Acta Neurologica Belgica
https://doi.org/10.1007/s13760-021-01740-z

LETTER TO THE EDITOR

# Recreational use of nitrous oxide may cause collateral neurological damage

Yasmine Sluyts[1,2] · Philippe Pals[2,3] · Rizvana Amir[3] · Pieternel Vanherpe[3]

Received: 4 June 2021 / Accepted: 22 June 2021


**Keywords** Nitrous oxide · Toxic · Vitamin B12 deficiency · Passive inhalation

## Introduction

The detrimental neurological and other toxic effects of nitrous oxide are well known in scientific literature and even by the broader public. Case reports discussing the toxic effects of nitrous oxide are plentiful, both in the context of use as a recreational drug or in clinical practice [1, 2]. Even so, there is a large margin for awareness-raising, including in clinical practice. Accidental exposure has been described [3]. If the physical properties of nitrous oxide render the probability of exposure substantial even for bystanders, many people could be at high risk.

In our neurology clinic, we recently admitted two patients with all the hallmarks of neurological damage due to functional vitamin B12 deficiency.

The first patient, a 30-year-old male, presented with subacute progressive sensory disturbances in both upper and lower limbs. There was a hypo-to areflexia. Sensation to light touch and pinprick was reduced. Vibration sense was absent below the knees.

The second patient, a 19-year-old woman, presented with a 1-week history of progressive limb numbness and paresthesia. Physical examination revealed a wide-based ataxic gait with absent deep tendon reflexes. There were sensory disturbances in upper and lower limbs, as well as an absent vibration sense in lower limbs. Romberg's sign was positive.

In the first patient, blood tests revealed a slightly reduced vitamin B12 level and an elevated homocysteine level. In the second patient, the B12 level was normal with an elevated homocysteine. In both patients, urine methylmalonic acid as well as methylcitrate levels were elevated. Even with a normal vitamin B12 level, described results are compatible with a functional vitamin B12 deficiency. MRI scan of the cervical spinal cord revealed an inverted V sign on T2 sequence with fat suppression in both patients.

They both consistently denied abusing the substance themselves but acknowledged frequent exposure to other people abusing it in their presence. This led us to question if this kind of 'accidental' exposure could be responsible for the toxic effects in our patients, and if so, whether this could reveal a larger safety issue for other 'accidental' users (Figs. 1, 2).

## Discussion

We believe that the concept of passive inhalation of non-metabolized (by the primary user) nitrous oxide may provide an explanation with our etiological problem, as both cases consistently denied substantial personal nitrous oxide use.

Data regarding potential (short term) toxic or lethal aerial concentrations of a compound are included in various datasets. In the US, the DOE (department of energy) PAC's (protective action criteria) database can be consulted, whereas in the BENELUX, the 'Intervention values of dangerous substances' are available. Both databases distinguish three levels of concern. The first concentration (PAC-1) causes mild, transient health effects. The second concentration (PAC-2) causes irreversible or other serious health effects that could impair the ability to take protective action. Finally, the third concentration (PAC-3) causes life-threatening health effects. For our purposes, we concentrate on the PAC-2 level of

✉ Pieternel Vanherpe
pieternel.vanherpe@emmaus.be

1 Department of Neurology, Antwerp University Hospital (UZA), Drie Eikenstraat 655, 2650 Edegem, Belgium

2 Faculty of Medicine and Health Sciences, University of Antwerp (UA), Universiteitsplein 1, 2610 Wilrijk, Belgium

3 Department of Neurology, AZ Sint-Maarten, Liersesteenweg 435, 2800 Mechelen, Belgium

Published online: 02 July 2021

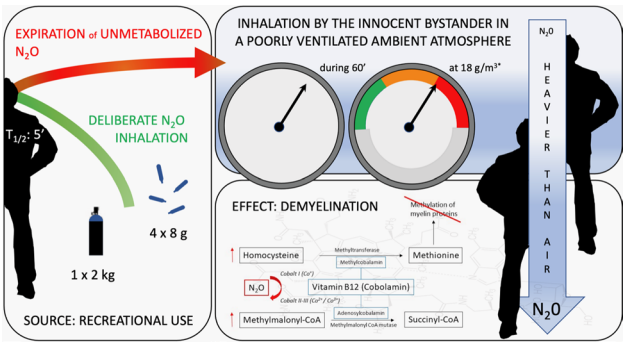


**Fig. 1** $N_2O$, stored in whippits or canisters, is inhaled by the recreational user. With a short biological half-life, the nearly unmetabolized $N_2O$ will readily be expired resulting in rising $N_2O$ concentration, especially in poorly ventilated and small spaces. Innocent bystanders, exposed to concentrations from 10 to 18 g/m$^3$ (depending on the standard used: see text for details) during more than an hour, may experience demyelination due to oxidative inactivation of vitamin B12. The irreversible oxidation of the B12 cobalt ion by $N_20$ also induces a diagnostically important rise of homocysteine and methylmalonyl-CoA levels.

