CASE SERIES

A Case Series of Acquired Methemoglobinemia Due to Pesticides: Conventional to Novel Therapies

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Abstract

Methemoglobinemia is a rare but life-threatening clinical condition which has to be rapidly diagnosed and treated to have a favorable outcome. There are multiple known causes for Acquired Methemoglobinemia of which pesticides are rare and less reported. We report a case series of Methemoglobinemia due to pesticide consumption, who had a varying response to treatment modalities. We discuss about the various treatment options for methemoglobinemia from conventional Methylene blue to novel treatments like Exchange transfusion and Hyperbaric Oxygen Therapy. We found that monitoring Methemoglobin levels may be required for a longer duration due to the possibility of relapse. For refractory cases not improving with Methylene blue, exchange transfusion is an effective alternate treatment.

Keywords: Acquired methemoglobinemia, Exchange transfusion, Hyperbaric oxygen therapy, Methylene blue.

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Introduction

Methemoglobinemia (MetHb) is a severe condition precipitated by oxidant stressors in the body. It occurs due to the oxidation of the ferrous ion in the heme molecule of hemoglobin, leading to the formation of the ferric ion. This dyshemoglobin has a reduced ability to bind oxygen. Hence, it reduces the oxygen-carrying capacity of blood and also causes the dissociation of oxygen, leading to tissue hypoxia.[1] It may be congenital or acquired. Drug-induced MetHb is common with dapsone, local anesthetics, and antimalarials. Here we discuss three patients with acquired MetHb due to a rare cause of pesticide consumption with varied presentation, severity, and treatment response (Table 1).

Case Description

Case 1

A 74-year-old gentleman was admitted to our hospital with hypoxia and frothy secretions from his mouth and nose following intentional insecticide (abamectin-avermectin group) consumption of an unknown quantity. On arrival at the emergency department, he was comatose, gasping, hypotensive, and hypoxic. He was intubated, and gastric lavage was done. On arrival at the intensive care unit (ICU), oxygen saturation (SpO_2) did not improve with a fraction of inspired oxygen (FiO_2) increments. However, the partial pressure of oxygen was 250 mm Hg with normal saturation on arterial blood gas. In view of this SpO_2 gap, co-oximetry was done, and it revealed MetHb (methemoglobin levels of 66%) with compensated metabolic acidosis. Intravenous (IV) methylene blue at a dose of 1 mg/kg was administered, and as there was no response, it was repeated after 30 minutes. His SpO_2 improved to 100%, and methemoglobin levels dropped to 2.5%. Acidosis improved, and hemodynamics were stable. The next day methemoglobin levels rose to 15% with dropping saturations, and the third dose of methylene blue (1 mg/kg) was administered. Methemoglobin level and saturation normalized, and did not have a relapse. He was weaned off ventilation and transferred to the ward, and discharged home on day 4.

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Case 2

A 57-year-old gentleman with an alleged history of (h/o) consumption of approximately 50–100 mL of a pesticide (1:2 compound, containing bioemulsifier 6%; oligosaccharide, 8%; fillers/carriers, 86%) at his home presented within 2 hours to a private hospital where gastric lavage was done and referred for deteriorating conscious level. On arrival, 5 hours from the time of consumption, he was stuporous. Glasgow Coma Scale (GCS) was 7/15, had central cyanosis, SpO_2—62% with severe hypotension, which responded to fluid. In view of poor GCS and low SpO_2, he was ventilated. Post intubation SpO_2—86% with 100% FiO_2. His blood gas revealed normal saturations, and co-oximetry showed a methemoglobin level of 63.5%. In view of raised MetHb, he was administered 2 mg/kg of methylene blue and shifted to ICU. In the subsequent arterial blood gas, methemoglobin levels remained high. Further boluses of methylene blue were tried upto a cumulative dose of 7 mg/kg without consistent reduction of methemoglobin levels to normalcy. Glucose-6-phosphate dehydrogenase (G6PD) deficiency was ruled out. A hematologist consultation was obtained, and one cycle of plasmapheresis was attempted, but the level did not decrease. An exchange

Table 1: Patient characteristics and outcome

Cases	*Patient parameters*	*ICU course*	*ICU outcome*
1	74-year-old male Abamectin–avermectin group	Ventilated Methylene blue 3 mg/kg	Discharged alive on day 4
2	57-year-old male 1:2 compound	Ventilated Methylene blue 7 mg/kg One cycle plasmapheresis Two cycles of 1 L exchange transfusion	Discharged alive on day 30
3	33-year-old female 1:2 compound	Ventilated Methylene blue 7 mg/kg HBOT one session Three cycles of exchange transfusion (350 mL + 1 + 1 L)	Discharged alive on day 12

transfusion was done with 1 L of packed red blood cells (RBC) twice in a period of 2 days. Subsequently, the methemoglobin levels started to decrease, and they reached 10.3 after the second session. Gradually, the levels came down, and he didn't require further methylene blue or exchange transfusion. He had a drop in his hemoglobin level, suspected to be due to hemolysis because of the high lactate dehydrogenase levels, and the peripheral smear picture got corrected with 1 unit of packed RBC. We were not sure whether the hemolysis was because of methylene blue itself. He remained drowsy and irritable. Magnetic resonance imaging of the brain showed cerebral edema and punctate hemorrhagic foci involving splenium of the corpus callosum, suggestive of MetHb intoxication. He was tracheostomized on day 11, gradually weaned from the ventilator and shifted to the ward. Supportive measures continued in the ward, and over a period of 2 weeks, his sensorium got better, and he was decannulated and discharged home on day 30 of hospitalization without any morbidity.

