Vitamin B12 deficiency–related polyneuropathy associated with chronic nitrous oxide use

Polineuropatía por déficit de B12 asociada al consumo crónico de óxido nitroso

To the Editor,

Nitrous oxide (N_2O) is a psychoactive substance whose recreational use is increasing, with potentially serious adverse effects. Its neurological toxicity is due to inactivation of vitamin B12, leading to axonal polyneuropathy. We present the case of a young man with functional vitamin B12 deficiency secondary to chronic N_2O use, with progressive neurological signs.

An 18-year-old male, with no relevant medical history, presented to the emergency department with progressive weakness and sensory disturbance in the lower limbs. He reported habitual N_2O consumption (20 cartridges per week). For one year he had experienced paresthesia in both feet, which progressed during the last month up to the ankles, accompanied by distal weakness interfering with gait. He was unable to specify a clear temporal onset of the worsening.

Physical examination revealed distal weakness in the lower limbs (strength 3/5), hypoactive Achilles reflexes, and distal sensory impairment predominantly affecting the dorsal and lateral regions. There were no cranial nerve abnormalities or sphincter dysfunction. He was admitted for further evaluation with a working diagnosis of neuropathy secondary to chronic N_2O use.

Laboratory tests showed low vitamin B12 levels (187 pg/mL) and elevated homocysteine (94.1 µmol/L), findings consistent with vitamin B12 dysfunction due to chronic N_2O use. Neurophysiological studies demonstrated moderate sensorimotor axonal polyneuropathy in the upper limbs and severe involvement in the lower limbs. Magnetic resonance imaging showed no involvement of the posterior or lateral spinal cord columns. High-dose intramuscular cyanocobalamin was initiated together with oral folic acid, with progressive clinical improvement. The patient showed stabilization of symptoms and partial improvement in gait, although sensory disturbances persisted at discharge.

N_2O is one of the most popular psychoactive substances in Europe, legally available and very easy to obtain. Its effects are rapid but short-acting, beginning 10–30 seconds after inhalation and ending within 1–5 minutes. Adverse effects are generally mild, but frequent use increases the risk of severe harm, including neurotoxicity.[2] Clinically, patients may present a spectrum of symptoms including sensory, motor, and autonomic disturbances, which are often underdiagnosed in emergency departments.[3]

The mechanism of N_2O toxicity lies in its ability to oxidize the cobalt ion of vitamin B12. This interferes with DNA synthesis and myelin formation, resulting in axonal neuropathy and, in severe cases, subacute combined degeneration of the spinal cord.[4] Its impact on vitamin B12 metabolism is due to inactivation of methionine synthase, leading to accumulation of homocysteine and methylmalonic acid, key markers for diagnosis.

Serum B12 levels may be normal; therefore, functional B12 tests using methylmalonic acid or homocysteine may help establish the diagnosis. Although vitamin B12 treatment is effective, its efficacy is limited if N_2O use continues, since neurotoxicity may progress despite supplementation.[5]

N_2O is a readily accessible psychoactive substance whose abuse can cause severe vitamin B12 dysfunction. This case highlights the importance of considering N_2O-related neuropathy in young patients presenting to the emergency department with progressive neurological symptoms. The need for early diagnosis supports improved training in clinical toxicology for emergency physicians and the performance of targeted history-taking based on such training. This would likely lead to earlier recognition of more cases of this clinical entity.

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Isotonitazene intoxication: thoughts on this new synthetic opioid

Intoxicación por isotonitazeno: consideraciones de este nuevo opioide sintético

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To the Editor,

Compounds belonging to the nitazene group were synthesized in the 1950s by the pharmaceutical company CIBA, but were not marketed or approved for clinical use in humans due to the high antinociceptive potency observed in preclinical in vivo studies, which raised concerns about their safety and risk profile in humans.[1] In recent years, the prohibition of the synthesis and commercialization of fentanyl analogues in China has promoted an increase in the production, distribution, and consumption of these alternative synthetic opioids, among which isotonitazene stands out.

