Original Research Paper

Volume - 13 | Issue - 10 | October - 2023 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Emergency Medicine

A RARE CAUSE OF REFRACTORY HYPOXIA

Dr. M. Ravi Krishna* Lead Consultant, Department Of Critical Care Medicine, KIMS ICON Hospital, Visakhapatnam. *Corresponding Author

Dr. Ravi Kanna Consultant, Department Of Internal Medicine, KIMS ICON Hospital, Visakhapatnam.

ABSTRACT Acquired methemoglobinemia is a rare but potentially life-threatening condition that is frequently associated in the primary care setting with topical anesthetics, dapsone, and antimalarial agents. This case report shows that recognition of acquired methemoglobinemia in a patient with sudden onset of cyanosis requires a high index of suspicion and a series of clinical and laboratory tests to exclude the most common causes. The definitive diagnosis is made using co-oximetry and detecting methemoglobin levels in the blood. The clinical presentation of methemoglobinemia varies from fatigue, anxiety, and dizziness, to disorders of consciousness, epileptic seizures, arrhythmia, and coma. The severity of symptoms is varied and depends on the percentage of methemoglobinemia in blood, the patient's hemoglobin level, and cardiopulmonary reserve. Treatment is primarily based on supportive care and discontinuation of the drug or substance that led to this condition.

KEYWORDS : hypoxia, methemoglobinemia, methylene blue, co-oxymetry

INTRODUCTION

Methemoglobinemia is a dangerous but uncommon condition that can be caused by medications such as topical anesthetics, dapsone, and antimalarial agents.

A 35-year-old man presented to the emergency department with an acute onset of breathlessness. Symptoms started approximately 1 hour after accidental exposure to N- (4-(Difluoromethoxy)-2-nitrophenyl) acetamide.

The patient maintained normal blood pressure (134/88 mm Hg) and heart rate (88/min) but was tachypneic, hypoxic (SpO2 82%). Physical examination findings were notable for acrocyanosis, and he was given 15 Lpm of oxygen via a non rebreathing mask. Upon obtaining an arterial blood specimen, a dark brown blood color was noticed.

Arterial blood gas was measured and showed a pH of 7.40, a Pco2 of 39.9 mm Hg, a bicarbonate level of 17 mmol/L, and a Po2 of 289.0 mm Hg with SaO2 of 98% with a lactate of 4 mmol/L. Chest X-ray, ECG and echocardiography were normal. Additional bloodwork results were unremarkable. In view of the SaO2- SpO2 gradient, a co-oximetry was also done, identified a methemoglobin level of 44.3%. G6PD levels were within normal limits. Slow intravenous injection of methylene blue 2 mg/kg over 15 min was started. The peripheral oxygen saturation (SpO2) gradually improved to 100% over the next 20 min. 8hrs later, blood gas analysis showed a methemoglobin level of 3.5% with a complete resolution of cyanosis; supplemental oxygen was, therefore, discontinued. During the next 36 h, the patient remained hemodynamically stable with good oxygenation on room air.

A man, 28, came to the ER with headache and loss of consciousness after being accidentally exposed to N-(4-(Difluoromethoxy)-2-nitrophenyl)acetamide.

The patient maintained normal blood pressure (RR 134/88 mm Hg) and heart rate (c/p 88/min) but was tachypneic, hypoxic (SpO2 82%). Physical examination findings were notable for acrocyanosis, and he was given 15 Lpm of oxygen via a non rebreathing mask. Upon obtaining an arterial blood specimen, a dark brown blood color was noticed.

Arterial blood gas was measured and showed a pH of 7.40, a Pco2 of 39.9 mm Hg, a bicarbonate level of 18 mmol/L, and a Po2 of 289.0 mm Hg with SaO2 of 98% with a lactate of 4 mmol/L. Chest X-ray, ECG and echocardiography were normal. Additional bloodwork results were unremarkable. In view of the SaO2- SpO2 gradient a co-oxymetry test was also done, identified a methemoglobin level of 28%. Slow intravenous injection of methylene blue 2 mg/kg over 15 min was started. G6PD levels were within normal limits. The peripheral oxygen saturation (SpO2) gradually improved to 100% over the next 20 min. 8hrs later, blood gas analysis showed a methemoglobin level of 3.2% with a complete resolution of cyanosis; supplemental oxygen was therefore, discontinued. During the next 36 h, the patient remained hemodynamically stable with good oxygenation on room air.