Case 3

A 33-year-old female with no known comorbidities presented with alleged h/o consumption of approximately 100 mL of a pesticide (1:2 compound—containing bioemulsifier 6%, oligosaccharide—8%, and fillers/carriers—86%). At the local hospital, she was given stomach wash and activated charcoal and found to have central cyanosis of the lips and tongue. Hence, she was suspected of having MetHb, for which she was given three doses of IV methylene blue of 100 mg each over a span of 24 hours. As there was non-improvement, she was referred to our hospital for further management. On admission to ICU, GCS was 15/15, had SpO_2 of 80% in 10 L of O_2, and was hemodynamically stable. Co-oximetry showed MetHb levels of 30%. She was given 50 mg of IV methylene blue. G6PD levels were normal. Repeat co-oximetry showed a MetHb level of 9.9% but rose within 12 hours to 24.5%. An exchange transfusion was planned. Only 350 mL venesection was done, as blood pressure dropped drastically. It was managed with colloids, 1 unit of packed RBC, and fresh frozen plasma was transfused. Repeat MetHb was 36%, and the patient was becoming drowsy. Hence, another dose of IV methylene blue of 100 mg was given. Subsequently, MetHb decreased to 14.2. Though there was a response to methylene blue, the effect was not sustained and was reaching the toxic dose. A single session of HBOT at 2.2 two atmospheres absolute for 90 minutes was done. Post-HBOT, MetHb paradoxically increased to 21.1 and then 33.8%. So, IV methylene blue 50 mg was again given. Repeat MetHb was 10.2 and then 14.1%. High volume exchange transfusion was planned, 1 L venesection done, with two units packed RBC replacement, noradrenaline, and colloid cover. MetHb levels dropped to 13% but again increased to 19%. So, another session of exchange transfusion with 1 L venesection was done the next day, and subsequently MetHb dropped to 12.7% and remained low. In total, IV methylene blue was used six times (7 mg/kg), exchange transfusion was done three times, and one session of HBOT was given. At last, the MetHb level was 8.5%, stopped increasing and was shifted to the ward on day 7. In subsequent days methemoglobin levels dropped to 0.3%. The patient was weaned off oxygen support, discharged on day 12 of the hospital stay, with normal SpO_2 and remained stable on follow-up after 1 week.

Discussion

Methemoglobinemia (MetHb) is a condition where methemoglobin levels in the blood exceed normal levels of 2%. It may be due to congenital causes like the absence of nicotinamide adenine dinucleotide (NADH) dependent enzyme, cytochrome B5 reductase, inherited as autosomal recessive disorders.[2] NADH-dependent reduction is the main system responsible for 99% reduction of endogenous methemoglobin produced in the body.

Acquired causes include exposure to various drugs and chemicals, sepsis, infants with severe gastroenteritis and dehydration, and sickle cell crisis.[3] Pesticides being a cause for acquired MetHb is less known, incidence not clearly known, but an important fact to know in a country where they are extensively used for agriculture. Indoxacarb, aluminium phosphide, and paraquat are the commonly implicated insecticides for MetHb. Other agrochemicals containing biological extracts, stabilizers, and fillers, like the compound used in our patients, are also known to cause MetHb. Biological extracts are rich in nitrogenous products and hence can potentially cause MetHb.

Clinically, it results in low SpO_2 on pulse oximetry, development of cyanosis, and chocolate brown color of blood, with the normal partial pressure of oxygen and calculated SpO_2 on arterial blood gas analysis.[3] Acute MetHb should be suspected in patients with central cyanosis with low peripheral SpO_2 not responding to high-flow oxygen therapy. To determine the SpO_2, the oximeter calculates the ratio of absorbance at the two wavelengths. MetHb absorbs light equally at both 940 and 660 nm. In the presence of 100% MetHb, the ratio of absorbance of light at 660 over 940 nm is about 1.0. Therefore, at higher MetHb levels, SaO_2 tends toward 85% regardless of the true percentage of oxyhemoglobin.[4]

A difference of >5% between the SpO_2 by pulse oximetry and blood gas analysis is abnormal. Patients with clinically significant MetHb usually have a saturation gap greater than 10%. Co-oximetry measures SpO_2 using different wavelengths of light to distinguish between fractions of oxyhemoglobin, deoxyhemoglobin, and methemoglobin, but it is not widely available.[4]

Methylene blue is the antidote of choice for MetHb. This is an oxidant dye that channels the NADPH-reductase pathway, which is an

alternate pathway in the metabolism of endogenous methemoglobin. Methylene blue acts as a co-factor for this enzyme and is reduced to methylene leucoblue, which then acts as an electron donor for methemoglobin. Symptomatic MetHb or levels above 20% are treated with 1–2 mg/kg IV bolus over 5–10 minutes. This will bring down the methemoglobin levels in 30–60 minutes. Additional doses of 1 mg/kg bolus can be given after rechecking levels. The total dose should not exceed 7 mg/kg as this can lead to chest pain, dyspnea, hypotension, and hemolysis with Heinz bodies.[5] Still, this total cumulative dose is not clear as to the time span in which this dose is acceptable. The first case that we described, though, responded to methylene blue treatment alone; the response varied from our previous experiences by requiring repeated doses three times.

