

Case Report

Methemoglobinemia caused by fungicide poisoning: A case report

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Abstract:

Methemoglobinemia is a potentially fatal condition at a level of more than 70%. It occurs when the ferrous iron in Haemoglobin is oxidized to ferric iron, forming methemoglobin (MetHb), causing decreased capability of hemoglobin to bind and deliver oxygen to tissues. Methemoglobinemia has been linked to a wide array of substances, including fungicides and industrial chemicals. We describe a patient who developed a high MetHb level of 70.7%, after deliberately consuming a fungicide, namely Mancozeb. The "oxygen saturation gap" is the difference between the calculated oxygen saturation from a standard blood gas machine and the reading from a pulse oximeter. If it is greater than 5%, the patient's hemoglobin may be abnormal, representing carbon monoxide poisoning, methemoglobinemia, or sulfhemoglobinemia. Disproportionate cyanosis not responding to supplemental oxygen, chocolate brown blood, and saturation gap of >5% raised the suspicion of methemoglobinemia secondary to ingestion of fungicide. An alternative approach to treatment including intravenous ascorbic acid, NAC, and multiple blood transfusions was given due to the unavailability of methylene blue. A high index of suspicion, early recognition, and an alternative approach to management resulted in a favorable outcome.

Keywords: Methemoglobinemia, saturation gap.

Introduction:

Methemoglobinemia is a potentially fatal condition when Methemoglobin (MetHb) reaches a level of more than 70%. Methemoglobinemia can be either inherited or acquired. Acquired Methemoglobinemia has been linked to a wide array of substances, like fungicides and industrial chemicals.

It occurs when the ferrous iron in hemoglobin is oxidized to ferric iron, forming methemoglobin (MetHb), causing decreased capability of hemoglobin to bind and deliver oxygen. Because red blood cells are continuously exposed to oxygen and free radicals, there is always a baseline level of MetHb present even after normal conditions. This accounts for approximately 1 % of the total hemoglobin at any given time. Higher concentrations of MetHb define the condition as methemoglobinemia. Various reduction systems prevent MetHb accumulation in the body. Primarily cytochrome-b5-metHb reductase system (nearly 95 %

reduction) and the reduced NADPH-MetHb reductase system (< 5%). To a very limited extent, non-enzymatic reduction systems may participate in the reduction of MetHb to Hb.

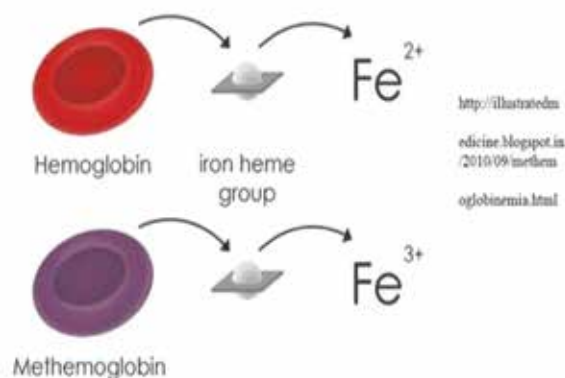


Fig 1: Formation of Methemoglobin ¹¹

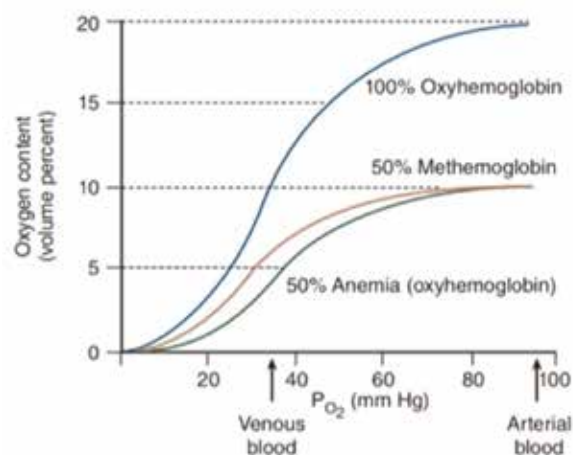


Fig 2 : Oxygen Dissociation curve ¹

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The primary adverse clinical effect of MetHb is the reduction of the oxygen content of the blood. Because Hb-bound oxygen accounts for the vast majority of the individual's oxygen-carrying capacity, as MetHb concentration rises, the oxygen-carrying capacity falls. Patients with Methemoglobinemia are often more symptomatic than patients with simple anemia that produces an equivalent reduction in oxygen-carrying capacity. This is caused by a leftward shift in the oxyhemoglobin dissociation curve, the consequently reduced release of oxygen from the erythrocyte to the tissue at a given partial pressure of oxygen occurs.^{1,4}

