Syncope and Methemoglobinemia Preceded by Amyl Nitrite 'Popper' Inhalation

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ABSTRACT

INTRODUCTION: Methemoglobinemia represents an uncommon but potentially serious cause of presentation to the emergency department, resulting in hypoxemia and even death. The symptoms and clinical findings in this condition can be nonspecific and therefore methemoglobinemia can be easily missed if the clinician is not familiar with it. This report presents a case caused by recreational drug use which has rarely been documented previously.

CASE REPORT: A 23-year-old male with a history of asthma presents to the emergency department for an episode of syncope after inhalation of amyl nitrite "poppers". He had normal vitals other than tachycardia but was found to have nailbed and perioral cyanosis, a classic but uncommon presentation that is demonstrated in the included clinical image. He was found to have methemoglobinemia caused by his use of amyl nitrite and received supportive care but did not require methylene blue.

CONCLUSION: Emergency physicians should familiarize themselves with the classic physical exam findings in methemoglobinemia in order to identify and treat this condition promptly. While this patient had a good outcome with only supportive care and observation, his presentation and the etiology of his condition offer an important teaching point. The possibility of methemoglobinemia after recreational "popper" use should be considered when working up a patient who presents with cyanosis and hypoxemia.

KEYWORDS: methemoglobin, amyl nitrite, inhalants, case report

INTRODUCTION

Methemoglobinemia refers to the condition where the iron in hemoglobin is oxidized, impairing its ability to carry oxygen and carbon dioxide.[1] It is uncommon but potentially life threatening as it causes hypoxemia, and therefore it is important for emergency physicians to be confident in diagnosing this condition. Unfortunately, patients with methemoglobinemia can present with nonspecific symptoms and have unusual pulse oximeter and blood gas findings, and there are a wide variety of causes which makes focused history-taking difficult. Environmental triggers include oxidizing agents such as nitrites, but genetic and dietary causes are also possible.

Recreational drugs have been implicated in methemoglobinemia, as well. Inhaled nitrites or "poppers" are a class of recreational drugs that cause vasodilation, producing a sensation of warmth and lightheadedness. They are sometimes used by men who have sex with men to facilitate anal intercourse due to their effects on the anal sphincter.[2] Since they are nitrites, they can have oxidizing effects on hemoglobin and cause methemoglobinemia. This report describes a case of methemoglobinemia that occurred after inhalation of amyl nitrite, a rare but serious complication of recreational "popper" use.

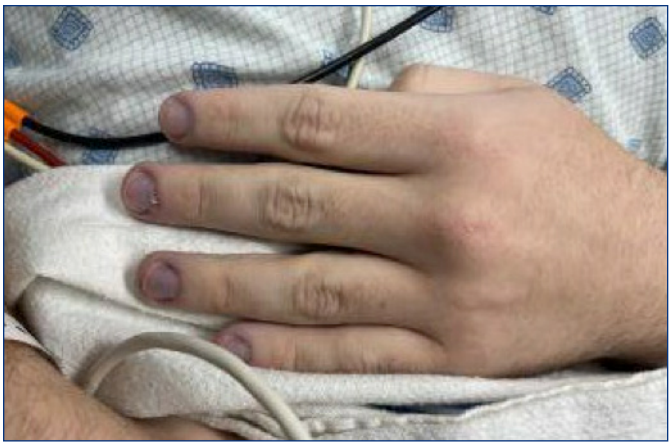
The cyanotic appearance of the patient's nailbeds on physical exam is documented in the clinical image, which is a classically reported finding that is rarely observed in practice. While the patient ultimately required only supportive care, learning about his clinical course will offer the emergency clinician a framework for diagnosing and managing this condition.

CASE REPORT

A 23-year-old male with a past medical history of asthma and depression presented to the emergency department for an episode of syncope followed by cyanosis of his fingernails. He reported that he had been "huffing poppers" earlier, which he and his partner do regularly for sexual enhancement. He had used three of them. Soon afterwards, he got in the shower, but felt lightheaded and transiently lost consciousness. He denied striking his head or sustaining any traumatic injuries. His partner reported that he quickly regained consciousness and behaved normally within seconds. He denied shortness of breath, palpitations, or chest pain. He would not have come to the hospital, but he noted that his fingernails were blue, and he became concerned.

