are more susceptible to this condition because of their underdeveloped renal functions.<sup>11</sup>In our second case, methemoglobin level was not increased although an overdose of metoclopramide was taken. It might be due to adolescent age or timely elimination of toxic agents by gastric lavage and catharsis. Furthermore, our second case was an attempted suicide which was not reported in literature previously.

## CONCLUSION

Two cases with two different reasons are reported to discuss and to draw attention to methemoglobinemia which is a rare but potentially lethal, life-threatening complication usually as a result of the use of oxidizing agents like prilocaine especially in newborns and infants. Doctors should be able to identify high risk patients, paying a special attention to infants younger than three months old who might be at an increased risk. Taking a detailed history should also help as methemoglobinemia might also rarely be as a result of a genetic defect and environmental exposure to oxidizing agents. Doctors should follow up infants following local anaesthesia administration and should not discharge them from the hospital too quickly. On the other hand, whether an adolescent or infant admitted to hospital due to drug intoxication, one should be aware of methemoglobinemia and timely intervention is warranted in the emergency department or in an intensive care unit.

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