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Research Article

Disturbances in Biological Parameters in Patients Exposed to Nitrous Oxide Abuse Experience of the Rene Dubos Hospital Centre in Pontoise

Yannick Thibaut Koffi[1, *], Samuel Nawa Yeo[1], Corinne Pottier[2], Philippe Niclot[2]

[1]Neurology Department, Bouake University Hospital Centre, Bouake, Ivory Coast

[2]Neurology Department, Rene Dubos Hospital, Pontoise, France

Abstract

Nitrous oxide abuse is increasingly common among young people. It's a gas consumed at parties, where access is easy and less expensive. It can cause vitamin deficiencies, leading to neurological and non-neurological clinical manifestations. The aim of this study was to establish the blood biology profile of patients hospitalized for neurological disorders in the context of nitrous oxide abuse. Methodology, we conducted a retrospective and prospective descriptive study from January 2021 to April 2023. We studied frequency of consumption, inhaled dose and time of exposure to nitrous oxide. Blood levels of vitamin B12 and B9 were measured. Methylmalonic acid and homocysteine were also measured in the blood. Results include 15 patients recruited during the study period. 7 of the 15 patients used nitrous oxide daily. One patient consumed 9600 grams per week. Ten patients had a delay in toxicity beyond one year. Vitamin B12 blood levels were normal in 8 of 15 patients. On average, vitamin B12 levels were normal at 207.57 pmol/l. Vitamin B9 was not routinely measured in 9 patients. Blood homocysteine levels were elevated in 12 of 13 patients, with a high mean of 83.36 µmol/l. In conclusion, blood homocysteine levels are a more reliable marker than vitamin B12 for demonstrating biological disturbances associated with laughing gas abuse.

Keywords

Homocysteine, Neurology, Nitrous Oxide, Vitamin B12

1. Introduction

Nitrous oxide is a gas legally used in various fields, notably medicine [1]. According to a study conducted by NSDUH (National Survey of Drug Use and Health), nearly 21% of teenagers worldwide use drugs, starting with nitrous oxide [2]. Nitrous oxide (N2O), or laughing gas, abused at parties is a growing problem [3, 4]. Vitamin B12 as a cofactor of several metabolic pathways becomes dysfunctional due to its oxidation linked to chronic N2O consumption [3]. Indeed, nitrous oxide inhibits the methionine synthetase enzyme in the liver [2, 5]. This inhibition leads to inactivation of vitamin B12, resulting in methionine deficiency and capture of the tetrahydrofolate molecule [6]. This leads not only to vitamin B12 deficiency, but also to a drop in intracellular folate concentration, with a consequent reduction in nucleotide synthesis. This enzymatic action is due to the fact that nitrous oxide inactivates methylcobalamin by oxidation of the cobalt ion it

*Corresponding author: koffiyannickthibaut@gmail.com (Yannick Thibaut Koffi)

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contains. Methylcobalamin no longer acts as a cofactor for methionine synthetase [6]. This blocks the various synthesis cascades of major cellular elements. Vitamin B12 deficiency can lead to myelopathy and/or encephalopathy, but mainly peripheral neuropathy [2-7]. Blood tests for vitamin B12, homocysteine, vitamin B9 and methyl melanonic acid should be carried out systematically.

Given the extent of nitrous oxide abuse during parties, the aim of our study was to measure biological parameters in patients to detect abnormalities in order to assess the severity of impairment and the effectiveness of management.

2. Materials and Methods

2.1. Setting of the Study

Neurology Department of the Centre Hospitalier René Dubois, Pontoise.

2.2. Type of Study

We conducted a retrospective and prospective descriptive study covering the period from January 2021 to April 2023

2.3. Study Population

The study population consisted mainly of patients with neurological disorders related to nitrous oxide abuse. These patients were admitted to neurological hospitals. Most of them came from the emergency department, the neurological consultation pool or general medicine. Patients hospitalized for peripheral and spinal neurological disorders without nitrous oxide consumption were not included in our study. Data were collected from patients' hospitalization records, using a standardized questionnaire.