Patients with methemoglobinemia typically present with skin discoloration ("chocolate cyanosis"), especially of nails, lips, and ears. Blood containing > 20 % MetHb has a characteristic "chocolate brown" colour when phlebotomized which could be used as a simple bedside test to guide treatment in limited resource settings.⁴ An easy bedside test involves applying a drop of blood to filter paper to assess its colour change after exposure to air. Blood that is rich in MetHb remains the chocolate-brown colour. At MetHb levels between 20 % and 30 %, anxiety, headache, weakness, and lightheadedness develop, and a patient may exhibit tachypnea and sinus tachycardia. MetHb levels of 50 % to 60 % impair oxygen delivery to the vital tissues, resulting in myocardial ischemia, dysrhythmias, depressed mental status (including coma), seizure, and lactate-associated metabolic acidosis. Levels above 70% are largely incompatible with life.^{1,3,6,9,11}

We describe a patient who developed a high MetHb level of 70.7%, after deliberately consuming a fungicide. The fungicide namely, Mancozeb, is a protective fungicide that reacts with, and inactivates sulfhydryl (SH) groups of amino acids and enzymes of fungal cells, resulting in disruption of lipid metabolism, respiration, and production of ATP but is reported to have a multisite action (on various organ systems) among mammals.⁸ Additionally, Mancozeb exposure produces neurotoxicity via yet an unknown mechanism. Mancozeb also has chelating properties, allowing it to possibly interfere with several enzyme systems that contain metals, such as zinc, copper, and iron (e.g., dopamine β -hydroxylase).^{2,5,6}

This case report highlights the importance of considering the possibility of methemoglobinemia in cases of exposure to a fungicide with biological compounds presenting with cyanosis out of proportion to respiratory status and normal PaO₂, which does not improve with administration of O₂, chocolate brown blood, and saturation gap.

Case Report

A 20 years old female with no premorbid illnesses allegedly consumed unknown quantities of a fungicide called 'Indofil M-45' (composition: Mancozeb fungicide) with the intent to suicide. She was found unresponsive following 2 episodes of vomiting and was taken to the emergency department (ED) of a tertiary hospital.

In ED, cyanosis of lips, tongue, and nails of both limbs was found. GCS was 11/15, and vitals were stable with a heart rate of 130/minute and a blood pressure of 110/70 mm Hg. Her SPO₂ measured by pulse oximetry was 88% with 15 liters of O₂ via a Non-rebreather mask and the corresponding SaO₂ was 95%, with a saturation gap of 7% (significant when >5%). The blood sample for ABG was chocolate brown. Disproportionate cyanosis not responding to supplemental oxygen, chocolate brown blood, and saturation gap of >5% raised the suspicion of methemoglobinemia-secondary to ingestion of fungicide, confirmed by ABG MetHb levels of 19% (At ED). She was referred to our intensive care unit for observation and monitoring. On arrival in the ICU (approximately 2.5 hours after ingestion of fungicide), she was drowsy with GCS of 10/15, agitated and marked cyanosis of lips, tongue, and nails of both limbs was noted. At ICU, she was intubated for airway protection and mechanically ventilated (assist control mode) following admission. The rest of the physical examination was normal.

MetHb level assessment was done from ABG analysis and serial estimation of metHb together with saturation gap is depicted in the table. All Lab parameters including renal function, liver function, and hematological panel (with attention to hemolysis) were normal. The urine strip test for pregnancy was negative.

