Original Research Paper

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General Medicine

METHEMOGLOBINEMIA

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ABSTRACT Methemoglobinemia is a life-threatening disease that must be treated promptly and efficiently. It is diagnosed by performing different diagnostic tests. Methylene blue is being used as a vital treatment for methemoglobinemia, but does not have proven efficacy in patient with G6PD deficiency. Here in the case study, we have reported the case of a 19-year-old male patient with an alleged history of industrial exposure to nitrobenzene (aniline dye exposure in textile factories), who developed methemoglobinemia, for which he was treated with methylene blue. However, there was no improvement in his symptoms. On the other hand, there was a drop in his hemoglobin level with worsening of kidney function due to hemolysis of red blood cells. On further examination, the patient was found to be G6PD deficient. The patient was provided with the only available method of treatment consisting of repeated blood transfusions and ascorbic acid with dialysis to which the patient responded, started recovering and after 26 days of intensive treatment, he was discharged from the hospital.

KEYWORDS : Methemoglobinemia, Nitrobenzene, G6pd, G6pd Deficiency, Hemolytic Anemia, Anemia, Aniline Dye

INTRODUCTION

Methemoglobinemia is a disease in which the level of methemoglobin (MetHb) is higher than the normal level in the blood. Methemoglobin is a type of hemoglobin in which heme iron is in the oxidized ferric state (Fe3+) rather than ferrous state (Fe2+). Ferric state does not combine with oxygen. MetHb shifts the oxygen dissociation curve to the left. This combination of decreased oxygen carrying capacity and diminished oxygen unloading predispose the system to profound tissue hypoxia despite normal partial pressure of oxygen in blood. Methemoglobinemia causes headaches, dizziness, shortness of breath, nausea, vomiting, fast heartbeat, convulsion, headache and blue-colored skin as the main symptoms. Acquired methemoglobinemia results when there is exposure to certain oxidizing agents, drugs and food. Hereditary methemoglobinemia are rare disorders caused by either a deficiency of NADH cytochrome b5 reductase or presence of abnormal hemoglobin variants (HbM).

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked genetic disorder characterised by low levels of the G6PD enzyme. G6PD deficiency is a risk factor for development of methemoglobinemia. It is estimated that G6PD deficiency affects about 5% of the global population. The enzyme G6PD is involved in the pentose phosphate pathway which is essential for red blood cell metabolism. It leads to formation of NADPH (reduced form of nicotinamide adenine dinucleotide phosphate) which keeps the hemoglobin heme iron in ferrous state. Affected individuals show premature breakdown of RBC (hemolysis) when triggered by infections, antibiotics, antimalarial and other drugs.

Diagnosis of methemoglobinemia is confirmed by a multiple wavelength co-oximeter. On blood gas, normal PaO2 concentrations are found. Clinical cyanosis in presence of normal arterial oxygen tension is highly suggestive of methemoglobinemia. Pulse oximetry is inaccurate and unreliable in this condition. Infusion of the drug methylene blue is the first treatment for MetHb. It accelerates the enzymatic reduction of methemoglobin by NADPH-methemoglobin reductase and it also reduces to leucomethylene blue that in turn reduces methemoglobin. Hyperbaric O2 and exchange transfusion are also useful in treatment of methemoglobinemia.

Here we present a case of serious nitrobenzene toxicity where treatment with intravenous (IV) methylene blue resulted in hemolytic anemia and acute kidney injury. The patient was deficient in glucose-6-phosphate dehydrogenase (G6PD) enzyme and hence unable to produce sufficient amounts of NADPH, which is required for methylene blue dependent reduction of MetHb. There occurs precipitation of hemolysis due to exposure of methylene blue in such patients, which is managed by repeated blood transfusion and hemodialysis.

CASE STUDY

A 19-year-old male patient with a weight of 47 kg was brought to the emergency department of a private hospital with a history of accidental fume exposure (20% nitrobenzene) for almost 24 hours in a fabric factory, with symptoms of sudden onset breathlessness and bluish discoloration of lips. The patient also showed discoloration of his palms and soles since the last two months suggestive of chronic dye exposure (Figure 1). Patient had been working in this dye factory since last three months, his colleagues also had this type of discoloration of their palms and soles, due to chronic occupational exposure of this aniline dye. He was treated with high flow oxygen, IV fluid, and IV methylene blue 50 mg. On the day of admission of the patient, his diagnostic tests for kidney and liver functions were normal with high enzyme level of serum cholinesterase 10,778 U/L. Patient did not show any deterioration of his symptoms for first 24 hours with the above treatment.

