Case Study

Shades of Blue: A Case Series of Acquired Methemoglobinemia

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Abstract

Methemoglobinemia is a significant medical condition that can result from oxidative stress in the body. It leads to reduced oxygen delivery to tissues due to altered hemoglobin, which decreases the ability to bind oxygen. As a result, a patient's oxygen saturation on pulse oximetry may be lower, even when supplemental oxygen is provided, while the SaO2 measured through blood gas analysis remains normal. This discrepancy creates a saturation gap. The treatment for methemoglobinemia is methylene blue, which can reverse the condition. We reported a case series of methemoglobinemia due to pesticide exposure. Both patients had low oxygen saturation despite oxygen therapy. On co-oximetry, we confirmed methemoglobinemia. Both patients responded well to methylene blue. Recognisingthat methemoglobinemia can be fatal if not addressed promptly is crucial. Early diagnosis through co-oximetry is essential. By identifying the saturation gap, healthcare providers can initiate early treatment with methylene blue, leading to better patient outcomes.

Key Words: Methemoglobinemia, Pesticide, Methylene blue

Introduction

Methemoglobinemia is an important condition that can result from oxidative stress in the body. When the ferrous ion in the heme molecule of hemoglobin is oxidized into a ferric ion, methemoglobinemia occurs. This leads to the formation of dyshemoglobin, which has a diminished capacity to bind oxygen, subsequently reducing the blood's ability to carry oxygen effectively[1]. The resulting decrease in oxygen delivery can lead to tissue hypoxia, which we must address proactively. In healthy individuals, the concentration of methemoglobin in the blood is typically below 2%. This condition can present as either congenital or acquired. Methemoglobinemia is relatively uncommon. The prevalence of methemoglobinemia is around 0.035%[1]. Risk factors are hospitalized

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patients, benzocaine-based anesthetics, infants and premature infants, the elderly, and G6PD (glucose-6-phosphate-dehydrogenase) deficiency. G6PD (glucose-6-phosphate-dehydrogenase) deficiency can induce methemoglobinemia by inhibiting NADPH-flavine reductase, which prevents methemoglobin reduction. Methylene blue, which is the treatment of choice for methemoglobinemia, is contraindicated in individuals with G6PD deficiency due to the risk of hemolytic anemia and potential for worsening methemoglobinemia. Long-term implications of methemoglobinemia can be cyanosis, fatigue, and in severe cases, seizure, coma, and death if not treated effectively. The mortality rate of methemoglobinemia can vary, but levels above 70% are often associated with death, while those below 70% can be treated successfully with methylene blue. A significant number of acquired cases are drug-related, often linked to medications such as dapsone, local anesthetics, and antimalarials. In this case series, we will explore two patients who developed acquired methemoglobinemia due to pesticide exposure, focusing on their treatment journey and the steps taken for effective management.

Case Report

Case-1

A 30-year-old female with no significant medical history was admitted to the Intensive Care Unit (ICU) two days after ingesting a pesticide. She presented with symptoms of dizziness and headache. After initial treatment at a local hospital, she arrived at the ICU exhibiting tachypnea and tachycardia, with an oxygen saturation of 78% in room air, measured by pulse oximetry. She received oxygen through a non-rebreathing mask at a flow rate of 10 liters per minute. On sampling for lab analysis, her blood appeared dark brown (Fig 1). The initial arterial blood gas analysis showed an oxygen saturation (sO2) of 90% and a partial pressure of oxygen (pO2) of 72.3 mm Hg while the patient was on room air. Additionally, the methemoglobin level was found to be 59%, later confirmed by a co-oximeter. Given a more than 10% saturation gap, the patient was treated with 2 mg/kg of methylene blue. After treatment, her urine changed to a blue hue (Fig 2). The patient's G6PD level was normal. A repeat arterial blood gas analysis performed two hours later revealed a methemoglobin level of 8.7%, and her oxygen saturation improved to 90% as measured by pulse oximetry. Further inquiry revealed that she had ingested an insecticide known locally as "ZERO INSECTICIDE," which contains the compound emamectin benzoate, recognized for causing methemoglobinemia. The patient's initial laboratory values are shown in Table 1. After two hours, the patient's oxygen saturation dropped again to 78%, and an arterial blood gas (ABG) analysis indicated a methemoglobin level of 20%. The patient received a repeat dose of methylene blue at 2 mg/kg. To address the potential for a rebound increase in methemoglobin levels, an infusion of methylene blue was initiated at a rate of 10 mg/hour for 24 hours. After six hours, the methemoglobin level decreased to 2%. After 24 hours, the patient's oxygen saturation improved as measured by pulse oximetry; however, the hemoglobin level decreased, and liver function tests (LFTs) worsened, with an increase in indirect bilirubin levels indicating hemolysis. A peripheral blood smear revealed fragmented cells, and lactate dehydrogenase (LDH) levels were elevated, as shown in Table 2. Methylene blue was discontinued, and after two days, the patient's liver function tests returned to normal. The patient was discharged after six days. At a follow-up appointment two months later, the patient was doing well.

