



Pancytopenia Caused by Nitrous Oxide Toxicity: Two Cases Report

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Abstract

Recreational nitrous oxide (N₂O) is increasingly common among young people, leading to attendant health disadvantages. Related complications primarily involve the hematological and neurological systems. We report two relatively uncommon cases of pancytopenia due to substantial N₂O inhalation. One possible cause is that N₂O toxicity results in vitamin B12 inactivation and an insufficient intake of nutrients. The patient's symptoms partially improved after cessation of N₂O inhalation and supplementation with vitamin B12. In conclusion, if the patients presented with unexplained bone marrow failure, a history of prolonged N₂O exposure should be considered, which would greatly help in early diagnosis, therapy, and the reduction of unnecessary costs.

Keywords

Nitrous Oxide, Pancytopenia, Hematological, Vitamin B12, Bone Marrow Failure

Abbreviations

ED: Emergency Department; EMG: Electromyography; MCV: Mean Corpuscular Volume, MRI: Magnetic Resonance Imaging; N₂O: Nitrous Oxide

Introduction

N₂O is widely used for anesthesia and as an analgesic in surgery. The related complications primarily involve hematological and neurological systems. We reported two cases of pancytopenia due to substantial N₂O inhalation, which was relatively uncommon. We hope that the report can provide a reference value for the diagnosis and treatment of long-term N₂O exposure.

Recreational nitrous oxide (N₂O) is a worldwide health problem with increasing incidence. A study from the 2014 Global Drug Survey confirmed N₂O as a very common addictive drug, in particular in the UK and the US (38.6% and 29.4% lifetime prevalence) [1].

However, this overuse is more likely to develop acute (hypoxia, barotrauma) and chronic complications (peripheral nervous system complications, anemia) [2].

We reported two cases of pancytopenia due to substantial N₂O inhalation over two months, which was uncommon in China. Written consent to publish the case report was obtained from the patients.

Case Presentation

Case-1:

A 23-year-old female patient presented to the emergency department (ED) for general fatigue,

Case Report

numbness, walking disability, and fecal incontinence. The patient reported a 2-month history of smoking N₂O. In the initial phase, she inhaled approximately three canisters weekly. When the patient tried to quit the inhalation of N₂O, she was often depressed and developed suicidal thoughts. Subsequently, the inhalation volume increased substantially and she inhaled 5-7 canisters daily. Ten days before admission, general fatigue, numbness, walking disability and fecal incontinence occurred. She was not eating for five consecutive days because of nausea, vomiting, and anorexia before admission. In addition, no significant medical history was noted.

In the ED, physical examination revealed that the temperature was 37.8°C, tachycardic to 110 beats per minute, tachypneic to 22 breaths per minute, and the blood pressure and oxygen saturation were normal. She had multiple oral ulcers and the muscle strength of both lower limbs was grade 4/5.

Initial laboratory analysis results showed pancytopenia with hemoglobin of 109g/L, red blood cell count of $3.62 \times 10^{12}/L$, mean corpuscular volume (MCV) of 82.3 fL, white cell count of $0.93 \times 10^9/L$, neutrophils $0.22 \times 10^9/L$ and platelets $57 \times 10^9/L$. The hemoglobin declined gradually and the lowest

hemoglobin was 69 g/L on the second day of admission. The peripheral blood smear reminded the red blood cell distribution width was increased (18.6%). Further details are provided in **Table-1**. The cranial magnetic resonance imaging (MRI) was normal. Regrettably, electromyography (EMG) was not performed.

The patient presented with history, exam findings, and labs that all supported the major diagnosis of N₂O exposure-induced pancytopenia. The primary treatment goal is complete abstinence from N₂O. The patient, combined with vitamin B₁ and folic acid supplements, was treated with intramuscular vitamin B₁₂ during admission. The antibiotic was used to treat possible infections. Owing to the factor that she suffered from emotional disturbances, some anxiolytic and antidepressant medications have been administered.

The patient showed improvement in sleep, diet, numbness, and limb muscle strength after one week of treatment. The psychiatric symptoms of anxiety, decreased energy, and depressed thoughts were partially improved and she still has the psychological craving for N₂O.

Table-1: Temporal Change of Hematologic Data

	Case-1				Case-2	
	Admission	Day 2	Day 5	Day 6	Admission	Day 2
HGB(g/L)	109	69	80	80	100	91
HCT (L/L)	0.3	0.19	0.23	0.24	0.27	0.26
MCV (fL)	82.3	86.2	89.1	93.8	88.8	92.6
WBC ($\times 10^9/L$)	0.93	2.02	5.33	6.59	2.26	5.49
NEUT ($\times 10^9/L$)	0.22	0.17	1.6	2.97	0.99	3.02
LYMPH ($\times 10^9/L$)	0.69	1.74	2.61	2.7	1.08	1.86
MONO ($\times 10^9/L$)	0.02	0.09	0.37	0.2	0.17	0.55
PLT ($\times 10^9/L$)	57	14	25	115	55	75
RET ($\times 10^{12}/L$)		0.0075			0.0177	

HGB, hemoglobin (#1 normal range, 115-150 g/L; #2 normal range 130-175 g/L); HCT, hematocrit (#1 normal range, 0.35-0.45 L/L; #2 normal range 0.4-0.5 L/L). The following data have the same normal range in #1 and #2. MCV, mean corpuscular volume (82-100 fL). WBC, white blood cell count ($3.5-9.5 \times 10^9/L$). ANC, absolute neutrophil count ($1.8-6.3 \times 10^9/L$). ALC, absolute lymphocyte count ($1.1-3.2 \times 10^9/L$). AMC, absolute monocyte count ($0.1-0.6 \times 10^9/L$). PLT, platelet ($100-300 \times 10^9/L$). RET, reticulocyte count ($0.024-0.084 \times 10^{12}/L$).