After 24 hours of admission, the patient experienced shortness of breath, yellowish discoloration of sclera and a drop in urine output to around 100 ml during the preceding 6 hours. For further treatment, the patient was referred to Civil Hospital, Ahmedabad. During his examination, he was pale, nauseous, tachypneic and his breath had a bitter almond-like pungent scent. The patient's pulse rate was 120/min, SpO2 86% by pulse oximeter, respiratory rate of 28/min, and blood pressure was 100/70 mmHg. Samples of arterial blood gas in the blood were dark-brown indicating respiratory alkalosis showing Ph 7.44, PaO2 108 mm hg, PaCo2 28mm hg, bicarbonate 16, Sao2 99.7%. In view of high Pao2 and low SpO2, where Saturation Gap (difference between SaO2 and SpO2) is more than 5%, so methemoglobinemia was suspected.

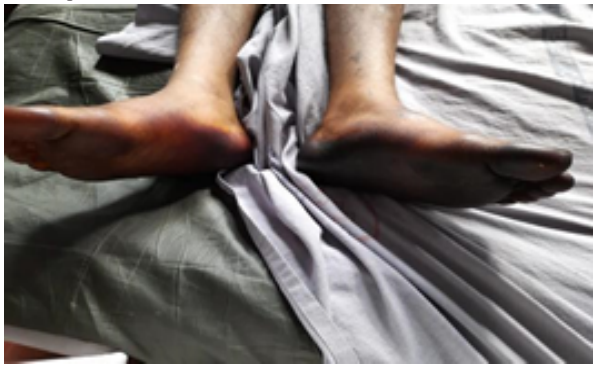


Figure 1. Discoloration of patient's feet

Electrocardiography indicated sinus tachycardia. The chest x-ray was under normal parameters. The blood withdrawn for investigations was dark brown, showing serum values as follows: total bilirubin was 2.8 mg/dl (direct 1.0 mg/dl and indirect 1.8mg/dl), with creatinine of 12.54 mg/dl and urea 349, decrease in hemoglobin level to 6.2 g/dl with high

LDH level 780 U/L suggestive of severe hemolytic anemia with acute kidney injury. It was decided to start urgent hemodialysis by double-lumen internal jugular blood transfusion catheter and the patient was referred to the Nephrology department for this purpose. Peripheral blood test reported normocytic, normochromic red blood cells that indicated hemolysis-compliant anisocytosis and teardrop cells. The Coombs test, both direct and indirect was negative. The urine was deep blue in color and 200 ml in the last 24 hours as shown in figure no.2.

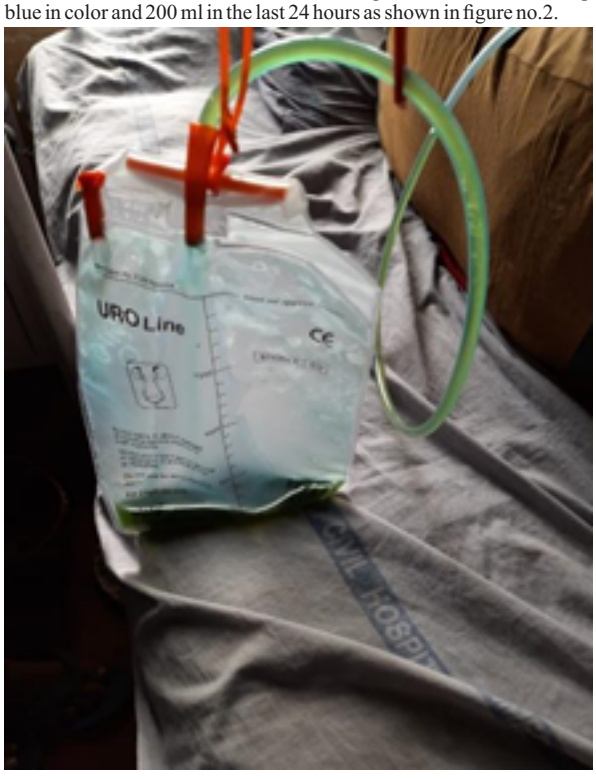


Figure 2. Urine collected from the patient

Arterial blood gas analysis with co-oximetry showed high levels of Methemoglobin (16.8%). MetHb was detected by spectrophotometry after addition of sodium cyanide, performed in a clinical biochemistry laboratory. This confirmed methemoglobinemia. Also, his G6PD enzyme level was found to be inadequate afterwards. The serum lactate dehydrogenase level was 186 U/L (decreased from 780 to 187 U/L). He was administered 500 mg of ascorbic acid three times a day along with supportive treatment of repeated blood transfusions (total 5 packed cell bag of volume 150 ml of each) on alternate days for the last 18 days. His urine output was steadily increased to 1000 ml on the 11th day after 4 cycles of hemodialysis on alternate day and his kidney functions began to recover. After 26 days of treatment, he was discharged from the hospital having normal lab report parameters and its comparison with previous reports is document below: – (as shown in table no 1).

