





## Poppers, A Potential Trigger for Hemolytic Anemia: A Case Report

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### ABSTRACT

**Background:** Hemolytic anemia is a rare but possible complication of inhaled nitrite use, particularly among patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. This occurs when the oxidative effect of nitrites exceeds the enzymatic reducing capacity of the erythrocytes. In patients with G6PD deficiency, this reducing capacity is impaired, making them more susceptible to hemolysis.

**Case Report:** A 36-year-old male with no relevant medical history was admitted to the Internal Medicine ward presenting with fever (38 °C), general malaise, and mucocutaneous jaundice. Laboratory tests revealed a non-autoimmune regenerative hemolytic anemia with a hemoglobin of 8.3 g/dL, reticulocytes of 12.8%, unesterified bilirubin of 7.7 mg/dL, LDH of 1590 U/L, haptoglobin <8 mg/dL, and a negative direct Coombs test. Notably, three days before symptom onset, the patient used inhaled nitrites (“Poppers”) recreationally. Further investigation confirmed G6PD deficiency.

**Conclusion:** Nitrite inhalation can trigger hemolytic anemia in both healthy and G6PD-deficient individuals.

**Keywords:** Glucose-6-phosphate (G6PD) deficiency, hemolytic anemia, inhaled nitrites, methemoglobinemia.



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### INTRODUCTION

We present a case of a male patient who developed hemolytic anemia following inhaled nitrite use and was subsequently diagnosed with glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD deficiency is the most common enzymatic disorder of red blood cells, affecting 400 to 500 million people worldwide.

Inhaled nitrites, including amyl nitrite - commonly known as “Poppers” - are recreational drugs primarily used in sexual contexts. Nitrites have been used for centuries, with their prevalence increasing particularly among younger populations. Through an oxidative mechanism that affects erythrocytes, they can induce hemolysis, although only a few cases have been documented in the literature.<sup>1-3</sup>

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## CASE REPORT

A 36-year-old male with no significant medical history presented to the Emergency Department with a 24-hour history of general malaise, fatigue, a fever reaching 38 °C, mucocutaneous jaundice, and dark urine. The patient denied any other accompanying symptoms. He admitted to using “*Poppers*,” inhaled nitrites, in a recreational context three days prior to clinical onset and denied the use of other drugs. Further history revealed no signs of infection in the preceding weeks. He had a stable female sexual partner, denied contact with animals, and had not traveled abroad. He lived in an urban area and worked as an office administrator.

Upon examination, his temperature was 37.1 °C, blood pressure 120/65 mmHg, heart rate 90 bpm, and oxygen saturation 98% on room air. He appeared in good general condition with evident mucocutaneous jaundice, but physical examination revealed no other significant findings.

The initial differential diagnosis considered, on the one hand, digestive causes of jaundice, such as biliary disorders, and, on the other hand, hematological causes.

Complementary tests were conducted, including blood tests, with the most relevant results presented in Table 1. Serological tests for syphilis; Epstein-Barr virus; toxoplasmosis; cytomegalovirus; hepatitis A, B, and C; HIV (antibodies and p24 antigen); and *Bartonella* spp were negative. The urine sediment was non-pathological, and both blood cultures and respiratory virus PCR tests were negative. The electrocardiogram and chest X-ray were normal, but an abdominal ultrasound revealed splenomegaly, measuring 13.6 x 6.5 cm. The patient received intravenous ceftriaxone, 1 g, for 5 days. Throughout his stay, he showed good clinical and laboratory improvement, with gradual normalization of hemoglobin and bilirubin levels. He was discharged after 7 days with complete clinical recovery and resolution of the anemia, which was suspected to be associated with consumption of inhaled nitrites (*Poppers*). Further laboratory tests revealed G6PD deficiency of 3 mU/10<sup>9</sup> erythrocytes (normal values 118-144 mU/10<sup>9</sup> erythrocytes), confirming the diagnosis of a hemolytic anemia episode in the context of inhaled nitrite consumption in a patient with G6PD deficiency. At a follow-up visit three months after discharge, the patient remained clinically stable and asymptomatic, with no new episodes. He denied any further use. Guidelines for foods and medications were provided, and the patient was discharged with follow-up by the primary care physician.