Co- Oxymetry Values Of Patient 1

Blood Gas	Pre-Treatment	Post-Treatment
pH	7.522	7.42
PCO2 mmHg	23.6	37.5
PO2 mmHg	147	112
ctHb g/dL	13.5	13.6
sO2 (%)	90.2	93.5
FO2Hb (%)	52.4	90.6
FCOHb (%)	0	0.4
FHHb (%)	3.3	6.3
FMetHb (%)	44.3	3.5
cLat mmol/L	1.9	1.4
cBase (Ecf),c mmol/L	-3.2	-0.3
cHCO3− (P,st),c mmol/L	19.3	23.9

Co- Oxymetry Values Of Patient 2

Blood Gas	Pre-Treatment	Post-Treatment
pH	7.374	7.395
PCO2 mmHg	34	39.4
PO2 mmHg	96.3	112
ctHb g/dL	10.2	10.6
sO2 (%)	94	92
FO2Hb (%)	69.4	91.5
FCOHb (%)	0.6	4.3
FHHb (%)	4.9	3.3
FMetHb (%)	25.1	0.9
cLat mmol/L	1.8	1.3
cBase (Ecf),c mmol/L	-4.7	-0.6
cHCO3− (P,st),c mmol/L	19.3	23

DISCUSSION

This case report shows that recognition of acquired methemoglobinemia in a patient with sudden cyanosis onset requires a high index of suspicion and a series of clinical and laboratory tests to exclude the possibility that cyanosis can depend on cardiovascular and/or respiratory problems.

Any cyanotic-appearing patient without demonstrable respiratory or cardiac disease whose SpO2 does not normalize with the administration of supplemental oxygen should raise the suspicion of methemoglobinemia. Clues that could help with diagnosis include brown blood, normal PaO2 levels, and an oxygen saturation gap of at least 5%.

However, particular attention must be paid to the methemoglobinemia pathogenesis to avoid the risk of recurrence.

Pathophysiology

Methemoglobin is an altered conformation of hemoglobin in which the

ferrous (Fe2+) state is oxidized to the ferric (Fe3+) state. The ferric heme in methemoglobin is unable to bind oxygen, resulting in an altered structure. The molecule has a stronger bond with oxygen, which shifts the oxygen dissociation curve to the left and disrupts oxygen delivery to tissues.

Under normal circumstances, a small amount of iron is oxidized to the ferric [Fe3+] state during the routine delivery of oxygen to tissue. Maintenance of methemoglobin levels is usually below 1% through the action of the enzyme cytochrome-b5 reductase. Cytochrome-b5 reductase utilizes NADH formed during glycolysis to reduce methemoglobin back to functional hemoglobin.[3]

An alternate pathway for the reduction of methemoglobin is through the function of nicotinamide adenine dinucleotide phosphate hydrogen methemoglobin (NADPH-MetHb) reductase. NADPH-MetHb reductase uses NADPH made by G6PD in the hexose monophosphate shunt.

Under normal physiologic circumstances, NADPH-MetHb reductase contributes very little to the reduction of methemoglobin, but under oxidative stress, the function of this alternative reduction pathway can be enhanced by the presence of exogenous electron donors, such as methylene blue.

Toxicokinetics

Methemoglobinemia secondary to toxic exposures occurs when cytochrome-b5 reductase's ability to reduce ferric hemoglobin, or methemoglobin, is overwhelmed by the induced oxidant stress. N-(4-(Difluoromethoxy)-2-nitrophenyl) acetamide may produce harmful gases like nitrogen oxides that can cause methemoglobinemia.

