Nitrous oxide induced neurotoxicity: a case report and literature review

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Abstract

Nitrous oxide is an increasingly popular recreational drug. However recurrent or prolonged use can be associated with nitrous oxide toxicity, with numerous reports of harm documented in the literature. Nitrous oxide irreversibly binds and inactivates vitamin B12, which is an important co-factor in metabolic pathways involved in DNA and myelin synthesis. Toxicity is therefore associated with vitamin B12 deficiency-related syndromes, primarily involving haematological and neurological systems. As a 'legal high', nitrous oxide use has attracted repeated health warnings from experts. An awareness and understanding of the pathophysiology and management of nitrous oxide toxicity is therefore important for clinicians. We discuss the case of a 29-year old man presenting with nitrous oxide-induced sensorimotor neuropathy and review the existing literature surrounding toxicity.

Introduction

Nitrous oxide (N_2O) is a drug used widely in medicine as an analgesic and sedative agent due to its rapid onset of action and high potency. It is also an increasingly popular recreational drug, considered a 'legal high' and surveyed to be in the top 10 most frequently used recreational drugs globally in 2019.[1] Nitrous oxide irreversibly binds, oxidises and inactivates vitamin B12, causing a functional deficiency.[2] Vitamin B12 deficiency is characterised by neurological and haematological abnormalities. There is an expanding body of evidence reporting nitrous oxide-associated vitamin B12 deficiency syndromes.[3] In this case report we discuss a 29-year-old man presenting with nitrous oxide-induced sensorimotor neuropathy and review the existing literature surrounding toxicity.

Case description

A 29-year old man presented with a two-week history of ascending lower limb numbness, pins and needles and difficulty walking. He reported symptoms developing three days after the abrupt cessation of nitrous oxide use. He described ascending symptoms from feet to thigh before developing right foot pain and unsteadiness, prompting his attendance to the emergency department.

At peak, he was using 60 nitrous oxide canisters (whippets) per day for the first five days followed by use every two to three days thereafter. Nitrous oxide was obtained using multiple catering canisters to fill up a balloon from which he would directly inhale. Prior to neurological symptoms, he experienced profuse sweating which began the day after stopping. He denied any unwell contacts, recent illness or travel, and disclosed intermittent low-level alcohol and cannabis use.

On examination he had an unsteady gait, reduced sensation to light touch and pinprick anteriorly from ankle to mid-thigh, absent deep tendon reflexes, and down going plantars. His neurological exam was otherwise unremarkable. Of note, his vitamin B12 levels were low at 164ng L^{-1} (normal range 197-771) and his homocysteine levels were high at 51.6μmol L^{-1} (normal range 0-15). His MRI spine was unremarkable. He was subsequently treated with intravenous vitamin B substances and ascorbic acid (Pabrinex®) and reported an

immediate improvement in symptoms, most notably in his gait and paraesthesia. He was discharged with a loading course of 1000μg of hydroxocobalamin intramuscularly twice weekly (for 10 doses) and 5mg daily folic acid.

Discussion

Nitrous oxide is a colourless gas used therapeutically for its analgesic and sedative properties. It is known commonly as 'laughing gas' due to feelings of euphoria experienced on inhalation with a rapid onset of action and short duration, which has made it an increasingly popular recreational drug. It is currently illegal to distribute nitrous oxide for recreational purposes however it is readily available and legal to buy for healthcare and catering purposes. According to the 2018/2019 Crime Survey of England and Wales, nitrous oxide is the second most used drug among 16 to 24 year olds (8.7%) (after cannabis) with its popularity related to its availability (23.9% of respondents reported ease of access within 24h citing multiple supply sources including friends, family and the internet).[4] According to The Global Drug Survey 2019 (GDS2019), which received data from 123,814 people from >30 countries, the lifetime prevalence of nitrous oxide use is 23.5% - highlighting the global scale of this problem.[1]

Nitrous oxide toxicity was first documented in 1956 when Lassen et al. described bone marrow suppression following the use of nitrous oxide to control spasms in patients with tetanus.[5] Subsequent studies showed an association with megaloblastic bone marrow aspirates[6] and it soon became hypothesised that nitrous oxide exerts its toxic effect on vitamin B12.

Vitamin B12 (cobalamin) is a water-soluble nutrient concentrated in animal tissue. It is absorbed in the terminal ileum using intrinsic factor produced by stomach parietal cells. Vitamin B12 is a co-factor for co-enzymes methionine synthase and methylmalonyl-CoA mutase which are involved in metabolic pathways necessary for haematological and neurological function. Methionine synthase converts homocysteine into methionine, which produces intermediate substrates used in DNA synthesis. Methylmalonyl CoA mutase converts L-methylmalonyl CoA into succinyl CoA (figure 1). In vitamin B12 deficiency these metabolic reactions are disrupted causing impaired DNA and myelin synthesis and maintenance. This leads to haematological and neurological deficits. Adverse effects of hyperhomocysteinuria, such as increased risk for cardiovascular disease, are also seen.[7]

Nitrous oxide exerts its toxic effect by irreversibly oxidising the cobalt ion of vitamin B12 rendering it inactive. This inhibits methionine synthase which uses the reduced form of vitamin B12 as a methyl carrier to function. It also indirectly reduces the activity of methylmalonyl CoA mutase. Levels of homocysteine and methylmalonic acid (MMA) therefore rise as metabolic pathways become disrupted, with recovery being dependant on the synthesis of new proteins.[2,8]

There is a growing body of evidence reporting a broad range of clinical abnormalities associated with nitrous oxide toxicity. These include haematological, neuropsychiatric, thrombotic and cutaneous presentations.[3]