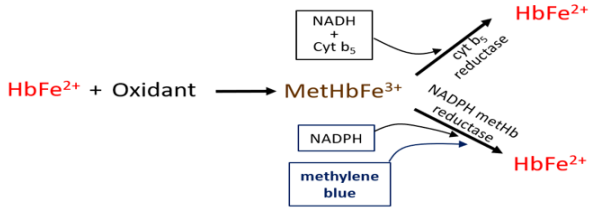
Table –1 Difference In Lab Reports Before And After Treatment

Tests	Before Treatment Values	At the time of discharge Values
Hemoglobin	6.2 g/dl	10.6 g/dl
platelet count	1.84 lakh/mm3	2.3 lakh/mm3
Total leukocytes count	12,100/mm3	6600/mm3
Serum creatinine	12.54 mg/dl	1.1 mg/dl
Blood Urea	349 mg/dl	40 mg/dl
Total Bilirubin	2.8 mg/dl	1.2 mg/dl
Direct Bilirubin	1.0 mg/dl	0.8 mg/dl
Indirect bilirubin	1.8 mg/dl	0.4 mg/dl
SGPT	89 U/L	40 U/L
SGOT	121 U/L	30 U/L
Serum lactic dehydrogenase	780 U/L	186 U/L

DISCUSSION

Nitrobenzene, a pale yellow oily liquid, with an odour of bitter almonds is used as an intermediate in the synthesis of solvents like paint, dyes, drugs, explosives, plastics, photographic and rubber chemicals. Nitrobenzene is quickly absorbed after dermal contact, inhalation and absorption. The toxic effects after inhalation are due to the rapid development of methemoglobinemia, a condition in which the iron within the haemoglobin is oxidized from the ferrous (Fe^{2+}) state to the ferric (Fe^{3+}) state, resulting in the inability to transport oxygen and causes a brownish discolouration of the blood.

When the MetHb level climbs above 10%, the first symptom to appear is cyanosis unresponsive to oxygen. Other clinical effects are consistent with hypoxia and include anxiety, lightheadedness, headache and tachycardia at MetHb levels of 20-30%; fatigue, confusion, dizziness and tachypnea at 30-50% and coma, seizures, dysrhythmias and acidosis at levels of 50-70%.The chocolate-brown blood is characteristic of methemoglobinemia at the bedside. Pulse-oximeter is unreliable in methemoglobinemia, as it will typically show saturation around 85%. This is because MetHb is detected by both oxyhemoglobin (940 nm) and deoxyhemoglobin (660 nm) sensors of the oximeters. SaO2 (Oxyhemoglobin saturation of arterial blood) given by ABG analyzers is derived from the PaO2 and will be near 100% if PaO2 is more than 100 (as per the oxygen dissociation curve). This oxygen "saturation gap" between the SaO2 and SpO2 greater than 5%, is a diagnostic clue to the presence of MetHb. To confirm methemoglobinemia, co-oximetry is required. Co-oximeters use multiple wavelengths to determine individual concentrations of oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin and MetHb by spectrophotometric technique. For symptomatic methemoglobinemia caused by drug or toxin exposure, Methylene blue is used as emergency choice of treatment. Its action depends on the availability of reduced nicotinamide adenine dinucleotide phosphate (NADPH) within the red blood cells, generated by G6PD. Methylene blue is an oxidant; its metabolic product leucomethylene blue is a reducing agent.



In patients with G6PD deficiency, methylene blue may not only be ineffective but also potentially dangerous, since it can lead to hemolysis and paradoxical methemoglobinemia. That is the reason why methylene blue is contraindicated in patients with G6PD deficiency. In this case, decreased urine output, jaundice, worsening of breathlessness and anemia occurred due to severe hemolysis induced by administering methylene blue to the patient with previously undiagnosed G6PD deficiency. Patient was then treated with ascorbic acid (vit-c), repeated blood transfusion and hemodialysis.

CONCLUSIONS

"BLUE CURES BLUE BUT BE CAUTIOUS."

Methylene blue is used for emergency life saving treatment of acquired symptomatic methemoglobinemia but while using it we should be careful about the possibility of associated G6PD deficiency, as in our case, which can worsen the clinical situation and lead to serious complications such as hemolysis with acute kidney injury. Methylene blue is contraindicated in patients with G6PD deficiency.

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