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Iatrogenic Anemia (Hemolysis) Following the Use of Methylene Blue Powder in Newborn: A Case Report

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Abstract

Introduction: Methylene blue was first described for the treatment of methemoglobinemia but practical usage of the compound for surgical purpose is common. The aim of this report is to describe a case of hemolysis in neonatal period as a potential hazard of methylene blue toxicity without presence of G6PD deficiency.

Case Presentation: In October 2015, a 36-week GA female infant with 2.05 kg weight was delivered by cesarean section with APGAR score of 9/9 from a healthy mother, with common type esophageal atresia. She underwent surgical repair with drainage tube placement on second day of life in our subspecialty referral center, Tehran, Iran. Her blood group type was A+ and her mother was AB+ with no family history of hematologic disease. On fifth day postoperative, 2 mL of methylene blue solution that was prepared by dissolving its powder in the hospital laboratory were fed per oral for confirmation of the integrity of esophagus after repair. 8 days after methylene blue ingestion, we met suddenly the occurrence of severe anemia and hyperbilirubinemia with Hb: 6 gr/dL (postoperative Hb: 15 gr/dL) , retic count: 4.8%, total bill/direct: 20/ 0.3, indirect coombs negative ,G6PD: sufficient, ALT: 30 U/L, and AST: 66U/L. At follow-up 2 months after the initial operation, barium meal showed moderate stricture at the site of anastomosis.

Conclusions: We considered two main reasons for hemolysis in our patient. The first explanation is that our patient received 20 mg/kg MB as solution which was nearly 5 - 10 times more concentrated than the recommended dose. The second is that the absorption of MB from mediastinal/plural space could be more than expected. Our justification for this event is the anastomosis site stricture at follow-up that was suggestive of Methylene blue leak to mediastinal/plural space on first day after repair. Therefore, paying attention to the preparation of methylene blue solution from its powder is essential. Determination of G6PD status as a risk factor for development of methylene blue toxicity is recommended. However, G6PD with two rechecks was sufficient for our patient.

Keywords: Anemia, Hemolytic, Hyperbilirubinemia, Methylene Blue

1. Introduction

Methylene blue (MB) is one of the most practical substances in medicine. Some medical applications of MB include diagnosis of recurrent aspiration, determination of endotracheal tube or jejunal feeding tube placement, detection of amniotic fluid prepartum leakage, treatment of methemoglobinemia, and detection of the fistulas leakage (1-4).

Glucose-6-phosphate dehydrogenase (G6PD) converts MB to leucomethylene blue (LMB) and can act as activator of reductase enzymes (5). Although MB is an effective antidote to methemoglobinemia due to its reductase activity, it can be an oxidative agent in high doses by producing hydrogen peroxide and also can induce methemoglobinemia and red blood cell hemolysis (4, 6, 7). Early in-vitro studies demonstrated that oxidative function can be increased in G6PD-deficient RBCs incubated with methylene blue (8). On the other hand, other studies failed to show any association between methylene blue-induced hemolysis and G6PD deficiency (8, 9). The purpose of this report is to describe a case of iatrogenic hemolysis in neonatal period in absence of G6PD deficiency after MB ingestion and mediastinal/plural absorption. This presentation has not been reported in literature.

2. Case Presentation

A female infant was delivered by cesarean section in our hospital (subspecialty referral center affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran) with 2.05-kg birth weight, 36 -week gestational age, and APGAR scores of 9/9 from a healthy mother with common type esophageal atresia. She was admitted to NICU ward in October 2015. The infant underwent esophagoplasty by drainage tube placement in extra pleural space on second day of life. The Blood group type of patient and her mother was A+ and AB+, respectively.

She had no family history of hematologic disease and

other significant medical history. Also, she did not have any transfusion before or after surgery.

On fifth day postoperative, 2 mL of MB solution were fed to the infant per oral for endorsement of integrity of esophagus after repair. We decided to prepare MB solution by dissolving its powder in hospital laboratory. We did not recognize clear leakage of MB through the chest drain, so oral feeding began and the drainage tube was removed after one day. On 8th day postoperative (3 days after MB ingestion), green color icteric appearance without rising in conjugated bilirubin (total bill/direct: 24/ 0.9) was prominent in our patient. The response to phototherapy was not favorable and our hospital laboratory on 15th day after birth (8 days after methylene blue ingestion) reported severe anemia and hyperbilirubinemia with Hb: 6 gr/dL (post-operative Hb: 15 gr/dL) , retic count: 4.8%, total bill/direct: 20/ 0.3, direct and indirect coombs: negative, G6PD : sufficient, ALT: 30 U/L, AST: 66U/L, antibody screening test: negative, anisocytosis and helmet cell on PBS(peripheral blood smear): moderate, and urinalysis: normal.

