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CASE REPORT

Methemoglobinemia induced by intentional phenazopyridine intoxication in an adolescent: a case report

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Abstract

Methemoglobinemia is a rare and often neglected cause of cyanosis in pediatric population. It can result from either congenital conditions or acquired processes from exposure to sub-stances that oxidizes hemoglobin. Phenazopyridine, a pain reliever for urinary tract symptoms, widely used, is one of those substances. The methemoglobinemia diagnosis can be a clinical challenge, and this hypothesis must be considered in patients with central cyanosis and persis-tent low saturation despite oxygen administration. Severe cases should be treated with meth-ylene blue, removal of the causal factor and aggressive oxygen therapy. This present case re-ports the diagnosis of a pediatric patient with methemoglobinemia induced by intentional in-toxication with phenazopyridine, that received fast and appropriate treatment, with satisfacto-ry outcome.

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INTRODUCTION

Methemoglobinemia is an uncommon, potentially severe, and diagnostically challenging condition in the pediatric population.[1] It may occur due to a congenital defect or as an acquired disorder from exposure to substances that oxidize hemoglobin.[2] It causes functional anemia, impairs oxygen delivery to tissues, and manifests as cyanosis and hypoxia refractory to oxygen therapy.[1-4]

Phenazopyridine is an over-the-counter medication used to treat dysuria that can cause acquired methemoglobinemia. The epidemiology of this condition needs to be better understood, with few cases described in the literature.[3] A cascade of reducing enzymes converts methemoglobin back to hemoglobin in healthy individuals. It has been suggested that phenazopyridine toxicity results in the overproduction of oxidized hemoglobin or the disruption of the reducing cascade.[3,5]

Although potentially severe, methemoglobinemia can be reversed with early diagnosis and adequate management. This article describes the case of an adolescent with methemoglobinemia due to intentional exogenous phenazopyridine poisoning, in which appropriate and timely treatment contributed to a satisfactory outcome.

CASE REPORT

A 13-year-old female was admitted to the emergency department of a tertiary hospital in southern Brazil with cyanosis and desaturation. According to the mother's account, she woke up with cyanosis of the lips and extremities and had an episode of vertigo that lasted 10 minutes and resolved spontaneously. During the school year, cyanosis and desaturation measured with a pulse oximeter worsened, and the mother decided to seek medical care.

The patient was awake, conscious, oriented in time and space, dyspneic, and with central and extremity cyanosis upon admission. Her heart rate was 120 bpm, respiratory rate 36 bpm, blood pressure 140x100 mmHg, temperature 36.7ºC, capillary blood glucose 146 mg/dL, saturation 88% on room air and below 90% even with on a non-rebreather at 10 L/min. Segmental physical examination had no specific findings. Her forearms had abrasions in different stages of healing.

She denied having other symptoms and reported normal bowel and bladder habits. The patient had a history of grade V vesicoureteral reflux and had undergone left ureteral reimplantation when she was five. She did not develop complications and was regularly followed by a nephrologist. She did not report a family history relevant to the case.

At first, the patient denied taking any medications. However, after extensive conversation, she admitted to having intentionally taken 18 phenazopyridine hydrochloride tablets 200 mg (a total of 75 mg/kg) to kill herself.

The patient was monitored upon admission and kept on oxygen therapy, with saturation measured with a pulse oximeter (SpO2) not improving despite treatment and remaining at 88 to 90% even with a non-rebreather at 10 L/min. Laboratory tests were performed once exogenous intoxication was suspected. Very dark arterial blood was collected in various punctures (Table 1).

The patient worsened with dyspnea and tachycardia and reported palpitation and dizziness. An electrocardiogram showed sinus tachycardia (heart rate 136 bpm). Given the diagnostic hypothesis of methemoglobinemia secondary to phenazopyridine intake and the evident deterioration of her condition, we decided to perform a methylene blue test for its diagnostic and therapeutic. This decision was made due to the unavailability of test results within a short period. Serum methemoglobin levels were sent to a support laboratory outside the hospital and measured before she was medicated. Methylene blue was administered intravenously at 2 mg/kg, diluted in 100 ml of 5% glucose solution for five minutes. A significant and immediate improvement in cyanosis and SpO2 was observed, confirming the hypothesis of methemoglobinemia. The patient was referred to the Intensive Care Unit for observation for 24 hours. She did not need additional methylene blue infusions.

The patient was discharged from the Intensive Care Unit and continued to be monitored by the social services, psychology, and psychiatry teams in the ward. SpO2 changed to 98% on room air, symptoms vanished, and her other vital signs were typical. After four days in the hospital, she was eventually discharged and started an outpatient follow-up program with the psychology and psychiatry teams. The serum methemoglobin levels measured on a UV/VIS spectrophotometer came in the day after she was discharged from the outpatient clinic, and the result was 0.68% (reference value lower than 1.5%). Despite the negative result, possibly affected by the time and distance until the test was processed, a diagnosis of methemoglobinemia was confirmed. The need for adequate protection against light and the inability to check whether proper measures were taken while transporting the blood samples complicated the test. The positive therapeutic test with methylene blue confirmed the diagnosis, resulting in immediate clinical improvement.

