Case Report

Methylene Blue Induced Methemoglobinemia with Acute Kidney Injury in a Glucose-6-Phosphate Dehydrogenase-deficient Patient

Abstract

Our case was treated with methylene blue for symptomatic nitrobenzene poisoning. After which he developed methemoglobinemia with acute kidney injury due to hemolysis and on further testing, he was found to be glucose-6-phosphate dehydrogenase (G6PD) enzyme deficient. Thus, afterward, the patient was treated with only available mode of treatment as repeated blood transfusions and ascorbic acid with dialysis support to which the patient responded. Thus, it is important to evaluate for the G6PD deficiency where methylene blue treatment is planned as an antidote to nitrobenzene compounds poisoning.

Keywords: *Acute kidney injury, glucose-6-phosphate dehydrogenase deficiency, methemoglobinemia, methylene blue, nitrobenzene poisoning*

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Introduction

A case of acute poisoning with nitrobenzene is presented where clinical evaluation and management, with antidote intravenous (IV) methylene blue, resulted in hemolytic anemia and methemoglobinemia with acute kidney injury as the patient was glucose-6-phosphate dehydrogenase (G6PD) enzyme deficient. It is important to prior evaluate the G6PD deficiency where methylene blue treatment is planned as an antidote to nitrobenzene compounds poisoning.

Case Report

A 34-year-old, 47 kg male farmer presented to the emergency department with a history of consumption of around 150 ml of plant growth stimulant (nitrobenzene 20%) about 8 h before admission with suicidal intention. On examination, he was pale, irritable, tachypneic, and there was bitter almond-like pungent smell from patient's mouth. Blood pressure was 100/70 mmHg with pulse rate of 128/min and respiratory rate of 28/min. Arterial blood gas blood samples were dark-brown, which was suggestive of respiratory alkalosis. Electrocardiogram showed sinus tachycardia. X-ray chest was within normal limits. He was treated with gastric lavage (with normal saline), IV fluids, and IV methylene blue 50 mg. His kidney and liver function tests were normal on the day of admission. His serum cholinesterase enzyme level was 10,778 U/L. After 24 h of admission, the patient developed hypoxia (O_2 saturation 86%), icterus, and decrease in urine output of about 100 ml in the last 6 h. Withdrawn blood for investigation was dark brown, which showed following serum values: total bilirubin 2.8 mg/dl (direct 1.0 mg/dl and indirect 1.8 mg/dl), serum glutamic oxaloacetic transaminase 121 U/L, serum glutamic pyruvic transaminase 45 U/L, alkaline phosphatase 45 U/L, creatinine 11.1 mg/dl, sodium 150 mEq/L, potassium 3.5 mEq/L, lactate dehydrogenase 780 U/L, and reticulocyte count of 4.0%; blood urea 279 mg/dl, hemoglobin 5.8 g/dl, total leukocyte count 11,800/mm^3, and platelet count 7.54 lakh/mm^3. Hemodialysis was initiated on an urgent basis through double-lumen internal jugular vein catheter with blood transfusions and was transferred to nephrology ward for the same. Peripheral blood smear showed normocytic, normochromic red blood cells that demonstrated anisocytosis and teardrop cells consistent with hemolysis. Coombs tests, both direct and indirect were negative. Urine was deep brown colored, and dipstick test was positive for hemeprotein. His methemoglobin level was

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sent and was found high (16.8%). Moreover, afterward, his G6PD enzyme level was found deficient. Hence, a diagnosis of methemoglobinemia in a G6PD-deficient patient due to compounds methylene blue and nitrobenzene with acute kidney injury was made. He was treated with ascorbic acid 500 mg three times a day along with supportive treatment. He was dialyzed on alternate days for the next 10 days with repeated blood transfusions. On the 11th day, his urine output gradually improved to 1000 ml and kidney functions started recovering. He was discharged after 20 days with following parameters: hemoglobin: 10.6 g/dl, total leukocyte count: 6600/mm^3, and platelet count: 1.7 lakh/mm^3. Serum creatinine was 1.1 mg/dl with normal serum electrolytes. Serum lactic dehydrogenase level was 186 U/L with normal liver function test.

Discussion

Nitrobenzene, a pale yellow oily liquid, with an odor of bitter almonds, is used as an intermediate in the synthesis of solvents, such as paint remover and flowering agent. The toxic effects after ingestion are due to the development of methemoglobinemia,[1] a condition in which iron within the hemoglobin is oxidized from ferrous (Fe^{2+}) state to ferric (Fe^{3+}) state, resulting in the inability to transport oxygen, and it leads to brownish discoloration of the blood.[2] Spontaneous formation of methemoglobin is normally counteracted by protective enzyme systems, for example, nicotinamide adenine dinucleotide methemoglobin reductase (cytochrome b5 reductase - major pathway), nicotinamide adenine dinucleotide phosphate (NADPH), and methemoglobin reductase (minor pathway),[3] and to a lesser extent by the ascorbic acid and glutathione enzyme systems. At methemoglobin levels of around 20%, cyanosis, headache, dyspnea, chest pain, tachypnea, and tachycardia develop. At 40%–50% levels, confusion, lethargy, and metabolic acidosis occur leading to coma, seizures, bradycardia, ventricular dysrhythmia, and hypertension. Levels around 70% are fatal. Anemic or G6PD-deficient patients suffer more severe symptoms.[1,4] G6PD is a metabolic enzyme involved in the pentose phosphate pathway, especially important in red blood cell metabolism. G6PD deficiency, an X-linked recessive hereditary disorder, is the most common human enzyme defect.[5] Individuals with G6PD deficiency exhibit nonimmune hemolytic anemia in response to a number of oxidative stresses. Methemoglobinemia is treated with methylene blue, but G6PD deficiency is a relative contraindication to the use of methylene blue.[6] G6PD-deficient individuals do not generate enough NADPH to efficiently reduce methylene blue to leucomethylene blue, which is needed for activation of the NADPH-dependent methemoglobin reductase system. G6PD-deficient individuals are prone to methylene blue-induced hemolysis as it may add to oxidative hemolysis. Moreover, in the presence of hemolysis, high-dose methylene blue can itself initiate methemoglobin formation.[7,8] Therefore, methylene blue is not the ideal mode of treatment for methemoglobinemia in G6PD-deficient patients since it can worsen the condition of the patient by increasing hemolysis. Thus, it is necessary to assess any G6PD deficiency before methylene blue administration. In this case, due to lack of facility for emergent enzyme G6PD testing, the patient was treated with antidote methylene blue for symptomatic nitrobenzene poisoning. Afterward, he developed methemoglobinemia with acute kidney injury due to hemolysis, and on further testing, he was found to be G6PD enzyme deficient. The only mode of treatment left now was either blood transfusion or exchange transfusion.[9] Finally, repeated blood transfusions (total of 7 units) were given during hemodialysis sessions and the patient responded. Fresh blood transfusion improved the oxygen carrying capacity and hemoglobin content, improving the patient symptomatically. The patient was treated with ascorbic acid 500 mg thrice a day afterward. Ascorbic acid is an antioxidant that may also be administered in patients with methemoglobinemia. N-acetylcysteine has been shown to reduce methemoglobin, but it is not yet an approved treatment for methemoglobinemia.[10]

Conclusion

Methylene blue cures methemoglobinemia, but we should be cautious about the presence of accompanying G6PD deficiency or else, as in our case, it can worsen the clinical scenario and lead to dangerous complications such as hemolysis with acute kidney injury.

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Conflicts of interest

There are no conflicts of interest

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