2.4. Variables Studied and Data Collection

*Characteristics of nitrous oxide consumption: frequency of exposure (day, week or month), approximate quantity inhaled (in grams) for each patient. Time to toxicity in number of months

*Biological parameters blood levels of vitamin B9, B12, homocysteine and methylmalonic acid. average blood rate of vitamine B12, B9, Homocysteine and methylmalonic.

.Qualitative data is expressed as a percentage. Quantitative data were expressed as mean +/- standard deviation. Data entry and results analysis were performed using Excel software. The confidentiality of the data collected was guaranteed by the anonymous nature of the data collection, based essentially on file numbers.

3. Results

3.1. Characteristics of Nitrous Oxide Consumption

We enrolled 15 patients during the study period. Data on nitrous oxide consumption are summarized in Table 1.

3.2. Biological Parameters

Vitamin B12 was not measured in 1 patient. Vitamin B9 dosage was only performed in 8 patients. Vitamin B12 deficiency was noted in 6 out of 11 patients; vitamin B9 deficiency in 2 out of 8 patients. On average, blood levels of vitamin B12 and B9 were normal (Table 2). Data on homocysteine and methylmalonic acid levels are summarized in Table 3.

Table 1. *Characteristics of nitrous oxide consumption.*

Patients	Consumption frequency	Average consumption (grams/week)	Toxicity time
1	3-6 times a week	Not specified	6 months
2	1 time a week	80	Less than 1 month
3	2times a week	160	More than 12 months
4	Daily	Not specified	More than12 months
5	Daily	1600	More than 6 months
6	Daily	3200	More than12 months
7	Daily	1600	More than12 months
8	Daily	4000	More than12 months
9	Daily	2400	More than12 months
10	Daily	3200	More than12 months

Patients	Consumption frequency	Average consumption (grams/week)	Toxicity time
11	2 times a week	3200	6 months
12	4 times a week	6400	2 months
13	4 times a week	9600	More than12 months
14	3 times a week	4800	More than12months
15	3 times a week	Not specified	More than12 months

Seven patients had been taking nitrous oxide daily for more than six to twelve months.

Table 2. *Vitamin B12 and B9 blood test results.*

Patients	Vitamin B12 assay (pmol/l)	Vitamin B9 assay (nmol/l)
1	213 (normal)	11 (limit of normal)
2	231 (normal)	11.7 (limit of normal)
3	254 (normal)	10.1 (deficiency)
4	<109 (deficiency)	11.3 (limit of normal)
5	289 (normal)	13.4 (normal)
6	124 (deficiency)	15.8 (normal)
7	172 (deficiency)	Not realized
8	278 (normal)	Not realized
9	186 (limit of normal)	Not realized
10	<109 (deficiency)	17.9 (normal)
11	342 (normal)	Not realized
12	363 (normal)	Not realized
13	123 (deficiency)	Not realized
14	Not realized	Not realized
15	113 (deficiency)	8.6 (deficiency)
Average	207.57 (normal)	12.47 (normal)

Eight out of fourteen patients had normal vitamin B12 levels. On average, vitamin B12 levels were normal. Vitamin B9 dosage was not routinely performed

Table 3. *Blood results for homocysteine and methylmalonic acid.*

Patients	Homocysteine assay (µmol/l)	Determination of methylmalonic acid (µmol/l))
1	120.67 (increased)	Not realized
2	17(increased slightly)	29.1 (normal)
3	110.91 (increased)	840 (increased)
4	2 (normal)	17 (normal)

Patients	Homocysteine assay (µmol/l)	Determination of methylmalonic acid (µmol/l))
5	56.4 (increased)	134.5 (normal)
6	61.39 (increased)	Not realized
7	152.14 (increased)	Not realized
8	146.85 (increased)	Not realized
9	101.37 (increased)	Not realized
10	21.23 (increased)	Not realized
11	46.24 (increased)	132.1 (normal)
12	126.31(increased)	Not realized
13	121.23(increased)	Not realized
14	Not realized	Not realized
15	Not realized	Not realized
Average	83.36 (increased)	230.5 (normal)

On average, homocysteine levels were normal.