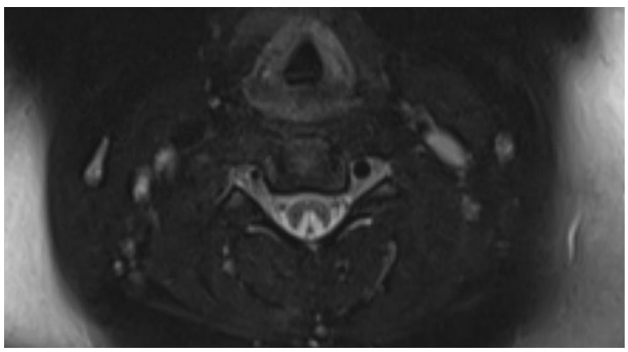

**Fig. 2** Inverted V-sign on axial T2 MRI with fat suppression

nitrous oxide in the US (18.000 mg/m$^3$) and in the BENELUX (10.000 mg/m$^3$).

Laughing gas can be obtained not only in whippit canisters (8 g of nitrous oxide), but also in larger containers upwards of 2 kg. Inhaled nitrous oxide has a biological half-life of 5 min. It leaves the body mainly by expiration. It is not or only poorly metabolized in the human body [4, 5]. Therefore, each milligram inhaled is exhaled, there is no storage in the body. Recreational use of nitrous oxide in a room of $3 \times 4 \times 2.5$ (w × l × h) m$^2$ leads to a PAC-2 concentration in case 300 g (BENELUX standard) or 540 g (US standard) nitrous oxide are released. This corresponds (assuming a standard ceiling height of 2.5 m) to 25 g/m$^2$ floor surface (BENELUX standard) or 45 g/m$^2$ floor surface (US standard). These values are likely to be high estimates. Indeed, nitrous oxide is heavier than air, which results in higher concentrations in the lower parts of the room. Furthermore, the PAC-2 concentrates mainly on acute apparent effects, whereas late-onset effect could be caused by even lower concentrations. When first responders enter a poorly ventilated room of 14 m$^2$ and find a total of 45 'whippits', they can calculate a total nitrous oxide use of 360 g. This may be enough to reach PAC-2 level (BENELUX standard).

We theoretically conclude that routinely used amounts of nitrous oxide in a recreational setting and in a poorly ventilated room may easily result in aerial concentrations that approach or even exceed the PAC-2 levels. Mainly due to poor metabolism and the weight of the gas, this may cause significant collateral damage to non-using, innocent bystanders. This theory can explain why our patients suffered from neurological damage due to vitamin B12 deficiency while denying nitrous oxide use.

History taking should, therefore, not only focus on personal nitrous oxide use, but also bear in mind the possibility of passive inhalation, including the specifics of the secluded area at issue, the quality of ventilation of the room, and the use of 'whippits' or larger containers.

**Acknowledgements** The authors would like to thank Jozefien Vanherpe for writing assistance, technical editing, language editing, and proofreading.

**Funding** The authors did not receive support from any organization for the submitted work. The authors have no relevant financial or non-financial interests to disclose.

**Data availability** Not applicable.

**Code availability** Not applicable.

## Declarations

**Conflicts of interest** None.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** No informed consent is required.

## References

1. Oussalah A, Julien M, Levy J et al (2019) Global burden related to nitrous oxide exposure in medical and recreational settings: a systematic review and individual patient data meta-analysis. J Clin Med 8:551. https://doi.org/10.3390/jcm8040551
2. Thompson AG, Leite MI, Lunn MP, Bennett DLH (2015) Whippits, nitrous oxide and the dangers of legal highs. Pract Neurol 15:207. https://doi.org/10.1136/practneurol-2014-001071
3. Krajewski W, Kucharska M, Pilacik B et al (2007) Impaired vitamin B12 metabolic status in healthcare workers occupationally exposed to nitrous oxide. Br J Anaesth 99:812–818. https://doi.org/10.1093/bja/aem280

4. Fernando R, Nissanka S (1991) Nitrous oxide. http://www.inchem.org/documents/pims/pharm/nitrusox.htm. (Accessed 12 Apr 2021)
5. Becker DE, Rosenberg M (2008) Nitrous oxide and the inhalation anesthetics. Anesth Prog 55:124–131