DISCUSSION

Methemoglobinemia is a rare, often neglected, potentially fatal disorder, potentially reversible when promptly diagnosed. It is characterized by an alteration in the state of hemoglobin that makes it dysfunctional.[4-6] In normal hemoglobin, iron is ferrous ($Fe^{2}+$), allowing oxygen to bind in the lungs and be released into the tissues.[4,6] Methemoglobin occurs when the iron atom loses an electron to an oxidant, with Fe2+ then converted to the ferric state (Fe3+).[1] Fe3+ cannot bind to oxygen and causes an allosteric change in the heme portion of partially oxidized hemoglobin, shifting the oxygen dissociation curve to the left. This process results in functional anemia, hypoxia, and impaired tissue oxygen supply.[1,4]

Table 1. Arterial blood gas analysis results and other laboratory tests on admission.

Test	Result	Reference value
Ph	7,40	7,34 a 7,45
pCO_2 (mmHg)	33	32 a 48
pO_2 (mmHg)	192	83 a 108
HCO_3 (mmol/L)	20,4	21 a 28
Base excess (mmol/L)	-3,5	-3 a +3
O_2 saturation (%)	100	95 a 99
Lactate (mmol/L)	1,4	0,6 a 2,2
Creatinine (mg/dL)	0,7	0,4 a 1,0
Urea (mg/dL)	24	7,8 a 21,6
Hemoglobin (g/dL)	12,2	11,5 a 15,5
Hematocrit (%)	38	33 a 46
C-reactive protein (mg/L)	6	<10
GOT (U/L)	31	23 a 41
GPT (U/L)	16	20 a 38

Under normal physiological conditions, hemoglobin undergoes oxidation to methemoglobin. However, natural reducing systems maintain methemoglobin levels below 2%.[4,6] Methemoglobinemia can occur due to a congenital defect in the methemoglobin reduction pathways or an acquired disorder resulting from exposure to substances that oxidize hemoglobin.[2] Exact prevalence rates are unavailable, but acquired cases appear to be more frequent than congenital ones.[4,5]

In acquired cases, exposure to exogenous oxidizing drugs and their metabolites can accelerate the rate of methemoglobin formation by up to 1,000 times. This overwhelms protective enzyme systems and acutely increases methemoglobin levels.[7] Few cases and no series have been published about pediatric phenazopyridine-induced methemoglobinemia since the first publication by Crawford et al. in 1951.[8]

Phenazopyridine has an analgesic effect on the urinary tract and is commonly prescribed to alleviate urgency and discomfort symptoms associated with lower urinary tract infections.[9] Its side effects include methemoglobinemia in <1% of the cases, with risk increasing proportionately to dosage and duration of treatment.[9] The literature indicates that methemoglobinemia results from the overproduction of oxidized hemoglobin or disruption of the reducing cascade induced by phenazopyridine toxicity.[10]

The signs and symptoms of methemoglobinemia are a direct consequence of inadequate oxygen transport. The range of symptoms depends on relative methemoglobin levels, normal hemoglobin levels, and associated comorbid conditions, including cardiovascular or pulmonary disease.[2,6,7] Healthy patients without anemia usually have few symptoms with methemoglobin levels below 15%. Levels from 20% to 30% may cause mental status alteration, headache, fatigue, exercise intolerance, and syncope. Levels above 50% can result in arrhythmia, seizure, and coma, and levels above 70% are usually fatal.[4,7]

Diagnostic signs include central cyanosis and low pulse oximetry saturation (SpO2) refractory to oxygen therapy.[4] Chocolate-colored arterial blood is often a sign of the condition. Test results reveal a discrepancy between SpO2 and the calculated arterial oxygen saturation (SaO2). This difference may be an early indicator of methemoglobinemia.[6] In blood gas analysis, hemoglobin saturation is not measured but estimated based on PaO2, pH, and the standardized oxygen-hemoglobin dissociation curve. Therefore, SaO2 results are imprecise and grossly erroneous in patients with methemoglobinemia. The most effective method of detecting methemoglobin is CO-oximetry, in which the concentrations of different types of hemoglobin in blood are measured using different wavelengths.[2,4,6] However, treatment decisions must be guided primarily by the severity of signs and symptoms, with blood methemoglobin levels having secondary importance in defining the approach.[4]

In mild cases, treatment generally consists of removing the inducing agent. It also includes administering high-flow oxygen, observing signs and symptoms, and analyzing CO-oximetry changes.[4] In situations with significant symptoms such as dizziness, headache, anxiety, dyspnea, low cardiac output, drowsiness, and seizures, in addition to the measures mentioned above, methylene blue administration is recommended.[4] This medication acts as a cofactor for NADPH methemoglobin reductase, accelerating its activity and increasing the conversion rate of methemoglobin to hemoglobin.[7] The usual initial dose is 1 to 2 mg/kg, infused intravenously over three to five minutes. The infusion may be

repeated at 1 mg/kg if methemoglobin levels fail to decrease significantly within 30 to 60 minutes.[5]

Other treatments include ascorbic acid, exchange transfusion, and hyperbaric oxygen therapy. However, the use of ascorbic acid in acquired cases has reportedly produced poor outcomes since the ability of ascorbic acid to reduce methemoglobin is much lower than that of endogenous enzyme systems.[1,4]

Our patient's signs and symptoms, the suspicion of methemoglobinemia, and the relatively low risk of empirical treatment with methylene blue guided the choice of treatment. The result of the serum methemoglobin test carried out after the onset of acute symptoms may have been affected by inadequate sampling, storage, and transportation conditions. Methemoglobinemia is a challenging condition. Timely diagnosis and treatment based on clinical signs and symptoms are paramount, given the condition's potential severity.

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