On arrival, the patient appeared pale but was alert and in no acute distress. His vital signs were notable for tachycardia but were otherwise within normal limits. On examination, he was found to have blue nail beds and perioral cyanosis but had no evidence of trauma and no other significant findings

Figure 1. Nail bed cyanosis on presentation to the ED



(**Figure 1**). His EKG showed sinus tachycardia with normal intervals and no ischemic changes. The patient's medications included duloxetine and albuterol as needed and he was a non-smoker.

Laboratory studies, including a CBC, CMP, lactate, troponin, carboxyhemoglobin, ethanol, acetaminophen, salicylates, and urine drug screen were normal. A venous blood gas demonstrated a pH of 7.36 and pCO2 of 47 mmHg (normal), but his pO2 and O2 saturation were low at <30 mmHg and 41%, respectively. His methemoglobin level on arrival was 25.6% (normal range 0–1.8%), confirming a diagnosis of methemoglobinemia. His cyanosis was attributed to his use of inhaled amyl nitrite. The etiology of his syncope was felt to be vasovagal due to the combined vasodilatory effects of amyl nitrite and the hot shower.

Because of the short half-life of both amyl nitrite and methemoglobin (both about one hour), poison control recommended foregoing treatment for the methemoglobinemia as the patient did not requiring supplemental oxygen and was minimally symptomatic. He was admitted to the internal medicine service and was monitored and treated with IV fluids. At 2 hours from arrival his methemoglobin level was 13.4%, which continued to downtrend to 2.5% at 6 hours and 1.7% at 12 hours. The next morning his cyanosis had resolved and his vital signs were within normal limits, so he was discharged home.

DISCUSSION

Methemoglobinemia can be due to a variety of causes including genetic or dietary but is commonly caused by exposure to an oxidizing chemical.[1] The most common categories of causative agents in the National Poison Data System include benzocaine, phenazopyridine, dapsone, and nitrites. **Table 1** summarizes common triggers.[3] Mild cases of methemoglobinemia can present with cyanosis, dyspnea, headache, and anxiety, while higher levels of methemoglobin can lead to arrythmias, acidosis, seizures, and coma. Pulse oximetry may show slightly reduced oxygen saturations, but at moderate to severe levels of methemoglobinemia will frequently over-estimate oxygen saturation. Co-oximetry is an accurate method of measuring levels of methemoglobin, and lab tests can determine the concentration of methemoglobin in the blood.[1] Interestingly, the patient in this case had a low pO_2 on presentation, an unexpected finding in this condition as methemoglobin is unable to transport and release O_2 effectively but does not affect the amount of oxygen in the blood. Typically, the pO_2 would be normal or even elevated in a patient with this condition.

Table 1. Common triggers of methemoglobinemia.[4]

Anesthetics	Benzocaine
	Prilocaine
Analgesics/anti-pyretics	Phenacetin
Antibiotics/anti-infectives	Trimethoprim
	Ciprofloxacin
	Dapsone
	Sulfonamides
	Primaquine
	Nitrofurantoin
	Chloroquine
Antiemetics	Metoclopramide
Psych/neurologic drugs	Phenelzine
	Phenobarbital
Cardiac drugs	Nitroglycerine
	Isosorbide dinitrate
	Nitroprusside
Environmental/occupational	Naphthalene
	Acetanilide
	Amyl nitrate
	Aniline
	Chlorate

Treatment for methemoglobinemia should begin with supportive care, including intravenous fluids and oxygen supplementation. Glucose supplementation may also be indicated, as endogenous reducing enzymes must have adequate glucose available. This is also important for the production of NADPH in the case of methylene blue administration. Methylene blue is the treatment that can be used to reduce methemoglobin levels, but should be used with caution in patients with G6PD deficiency, pregnant patients, those on serotonergic medications and those with renal failure.[5] Treatment thresholds differ between providers and are primarily based on symptoms, as some patients can have severe symptoms at only moderate levels of methemoglobin in the

blood.[6] Poison control or a toxicologist should be involved in the treatment plan when possible. Methylene blue should be administered if blood levels of methemoglobin are 20–30%, but should not be withheld in cases where symptoms are significant and blood levels are lower or unavailable.[7]

Nitrites are a known cause of methemoglobinemia, but it is rare for this condition to be caused by recreational inhalation of nitrites. Upon review of the literature, 10 cases of methemoglobinemia from inhalation of isobutyl (amyl) or butyl nitrite have been described between 1979–2022. Patients ranged in age from 21 to 62 years old, with most in their third or fourth decade of life. Most reported exam findings of cyanosis and hypoxemia, and the majority of these patients received treatment with methylene blue. Almost all of these patients made a full recovery within 24–36 hours of arrival to the emergency department.[8-17]