Table 1: Drugs Associated With Methemoglobinemia

Drug group	Examples
Local anesthetics	Benzocaine (often used in endoscopic procedures) Prilocaine, tetracaine, lidocaine
Nitrates	Nitroglycerin Inhaled nitric oxide Nitroprusside, oral nitrates, amyl-nitrate
Antibiotics	Dapsone Rifampicin, sulfonamides, antimalarials
Other drugs	Rasburicase (especially in G6PD deficiency) Oncological drugs: cyclophosphamide Metoclopramide Various drugs in which some oxidizing substance is used in the making
environmental/occupational exposures	Fertilizers, weed killers. Plastics. Dyes, paints, rubber.

The symptoms of methemoglobinemia vary and depend on the level of methemoglobin, the patient's usual hemoglobin level, and cardiovascular reserve. The normal percentage of methemoglobin is below 25%.

Table 2: Methemoglobin Level & Relationship To Symptoms

Range	symptoms
3-15%	Asymptomatic. Cyanosis can occur at levels above 5-10%
20-30%	Moderate symptoms. Fatigue, tachypnea, dyspnea, tachycardia. Anxiety, dizziness, confusion. Nausea, vomiting.
>40%	Severe symptoms can occur: Seizure, coma. Arrhythmia. Hyperlactatemia. Death.

The final diagnosis is made using co-oximetry, but clinical suspicion itself can be made based on the following three entities:

Refractory hypoxia: methemoglobinemia can typically be suspected in a patient with oxygen saturation between 82-86%, who is at high oxygen flows (FiO2 100%), and no other explanation for hypoxia.

"Cyanosis-saturation gap": methemoglobinemia leads to the development of central cyanosis (attention to the color of the tongue). Oxygen saturation of 80-90% usually does not lead to cyanosis, so patients with 80-90% saturation who present with central cyanosis are clinically suspicious of methemoglobinemia.

Brown blood color: methemoglobinemia causes a change of blood color to chocolate-like. Also, if we put a patient's blood on white gauze, the blood will remain brown when dry, unlike deoxygenated blood, which will absorb oxygen in the air and turn red again.

Diagnosis

There are a variety of approaches, which may depend on local resources and pre-test probability.

Simple tests can be used for rough assessment, which, based on the color of the blood on a white paper, provide an estimate of the level of methemoglobinemia.

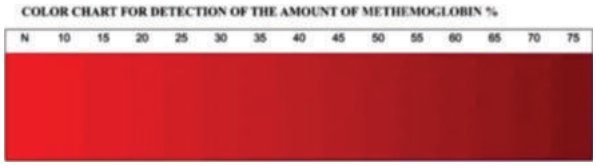

Figure 1: Color Shades And The Level Of Methemoglobin

Treatment:

Treatment of methemoglobinemia is primarily based on supportive care and discontinuation of the drug or substance use that leads to this condition. The drug of choice for treating methemoglobinemia is methylene blue, which reduces it to a non-oxidized state. Methylene blue, along with nicotinamide-adenine dinucleotide phosphate (NADPH), is a co-factor of the enzyme NADPH-methemoglobin reductase. It works by accepting an electron from NADPH and in this form reduces trivalent iron from ferric form to ferrous form.[4]

Figure 2: Mechanism Of Action Of Methylene Blue

The use of methylene blue is indicated in symptomatic methemoglobinemia regardless of methemoglobin level, and in cases where the methemoglobin level is above 30%. The drug is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and caution is required in patients at risk of developing serotonin syndrome. Methylene blue is a monoamine oxidase (MAO) inhibitor and can lead to the development of serotonin syndrome in interaction with other drugs. The drug dose is 1-2 mg/kg IV over five minutes, while the clinical effect is visible within a few minutes. Cyanosis resolves within one hour after drug delivery. The drug can lead to a dip in oxygen levels because it turns the blood blue, which interferes with the accuracy of pulse oximetry readings. The drug can be administered again after 60 minutes if the patient is still cyanotic, although a dose failure of 2 mg/kg raises suspicion of G6PD deficiency. Rebound-methaemoglobinaemia may recur within 12 hours after drug administration, after which continuous infusion of methylene blue may be considered[5] treatment options in G6PD deficient patients.