4. Discussion

4.1. Characteristics of Nitrous Oxide Consumption

It was difficult to specify exactly how much was inhaled. However, based on the fact that a cartridge for a whipped cream siphon contained 8 grams of nitrous oxide, we were able to accumulate the dose consumed per week. The dose varied from 80 grams to 9600 grams per week, with the majority of patients consuming every day. Accordind to Agarwal and al, the use of nitrous oxide is still legal and beyond the reach of the Drug Enforcement Administration [8]. This exposure took place at parties. 10 out of 15 patients had a toxicity delay of over a year. This shows the addictive nature of this drug. According to Van and al Recreational N2O users, however, voluntarily and repeatedly expose themselves to (very) high doses of N2O [8].

4.2. Biological Parameters

Overuse of inhaled nitrous oxide is becoming increasingly common. It leads to altered concentrations of vitamin B12, a cofactor for methionine synthase and methylmalonyl-CoA mutase activity. Consequently, the measurement of biomarkers of cobalamin metabolism, including vitamin B12, homocysteine and methylmalonic acid, could help in the management of patients with complex clinical presentations or those who deny nitrous oxide consumption [3-11]. We observed vitamin B12 deficiency in 6 of 14 patients. Mean vitamin B12 levels were normal at 207.57 pmol/l. On the other hand, Mondesert et al reported a vitamin B12 deficiency in their study, with a mean blood level estimated at 134.6 pmol/L [12]. It was difficult to assess vitamin B9 levels, as these are not routinely measured. Homocysteine levels were elevated in 13 patients, with a mean level of 83.36 µmol/l.

Methylmalonic acid levels were increased in 1 of the 5 patients who benefited from this assay.

Methylmalonic acid levels were increased in 1 of the 5 patients who benefited from this assay. As homocysteine is a reliable biomarker of N_2O toxicity, it should be routinely measured. In their cohort, Swart and al noted vitamin B12 deficiency in 10 out of 20 patients [13]. They reported profiles of nitrous oxide abusers with neurological signs but normal blood levels of vitamin B12. Vitamin B12 levels did not correlate significantly with cumulative nitrous oxide use. Also in their study, Swart et al reported elevated homocysteine in virtually all patients, which may be a more sensitive marker than vitamin B12 levels [13]. In the same vein, Grzych et al report that there is no specific marker of nitrous oxide abuse according to the level of consumption, and the total decrease in vitamin B12 can be used neither as a marker of consumption nor as a marker of severity. Nevertheless, homocysteine is systematically increased and could be used as a marker of recent N2O consumption. On the other hand, they reported that methyl malonic acid could be used as a marker of clinical severity [14]. A recent neurodiagnostic study identified greater motor axonal dysfunction in patients with N2O abuse than in those with vitamin B12 deficiency (who had greater sensory axonal dysfunction) [15]. This suggests a unique pathophysiology, not solely dependent on vitamin B12 function [15].

5. Conclusion

Recreational nitrous oxide abuse is a real public health problem. Classified as a drug, it is responsible for biological disturbances in chronic users. To confirm the diagnosis outside the clinic, biological parameters such as vitamin B12, B9, homocysteine and methylmalonic acid need to be measured. Homocysteine is a reliable marker for the impact of nitrous oxide abuse, while vitamin B12 may be normal. Moreover, there is no cumulative correlation between inhaled dose and vitamin B12 deficiency. In addition to homocysteine, methylmalonic acid should also be systematically measured, to reinforce the biological diagnosis and clarify the severity of the clinical picture, as well as for proper follow-up after treatment.

Abbreviations

N_2O	Nitrous Oxide

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Author Contributions

Yannick Thibaut Koffi: Conceptualization, Data curation
Corrine Pottier: Supervision, Validation
Samuel Nawa Yeo: Data curation
Philippe Niclot: Resources

Data Availability Statement

The data is available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no Conflicts of Interest.

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