CASE REPORT

A case of Occupational Methemoglobinemia (MetHb): A Rare Entity and Unique Treatment

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Abstract:

Methemoglobinemia is acute emergency which have precise and effective treatment if instituted in time. Methemoglobinemia due to chemical exposure is a known entity. But it required a high index of suspicion to look for it in busy casualty. Treatment with methylene blue is safe and truly lifesaving if instituted in time. Here we are presenting a case of Occupational methemoglobinemia who was treated successfully.

Key words:

MetHb, Normal partial O2 pressure, Methylene Blue, Potassium ferricyanide test, NADPH dependent MetHb Reductase, Riboflavin.

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Introduction:

Case Report:

24 years old chemical factory worker from Industrial Area was admitted to hospital in gasping condition at 6.30 p.m. His friends gave history, that on the day of incidence he was working in a factory since 10 a.m. had lunch at 2 p.m. and then started feeling giddy. He had nausea, vomiting andhis skin, nails, and lips turns muddy to blue. He was brought to the hospital in unconscious state. He had history of exposure to noxious gases and chemicals in one of the chemical company in Industrial area. The nature of exposure could not be detailed out and substantiated for various reasons.

There was no past history of cyanotic heart disease and no history of any drug consumption.

Clinical examination showed that Comatose, Pulse rate was100/ min. Blood pressure was 90/60 mm Hg. Respiration was shallow. Tongue was cyanosed. Extremities werecold, clammy and cyanosed. Pupils were bilaterally equally reacting to light. Laboratory investigations shows that his Sa $O_2$was 80%, Blood Sugar was 84mg%.

He was started with 100 % O_2 by mask. IV fluids Ringer lactate and 5%DNS given fast. No improvement in arterial O_2 saturation. Endotracheal intubation was done. The arterial O_2 saturation did not improved even after intubation. ABG reports shows pH=7.32, pCO_2 =32mm of Hg, pO_2 =134 mm of Hg, HCO_3 = 16 mEq/L. Glucose -6-Phosphate dehydrogenase activity was normal. Colour of blood was chocolate brown.

Clinical impression:

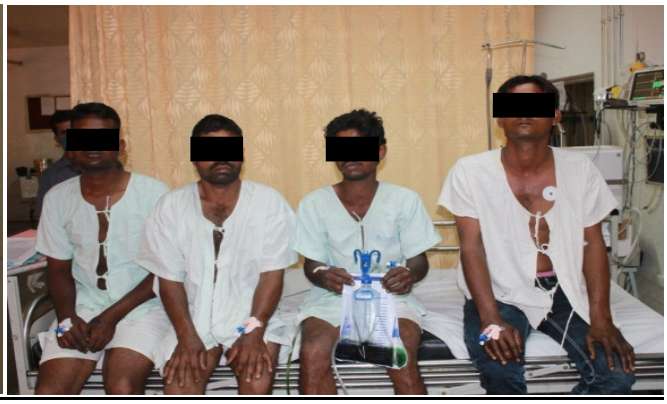
Based on clinical examination and laboratory investigations it reveals that the case was methemoglobinemia. Following laboratory tests were performed to confirm the diagnosis of methemoglobinemia.

1. **Blotting paper Test:** Drop of blood was put on the paper and color was observed. Chocolate brown color did not change even after oxidation.[1]

2. **Potassium ferricyanidetest:** 5ml distilled water + 3 -5 drops of blood + a pinch of potassium ferricyanide powder. Mix gently by inversion and observe through hand spectroscope. A single prominent band in red region of spectrum (630nm) is observed. [2,3] It was also observed that Chocolate brown colour changed to red pink after serially diluting with potassium ferricyanide ($K_3Fe(CN)_6$).

3. **Urine colour:** The colour of urine was brown.

Blotting paper test



After extubation

Result:

Above tests confirmed the presence of abnormal hemoglobin (more than 5% of total Hb), most likely methemoglobin.

Methemoglobin estimation assay facility was not available.

