Toxic bone marrow aplasia

Aplasia medular tóxica

Nitrous oxide is a colorless, odorless, non-flammable gas with multiple applications in our environment. It is an inhalational anesthetic agent that has been used for years in dental procedures or minor surgical interventions in pediatric patients.[1] It is also a food additive (E942) used in multiple propellant systems and as a stabilizer for packaged products, and it is employed in the automotive industry as a fuel performance enhancer in the engine cylinder.[2]

The first reference to its recreational use dates back to 1800, in a scientific publication that described its effect as "hilarious and pleasant".[3]

Currently, it is part of the broad spectrum of drugs of abuse. In a survey of more than 900,000 drug users, 22.5% reported having used it at least once in their lifetime, and 9.7% had done so during the previous year.[4] Meanwhile, the EMCDDA (European Monitoring Centre for Drugs and Drug Addiction), in a special report dedicated to this substance, reported a global increase in the number of cases notified to poison control centers in various countries: in Denmark, from 16 cases in 2015 to 73 in 2021; in France, from 10 cases in 2017 to 134 in 2020; and in the Netherlands, from 10 cases in 2017 to 144 in 2020.[5]

The desired effects of recreational use include euphoria, laughing fits, hallucinations, and distortion of perception, which appear approximately 30 seconds after inhalation and subside within one minute after stopping it.

Most users obtain nitrous oxide in small metal cylinders, known as whippets (easily available online or in hospitality supply stores). The gas is released into balloons, which are then inhaled. Less common methods include bags or masks connected to large medical or industrial nitrous oxide cylinders.[6]

Chronic or high-dose use has been associated with myelopathy,[7] thromboembolic disease,[8] and skin hyperpigmentation.[9]

We present the case of a young man who presented to the emergency department of a university hospital in Barcelona with hematologic and neurological alterations secondary to nitrous oxide use.

A 22-year-old male, smoker of 20 cigarettes per day and five cannabis joints daily (denied other drug use), presented to the emergency department with a three-week history of dizziness not related to position changes, gait instability, tinnitus, distal tingling in all four limbs, fine motor difficulty (buttoning, tying shoelaces), loss of appetite, and marked asthenia. He also reported gum bleeding when brushing his teeth, without other bleeding sites. On the day of presentation, he experienced a fainting episode after showering (the fourth similar episode since symptom onset). He denied weight loss, fever, or night sweats.

On physical examination, vital signs were normal, but marked pallor of the skin and mucosae was noted. Neurological assessment showed upper-limb muscle weakness (4/5) with normal lower-limb strength (5/5), distal tactile and pain hypesthesia in upper limbs and from the distal third of the calves downward in the lower limbs, with a gradient pattern, positive Romberg sign, and impaired tandem gait. No alterations were observed in proprioception or vibratory sensation.

Admission blood tests showed macrocytic anemia, leukopenia with neutrophil hypersegmentation, thrombocytopenia, and decreased reticulocytes, with increased indirect bilirubin and LDH (Table 1).

Further anamnesis revealed that the patient had used nitrous oxide recreationally one week before symptom onset (he provided a photograph of the product used), inhaling it for several hours over a weekend (Figure 1). The exact amount consumed was not specified.

He was diagnosed with pancytopenia of probable toxic origin and admitted for evaluation and treatment.

During hospitalization, plasma concentrations of vitamin B_{12} ($VitB_{12}$) and homocysteine were determined, revealing a $VitB_{12}$ deficiency (81 pg/mL; normal > 200 pg/mL) and elevated homocysteine (106.5 µmol/L; normal < 15 µmol/L). As part of the diagnostic algorithm

Authors:
Solanche Santillán Zorrilla[1], Miguel Galicia[2].

Author Affiliations:
[1]Servicio de Oncología Radioterápica, Hospital Clinic, Barcelona, Spain.
[2]Área de Urgencias, Unidad de Toxicología Clínica, Hospital Clinic, SoCMUETox.

Corresponding Author:
Miguel Galicia.
Área de Urgencias.
Unidad de Toxicología Clínica.
Hospital Clínic.
C/ Villarroel 170.
08036 Barcelona, Spain.

E-mail:
mgalicia@clinic.cat

Ethical Responsibilities:
All authors have confirmed their authorship, the nonexistence of external funding, and the maintenance of confidentiality and respect for patients' rights in the author's responsibilities document, publication agreement, and assignment of rights to Revista Española de Urgencias Emergencias.

