

Methylene blue unresponsive methemoglobinemia

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Abstract

Acquired methemoglobinemia is an uncommon blood disorder induced by exposure to certain oxidizing agents and drugs. Although parents may not give any history of toxin ingestion; with the aid of pulse-oximetry and blood gas analysis, we can diagnose methemoglobinemia. Prompt recognition of this condition is required in emergency situations to institute early methylene blue therapy. We report an unusual case of severe toxic methemoglobinemia, which did not respond to methylene blue, but was successfully managed with exchange transfusion.

Keywords: Co-oximetry, exchange transfusion, methemoglobinemia, methylene blue

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Introduction

Acquired methemoglobinemia results from exposure to the various drugs and toxins. It often goes unrecognized and thus untreated. Moderate to severe symptoms are treated with methylene blue 1% solution. Refractory cases of methemoglobinemia may occasionally require exchange transfusion therapy.

Case Report

A boy aged 18 months, was referred as suspected unknown poisoning and presented in pediatric emergency with a history of vomiting, excessive irritability and seizure. On examination, the child had tonic posturing and was cyanotic. Pulse-oximetry revealed oxyhemoglobin saturation (SpO₂) to be only 86%. Heart rate was 146/min, respiratory rate was 45/min and blood pressure 86/50 mmHg. Chest was clear. Heart sounds were normal and there was no murmur. His sensorium deteriorated, so he was intubated and shifted to the pediatric intensive care unit (PICU).

In PICU, he was hemodynamically stable, but SpO₂ remained only 86%. His blood was chocolate brown in color. Arterial blood gas analysis on radiometer ABL 80 machine revealed pH 7.24, PaO₂ 205 mmHg, PaCO₂ 28 mmHg, bicarbonate 16 mmol/L and SaO₂ 99.7%. Chest X-ray was normal. In view of high PaO₂ and low SpO₂, methemoglobinemia was suspected. Arterial blood gas analysis with co-oximetry showed Methemoglobin (MetHb) level to be 39%. MetHb was detected by spectrophotometry after addition of sodium cyanide, performed in the Clinical Biochemistry laboratory. This confirmed methemoglobinemia. G6PD level was 9.6 U/g Hb (normal > 6.5).

Mechanical ventilation was continued; intravenous methylene blue 2 mg/kg was started along with tablet ascorbic acid. Methylene blue was repeated to a dose of 7 mg/kg over 24 h. 150 ml of packed cell was transfused as his hemoglobin level was only 8 g%.

Despite treatment with methylene blue, he continued to be cyanotic and the MetHb level by co-oximetry, as well as that estimated by adding sodium cyanide, remained elevated (32%). In view of refractory methemoglobinemia, single volume exchange transfusion was performed twice in an interval of 12 h after establishing femoral venous and arterial lines. Following the procedure the SpO₂ increased to 92%, sensorium improved and he was extubated the next day. The MetHb level gradually decreased to 7.8%. He was discharged on the 8th day of hospitalization.

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Follow-up after 1 week revealed a neurologically intact child with no cyanosis. MetHb level was 1%.

Discussion

When any child presents with cyanosis and desaturation, an urgent search for the etiology is vital. Once congenital cyanotic heart disease and respiratory disease are excluded, evaluation for abnormal hemoglobin is warranted. MetHb is produced when normal ferrous ion in heme complex of hemoglobin is oxidized to ferric ion. The ferric state does not combine with oxygen. MetHb shifts the oxygen dissociation curve to the left. The combination of decreased oxygen carrying capacity and diminished oxygen unloading predisposes the system to profound tissue hypoxia despite normal partial pressure of oxygen in the blood.^[1]

Under normal conditions, red cells contain several reducing enzymes such as cytochrome b5 reductase, glutathione reductase and catalase that maintain MetHb level below 1%.^[2] Hereditary methemoglobinemias are rare disorders caused by either a deficiency of nicotinamide adenine dinucleotide (NADH) cytochrome b5 reductase or the presence of certain abnormal hemoglobin variants (HbM). Acquired methemoglobinemia occurs due to exposure to drugs and toxins with oxidising effects.^[1]

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%.^[3]

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.^[1,3]

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.^[4]

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. Even co-oximeters cannot distinguish between MetHb and sulfhemoglobin due to similar absorbance peaks at 630 nm.^[5,6]

For methemoglobinemia caused by drug or toxin exposure [Table 1], the treatment of choice is methylene blue, whose action depends on the availability of reduced nicotinamide adenine dinucleotide phosphate (NADPH) within the red blood cells. Methylene blue is an oxidant; its metabolic product leucomethylene blue is a reducing agent. Treatment should be considered when MetHb reaches 30% in an asymptomatic patient and 20% in a symptomatic patient. Patients with anemia or cardiorespiratory problems should be treated at lower levels.^[7] The recommended dose is 2 mg/kg for infants, 1.5 mg/kg for older children and 1 mg/kg for adults diluted in 1% sterile aqueous solution infused over 5 min. MetHb levels are generally brought below 10% within 30 min. The dose can be repeated hourly up to a maximum of 7 mg/kg over 24 h.^[8,9]

If the patient fails to respond to methylene blue this may reflect an incorrect diagnosis (e.g. sulfhemoglobinemia), inadequate gastrointestinal decontamination with ongoing toxin absorption, G6PD deficiency, congenital NADPH MetHb reductase deficiency or a rare toxin. In G6PD deficiency NADPH production is insufficient to reduce methylene blue to leucomethylene blue. In this situation, methylene blue therapy is not only ineffective, but may even result in higher levels of methylene blue than of leucomethylene blue leading to paradoxical methemoglobinemia. Toxins like analine can cause prolonged absorption and cyclic MetHb production. In cases of unresponsive methemoglobinemia, hyperbaric oxygen or exchange transfusion may be required.^[4] Methemoglobinemia due to HbM does not respond to ascorbic acid or methylene blue.^[7]

Table 1: Drugs and chemicals capable of inducing methemoglobinemia

Chloroquine	Primaquine	Sodium nitrate	Nitric oxide
Ammonium nitrate	Silver nitrate	Nitroglycerine	Nitroprusside
Nitrous oxide	Nitrites	Lidocaine	Benzocaine
Prilocaine	Bupivacaine	Sulfadiazine	Sulfones
Dapsone	Sulfamethoxazole	Flutamide	Nitrofurantoin
Phenyton	Valproate	Naphthalene	Alloxan
Metoclopramide	Butyl nitrite	Isobutyl nitrite	Paraquat
Anilines	Benzene	Burning wood plastics	Trinitro toluene
Automobile exhaust fumes	Oral hypoglycemics	Bivalent copper	Bismuth subnitrate
Toluidine	Chlorates		

Source: Reference no [1, 2 and 8]

We were not able to establish the exact etiology. The parents, of agriculture background, informed us that the house had been cleaned up in preparation for the Hindu Pooja festival. It is likely that the child was exposed to some chemical. Ash-Bernal *et al.* in their study of 138 cases of methemoglobinemia described 24 cases of unknown etiology.^[10]

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