Treatment:

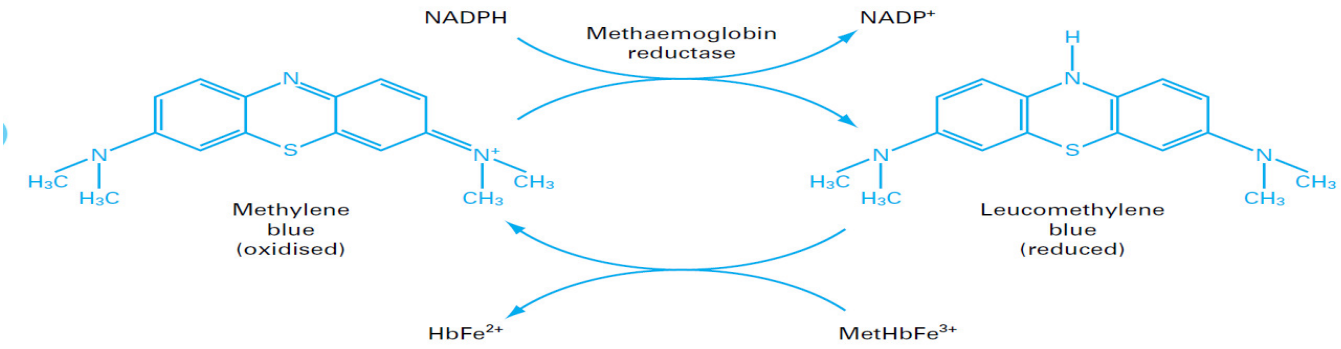
After confirmation of diagnosis of methemoglobinemia, intravenous methylene blue was infused (1 mg /kg.) over 10 minutes. Saturation of oxygen was monitored continuously. Dose was repeated till patient maintained SaO_2>95%.Blood was collected for blotting paper test. Oneunit of blood was infused as SaO_2 was improving. Next day morning patient was conscious, SaO_2 was 100% and extubated.

There were 3 more patients with same history of working in the same company. They were put on non-invasive ventilation, methylene blue infusion and all of them recovered well.

Clustering of patients in the same chemical company, around the same time confirmed the exposure to single methemoglobin causing agent at work place. This gave valuable information for occupational safety in the similar (???Benzocaine/ benzene related compounds) chemical factories.

Discussion:

Methemoglobinemia refers to the oxidation of ferrousiron (Fe^{++}) to ferric iron (Fe^{+++}) within the hemoglobinmolecule.[4] This reaction impairs the ability of hemoglobin to transport oxygen and carbon dioxide, leading to tissue hypoxemia and in severe cases, death. Methemoglobinemia is most commonly results from exposureto an oxidizing chemical, but may also arise fromgenetic, dietary, or even idiopathic etiologies Hemoglobin molecules contain iron within a porphyrinheme structure.[5,6] The iron in hemoglobin is normallyfound in the Fe^{++}state. If Fe^{++} of hemoglobinis oxidized to Fe^{+++} methemoglobin is formed. Once methemoglobin is formed; the molecule loses its ability to carry molecular oxygen. Additionally hemoglobin molecule loses the ability to release oxygen at tissue level leading to leftward shift of Hb-O_2 dissociation curve.[4][7] Because RBCs are bathed in oxygen, acertain amount of physiologic methemoglobin formation occurs continuously. Several endogenous reduction systemsexist to convert methemoglobinto functional Hb. Only about 1% of total hemoglobin ismethemoglobin at any given time. Excess of methemoglobinlead to impaired aerobic respiration, metabolic acidosis, and in severe cases, death. Methylene blue (MB) is the treatment for methemoglobinemia. Methylene blue reduces methemoglobin to functional Hb with the utilization of NADPH dependent methemoglobin reductase enzyme. (fig) This enzyme system donot play active role in normal conditions and is stimulated by the presence of methylene blue and riboflavin which forms the basis of treatment.[8–10]The constant supply of NADPH in RBCsis ensured by functioning HMP pathway which is impaired in G-6PD deficiency. Nonresponsiveness to MB should arose