For refractory cases, such as our second and third cases, not improving with methylene blue, the next option is to consider either HBOT, plasmapheresis, or exchange transfusion.[6] There are multiple case reports published on the use of HBOT, but there is no clear recommendation for its use.[7,8] HBOT is not commonly available in all the centers, and the dose and treatment protocol are not clearly defined. The efficacy of hyperbaric oxygen is also not proven. In one of our patients described with refractory MetHb, we tried one session of HBOT, and it did not even have a temporary response.

In a systematic review, therapeutic whole blood exchange (TWBE) led to a survival rate of 81.6% in patient's refractory to methylene blue.[9,10] TWBE, though it has good efficacy, still has setbacks like the availability of good blood bank support and the difficulty of the technique when the special exchange equipment is not available. The exact volume to be exchanged and the number of sessions is also not validated. The complications during the procedure, such as hypotension, need close monitoring in ICU, and we encountered it in our last patient in the first session where we reduced the volume exchanged, and it did not have a desirable effect. The subsequent sessions were done with a dialysis line dedicated to the exchange and adequately volume resuscitating the patient simultaneously with colloids. In both the refractory patients where we tried exchange transfusion, two good, carefully performed sessions of 1 L exchange on subsequent days were found to be efficacious without many complications. Plasmapheresis was tried in one of the refractory patients but was not beneficial. Methylene blue use is contraindicated in G6PD deficient patients and makes it mandatory to consider exchange transfusion as the option in higher levels of symptomatic MetHb.

Conclusion

Pesticide poisoning is a rarely reported cause of acquired MetHb. A high index of suspicion in these patients leads to early diagnosis and appropriate management. Methylene blue can be used to treat this condition when the patient is symptomatic, or levels of methemoglobin exceed 20%. Monitoring of methemoglobin levels may be required for a longer duration due to the possibility of relapse. For refractory cases not improving with methylene blue, exchange transfusion is an effective alternate modality of treatment.

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References

1. Darling RC, Roughton FJW. The effect of methemoglobin on the equilibrium between oxygen and hemoglobin. Am J Physiol 1942;137(1):56–58. DOI: 10.1152/ajplegacy.1942.137.1.56
2. Yubisui T, Takeshita M, Yoneyama Y. Reduction of methemoglobin through flavin at the physiological concentration by NADPH-flavin reductase of human erythrocytes. J Biochem 1980;87(6):1715–1720. DOI: 10.1093/oxfordjournals.jbchem.a132915
3. Garg D, Edwin N. A case report of methemoglobinemia due to benzonitrile. J Clinic Toxicol 2012;2(4):131. DOI: 10.4172/2161-0495.1000131
4. Barker SJ, Tremper KK, Hyatt J. Effects of methemoglobinemia on pulse oximetry and mixed venous oximetry. Anesth 1989;70(1):112–117. DOI: 10.1097/00000542-198901000-00021
5. Monechi G, Fabrizi de Biani G, Colasanti L. A case of methemoglobinemia due to 4-nitrobenzonitrile exposure. Med Lav 1991;82(2):137–141.
6. Iolascon A, Bianchi P, Andolfo I, et al. Recommendations for diagnosis and treatment of methemoglobinemia. Am J Hematol 2021;96(12):1666–1678. DOI: 10.1002/ajh.26340
7. Cho Y, Park SW, Han SK, et al. A case of methemoglobinemia successfully treated with hyperbaric oxygenation monotherapy. J Emerg Med 2017;53(5):685–687. DOI: 10.1016/j.jemermed.2017.04.036
8. Lindenmann J, Matzi V, Kaufmann P, et al. Hyperbaric oxygenation in the treatment of life-threatening isobutyl nitrite-induced methemoglobinemia—a case report. Inhal Toxicol 2006;18(13):1047–1049. DOI: 10.1080/08958370600904629
9. Singh P, Rakesh K, Agarwal R, et al. Therapeutic whole blood exchange in the management of methaemoglobinemia: case series and systematic review of literature. Transfus Med 2020;30(3):231–239. DOI: 10.1111/tme.12666
10. Bhasker B, Ramakrishna AA. Therapeutic whole blood exchange using plasma exchange kit on a cell separator in a patient with refractory methemoglobinemia. Transfus Apher Sci 2020;59(6):102910. DOI: 10.1016/j.transci.2020.102910