The following treatments are safe and should arguably be used (but may not be the most effective):

(a) IV vitamin C is a reducing agent which doesn't require NADPH. Doses vary widely in the literature, but ~1.5-3 grams IV q6hr seems reasonable.[6–8]
(b) Riboflavin (vitamin B2) can function as an electron shuttle, analogous to methylene blue. This seems to be an acceptable treatment here (although theoretically it could cause the same problem as methylene blue with regard to NADPH depletion).
(c) Trial of methylene blue might be considered
(d) Exchange transfusion

(e) Hyperbaric oxygen therapy

Side effects of methylene blue are as follows: systemic and/or pulmonary hypertension (via a reaction that prevents nitric oxide-mediated vasodilation), motor restlessness, dyspnea, nausea, vomiting, sweating, and anaphylaxis.

CONCLUSION

Methaemoglobinaemia is a rare disorder characterized by elevated levels of methemoglobin, a hemoglobin molecule that contains an oxidized form of iron that cannot bind oxygen and results in an inadequate oxygen supply to tissues. Acquired methemoglobinemia, on the other hand, is an acute condition that is most often the result of poisoning by certain drugs and compounds, which can be fatal. The severity of symptoms depends on the percentage of methemoglobin in the blood, and clinical presentation varies from fatigue, anxiety, dizziness, and cyanosis, to qualitative disorders of consciousness, epileptic seizures, arrhythmia, and coma.

Unexplained symptoms of refractory hypoxia, cyanosis-saturation gap, and chocolate-colored blood may raise suspicion of methemoglobinemia, but the definitive diagnosis is made using co-oximetry and detecting methemoglobin levels in the blood. Treatment of methemoglobinemia is based on supportive care and discontinuation of the drug or substance that led to this condition.

Despite being a rare condition, acquired methemoglobinemia can be a life-threatening condition and emergency services should be provided with antidotes - methylene blue and vitamin C

REFERENCES

1. Ash-Bernal R, Wise R, Wright SM. Acquired methemoglobinemia: a retrospective series of 138 cases at 2 teaching hospitals. Medicine [Internet]. 2004 Sep [cited 2023 Jul 11];83(5):265–73. Available from: https://pubmed.ncbi.nlm.nih.gov/15342970/
2. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: Etiology, pharmacology, and clinical management. Ann Emerg Med [Internet]. 1999 [cited 2023 Aug 19];34(5):646–56. Available from: https://pubmed.ncbi.nlm.nih.gov/10533013/
3. Skold A, Cosco DL, Klein R. Methemoglobinemia: pathogenesis, diagnosis, and management. South Med J [Internet]. 2011 Nov [cited 2023 Aug 19];104(11):757–61. Available from: https://pubmed.ncbi.nlm.nih.gov/22024786/
4. Benzocaine-induced methemoglobinemia in an adult: accuracy of pulse oximetry with methemoglobinemia - PubMed [Internet]. [cited 2023 Aug 19]. Available from: https://pubmed.ncbi.nlm.nih.gov/3189900/
5. Severe Methemoglobinemia and Hemolytic Anemia from Aniline Purchased as 2C-E (4-ethyl-2,5-dimethoxyphenethylamine), a Recreational Drug, on the Internet — Oregon, 2011 [Internet]. [cited 2023 Aug 19]. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6105a1.htm
6. Marik PE. Is intravenous vitamin C contraindicated in patients with G6PD deficiency? Crit Care [Internet]. 2019 Apr 3 [cited 2023 Aug 19];23(1). Available from: https://pubmed.ncbi.nlm.nih.gov/30944032/
7. Reeves DJ, Saum LM, Birhiray R. I.V. ascorbic acid for treatment of apparent rasburicase-induced methemoglobinemia in a patient with acute kidney injury and assumed glucose-6-phosphate dehydrogenase deficiency. Am J Health Syst Pharm [Internet]. 2016 May 1 [cited 2023 Aug 19];73(9):e238–42. Available from: https://pubmed.ncbi.nlm.nih.gov/27099330/
8. Rehman A, Shehadeh M, Khirfan D, Jones A. Severe acute haemolytic anaemia associated with severe methaemoglobinaemia in a G6PD-deficient man. BMJ Case Rep [Internet]. 2018 [cited 2023 Aug 19];2018. Available from: https://pubmed.ncbi.nlm.nih.gov/29592989/