CASE 2

A 38-year-old female was admitted with an alleged history of pesticide (PERFECT ZENE and ANTH 505), which contains chlorpyriphos and cypermethrin, and nitrate compound. She was treated at a local hospital and shifted to the ICU. On arrival, the patient was tachypneic, with a heart rate of 60 beats per minute, and room air saturation of 82%. Arterial blood gas analysis showed SO2 of 97%, PO2 of 80 mmHg, and methemoglobin % of 30.7, which was later confirmed by cooximetry. The patient's blood was found to be a chocolate color (Fig 3). A serum choline esterase level was sent, and a G6PD level was sent(found out to be normal). Atropine infusion was started, and methylene blue at a dose of 2mg/kg body weight was administered. After methylene blue, the urine changed to a bluish hue(Fig 4). After 3 hours, the patient's saturation improved to 94% on 3 lt of oxygen, and the methemoglobin

percentage on arterial blood gas analysis was found to be 4.1%. Initial lab values are as follows (Table 4). The patient was having tachycardia and tachypnoea and was restless and agitated, probably because of atropine. The patient also received Vitamin C as an antioxidant. Gradually atropine was stopped, and the patient clinically improved, subsequently discharged on day 7 of admission. On follow-up,the patient was doing fine after 30 days.

Figure 1 shows dark brown blood on the left picture due to methemoglobinemia in case 1

Figure 2 shows a blue hue in urine due to the methylene blue treatment in case 1

Figure 3 shows chocolate blood on the left picture due to methemoglobinemia in case 2

Figure 4 shows a bluish hue in urine after methylene blue in case 2

Table-1

LAB TESTS	LAB VALUE ON ADMISSION DAY	LAB VALUE ON THE NEXT DAY OF ADMISSION
HB/TLC/TPC	10/18K/2.6L	9.7/17K/3.0L
UREA/CREAT	21/0.68	14.5/0.55
NA/K	138/3.79	139/4.1
BILLIRUBIN (T/D/I)	1.1/0.5/0.6	
SGOT/PT	38/18	
ALBUMIN	4.34	
CHOLINE ESTERASE	6356(4650-10440)	

Table 1 shows the Initial lab value on admission day, and the next day, the serum cholinesterase level was normal in case 1

Table-2

LAB INVESTIGATIONS	LAB VALUES AFTER ADMINISTRATION OF METHYLENE BLUE
HB/TLC/TPC	8.2/20K/3.0L
UREA/CREATININE	17/0.49
BILLIRUBIN(T/D/I)	3.40/0.9/2.48
SGOT/PT	37/12.6
LDH	433.6 (NORMALLY LESS THAN 247)

Table 2 shows lab values of hemolysis after administration of methylene blue, also peripheral smear showing fragmented red cells in case 1.