Table 1: Serial ABG Values and saturation gap

Parameters	Day 1(ED)	Day 1(ICU)	Day 2	Day 3	Day 4	
MethHb level (from ABG)	19	34	70.7	55	43	28.8
pH	7.39	7.49	7.47	7.63	7.61	7.52
PaO ₂	108	313	230	469	421	429
SPO ₂	88	83	79	86	89	91
SaO ₂	95	95	98	98.8	98.9	99
Saturation Gap (SaO ₂ -SPO ₂)						
**significant when >5%	7	12	19	12.8	9.9	8
FiO ₂	100	100	100	100	100	90

An alternative approach to treatment was followed as methylene blue was unavailable. The patient received activated charcoal at 1 gm/kg BW dose considering unknown poisoning. Initially, large doses of ascorbic acid (0.5 gm/8 hourly -total 9 doses) and N-acetyl cysteine (600 mg 3 doses each day till discharge) were given. The patient was given supportive care in the form of mechanical ventilation with FiO₂ 100%, Fentanyl infusion, dextrose infusion, and ICU nursing care. Three units of fresh whole blood were transfused during the ICU course (one unit each day till day 3).

On day 2, her sensorium improved further but SpO₂ continued to be low despite high oxygen administration, the lowest recording was 79 %, the SpO₂ increased to 89% on day 3, and to 91-93% on day 4, and she was successfully weaned off the ventilator after 5 days continued to maintain a SpO₂ of 98% on a face mask with 5 L/minute of oxygen. MetHb levels slowly decreased and reached levels of <5 on the day of discharge (day 6).

ACID-BASE 37.0 °C			ACID-BASE 37.0 °C			ACID-BASE 37.0 °C		
pH	7.391		pH	7.498		pH	7.478	
pCO ₂	38.3	mmHg	pCO ₂	23.4	mmHg	pCO ₂	23.8	mmHg
pO ₂	109.8	mmHg	pO ₂	363.6	mmHg	pO ₂	230.8	mmHg
HCO ₃ ⁻ act	22.7	mmol/L	HCO ₃ ⁻ act	17.8	mmol/L	HCO ₃ ⁻ act	17.5	mmol/L
HCO ₃ ⁻ std	22.9	mmol/L	HCO ₃ ⁻ std	21.3	mmol/L	HCO ₃ ⁻ std	20.9	mmol/L
BE (act)	-1.9	mmol/L	BE (act)	-3.8	mmol/L	BE (act)	-4.9	mmol/L
BE (std)	-2.2	mmol/L	BE (std)	-5.5	mmol/L	BE (std)	-6.3	mmol/L
cCO ₂	23.9	mmol/L	cCO ₂	18.5	mmol/L	cCO ₂	18.0	mmol/L
CO-OXIMETRY			CO-OXIMETRY			CO-OXIMETRY		
Hct	38	%	Hct	35	%	Hct	36	%
Hgb	12.8	g/dL	Hgb	12.0	g/dL	Hgb	12.4	g/dL
SO ₂	97.4	%	SO ₂	98.0	%	SO ₂	99.0	%
COHb	0.5	%	COHb	0.3	%	COHb	0.0	%
MetHb	19.4	%	MetHb	34.3	%	MetHb	70.7	%
FHb	2.1	%	FHb	1.3	%	FHb	0.3	%
nBili	<2	mg/dL	nBili	<2	mg/dL	nBili	<2	mg/dL

ACID-BASE 37.0 °C			ACID-BASE 37.0 °C			ACID-BASE 37.0 °C		
pH	7.347		pH	7.436		pH	7.476	
pCO ₂	18.4	mmHg	pCO ₂	24.0	mmHg	pCO ₂	22.1	mmHg
pO ₂	308.4	mmHg	pO ₂	381	mmHg	pO ₂	444.6	mmHg
HCO ₃ ⁻ act	15.6	mmol/L	HCO ₃ ⁻ act	12.8	mmol/L	HCO ₃ ⁻ act	12.5	mmol/L
HCO ₃ ⁻ std	20.1	mmol/L	HCO ₃ ⁻ std	18.9	mmol/L	HCO ₃ ⁻ std	22.5	mmol/L
BE (act)	-5.5	mmol/L	BE (act)	-6.9	mmol/L	BE (act)	-2.9	mmol/L
BE (std)	-6.8	mmol/L	BE (std)	-8.4	mmol/L	BE (std)	-4.0	mmol/L
cCO ₂	16.2	mmol/L	cCO ₂	16.5	mmol/L	cCO ₂	20.4	mmol/L
CO-OXIMETRY			CO-OXIMETRY			CO-OXIMETRY		
Hct	30	%	Hct	32	%	Hct	33	%
Hgb	10.1	g/dL	Hgb	11.0	g/dL	Hgb	11.2	g/dL
SO ₂	98.8	%	SO ₂	99.9	%	SO ₂	99.9	%
COHb	7.5	%	COHb	2.5	%	COHb	2.4	%
MetHb	23.2	%	MetHb	21.3	%	MetHb	24.4	%
FHb	0.9	%	FHb	0.1	%	FHb	0.4	%
nBili	<2	mg/dL	nBili	<2	mg/dL	nBili	<2	mg/dL

