



## Case Report on Methylene Blue Induced Hemolytic Anemia

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### ABSTRACT

A 22-years old male patient was admitted to a tertiary care hospital with complaints of an alleged history of intentional poisoning (organophosphorus compound and nitrofurantoin) and developed hemolytic anemia after receiving methylene blue for 8 days. The patient presented with hematuria and hemoglobin level 3.1 which confirmed hemolytic anemia G6PD level was normal. Methylene blue was discontinued and PRBC transfusion (3 pints) was given. After 4 days of blood transfusion, the patient's Hb level became 9.4 g/dl. Causality assessment was suggestive of a probable relationship between the drug and reaction.

**Keywords:** Hemolytic anemia, Methylene blue, G6PD

**Abbreviations:** G6PD: Glucose-6-phosphate Dehydrogenase; PRBC: Packed Red Blood Cells; LMB: Leucomethylene Blue; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; OP: Organophosphorus; SPO<sub>2</sub>: Saturation of peripheral oxygen; CBC: Complete Blood Count

### INTRODUCTION

Methylene blue (tetramethylthionine chloride) is a diagnostic agent in kidney function, anti-infective agent, antidote, antiseptic and nutraceutical. It has been recommended and used frequently for the treatment of acquired methemoglobinemia due to nitrobenzene poisoning. It helps checking anastomotic integrity, determining tissue dysplasia (chromoendoscopy), treatment of ifosfamide neurotoxicity and methemoglobinemia.

It promotes non-enzymatic redox conversion of methemoglobin to leucomethylene blue (LMB) via NADPH reductase which further reduces the ferric iron of methemoglobin to the ferrous state of hemoglobin. When given in high doses, it oxidizes ferrous iron of reduced hemoglobin to ferric iron, resulting in the production of methemoglobin, thus accentuating toxic methemoglobinemia. Therefore, only recommended doses should be administered over several minutes. Toxicity includes skin and urine discoloration, phototoxicity, and respiratory distress. Additionally, methylene blue at toxic doses can precipitate serotonin syndrome due to monoamine oxidase inhibition [1]. Unusual or toxic effects following intravenous methylene blue have rarely been referred to in publications on methemoglobinemia. The possibility that hemolytic anemia is caused by methylene blue has been discussed rarely [2]. Here, we report a case of drug-induced hemolytic anemia in a patient who is not a known case of G6PD deficiency.

A 22-years old male patient admitted to a tertiary care hospital with the complaints of an alleged history of intentional poisoning and developed respiratory distress. Initially, he was admitted to a local hospital wherein a gastric lavage was done and intubated in view of respiratory distress, later, referred to the tertiary care hospital.

The diagnosis was made as OP compound poisoning with nitrobenzene poisoning. He was prescribed with atropine, pralidoxime (2 g stat, 1g iv), cefoperazone+tazobactam (1.5 g iv), Esomeprazole 40 mg, Ondansetron (4 mg), noradrenaline (5 mcg/min), methylene blue (60 mg in 50 ml NS over 5 minutes repeat the same after 1 hour), baclofen (10 mg), sodium alginate, sodium bicarbonate and calcium carbonate syrup (2 tsp), ambroxol 15 mg (Q6H).

On admission, his blood pressure was 100/70 mmHg, pulse rate was 88 bpm, SPO<sub>2</sub> was 75%, FiO<sub>2</sub> was 100%, Hb was

13.1 mg/dl, and RBC was 3.5 million cells per cmm. Other lab investigation reports were found to be near normal. After receiving 8 days of methylene blue, he developed blood colored urine. Relevant investigations like G6PD, CBC levels, and urine analysis were done to confirm hemolytic anemia. The patient's Hb level was 3.1, G6PD level (methylene blue in G6PD deficiency can cause hemolytic anemia) was near normal and urine analysis showed blood red color of it which could be considered as a confirmatory of hemolytic anemia.

Methylene blue was discontinued and the patient was transfused with 3 pints of PRBC. Following 4 days of blood transfusion, the patient's Hb level raised to 9.4 g/dl. Patient's general condition was stable by day 11. On discharge, he was prescribed with *T. acetaminophen* 650 mg sos, *C. multivitamin* 0-1-0 for 30 days, *T. baclofen* 10 mg 1-1-1 for 3 days, *T. chlorpromazine* 25 mg 1-1-1 for 3 days, syp Sucralfate 2 tsp 1-1-1 and *T. folic acid* 5 mg 1-0-0 for 30 days.

The Naranjo's criteria and WHO probability scale was applied to determine the causality for suspected ADR. The causality assessment with both scales suggests that the ADR due to methylene blue, in this case, was "probable". The severity of the ADR was determined by using the Modified Hartwig and Siegel scale and was found to be moderate (level 3b) reaction.

### DISCUSSION

Here we report a case of a 22-year old male who developed hemolytic anemia following the administration of methylene blue; which was rarely reported in individuals without G6PD deficiency and was common among neonates. Thus, this may be the earliest report of adults without G6PD deficiency developing hemolytic anemia on methylene blue use [3].

The major adverse effects of methylene blue are hemolytic anemia, anaphylaxis, serotonin syndrome, hypertension, discoloration of the skin, hyperhidrosis, nausea, dizziness, headache, and abnormal urine color.

Hemolytic anemia is a condition in which red blood cells are destroyed and removed from the bloodstream before their normal lifespan is over which is characterized by the lowering of hemoglobin levels and reddish discoloration of urine. Hemolytic anemia may be due to immune disorders, infections, reactions to medicines, blood transfusions or hypersplenism [4].

In this case, the reaction was observed after receiving methylene blue for 8 days. The patient's Hb level was 3.1 g/dl, G6PD level was near normal and urine analysis showed blood red color of it which was confirmatory of hemolytic anemia. Methylene blue has rare reports of causing hemolytic anemia in pediatrics and few reports in G6PD deficient adults. Till date, there are no case reports suggesting methylene blue-induced hemolytic anemia in adults without G6PD deficiency [5]. Thus in this patient, the temporal relationship between methylene blue use, the onset of hemolytic anemia and its resolution when the drug was stopped are plausible and strongly indicates, methylene blue is responsible for the suspected reaction.

### CONCLUSION

Although methylene blue is known to cause hemolytic anemia, the reports are rare. Thus, our case report of methylene blue-induced hemolytic anemia adds newer information. The physician should be vigilant for the potential of drugs to cause some rare side effects like hemolytic anemia so that a safer alternative treatment can be started. The patient should be identified and promptly reported if any adverse drug reactions occur.

### DECLARATIONS

#### Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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