Table-3

LAB INVESTIGATION	LAB VALUES ON DAY OF ADMISSION	LAB VALUES ON THE NEXT DAY OF ADMISSION
HB/TLC/TPC	12.9/12k/2lakh	11.2/16k/2.3lakh
UREA/CREAT	34.8/0.51	30.7/0.59
NA/K	137/4.40	133/3.75
BILLIRUBIN(T/D/I)	0.97/0.16/0.81	
SGOT/PT	16.2/12.6	
ALBUMIN	4.59	
CHOLINE ESTERASE	740.9(4650-10440)	

Table 3 shows the initial lab values of case 2. The cholinesterase level was low because it was an organophosphorus poison.

Table-4

DRUG GROUP	EXAMPLE OF DRUGS CAUSING METHEMOGLOBINEMIA
Local anesthetics	Benzocaine (often used in endoscopicprocedures)
Nitrates	Nitroglycerin,inhaled nitric oxide, Nitroprusside, oral nitrates, amyl-nitrate
Antibiotics	Dapsone
Other drugs	Rasburicase (especially in G6PD deficiency)
Environmental causes	fertilizers, herbicides, Plastic (various types), Paints, and rubber

Table 4 shows common drugs causing methemoglobinemia.

Discussion

Methemoglobinemia is a rare disorder where hemoglobin's iron changes from the ferrous to the ferric state, impairing its ability to bind oxygen. This condition shifts the oxygen-hemoglobin dissociation curve to the left, reducing oxygen delivery to tissues and resulting in hypoxia and functional anemia, even with normal hemoglobin levels[2]. Understanding its health implications is crucial.

Methemoglobinemia is classified into two types: congenital and acquired. Acquired methemoglobinemia is more common and results from exposure to substances that oxidize hemoglobin. In contrast, congenital methemoglobinemia is caused by genetic factors, primarily mutations in the CYB5R3 gene. Hereditary forms lead to NADH-cytochrome reductase deficiency. Acquired methemoglobinemia usually stems from specific drugs or toxins that oxidize hemoglobin from its ferrous (Fe2+) to ferric (Fe3+) form. A table listing common drugs that contribute to this condition is provided (Table 4).

The clinical manifestations of methemoglobinemia vary according to the percentage of methemoglobin in the blood[3]. Levels between 3% and 15% are typically asymptomatic. However, mild symptoms may occur when levels rise to between 20% and 30%, including fatigue, rapid breathing, shortness of breath, increased heart rate, anxiety, dizziness, nausea, and vomiting. At levels above 40%, more severe symptoms can manifest, such as seizures, coma, arrhythmias, and even death. Diagnosis is confirmed through co-oximetry, but healthcare professionals may suspect methemoglobinemia based on three key indicators[3].

1. **Refractory Hypoxia**: This condition is suspected in patients with an oxygen saturation level between 82% and 86% and who are receiving 100% oxygen, provided there are no other identifiable causes of their hypoxia.

2. **Cyanosis-Saturation Gap**: The presence of central cyanosis in patients with an oxygen saturation level between 80% and 90% may suggest the possibility of methemoglobinemia.

3. **Brown Blood Color**: Blood may exhibit a chocolate brown appearance. If a sample is placed on white gauze, it will remain brown when dry, in contrast to deoxygenated blood, which turns red upon oxygenation.

Methemoglobinemia is diagnosed using co-oximetry, which measures light absorption at four wavelengths: 600 nm (carboxyhemoglobin), 631 nm (methemoglobin), 660 nm (deoxyhemoglobin), and 940 nm (oxyhemoglobin). This method can identify disorders like carboxyhemoglobinemia and methemoglobinemia.[4] A "saturation gap" of over 5% between co-oximetry and pulse oximetry readings may indicate methemoglobinemia.

The primary treatment for methemoglobinemia is supportive care and discontinuing any offending drugs. Methylene blue is the definitive treatment, helping convert methemoglobin back to its non-oxidized form. It is recommended for symptomatic patients, especially when methemoglobin levels exceed 30%, but is contraindicated in those with G6PD deficiency and should be used cautiously due to possible serotonin syndrome. The standard dosage is 1-2 mg/kg intravenously over five minutes, with effects often seen within minutes and cyanosis typically resolving in an hour. A second dose may be necessary if cyanosis persists after 60 minutes. Rebound methemoglobinemia can occur within 12 hours, potentially requiring continuous infusion. For patients with G6PD deficiency, alternatives like high doses of vitamin C or riboflavin may be needed.