We present the case of a 21-year-old man, a pharmacy technician student, with a past medical history of habitual consumption of multiple psychoactive substances, including opioids. Six months earlier, he had experienced an episode in which he was treated at the same hospital for respiratory arrest due to opioid use, with a positive urine toxicology screen for natural opioids.

In the current episode, the patient was attended by prehospital emergency services following an alert from a witness. According to the history obtained, the patient had recreationally consumed, via the intranasal route (snorting), an indeterminate dose of a new synthetic opioid identified as isotonitazene (colloquially referred to as "toni"), supplied by an acquaintance.

Upon arrival of emergency medical personnel, the patient was unconscious, with a Glasgow Coma Scale score of 6 (E1 V1 M4). He had shallow spontaneous breathing, bradypnea (6 breaths per minute), and tolerated an oropharyngeal airway. Oxygen saturation was not detectable due to peripheral hypoperfusion, with central cyanosis observed. The carotid pulse was palpable, with blood pressure of 73/38 mmHg and heart rate of 88 bpm. Bilateral miosis with symmetric and poorly reactive pupils was noted. Given the clinical suspicion of opioid intoxication, IV naloxone (0.4 mg) was administered. After the first bolus there was no significant clinical improvement, so two additional doses (0.4 mg each) were administered at 2-minute intervals. After the third bolus of naloxone (total dose 1.2 mg), progressive improvement in level of consciousness and ventilatory function was observed. The patient was transferred to the referral hospital in hemodynamically stable condition. No adverse reactions related to naloxone administration were recorded, and the patient remained cooperative during transport.

Upon arrival at the emergency department, the patient was conscious, with blood pressure 141/94 mmHg, heart rate 108 bpm, respiratory rate 16 breaths per minute, and oxygen saturation 100 % breathing room air. Venous blood gas analysis showed metabolic acidosis (pH 7.22, normal pCO_2, lactate 5 mmol/L, base excess −7 mEq/L). PEWS score was 1 point (high risk of adverse

events). Basic laboratory tests showed no relevant abnormalities. Continuous naloxone infusion was initiated (2.4 mg diluted in 500 mL of 0.9 % saline at a rate of 21 mL/hour). Urine toxicology screening was negative for natural opioids and positive for amphetamines, methamphetamines, cannabis, and cocaine, confirming a history of polysubstance use.

After 4 hours of observation, the patient requested discharge against medical advice. After medical assessment and in the absence of signs of resedation following discontinuation of naloxone infusion, and with no contraindications, discharge was granted with the diagnosis of opioid syndrome secondary to isotonitazene use and polysubstance abuse.

Despite pharmacodynamic differences compared with fentanyl analogues, nitazenes have proven to be a viable and, at the time, legal alternative for supplying international markets with new synthetic opioids. These compounds are characterized by the presence of a 2-benzylbenzimidazole ring, to which different chemical radicals attach, generating a wide variety of derivatives with potent pharmacological effects. They are high-potency agonists of the μ-opioid receptor, with significantly greater affinity compared with conventional opioids. This high μ-receptor affinity results in more pronounced respiratory depression compared with fentanyl and requires a prolonged time for normalization of respiratory rate, leading to a high incidence of fatalities from this cause. Similarly, this strong affinity may contribute to a slower response to naloxone, posing therapeutic challenges in intoxication cases.

Different forensic studies have documented the presence of nitazenes as a cause of death in the United States since 2019[4] and in Europe. These compounds are not detectable by conventional urine screening analysis, and furthermore, a positive result for natural opioids does not exclude their presence (mainly due to their fraudulent introduction into markets as adulterants of other opioids or substances). The test of choice for their detection is liquid chromatography coupled with gas-mass spectrometry. In addition, rapid tests based on enzymatic immunoassays have been developed for qualitative detection of synthetic opioids such as isotonitazene in compounds, drugs, or surfaces, but these tests are primarily intended for forensic use and for consumers to rapidly identify these highly lethal substances.[6] Their current use has been identified as adulterants in known opioids (such as fentanyl or heroin) and in black-market drugs such as benzo-dope (benzodiazepines and isotonitazene, 2022) and tranq-dope (xylazine and isotonitazene, 2021), among others.[7]

Treatment of nitazene intoxication continues to rely on naloxone, which remains the opioid antagonist of choice. However, due to the high potency and receptor affinity of these compounds, significantly higher doses and close monitoring may be required to ensure adequate reversal of respiratory depression. Clinicians must maintain a high index of suspicion in opioid syndromes with slow or incomplete response to naloxone, as this may suggest possible nitazene intoxication—an emerging group of opioids that poses a challenge for both healthcare professionals and users.

