The diagnostic clues of acquired methemoglobinemia in herbicide-induced poisoning: A case report with literature review

Mohd Fazrul M.[1], Fatinhanim AS[2], Nursaleha MP[2]

Abstract

Methemoglobinemia has been linked to many substances, such as antibiotics, local anesthetics, and industrial chemicals. It is an altered state of hemoglobin whereby oxygen delivery to tissues is impaired. Diagnosis of methemoglobinemia is often difficult due to its non-specific symptoms, coupled with the absence of accurate history and the non-availability of the diagnostic test. We report a case of methemoglobinemia in a schizophrenic patient who deliberately ingested herbicide containing N-(3,4-dichloropropionanilide) or propanil. Toxicity from herbicides containing propanil is under-reported in Malaysia, especially propanil-induced methemoglobinemia. Low oxygen saturation was seen even at a methemoglobin level of 8.4%. Early recognition of such poisoning and early administration of methylene blue remains the mainstay of treatment. Recognizing the chemical contents of herbicide is important to explain the clinical abnormalities of a poisoned patient.

Key words: Methemoglobin, methemoglobinemia, propanil, herbicides.

Introduction

Poisoning by pesticides has been a major concern in many developing nations. Self-poisoning is the leading cause of death, while occupational and accidental poisonings are widespread. Propanil [N-(3,4-dichloropropionanilide)] is a widely used herbicide for rice cultivation. Propanil and its primary metabolite, 3,4-dichloroanilide salt, stimulate the conversion of Fe^{2+} to Fe^{3+} in hemoglobin, resulting in the formation of methemoglobin (MetHb) and a decrease in the oxygen-carrying capacity of the blood. Upon exposure to this oxidizing chemical, the onset of hypoxia symptoms is typically quite sudden. However, the diagnosis of methemoglobinemia is often difficult due to its non-specific symptoms, coupled with the absence of accurate history and the non-availability of the diagnostic test. We report a case of propanil-induced methemoglobinemia.

Case presentation

A 21-year-old male with underlying schizophrenia and not receiving treatment was presented for alleged herbicide ingestion. He was discovered semi-conscious in his residence, with vomitus on the floor. A bottle labeled 'Satunil' was found alongside him, and he smelled strange. 'Satunil' is a herbicide that contains 40% thiobencard and 20% propanil.

Upon arrival, the Glasgow coma score (GCS) was E3V3M6, he was pink, and his pupils were normal. The oxygen saturation under room air was 100%. Other parameters were within normal limits. The capillary blood glucose was 9.4 mmol/l. Systemic examinations were unremarkable. While early resuscitation steps were carried out, external decon-

[1.] Department of Emergency Medicine, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh Campus, Selangor Branch, Selangor, Malaysia
[2.] Department of Emergency and Trauma, Hospital Queen Elizabeth, Kota Kinabalu, Sabah, Malaysia

Address for correspondence:
Mohd Fazrul Mokhtar
Department of Emergency Medicine, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh Campus
Jalan Hospital, Sungai Buloh, Selangor, Malaysia
Email: fazrul2293@uitm.edu.my

tamination using water and soap was also performed.

During venipuncture, we observed that his blood sample was brown in color. The first blood gas showed metabolic acidosis with a normal partial pressure of oxygen (PaO2) and arterial oxygen saturation (SaO2) levels. Considering the effect of propanil, the MetHb level was sent, and it was elevated (8.4%). The urine paraquat test was negative. The glucose-6-phosphate dehydrogenase (G6PD) was normal.

Subsequently, he desaturated. The pulse oxygen saturation (SpO2) ranged between 80% to 85%, with a good normal PaO2 and SaO2. He was subsequently started on intravenous methylene blue. After a few days, he regained consciousness, and the oxygen supplement was weaned. The MetHb level was reduced from 8.4% to 1.4%.

Discussion

Methemoglobinemia is a condition whereby there is an increased MetHb level in the blood. This condition may result from congenital disease due to a lack of certain enzymes that protect hemoglobin from oxidation reactions or abnormal structure of hemoglobin molecules. This process may also be acquired from poisoning. Examples include poisoning from antimalarial agents, (1,2) topical anesthetics, (3) inhaled nitric oxide, (4) and agrochemicals. These agents increase the rate of hemoglobin oxidation by 100 to 1000 times, thus surpassing the body's natural protective ability. (5)

There are many case reports of agrochemical ingestions as the cause of methemoglobinemia. (6-8) However, propanil-induced methemoglobinemia is rarely discussed in toxicology textbooks, and there are only a few case reports in the literature search. “Satunil” is a widely used herbicide in rice cultivation. It contains thiobencarb 40% and propanil 20%. Local data from a single center in India showed 16 admissions for severe propanil poisoning between 1998 and 2002, with more than half being brought to intensive care units and seven deaths occurring within 24 hours of ingestion. (9) Confusion, decreased consciousness level, cyanosis, and respiratory depression were common clinical characteristics.

MetHb is the oxidized form of hemoglobin where the heme ferrous ion (Fe^{2+}) is oxidized to a ferric state (Fe^{3+}), so it cannot bind oxygen. This ferric ion also causes a change in the structure of the heme portion of partially oxidized hemoglobin. It increases its oxygen affinity, thus hindering the release of oxygen into the tissues. Naturally, hemoglobin is constantly oxidized; however, a few regulatory systems help maintain the levels of MetHb under 2%. (10,11) A concentration below 2% is considered physiological, while a level of 10%-20% generally causes cyanosis. A level of 20%-70% may cause respiratory disorders, and a level above 70% is generally fatal. In this case, we observed a patient with altered consciousness and low SpO2 with a MetHb level of 8.4%.