Emergency Department, ICU

Fig 3 : Serial ABGs of the patient

Discussion :

Diagnostic suspicion of methemoglobinemia should be considered on clinical findings: cyanosis out of proportion to respiratory status and normal PaO₂, which does not improve with administration of O₂, "oxygen saturation gap," and chocolate brown colour on blood sampling.

The oxygen saturation gap refers to the gap between oxygen saturation as measured by pulse oximetry and the actual arterial oxygen hemoglobin saturation. Some refer to it as the difference between the oxygen saturation calculated from routine blood gas analysis and the oxygen saturation measured by pulse oximetry. Others use this term for the difference between the calculated oxygen saturation from a standard blood gas machine and the measured value from a co-oximeter. An oxygen saturation gap is present when there is more than a 5% difference. The 'oxygen saturation gap' is readily available and is a clinically important phenomenon beyond historical interest. It should be calculated on patients when there is a suspicion of carbon monoxide, methemoglobinemia, or hydrogen sulfide toxicity. An oxygen saturation gap should clue in the diagnosis to the evaluation of carbon monoxide, methemoglobinemia, and hydrogen sulfide to avoid neurological, metabolic, and cardiovascular sequelae.²

Pulse oximetry is based on the measurement of a ratio of light absorption by tissues at a red wavelength (660 nm) and at an infrared wavelength (940 nm). This measured absorption ratio is related to arterial oxygen saturation levels by empirically derived calibration curves developed by simultaneously measuring absorption ratios and sampling arterial blood in healthy adult human volunteers subjected to varying levels of hypoxia. The curves assume that only two hemoglobin species are present: O₂Hb and reduced hemoglobin.^{1,2,4}



Figure 3: Chocolate cyanosis of the lips and nails

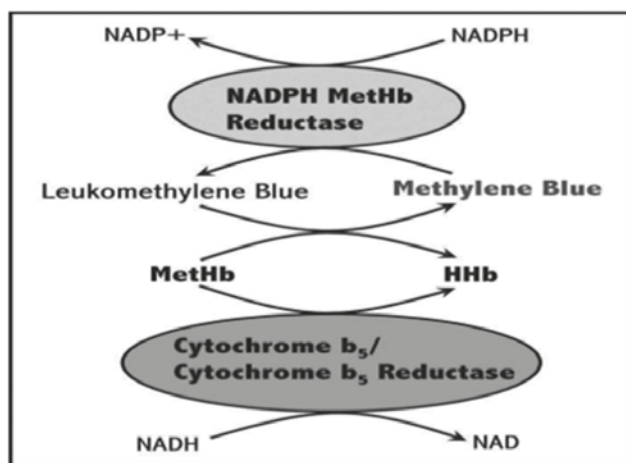


Figure 4: Mechanism of action of Methylene Blue

The arterial blood gas analysis calculates oxygen saturation from the measured oxygen tension using an assumed standard oxygen-hemoglobin dissociation curve. In patients with methemoglobinemia, the pulse oximeter will report a falsely elevated value for arterial oxygen saturation percentage. Arterial blood gas results may be initially deceptive because the partial pressure of oxygen, a measure of dissolved, not bound, oxygen is normal. This discrepancy is used to calculate the saturation gap which gives a clue to the diagnosis.^{1,2,6}

Co-oximetry determines oxygen saturation by detecting the absorption of four wavelengths allowing definitive identification of dyshemoglobinemias. Co-oximetry is a spectrophotometric method capable of differentiating oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin species. Co-oximetry is superior in the detection of MHb but a standard ABG machine served our purpose. The advantage of co-oximetry in evaluating MetHb is that it measures light absorbance at two additional wavelengths compared to pulse oximetry.^{1,2,6}