Death has also been reported with evidence suggesting nitrous oxide impairs physiological responses to rising hypoxia and hypercapnia.[9] While the pathophysiology of nitrous oxide-induced toxicity is attributed to vitamin B12 dysfunction, there are reports in the literature suggesting other mechanisms such as the inhibition of N-methyl-D-aspartate (NMDA) receptors.[10] Of interest, a recent neuro-diagnostic study identified more prominent motor axonal dysfunction in patients with nitrous oxide abuse, compared to patients with vitamin B12 deficiency (who had more prominent sensory axonal dysfunction). This suggests a unique pathophysiology independent of vitamin B12 function.[11]

In the present case we discuss a presentation of nitrous oxide-induced sensorimotor neuropathy which highlights the effect of nitrous oxide on vitamin B12 metabolism and describes a clinical presentation of acute toxicity following two weeks of heavy recreational use. These observations are consistent with previously reported cases of nitrous oxide toxicity, most broadly summarised by Oussalah et al. in a systematic review and individual patient meta-analysis of 85 studies, reporting on 100 patients.[3] In this study authors described the majority of patients to be male (60%), young (median 27 years [range 0.4 - 76]) and exposed to nitrous oxide through recreational use (57%). The median nitrous oxide exposure was 18.5 cartridge-years, with one cartridge defined as an 8g canister, and exposure defined as the average number of cartridges consumed per day, multiplied by the duration of exposure (expressed in years). Other sources of exposure included surgery, occupational exposure and analgesia. Of relevance to our observations, Oussalah et al. reported that in 96% of patients, at least one neurological symptom was present, which included paraesthesia in extremities, gait abnormalities and weakness. In 68% of patients who underwent MRI of the spinal cord, there was T2 signal hyperintensity, with the three most frequently reported diagnoses being subacute combined degeneration (28%), myelopathy (26%) and generalised demyelinating polyneuropathy (23%).

Oussalah et al. also reported that in 71.7% of patients at least one haematological abnormality was observed with patient having a high risk of macrocytic anaemia (median MCV 100fL (IQR 94-103) and Hb 12.8g dL^{-1} (IQR 10.8-14.2) and 10.7g dL^{-1} (IQR 8.3-12.4) in males and females respectively). In 70.7% of patients there was vitamin B12 deficiency (<150 pmol L^{-1}). In 90.3% and 93.8% of patients there were high levels of homocysteine (>15 μmol L^{-1}) and MMA (>0.4 μmol L^{-1}) respectively. These findings suggest the presence of symptomatic functional vitamin B12 deficiency with normal vitamin B12 serum levels. This highlights the use of homocysteine and MMA as indirect markers of functional B12 deficiency, which should be considered in patients with high clinical suspicion for deficiency but normal vitamin B12 levels.

In healthy patients, mild megaloblastic bone marrow changes can occur after 12h of exposure to 50% nitrous oxide, with changes becoming marked after 24h exposure.[12] The minimum duration required to cause neurological complications is not known. However a recent study of data from the Global Drug Survey from 2014-2016 reported a strong dose-response relationship between the dose of nitrous oxide per session and the probability of survey respondents reporting paraesthesia, with a 5-fold increase in symptoms comparing people who use up to 2 doses per session to those using 100 doses per session.[13]

There is currently no standardised regimen for treating nitrous oxide toxicity, with the literature varying widely in terms of duration and frequency of reported treatment in addition to the preparation of cobalamin used. [14,15] However, the principles of treatment involve the cessation of nitrous oxide use and intramuscular vitamin B12 replacement. The degree of, and time to recovery in patients with acquired myelopathy due to vitamin B12 deficiency is highly variable. In one observational study of patients with subacute combined degeneration of the spinal cord, 14% of patients treated with vitamin B12 showed complete recovery by a median of 6 weeks (range 2 to 24 weeks). The remaining 86% had some degree of improvement of symptoms by a median of 12 weeks but with a range of 1 to 84 weeks.[16]

Oussalah et al conducted a systematic review of PubMed from January 1966 to August 2018. Using the same search strategy and study inclusion criteria, we conducted a literature search looking for additional publications from Sept 2018 to present. At the time of writing, 53 articles were identified (excluding Oussalah's review) of which 32 were English-language case reports or series reporting on 218 patients with nitrous oxide exposure. Of these, 30 articles, reporting on 176 patients, were related to recreational nitrous oxide use while two, reporting on 42 patients, were in the context of nitrous oxide analgesia for sickle cell crises. Clinical and laboratory features were broadly similar to those reported by Oussalah et al; the majority of patients were young and used nitrous oxide regularly for recreational purposes with abnormalities seen including myelopathy, encephalopathy, pancytopenia, venous thromboembolic events and rashes.[17-22]

Conclusion

There has been a marked increase in the number of cases of recreational nitrous oxide-related toxicity reported in the literature over the last few years. This reflects an increase in the incidence of such cases, as nitrous oxide has gained popularity as a recreational drug. However, it may also reflect an increase in diagnosis and/or reporting, as clinicians become more aware of the phenomenon.

In a recent expert opinion piece, authors issued a warning about the increasing prevalence and use of nitrous oxide, raising concerns about the current COVID-19 pandemic potentially exacerbating the situation through drug market disruptions and social isolation driving consumers towards easily accessible 'highs'.[23] In the past two years there has been a rise in the number of patients being reported with nitrous oxide related toxicity highlighting the urgency of the situation and the need for clinicians to be aware of the pathophysiology and management of acute nitrous oxide toxicity, which may be an increasingly common presentation on the acute medical take.

Data Availability Statement

Data sharing not applicable – no new data generated

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