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From historical demand to educational opportunity: a professional view on the specialty of Emergency in Spain

De reivindicación histórica a oportunidad formativa: visión profesional sobre la especialidad de Urgencias y Emergencias

To the Editor,

The specialty in Emergency and Urgent Care Medicine (EUCM) will begin its effective implementation in Spain with the incorporation of the first MIR residents in 2026.[1] To assess the perceptions of physicians working in the services where MIR residents in this specialty will be trained, a cross-sectional study was conducted in Castile and León (Spain) using an anonymous digital survey administered between February and March 2025. The questionnaire included sociodemographic variables (age group, sex, hospital level) and five items assessing the specialty, with closed responses (Yes, No, I don't know), as well as two open-ended questions ("write something positive about the new specialty" and "write something negative or something that worries you about the new specialty"—maximum 3 words).

Out of a target population of 520 hospital emergency and prehospital emergency professionals, 169 participated (32.5 %), including 42 % prehospital emergency (EMS) professionals. Overall, 70 % believed that EUCM will improve the image of emergency and prehospital emergency professionals; 77 % felt it will improve the way of working and the updating of knowledge and techniques; 65 % believed it will improve patient care and therefore patient satisfaction with the care received; and 76 % considered it an attractive specialty for future MIR residents, with a potential to improve retention of professionals in emergency and prehospital emergency services estimated at 76 % (Table 1). There were no statistically significant differences in the percentages of positive responses by level of care, nor in relation to sex, despite women being predominant (62.1 %, $P = .046$). Among those > 55 years, 80.5 % stated that the specialty would improve their professional image vs 66.1 % of those aged 30–

Table 1. Opinion of emergency professionals on the impact of implementing the Specialty in Emergency and Urgent Care Medicine (EUCM)

		Total 169 (100) n (%)	EMS 71 (42) n (%)	Hospital Level I 12 (7,1) n (%)	Hospital Level II 44 (26) n (%)	Hospital Level III 42 (24,9) n (%)	*P* value
Sex	Female	105 (62.1)	51 (71.8)	9 (75)	21 (47)	24 (57)	.046
Age group	< 30 yrs	5 (3)	1 (20)	0	2 (40)	2 (40)	.37
	30-55 yrs	123 (72.8)	54 (43.9)	11 (8.9)	27 (22)	31 (25.2)	
	> 55 yrs	41 (24.2)	16 (30)	1 (2.4)	15 (36.6)	9 (22)	
Will improve professional image	Yes	118 (69.8)	52 (73.2)	9 (75)	28 (63.6)	29 (69)	.57
	No	17 (1.1)	9 (12.7)	0	5 (11.4)	3 (7.2)	
	Do not know	34 (2.1)	10 (14.1)	3 (25)	11 (25)	10 (23.8)	
Will improve working methods	Yes	130 (76.9)	51 (71.8)	9 (75)	34 (77.3)	36 (85.8)	.64
	No	17 (1.1)	10 (14.1)	1 (8.3)	3 (6.8)	3 (7.1)	
	Do not know	22 (13)	10 (14.1)	2 (16.7)	7 (15.9)	3 (7.1)	
Will improve patient care	Yes	109 (64.5)	49 (69)	5 (41.7)	27 (61.4)	28 (66.7)	.58
	No	24 (14.2)	10 (14.1)	2 (16.6)	6 (13.6)	6 (14.3)	
	Do not know	36 (21.3)	12 (16.9)	5 (41.7)	11 (25)	8 (22.2)	
Will be attractive specialty for MIR	Yes	129 (76.3)	55 (77.5)	10 (83.4)	32 (83.4)	32 (76.2)	.97
	No	16 (9.5)	7 (9.9)	1 (8.3)	5 (8.3)	3 (7.1)	
	Do not know	24 (14.2)	9 (12.7)	1 (8.3)	7 (8.3)	7 (16.7)	
Will help retain professionals	Yes	128 (75.7)	48 (67.6)	9 (75)	38 (86.4)	33 (78.6)	.35
	No	17 (1.1)	9 (12.7)	2 (16.7)	3 (6.8)	3 (7.1)	
	Do not know	24 (14.2)	14 (19.7)	1 (8.3)	3 (6.8)	6 (14.3)	