For cases that do not improve with methylene blue treatment, the next options to consider are hyperbaric oxygen therapy (HBOT), plasmapheresis, or exchange transfusion[6]. Although several published case reports on the use of HBOT exist, there are no clear recommendations for its application[7]. Additionally, HBOT may not be available at all medical centers, and the dosing and treatment protocols are not well-defined. The efficacy of hyperbaric oxygen remains unproven. In a systematic review, therapeutic whole blood exchange (TWBE) demonstrated a survival rate of 81.6% in patients who were refractory to methylene blue[8]. While TWBE shows promising efficacy, it has some limitations, including the need for reliable blood bank support and the complexity of the procedure, especially if specialized exchange equipment is unavailable. The appropriate volume to be exchanged and the number of sessions required have yet to be validated. Furthermore, complications such as hypotension can occur during the procedure, requiring close monitoring in an intensive care unit (ICU).

Similar to our case, these are some case reports that benefited from methylene blue treatment due to acquired methemoglobinemia.

Liwen Zhao and colleagues managed a case of acquired methemoglobinemia caused by a nitrobenzene compound, treating it with methylene blue and other antioxidants[2].

Tarun George and associates handled a case of methemoglobinemia resulting from insecticide poisoning, using methylene blue, vitamin C, and riboflavin for treatment[3].

Angela Mauro and her team reported two cases of methemoglobinemia resulting from nitrate ingestion from vegetable sources, both successfully managed with methylene blue[4].

Giulia Cannata and colleagues documented a case of methemoglobinemia resulting from consuming homemade vegetables, which was effectively treated with methylene blue.[5]

Lakshmikanthcharan Saravanabavan and his team managed three cases of methemoglobinemia due to pesticide poisoning. In addition to methylene blue, they used hyperbaric oxygen therapy and exchange transfusion for refractory cases, with successful outcomes[6].

Ida Ivek and her team managed a case of methemoglobinemia due to poisoning from an unknown substance, successfully treated with methylene blue and other antioxidants[7].

Mona J. Malik and colleagues reported a case of methemoglobinemia linked to substance ingestion at a rave party, which was successfully treated with methylene blue[8].

Conclusion

Methemoglobinemia is a rare disorder characterized by elevated levels of methemoglobin, an oxidized form of hemoglobin that cannot bind oxygen. This results in an inadequate supply of oxygen to tissues. There are two types of methemoglobinemia: genetic and acquired. Genetic methemoglobinemia is chronic and typically presents as cyanosis (a bluish discoloration of the skin) without other symptoms. In contrast, acquired methemoglobinemia, which is often

caused by exposure to certain drugs and chemicals, is acute and can be potentially life-threatening. Symptoms of methemoglobinemia vary depending on the level of methemoglobin present and may include fatigue, dizziness, altered consciousness, seizures, and even coma. It should be suspected when a person shows low oxygen saturation on pulse oximetry and has chocolate-colored blood. Methemoglobin levels may need to be monitored for up to 7 days as they can remain elevated. Diagnosis is confirmed through co-oximetry, a specialized test to measure blood methemoglobin levels. Treatment involves supportive care and discontinuing the use of the offending substance. Emergency responders should have antidotes such as methylene blue and vitamin C, as acquired methemoglobinemia can be serious.

Clinical Significance

1. Methemoglobinemia is a rare acquired condition caused by herbicide ingestion.
2. Careful clinical judgment is required for accurate diagnosis and treatment.
3. Methylene blue is used to treat methemoglobinemia, but it may lead to hemolytic anemia.

Declaration of Conflicting Interests:

The authors declared no potential conflicts of interest regarding this article's research, authorship, and/or publication.

Patient Consent Statement

We hereby confirm that we have obtained written informed consent from the patients in these case reports for publication of their clinical information.

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