We considered exchange transfusion (ET) for correcting the anemia and hyperbilirubinemia. The bilirubin and hemoglobin level did not rise after one time ET. Ultimately, she recovered and discharged at 18 days with good condition. At follow-up tests, carried out 2 months after the initial operation, barium meal showed moderate stricture at the site of anastomosis.

3. Discussion

Methylene blue (international nonproprietary name (INN): methylthioninium chloride blue) was first synthesized in 1876 by German chemist Heinrich Caro (1834 -1910). It is a dark green powder and odorless substance at room temperature. The blue solution after dissolving its powder in water is the end-use product in practice. MB, according to World Health Organization report, is an important medication in the basic health system. It is a part of hyoscyamine sulfate, urinary analgesic/anti-infective/antispasmodic known as “Prosed” that is prescribed for child and adult patients (10).

The other usage of Methylene blue is to treat methemoglobinemia, heal resistant psoriatic plaque, treat Kaposi’s sarcoma (AIDS), and inactivate staphylococcus aurous, HIV-1, adenovirus vectors, hepatitis C, and hepatitis B. Currently, MB as a diagnostic modalities is widely used in applications such as confirmation of the integrity of esophagus after esophageal atresia repair (1).

Drug-induced hemolytic anemia is rare in children. This type of hemolytic anemia can be related to immune system and occurs when a medicine triggers the body’s defense system to break down RBC earlier than normal.

Cephalosporins, Dapsone, Levodopa, Levofloxacin, Methyldopa, Nitrofurantoin, Nonsteroidal

anti-inflammatory drugs (NSAIDs, Phenazopyridine (pyridium), Quinidine), and Penicillin can stimulate human immune system. Another rare form of hemolytic anemia is associated with the breakdown of red blood cells due to a certain type of stress in the cell with lack of glucose-6 phosphate dehydrogenase (G6PD) (4).

Methylene blue has contradictory effects at high and low doses. At high doses, MB is oxidative and can induce methemoglobinemia; it is also used as a therapy for methemoglobinemia by shortening the half-life of methemoglobin from hours to minutes (3, 4).

Leucomethylene blue, which is the product of Methylene blue metabolism in red blood cells, can produce hydrogen peroxide as an oxidative product. Hexose monophosphate shunt that initially detoxifies leucomethylene blue will overcome if reduced glutathione is depressed; so oxidation of lipid components and hemoglobin in RBC cannot be prevented. However, adult can tolerate higher doses of Methylene blue without toxicity presentation. but its toxicity on neonates and the appearance of Heinz body hemolytic anemia and hyperbilirubinemia has been well described. Although we exactly do not know the cause of neonatal high sensitivity to this dye, this response must be considered when this agent is administered for diagnostic or therapeutic reasons.

One of the precautions of MB administration is when it is going to be used for its visibility in diagnostic procedures. Although the MB toxicity mostly appears with excessive doses, even a lower dose (2 to 4 mg/kg) can cause hemolytic anemia. The recommended dose of MB in newborn is 2 mg/kg. The time of anemia and hyperbilirubinemia occurrence after MB administration in literature is within 24 hours of injection up to 12 days (with an approximate peak of 5 days). Most commonly described hemolysis and hyperbilirubinemia is after MB administration as intra- amniotic or intravenous injections. Thus, the interesting point of our case is the appearance of hemolysis at 8 days after oral MB administration (6, 7).

We considered two main reasons for hemolysis in our patient. The first explanation is that our patient received 20 mg/kg MB as solution which was nearly 5 -10 times more concentrated than the recommended dose.

The second is that the absorption of MB from mediastinal/plural space could be more than expected. Our justification for this event is the occurrence of anastomosis site stricture at follow-up that is suggestive of Methylene blue leak to mediastinal/plural space at first day after repair.

Another considerable point in our patient was changing the skin color to dark yellow green (like bronze baby syndrome) after phototherapy followed by MB ingestion as a precursor of hemolysis detection.

This presentation after MB ingestion has not been reported in literature although varying degrees of skin staining related to prenatal exposure to MB have been reported. The described effect of MB on skin as a known photo sensitizer is redness within hours after exposure to phototherapy on all exposed areas of the patient's skin, followed by bulla and epithelial desquamation due to breakdown of lysosomal membranes after interacting with light.

We probably introduce the first case of mediastinal/plural MB absorption after a diagnostic procedure for confirmation of esophageal anastomosis repair. At present, some medical centers consider MB instead of barium meal for assessment of esophageal repair due to inexistence of this modality or patient transfer impossibility.

Our goal is drawing physicians and practitioners' attention to prepare the recommended dose of MB solution (2 to 4 mg/kg) for infants. If possible, it is safer to use methylene blue vials instead of powder.

Also, we recommend G6PD status determination as the most common enzymopathy with the development of MB toxicity (3).

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