suspicion of G-6PD deficiency (Haemolysis should be ruled out) Normally, through the NADH dependent methemoglobin reductase enzymes, methemoglobin is reduced back to hemoglobin. This spontaneous reaction is slow and it contribute upto 5 % for conversion of methemoglobin to functional Hb. When large amount of methemoglobin is formed, methemoglobin reductases are overwhelmed. Methylene blue, when injected intravenously as an antidote, is itself first reduced to leucomethylene blue, which then reduces methemoglobin to hemoglobin. Methylene blue reduce the half-life of methemoglobin from hours to minutes.[11][12]Methylene blue is quiet safe drug till 2mg/kg and have wide therapeutic window. MB induced hemolysis which is expected in G-6PD deficient patients is seen in the dose range of 2-4 mg/kg and beyond.[13] NADPH dependent methemoglobin reductase is either MB or flavin dependent for its activity. This make flavin or MB as choice of activator for this enzyme.[14]One in-vitro study have shown the effectiveness of riboflavin in reducing the half-life of methemoglobin though less effective than MB.[15] One case study clearly underlined the utility of riboflavin in familial methemoglobinemia.[16] But we could not find the recent data on human studies establishing the benefit of riboflavin over MB. But certainly, riboflavin could be used safely (Being water soluble vitamin, no risk of overdose toxicity) in MB intolerant patients. Doses in the range of 30 to 60 mg/day of riboflavin (Vit B2) were found useful in controlling methemoglobinemia(<5%) in familial methemoglobinemia.[16] Vitamin C could be used as adjuvant or second line of drug owing to its antioxidant properties though exact mechanisms not established.[17]

In emergency medicine, cases due to exposure to various drugs is common but cases due to industrial exposure is on decline. [5] Acute Hypoxia with relatively stable patient, normal pO_2 on ABG and non effective oxygen treatment is highly suggestive of methemoglobinemia. Methylene blue is the only effective medicine which can revert methemoglobin to hemoglobin. Methylene blue is a rarely availablein any ICU.In our case, clinical diagnosis,high index of suspicion of methemoglobinemia and blotting paper test and very critical condition of patients made us to use this drug. Timely use of methylene blue proved highly effective in these cases.

Table enlisting the causes of Methaemoglobinemia:

Industrial Chemical	Drugs	Clinical conditions
Acetanilid Alloxan Aniline Arsine Benzene derivatives Chlorates Chromates Exhaust fumes Naphthalene Nitrates Phenol Smoke inhalation Trinitrotoluene	Benzocaine Bivalent copper Bismuth subnitrate Bupivacaine hydrochloride Chloroquine Clofazimine Dapsone Dimethyl sulfoxide Dinitrophenol Ferricyanide Flutamide Hydroxylamine Lidocaine hydrochloride Metoclopramide hydrochloride Methylene blue Nitric oxide Nitrites Nitrofuran Nitroglycerin Sodium nitroprusside Phenacetin Phenytoin Prilocaine hydrochloride Primaquine phosphate Rifampin Silver nitrate Sodium valproate Sulfasalazine Sulfonamides	Sepsis [18][19]

Highlights of Clinical presentation of Methemoglobinemia:

1. History of exposure to offending agent. (Separate list of industrial compounds and drugs causing MetHb is attached)
2. Features of Hypoxia , (May appear cyanotic, Not always), relatively stable patient, Normal Partial pressure of

oxygen , Non-responsive to Oxygen therapy

3. Dark brown color of blood on tissue paper and not turning pink after exposure to air
4. Pulse oximetry is not useful to monitor recovery of methemoglobinemia.
5. Spectroscopic analysis of Hb/ assay based on co-oximetry for definitive diagnosis
6. Quick clinical response to IV methylene blue treatment.
7. Rule out Haemolysis/G-6PD deficiency in cases nonresponsive to MB
8. Observation needed till 24 hours as late activation of offending agent is possible.

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