Editor in Charge:
Guillermo Burillo-Putze.

Table 1. Complementary tests performed upom admission

Laboratory studies		Imaging and other studies
Day 0	Hct 15% MCV 107.8 fL (80–100) Plt 33,000 (130,000–400,000) Leukocytes 1,820 (4,000–11,000) LDH 4,878 U/L (< 234)	BONE MARROW ASPIRATE – Hypercellular bone marrow aspirate with absence of fat. – Presence of all three hematopoietic lineages. – Abundant megakaryocytes with overall preserved morphology. – Inverted myeloid-to-erythroid ratio; lack of maturation in terminal stages. – Severe signs of megaloblastosis, mainly in the red lineage. Conclusion: Findings compatible with megaloblastic anemia.
Day 1	Hb 5.5 g/L (13–17) Hct 16% MCV 108.4 fL (80–100) Plt 34,000 (130,000–400,000) Leukocytes 2,180 (4,000–11,000) LDH 4,939 U/L (< 234) Vitamin B_{12} 81 pg/mL (199–300) Homocysteine 106 µmol/L (< 15) Folic acid 8.32 ng/mL (3–5)	BRAIN MRI – Cerebellum, brainstem, and cerebellopontine angles of normal appearance. – Ventricular system of normal size, position, and morphology. – No signal alterations or parenchymal space-occupying lesions. – No acute ischemic lesions, extra-axial collections, or hemorrhagic lesions. – Basal cisterns are clear. Sella turcica appears normal.
Day 2	Hb 5 g/L (13–17) Hct 15% MCV 109.4 fL (80–100) Plt 30,000 (130,000–400,000) Leukocytes 3,140 (4,000–11,000) LDH 4,679 U/L (< 234) Hb 5 g/L (13-17)	SPINAL MRI – Spinal cord with preserved signal and size, without lesions related to vitamin B_{12} deficiency. – Vertebral bodies with preserved signal and height. – Focal central hernia at T7–T8 without spinal canal compromise. – No pathological enhancement detected.
Day 3	Hb 6.6 g/L (13–17) Hct 19% MCV 104.4 fL (80–100) Plt 47,000 (130,000–400,000) Leukocytes 5,250 (4,000–11,000)	ELECTROMYOGRAPHY / EVOKED POTENTIALS – Both studies within normal limits.
Day 5	Hb 7.7 g/L (13–17) Hct 24% MCV 108.2 fL (80–100) Plt 40,000 (130,000–400,000) Leukocytes 3,710 (4,000–11,000) LDH 2,369 U/L (< 234)	
Day 7	Hb 8.8 g/L (13–17) Hct 28% MCV 105.7 fL (80–100) Plt 172,000 (130,000–400,000) Leukocytes 3,390 (4,000–11,000) LDH 1,729 U/L (< 234)	
Day 19	Hb 11.6 g/L (13–17) Hct 39% MCV 97.8 fL (80–100) Plt 440,000 (130,000–400,000)	

Hb: hemoglobin; Hct. hematocrit; LDH: lactate dehydrogenase; MCV: mean corpuscular volume; Plt: platelets.

for pancytopenia and polyneuropathy, bone marrow aspiration, brain and spinal MRI, electromyography, and evoked potentials were performed—all within normal ranges (Table 1).

Treatment consisted of intramuscular $VitB_{12}$ replacement and oral folic acid, resulting in clinical improvement and increased cell counts by day three; the patient was discharged after 7 days, requiring only 1 packed red blood cell transfusion.

At discharge, intramuscular $VitB_{12}$ supplementation was prescribed for an additional 4 weeks.

At the outpatient follow-up visit, 19 days after admission, hemoglobin was 11.6 g/L, hematocrit 39%, MCV 97.3 fL, and platelet count 440,000/µL. No follow-up tests for $VitB_{12}$ or homocysteine were performed.

VitB12 is a metabolite required for red blood cell and myelin sheath synthesis. It is also a cofactor in several reactions, including the conversion of homocysteine to methionine, 5-methyltetrahydrofolate to tetrahydrofolate, and methylmalonyl-CoA to succinyl-CoA. Nitrous oxide inactivates methylcobalamin by oxidizing the cobalt ion in $VitB_{12}$, leading to homocysteine accumulation and disrupted myelin lipid synthesis.[10,11] As a result, anemia, polyneuropathy, and hypercoagulable states due to homocysteine accumulation may occur.