Poisoning is a huge public health issue that affects people of all ages. Poisoned patients frequently present to the Emergency Department (ED); hence a quick diagnosis and therapy are critical to achieving the best possible outcomes. The situation may pose a challenge if there are no witnesses to the incident, no drug or chemical found at the site, and the non-specific clinical findings of the patient. Our patient was found together with the insecticide and was semi-conscious. The findings of brown-colored blood also provided a helpful clue. In contrast to the dark red-violet of deoxygenated blood, blood carrying high amounts of MetHb appears brown. Two drops of our patient’s blood were placed on a white filter paper by the bedside as we observed MetHb retained its brownish color over time. In contrast, deoxyhemoglobin will appear dark red-violet but brightens following contact with oxygen. (12)

At the time of the patient's arrival, the pulse oximetry measurement was 100%; nevertheless, this value declined with time. This phenomenon can be explained when the pulse oximeter measures light absorbance at two wavelengths, i.e., 660 nm and 940 nm. In this wavelength range, both oxy- and deoxyhemoglobin absorb light. MetHb absorbs nearly equal amounts of light at 660 and 940 nm. In the presence of lower levels of MetHb, pulse oximetry results are comparable to those of healthy individuals. However, when MetHb levels reach 30 to 35%, light absorption reaches a plateau, and the pulse oximeter reading stabilizes in the 82-86% range, regardless of real MetHb levels. Only deoxyhemoglobin can bring the pulse oximeter measurement below this threshold. (12) As a result, the pulse oximeter measurement can be erroneous; it can detect high amounts of MetHb as mild to moderate oxygen desaturation, but it cannot determine the exact concentration of MetHb in the blood.

We also noticed an “oxygen saturation gap” whereby the patient had low SpO2 with a normal PaO2 and SaO2 measured on the arterial blood gas analysis. PaO2 refers to dissolved gas and not to oxygen molecules bound to hemoglobin. The "saturation gap" is the disparity between the depressed SpO2 measurement and the falsely normal SaO2 computation. This extra diagnostic clue should indicate the existence of hemoglobinopathies such as

carbon monoxide poisoning, methemoglobinemia, or sulfhemoglobinemia. In humans, the severity and symptoms of propanil poisoning differ depending on MetHb levels.

Treatment is supportive. For severe symptoms and/or MetHb levels above 30%, methylene blue is recommended and served either orally or intravenously (grade 2C). Repeating dosing may be required based on the patient's progression and MetHb levels. However, methylene blue is contraindicated for persons with G6PD deficiency because it may promote hemolysis. We recommend ascorbic acid for those with severe or symptomatic methemoglobinemia who should not get methylene blue (grade 2B).

Conclusion

MetHb can be life-threatening; thus, recognizing the chemical contents of a herbicide is important in a poisoned patient. Rapid diagnosis and early intervention with antidote therapy could prevent a fatal outcome.

References

1. Naymagon L, Berwick S, Kessler A, Lancman G, Gidwani U, Troy K. The emergence of methemoglobinemia amidst the COVID-19 pandemic. Am J Hematol 2020;95:E196-7.
2. Kuipers MT, van Zwieten R, Heijmans J, Rutten CE, de Heer K, Kater AP, et al. Glucose-6-phosphate dehydrogenase deficiency-associated hemolysis and methemoglobinemia in a COVID-19 patient treated with chloroquine. Am J Hematol 2020;95:E194-6.
3. Kane GC, Hoehn SM, Behrenbeck TR, Mulvagh SL. Benzocaine-induced methemoglobinemia based on the Mayo Clinic experience from 28 478 transesophageal echocardiograms: incidence, outcomes, and predisposing factors. Arch Intern Med 2007;167:1977-82.
4. Bizzarro M, Gross I, Barbosa FT. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. Cochrane Database Syst Rev 2014:CD005055.
5. Baraka AS, Ayoub CM, Yazbeck-Karam V, Kaddoum RN, Gerges FJ, Hadi UM, et al. L'administration prophylactique de bleu de méthylène chez un patient atteint de méthémoglobinémie congénitale. Can J Anaesth 2005; 52:258-61.
6. Casey PB, Buckley BM, Vale JA. Methemoglobinemia following ingestion of a monolinuron/paraquat herbicide (Gramonol). J Toxicol Clin Toxicol 1994;32:185-9.
7. Sun KH, Kim JK, Ryu CY, Kim SJ, Jo HK, Yoo TH, et al. A Case of a Herbicide Poisoning Induced Methemoglobinemia Patient Treated with High-dose Vitamin C. J Korean Soc Clin Toxicol 2017;15:148-51.
8. Sudheer VR, Krishnapriya R, Kumar NV, Umarani R. Management of Herbicide Induced Methemoglobinemia. J Drug Metab Toxicol 2018;9:1-2.
9. Eddleston M, Rajapakshe M, Roberts D, Reginald K, Sheriff MHR, Dissanayake W, et al. Severe Propanil [N-(3,4-dichlorophenyl) propanamide] Pesticide Self-Poisoning. J Toxicol Clin Toxicol 2002;40:847-54.
10. Chui JSW, Poon WT, Chan KC, Chan AYW, Buckley TA. Nitrite-induced methaemoglobinaemia - aetiology, diagnosis and treatment. Anaesthesia 2005;60:496-500.
11. Suyama H, Morikawa S, Noma-Tanaka S, Adachi H, Kawano Y, Kaneko K, et al. Methemoglobinemia induced by automobile exhaust fumes. J Anesth 2005;19:333-5.
12. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: Etiology, Pharmacology, and Clinical Management. Ann Emerg Med 1999;34:646-56.