EMS: Emergency Medical Services; MIR: Medical Intern Resident.

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55 years (P = .3). Regarding attractiveness for MIR residents, 84 % of the 30–55-year group considered it attractive vs 81.6 % of those older than 55 years (P = .31). In the free-text questions, the most frequently mentioned advantages were specific training, professional recognition, and historical need; while perceived concerns included conflict with other specialties, possible initial disorganization, and lack of training among attending physicians.

As expected,[2] broad support for the creation of EUCM was observed among emergency and prehospital emergency professionals in Castile and León. Positive expectations were also identified in terms of quality of care, professional development, and talent retention, similarly to what has been described in our closest setting.[3,4] In this regard, as early as 2010, a survey conducted among MIR applicants immediately after selecting their residency position indicated that 40.5 % of MIR applicants might choose this EUCM specialty, and 9 % would have chosen it as their first option, ahead of 44 other specialties.[5] Concern was also raised about the ESEM implementation process, specifically the training or updating of current specialists and coordination with other specialties. Far from being a drawback, these concerns should be understood as a sincere and responsible professional engagement with the training process,[6] recognizing certain shortcomings and pointing toward areas for educational improvement,[7] always in collaboration with other specialties, as medicine in the 21st century should be understood.[8]

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Renopulmonary syndrome with a fatal outcome and an unusual etiology in a young patient: suspect early to act early

Síndrome renopulmonar de desenlace fatal y etiología poco usual en paciente joven: sospechar rápido para actuar rápido

To the Editor,

Renopulmonary syndrome (RPS) combines diffuse alveolar hemorrhage (DAH) and rapidly progressive glomerulonephritis, and its most frequent cause is antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis, which carries high mortality if not treated early.

We present the case of a previously healthy 24-year-old man who came to the emergency department with a 3-day history of fever to 40°C, cough, and dyspnea after a positive self-test for influenza B. In the hours prior to consultation, he reported blood-tinged sputum and one episode of frank hemoptysis. On arrival at the emergency department, he appeared in fair general condition, with blood pressure 90/50 mmHg, heart rate 130 bpm, and respiratory rate 50 breaths per minute. Lung auscultation revealed rhonchi and bilateral crackles extending to the apices.

Laboratory results on arrival are detailed in Table 1.

The chest radiograph showed fluffy infiltrates throughout the entire right lung and in the middle and lower fields of the left lung. Contrast-enhanced chest computed tomography revealed a "crazy-paving"

Table 1. Analytical parameters upon arrival at the emergency room

Venous blood gas analysis	
pH	7.01
pCO_2	64.6 mmHg
Bicarbonate	11.6 mmol/L
Lactic acid	14.5 mmol/L
Complete blood count	
Hemoglobin	15.8 g/dL
Leukocytes	710/µL
Platelets	48,000/µL
Coagulation	
INR	2.03
APTT ratio	1.61
Biochemistry	
Creatinine	2.36 mg/dL
Urea	46 mg/dL
C-reactive protein	196.3 mg/L

INR: International normalised ratio.