## DISCUSSION

Inhaled nitrites, including amyl nitrite —colloquially known as “*Poppers*” — are widely used recreationally, particularly in sexual contexts. They produce a pleasurable effect and

**Table 1.** Principal findings of the blood analysis

Parameter	Value	Unit
Hemoglobin	8.3	g/dL
Hematocrit	24	%
MCV	98	µm <sup>3</sup>
MHC	33	pg
Reticulocytes	12.8	%
Fraction of immature red blood cells	0.6	%
Peripheral blood morphology	Polychromatophilia without notable morphological alterations	–
Direct Coombs test	Negative	–
Hemoglobin electrophoresis	HbF 0.3, HbA2 2.3	%
Fibrinogen	733	mg/dL
D-dimer	3990	FEU/mL
Creatinine	0.84	mg/dL
GFR	>90	mL/min/1.73 m <sup>2</sup>
Total bilirubin	8.5	mg/dL
Esterified bilirubin	0.8	mg/dL
Unesterified bilirubin	7.7	mg/dL
GGT	11	U/L
LDH	1590	U/L
PCT	0.53	ng/mL
CRP	83	mg/L
Haptoglobin	<8	mg/dL
Folic acid	14	µg/L
Cobalamin	236	ng/L
Transferrin	150	mg/dL
TSI	37	%
Ferritin	1953	µg/L
Iron	78	µg/dL
Complement C3	116	mg/dL
Complement C4	26	mg/dL
Lupus anticoagulant	Negative	–
Beta 2 microglobulin	Negative	–
Anticardiolipin antibodies	Negative	–
Proteinogram	Negative	–
Venous pH	7.39	–
Venous HCO <sub>3</sub> <sup>-</sup>	22.4	mmol/L
Venous lactate	1.3	mmol/L

MCV: Mean corpuscular volume; MHC: Mean corpuscular hemoglobin concentration; GFR: Estimated glomerular filtration rate; GGT: Gamma-glutamyl transferase; LDH: Lactate dehydrogenase; PCT: Procalcitonin; CRP: C-reactive protein; TSI: Thyroid-stimulating Immunoglobulin.

function as vasodilators, enhancing penile erection and promoting relaxation of the anal sphincter.<sup>1,2</sup>

Inhaled nitrites are highly oxidizing substances. From a hematological perspective, they present two potentially life-threatening complications. First, they induce the formation of methemoglobin by oxidizing hemoglobin from its ferrous to ferric form, rendering it incapable of performing its physiological oxygen transport function, thus causing functional hypoxia.<sup>1,2</sup> Second, it can lead to hemolysis through an oxidative stress mechanism. Under normal conditions, erythrocytes protect their cell membranes from oxidation by producing reduced glutathione. G6PD catalyzes the first reaction in this pathway. Various chemical agents can overwhelm this physiological system and cause oxidation at multiple levels. Oxidation of the erythrocyte membrane impairs its flexibility, promotes cellular lysis, and results in intravascular hemolysis. On the other hand, oxidation of hemoglobin leads to dissociation of the heme group from globin, generating insoluble aggregates known as Heinz bodies. These aggregates can attach to the inner surface of the erythrocyte membrane, making the cell susceptible to lysis as it passes through the splenic sinusoids, thereby also contributing to extravascular hemolysis.<sup>1-3</sup>

Several studies have analyzed the mechanisms underlying hemolysis induced by inhaled nitrites. A dose-dependent relationship has been demonstrated, with a reported threshold of 30 mL of amyl nitrite required to induce hemolysis.<sup>1</sup> Hemolysis can occur in patients with normal G6PD levels, as nitrites possess sufficient oxidative potential to induce a hemolytic crisis, even in the presence of adequate enzymatic activity. However, in patients with G6PD deficiency, reduced enzymatic activity increases individual susceptibility to these substances, leading to hemolysis at lower concentrations than in healthy individuals.<sup>3,4</sup>

The treatment of hemolytic anemia caused by nitrite inhalation is based on supportive measures and the discontinuation of exposure to the triggering agent. In cases of hemolytic crisis, methylene blue is the treatment of choice.

However, methylene blue is contraindicated in patients with G6PD deficiency. In such cases, ascorbic acid can be used because of its strong reducing capacity.<sup>1</sup>

The clinical presentation was consistent with previously reported cases, although some patients exhibited more severe manifestations requiring intensive care support. G6PD deficiency was present in most cases, known beforehand in

some cases and diagnosed after the event in others, as in this case. In one report, ascorbic acid was administered because the enzymatic deficiency had already been established.

## CONCLUSION

The inhalation of nitrites can lead to hemolytic anemia. Although a few cases have been reported in the literature, nitrites appear to act as triggers in both healthy individuals and patients with G6PD deficiency. The use of inhaled nitrites has become increasingly common among young people, particularly in recreational settings. Therefore, it is important to consider them potential causes of non-autoimmune hemolytic anemia.

**Ethics Committee Approval:** This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

**Informed Consent:** Written informed consent was obtained from the patient.

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