Treatment should be guided by the severity of the disorder and blood levels of MetHb represent a secondary parameter in the definition of the treatment. The first-line treatment of methemoglobinemia is the intravenous administration of methylene blue (MB). This antidotal therapy with MB is reserved for symptomatic patients or those asymptomatic patients with MetHb > 25%.⁴ Administering MB at a dose of 1-2 mg/kg loading dose over 30-60 minutes, to a maximum of 7 mg/kg, followed by 50-100 mg twice or thrice daily and other supportive measures as required. Alternative treatments, such as intravenous ascorbic acid, N-acetylcysteine, and hyperbaric oxygen, can also be used if methylene blue is unavailable or contraindicated. Exchange blood transfusion, beneficial in severe cases, is recommended when methylene blue or alternative treatments are ineffective. As neither G6PD evaluation nor MB was available, we opted for alternative therapies such as fresh whole blood transfusion and intravenous ascorbic acid. These alternative therapies were found safe⁷, effective, easily available⁷, and devoid of any side effects (hemolysis, pain, and dose dependant hypotension) or treatment failures^{3,4,5,6,7,9,10,11} MB has a short

half-life, rebound MB can occur up to 12 hours after its administration.⁶

Intravenous ascorbic acid is a strong, water-soluble reducing agent and a donor anti-oxidant that takes part in oxidation-reduction reactions, so ascorbic acid directly reduces MetHb and is proven to treat the diagnosis.^{7,9,11} There is no consistent recommendation regarding the dosage of ascorbic acid for the treatment of methemoglobinemia provided in the literature. In our case lowering of MetHb level from 70.7 to 28.8 occurred over 48 hours, being given 0.5-gram ascorbic acid 8 hourly during that period. The dosage and duration of treatment with ascorbic acid vary widely across these cases ranging from 1 g ascorbic acid as a one-time dose [reportedly lowering the patient's MetHb level from 26.2% to 2.1% within 6 hours of dosing to high-dose 10 g ascorbic acid every 6 h. Dosing recommendations from four case reports of successful resolution of methemoglobinemia using only ascorbic acid have been outlined in a 2016 review by Sahu et al. On the other hand, another study reported that acquired Methemoglobinemia may not respond to ascorbic acid because its capacity to reduce MetHb is much inferior to that of endogenous enzymatic systems.^{9,10,13} Oral ascorbic acid may not be beneficial in reducing methemoglobinemia.¹⁰ However failure of ascorbic acid in the treatment of methemoglobinemia is attributed to lower doses and short duration of therapy.^{7,10}

In similar reported cases⁷, with higher MetHb level as high as 90%, fresh whole blood transfusion was tried as a therapy option.⁷ Our case also had a MetHb level > 70 %, and hence 3 units of fresh whole blood were transfused, one unit each day for 3 days.

No effective antidote exists for individuals with G6PD deficiency who develop drug-induced methemoglobinemia. It was previously reported on the use of N-acetylcysteine (NAC) to reduce MetHb in normal blood. As it is not associated with hemolysis, NAC should be a safer antidote than methylene blue in patients with G6PD deficiency, renal insufficiency along with methemoglobinemia. Oral NAC dosing would undergo significant first-pass liver metabolism, which may limit blood concentrations. In our patient IV NAC used as G6PD deficiency could not be determined. There is conflicting data regarding the efficacy of NAC and its ability as a reducing agent in MetHb. In vitro studies have demonstrated positive results. Serial measurements of MetHb levels should be performed, as per recommendations it was done in our case.

Activated charcoal in multiple doses has been proven to be effective, which was given at ER and the rest of the doses at the ICU. The use of activated charcoal improves the clearance rates of MetHb.¹⁰

She also received dextrose-containing fluids for supplementing NADH/NADPH which is needed for the reduction of methemoglobin by the NADPH reductase enzyme.¹¹

MetHb levels may remain elevated for up to 7 days and need monitoring. With a steady decline after 4th day, the patient was discharged at the end of day 6.

Conclusion :

In conclusion, as more and more products are being marketed, treating clinicians should be cautious of the numerous compounds which can cause methemoglobinemia. This should be kept in mind while dealing with such cases of fungicide poisoning. Methemoglobinemia must be considered in the differential diagnosis in unknown poisoning with unexplained cyanosis, saturation gap >5% and the presence of chocolate-colored blood. A high index of suspicion, early recognition, and management can result in a favorable outcome.

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