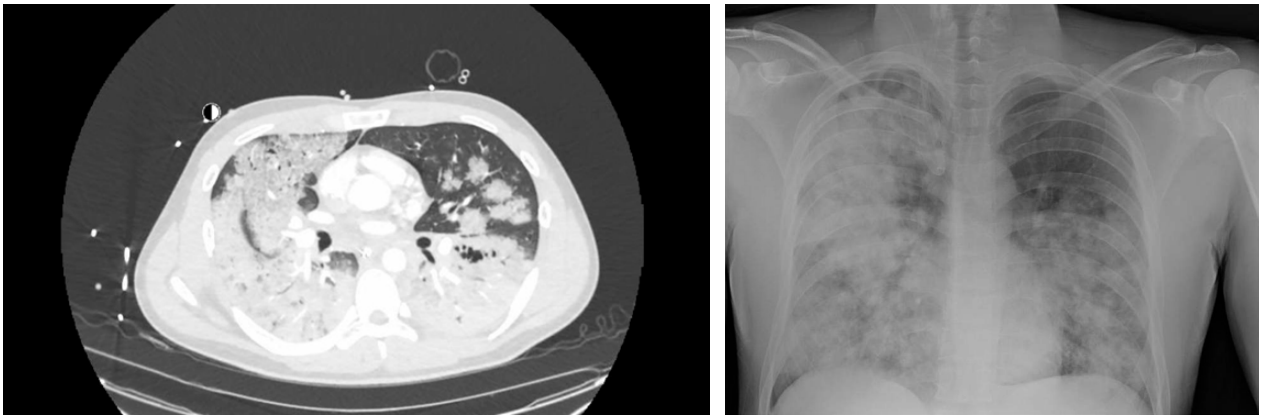

Figure 1. Chest radiograph and contrast-enhanced chest computed tomography, lung window, at the time of patient admission.

pattern compatible with alveolar hemorrhage and areas of alveolar consolidation with cavitations, suggestive of bilateral necrotizing pneumonia (Figure 1). Blood cultures grew *Staphylococcus aureus*, and nasopharyngeal PCR confirmed the presence of influenza B viral RNA.

Due to respiratory deterioration, orotracheal intubation was performed, with bloody contents emerging from the airway. He was transferred to the intensive care unit, where he developed persistent hypoxemia, shock refractory to vasoactive drugs, and ventilatory difficulties even after prone positioning. He ultimately developed multiple organ dysfunction syndrome and died a few hours later.

Autopsy showed DAH and necrotizing small-vessel vasculitis with mixed inflammatory infiltrate and polymicrobial bacterial superinfection. In addition, sclerosed and hypertrophic glomeruli were observed.

Influenza–*Staphylococcus aureus* coinfection, especially with PVL (Panton–Valentine leukocidin) strains, is associated with necrotizing pneumonia and DAH.[1] In addition, influenza A infection has been linked to renopulmonary syndrome in the context of de novo ANCA-associated vasculitis and anti–glomerular basement membrane (anti-GBM) disease.[2] Among poor prognostic factors is severe leukopenia which, as in our patient, predicts a fatal outcome.[3] In our case, PCR confirmed influenza B, which has been less frequently described as a trigger of renopulmonary syndrome. Furthermore, the patient's age is considerably younger than that of cases described in the literature.[4]

Given the poor prognosis of this entity, the following therapeutic algorithm is proposed in the emergency department when renopulmonary syndrome is suspected without a prior diagnosis, supported by KDIGO (Kidney Disease: Improving Global Outcomes) guidelines:[5]

1. Assessment of airway, breathing, and circulation, with early protective ventilation, active control of hemoptysis, and immediate evaluation for admission to the intensive care unit.

2. Collection of blood cultures, urine culture, and sputum culture, and initiation of broad-spectrum antibiotic therapy before starting immunosuppressive treatment.

3. Standard urgent laboratory tests: arterial blood gas, complete blood count, coagulation studies, renal function, acute-phase reactants, and urinalysis with urine sediment. In addition, ANCA and anti-GBM serologies are recommended to guide etiologic diagnosis.

4. Initiate immunosuppression in cases with multiple organ involvement and high suspicion of vasculitis: 1 g IV methylprednisolone bolus and induction with cyclophosphamide or rituximab. Both drugs have been shown to be equivalent for induction. Regarding plasmapheresis, it is recommended only in patients with creatinine > 3.4 mg/dL, those requiring dialysis, or those with DAH and persistent hypoxemia. KDIGO indicates that it may reduce the risk of kidney disease at 12 months, although it does not improve mortality and increases the risk of severe infections.

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