Typical clinical signs include paresthesia and numbness of the extremities, followed by gait instability and fine motor impairment.[7]

Nitrous oxide is a liposoluble gas that easily crosses the blood-brain barrier, exerting effects on µ-, δ-, and κ-opioid receptors and acting as an NMDA receptor antagonist.[12] It has a rapid onset (seconds) and cannot be detected by most routine emergency department drug screening kits.

The progressive rise in its use among drug users[13] in our setting underscores that in young patients pre-

Figure 1. Nitrous oxide canister used (photo courtesy of the patient).

senting to emergency departments with paresthesia and macrocytic anemia or elevated MCV, nitrous oxide use must be specifically investigated in the anamnesis. Suspicion of this etiology may also reduce unnecessary complementary testing and hospital stay.

Note of the editors: This is a BOWMAN-generated English translation of the officially indexed Spanish-language article, which should be cited as Rev Esp Urg Emerg. 2024;3:122-124. In this translated version, the editors have supervised the process; however, it cannot be ruled out that some errors resulting from the artificial intelligence translation process may have gone unnoticed.

REFERENCES

1. Gómez B, Capapé S, Benito FJ, Landa J, Fernández Y, Luaces C, et al. Efectividad y seguridad del uso de óxido nitroso para sedoanalgesia en urgencias. An Pediatr (Barc). 2011;75:96-102.
2. E942 Óxido Nitroso. (Accessed 20 October 2023). Available at: https://www.aditivos-alimentarios.com/2016/01/E942.html
3. Davy H. Researches, chemical and philosophical chiefly concerning nitrous oxide, or diphlogisticated nitrous air, and its respiration. Bristol, London: J. Johnson, St. Paul's Church-Yard; 1800.
4. Winstock AR, Maier LJ, Zhuparris A, Davies E, Puljevic C, Kuypers KPC, et al. Global Drug Survey (GDS) 2021 Key findings report. (Accessed 20 October 2023). Available at: https://www.globaldrugsurvey.com/wp-content/uploads/2021/12/Report2021_global.pdf
5. Recreational use of nitrous oxide — a growing concern for Europe. (Accessed 20 October 2023). Available at: https://www.emcdda.europa.eu/publications/rapid-communication/recreational-use-nitrous-oxide-growing-concern-europe_en
6. Evans EB, Evans MR. Nangs, balloons and crackers: Recreational nitrous oxide neurotoxicity. AJGP. 2021;50:834-8.
7. McCormick JP, Sharpe S, Crowley K, Dudley A, O'Laoi R, Barry M, et al. Nitrous oxide-induced myeloneuropathy: an emerging public health issue. Vol. 192, Irish Journal of Medical Science. Springer Science and Business Media Deutschland GmbH; 2023. p. 383-8.
8. Vollenbrock SE, Fokkema TM, Leijdekkers VJ, Vahl AC, Konings R, Van Nieuwenhuizen RC. Nitrous Oxide Abuse associated with severe thromboembolic complications. Eur J Vasc Endovasc Surg. 2021;62:656-7.
9. Fang X, L Weishuai, Gao H, Ma Y, Dong X, Zheng D. Skin hyperpigmentation: a rare presenting symptom of nitrous oxide abuse. Clin Toxicol (Phila). 2020;58:476-81.
10. Brunt TM, van den Brink W, van Amsterdam J. Mechanisms Involved in the Neurotoxicity and Abuse Liability of Nitrous Oxide: A Narrative Review. Int J Mol Sci. 2022;23:14747.
11. Van Amsterdam J, Nabben T, Van der Brink W. Recreational nitrous oxide use: prevalence and risk. Regulatory Toxicology and Pharmacology. 2015;73:790-6.
12. Winstock AR, Ferris JA. Nitrous oxide causes peripheral neuropathy in a dose dependent manner among recreational users. J Psychopharmacol. 2020;34:229-36.
13. Gendre T, Ovaska H, Nguyen R, Bachoud-Levi AC, Khellaf M, Remy P. Ataxia aguda inducida por el abuso de óxido nitroso en adultos jóvenes durante la pandemia de COVID-19. Emergencias. 2023;35:225-7.