CONCLUSION

This case of a young man who presented to the ED after amyl nitrite inhalation with syncope and cyanosis provides an example of how a patient can present with methemoglobinemia. The history of "popper" use contributing to his condition is rare and has not been frequently documented in the literature. Emergency clinicians can learn from this unusual case and refine their history-taking in a patient who presents with hypoxemia and cyanosis and should keep methemoglobinemia on their differential when evaluating a patient with these symptoms and a history of recreational drug use.

References

1. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. Annals of emergency medicine. 1999;34(5):646-656.
2. Romanelli F, Smith KM, Thornton AC, Pomeroy C. Poppers: Epidemiology and Clinical Management of Inhaled Nitrite Abuse. Pharmacotherapy. 2004;24(1):69-78. doi:10.1592/phco.24.1.69.34801
3. Wills BK, Cumpston KL, Downs JW, Rose SR. Causative Agents in Clinically Significant Methemoglobinemia: A National Poison Data System Study. American Journal of Therapeutics. 2021;28(5):e548-e551. doi:10.1097/mjt.0000000000001277
4. Vazquez E, Jamison A, Kwok J. Undiscovered Methemoglobinemia During Surgery and Review of Literature. Journal of Case Reports. 2020;10(2):90-94.
5. Iolascon A, Bianchi P, Andolfo I, et al. Recommendations for diagnosis and treatment of methemoglobinemia. American Journal of Hematology. 2021;96(12):1666-1678. doi:10.1002/ajh.26340
6. El-Husseini A, Azarov N. Is threshold for treatment of methemoglobinemia the same for all? A case report and literature review. The American journal of emergency medicine. 2010;28(6):748.e5-748. e10.
7. Ludlow JT, Wilkerson RG, Nappe TM. Methemoglobinemia. In: StatPearls. StatPearls Publishing, Treasure Island (FL); 2022. PMID: 30726002.
8. Horne III MK, Waterman MR, Simon LM, Garriott JC, Foerster E. Methemoglobinemia from sniffing butyl nitrite. Annals of Internal Medicine. 1979;91(3):417-418.
9. Laaban J, Bodenan P, Rochemaure J. Amyl nitrite poppers and methemoglobinemia. Annals of internal medicine. 1985;103(5):804-805.
10. Edwards RJ, Ujma J. Extreme methaemoglobinaemia secondary to recreational use of amyl nitrite. J Accid Emerg Med. Jun 1995;12(2):138-42. doi:10.1136/emj.12.2.138
11. Machabert R, Testud F, Descotes J. Methaemoglobinaemia due to Amyl Nitrite Inhalation: A Case Report. Human & Experimental Toxicology. 1994;13(5):313-314. doi:10.1177/096032719401300505
12. Lin C-H, Fang C-C, Lee C-C, Ko PC-I, Chen W-J. Near-fatal methemoglobinemia after recreational inhalation of amyl nitrite aerosolized with a compressed gas blower. J Formos Med Assoc. 2005/11// 2005;104(11):856-859.
13. McCabe A, McCann B, Kelly P. Pop goes the O2: a case of popper-induced methaemoglobinamia. Case Reports. 2012;2012 (nov21 1):bcr2012007176-b. doi:10.1136/bcr-2012-007176
14. Lefevre T, Nuzzo A, Mégarbane B. Poppers-induced Life-Threatening Methemoglobinemia. American Journal of Respiratory and Critical Care Medicine. 2018;198(12):e137-e138. doi:10.1164/rccm.201806-1044im
15. Ramonell R, Daniels L, Neveu W. Using Poppers Until You're Blue in the Face. B42 DYSPNEA CASE REPORTS. American Thoracic Society; 2019:A3177-A3177.
16. Elgendy F, Rio-Pertuz GD, Nguyen D, Payne D. "Popper" induced methemoglobinemia. Baylor University Medical Center Proceedings. 2022;35(3):385-386. doi:10.1080/08998280.2022.2030188
17. Sonck E, Bourmanne E, Bruteyn J, Dolip W. Methemoglobinemia due to use of poppers: a case report. Journal of Medical Case Reports. 2022;16(1)doi:10.1186/s13256-022-03475-8

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Disclosures

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