Case-2:

A 26-year-old male patient was found confused, irritable, babbling, with general fatigue on the couch by his mother, he looks decadent and sloppy. The family members and friends reported that he presented with a two-month history of inhaling N₂O and inhaled several canisters daily. Physical examination revealed that his heart rate, respiratory rate, blood pressure, and peripheral oxygen saturation were normal.

He had redness and ulceration of the skin involving bilateral thigh tattoo areas of skin. There were many rashes on the chest wall skin. He was unable to walk and presented hypoesthesia of the skin. The muscle strength of both lower limbs was grade 3/5.

Initial laboratory analysis results showed pancytopenia with hemoglobin of 100 g/L, MCV 88.8 fL, white blood cell count 2.26×10^9 /L, neutrophils 0.99×10^9 /L, and platelets 55×10^9 /L. Subsequently, reticulocyte count was decreased to 0.0177×10^{12} /L. The details were provided in **Table-1**. The further medical examination included a negative viral screen (HIV, hepatitis B, and C), a negative autoimmune screen, and normal thyroid hormones. The test showed a serum iron of 6.5 umol/L (normal range, 10.6–36.7 umol/L), transferrin saturation of 27.3% (20–55%), transferrin of 1.12 g/L (2.5–4.3 g/L), and ferritin of 1327 ng/ml (24–336 ng/ml). Serum vitamin B12 level increased to over 1550 Pg/ml (180–914 Pg/ml). Head and neck MRI were normal and a T2-weighted MRI of the cervical spine didn't show inverted V-shaped hyperintensity.

The major diagnosis of N₂O exposure induced pancytopenia. The primary treatment included supplements of vitamin B12, vitamin B1, and folic acid. The antibiotic was used to treat skin ulcers with infection. The hematological test showed clear improvement, but he was unable to walk independently at discharge. Rehabilitation therapy was commenced in the rehabilitation hospital. One-month follow-up after discharge showed that the patient was emotional stability, and whose sleep and diet have been even normalized, he was able to walk without the help of crutches, but the numbness

of his feet and hands remains.

Discussion and Conclusions

N₂O is widely used for anesthesia and as an analgesic, but now it is increasingly used as a recreational drug. The N₂O influences hematopoiesis similar to that found in the case of vitamin B12 deficiency. N₂O can inactivate vitamin B12/ cobalamine due to prolonged or repeated exposure, which is a crucial co-factor in metabolic pathways involved in myelin and DNA synthesis [3]. The related complications primarily involve hematological and neurological systems [4]. A systematic review reported on 100 patients of N₂O exposure with a median age of 27 years. The most frequent outcomes were subacute combined degeneration (28%), myelopathy (26%), and generalized demyelinating polyneuropathy (23%). At least one hematological abnormality was retrieved in 71.7% of cases. However, this review did not report cases related to pancytopenia [4].

In our study, the cases of two patients had an identifiable history of inhalation of N₂O and were found to be pancytopenia. Intriguing is the rarity of such reports everywhere. Three case reports of N₂O toxicity resulting in pancytopenia have been reported previously to our knowledge. Felicity Norris et al [5] reported a female patient had non-specific neurological and gastrointestinal symptoms. She was diagnosed initially with pyelonephritis. Subsequently, she was found to be an N₂O use disorder and started Vitamin B12 supplement daily on day six of admission. Another case reported a pregnant patient presented after prolonged N₂O exposure with altered mental status and pancytopenia. However, there may be other reasons for pancytopenia in this patient including pregnancy, and possible viral infection [6]. Vozy et al. reported a 16-year-old girl who presented with secondary bone marrow failure following an allogeneic haploidentical stem cell transplant. This was mainly because of the heavy use of N₂O (analgesia) over a prolonged period [7].

In addition, we summarized two cases of pancytopenia in our hospital. Firstly, both patients

presented with symptoms of loss of appetite. Case-1 even presented with vomiting and anorexia which were relatively infrequent and she was not eating for five consecutive days before admission, which may further deteriorate toxic effects such as anemia. Secondly, both patients showed signs of infection. Due to pancytopenia, the patients were immunosuppressed and prone to infection. They were administered with antimicrobials. Thirdly, the primary treatment was administrated with supplements of vitamin B12. The white blood cell count, neutrophils, and platelet levels of patients returned to normal and anemia was partially ameliorated before discharge. The recovery speed was much faster than damage to the spinal cord. Furthermore, they all showed typical neurological damage, mainly manifested by decreased limb muscle strength and sensory disturbance. Regrettably, electrodiagnostic testing such as EMG and nerve conduction study were not performed. One possible reason was their symptoms improved in the early stage of treatment.

Summarily, N₂O was widely used under the name 'narcotic balloon' or 'happy balloon' with its attendant health disadvantages. Physicians particularly included ED physicians, anesthesiologists and psychiatrists should be aware of the pathophysiological, symptoms, and treatment of recreational N₂O exposure. The related complications primarily involve hematological and neurological systems. Pancytopenia is not so frequent when using N₂O for patients with normal hematopoiesis [6]. If the patients presented with unexplained bone marrow failure, a history of N₂O use should be considered, which would greatly help in early diagnosis, therapy, and the reduction of unnecessary costs.

Disclosure

Jia-Li Jiang: This author helped to design the study, collect, and analyze the data, and prepare the manuscript.

Yi-Qin Xia: This author helped to design the study and modify the manuscript.

Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

Ethical Approval

This article does not contain any studies with human participants performed by any of the authors. We only analyzed the data retrospectively.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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Case Report

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