Lesson of the month 2: A case of nitrous oxide-induced pancytopenia

Authors: Felicity Norris[A] and Patrick Mallia[B]

ABSTRACT

An 18-year-old female patient presented to the emergency department with non-specific neurological and gastrointestinal symptoms and was found to be pancytopenic. Her vitamin B_{12} level was low with a normal mean corpuscular volume and her full blood count 2 months previously had been within normal range. She reported heavy use of nitrous oxide over the previous 2 weeks and other investigations revealed no cause for her pancytopenia. Her pancytopenia resolved with discontinuation of nitrous oxide and vitamin B_{12} treatment. Heavy use of nitrous oxide should be considered as a cause of pancytopenia.

KEYWORDS: Pancytopenia, nitrous oxide, vitamin B_{12} deficiency

An 18-year-old female patient presented to the emergency department following a collapse at home. She reported feeling dizzy on walking to her bed and then collapsed and was found unconscious on the floor by her partner who reported that she was unresponsive for 1 minute. On further questioning the patient reported a 1-week history of dizziness, nausea and vomiting, and a 1 day history of urinary frequency, dark urine and intermittent lower abdominal pain. She had no past medical history other than a previous appendicectomy and was not on any regular medications. On examination she was haemodynamically stable and afebrile. She had multiple oral ulcers and some tenderness on palpation of the left flank but otherwise examination was unremarkable.

Initial investigations revealed a pancytopenia with a haemoglobin of 101 g/L, mean corpuscular volume (MCV) 86.7 fL, white cell count 2.0 x 10^9/L (neutrophils 0.7 x 10^9/L) and platelets 83 x 10^9/L. The blood film was reported as: 'Occasional small platelet clumps although platelet count does appear to be genuinely low. Moderate neutropenia, the neutrophils seen appear well granulated and mature'. Other routine blood investigations were normal other than a slightly raised C-reactive protein of 10.3 mg/L, and chest radiography was unremarkable. Urinalysis was positive for nitrites with traces of leucocytes, blood and protein, β-human chorionic gonadotrophin was negative. She was diagnosed with pyelonephritis and treated with gentamicin and co-amoxiclav. Her haematological parameters continued to deteriorate (see Table 1) so she was reverse barrier nursed and her antibiotics changed to piperacillin/tazobactam, but she remained clinically well and afebrile. Urine cultures were negative. Further investigations included a negative viral screen (HIV, hepatitis B and C, Epstein-Barr virus and cytomegalovirus), negative autoimmune screen and unremarkable abdominal ultrasound. Her haematinics showed a ferritin of 185 µg/L (10–120 µg/L), serum iron 10 mmol/L (9–30 mmol/L), transferrin 2.3 g/L (1.7–3.4 g/L), transferrin saturation 17% (16–55%), folate 17.1 µg/L (>2.7 µg/L) and vitamin B_{12} <125 ng/L (160–800 ng/L). A full blood count 2 months prior to admission was normal (Table 1).

On further questioning the patient admitted to having inhaled approximately 350 canisters of nitrous oxide (N_2O) over the preceding fortnight and prior to this inhaling approximately two canisters weekly for 4 months. On discussion with a haematologist, vitamin B_{12} replacement was commenced in the form of intramuscular hydroxocobalamin 1 mg daily on day six of admission. By day nine her haematological parameters had recovered sufficiently for her to be discharged and her treatment was continued in primary care. A full blood count 6 weeks after her admission was within normal limits (Table 1).

Discussion

N_2O is a colourless, sweet-tasting gas that was discovered by Joseph Priestley in 1772, and its medical use was popularised by Sir Humphrey Davy who reported its pain relieving and euphoric effects in 1784. It is used as an anaesthetic for dental operations, during labour and for acute pain. However its euphoric and relaxing effects and hallucinogenic properties have led to its use as a recreational drug known as 'hippy crack' or 'laughing gas'. In 2014 the Global Drug Survey reported that 38.6% of UK respondents reported ever using N_2O and 20.4% of respondents reported N_2O use in the last year.[1] Most consumers of N_2O use it infrequently but some are heavy users who are at higher risk of adverse effects. Awareness of the potential adverse effects of N_2O among users is low.[2] Vitamin B_{12} deficiency has been reported as a cause of pancytopenia and can occur even with a normal MCV.[3] An effect of N_2O on vitamin B_{12} metabolism was first reported in 1956 with the occurrence of megaloblastic pancytopenia in patients with tetanus treated with N_2O.[4] N_2O causes oxidation of cobalt ions in B_{12}, leading to its irreversible inactivation. This results in inhibition of methionine synthase and impaired conversion of homocystine to methionine and

Authors: [A]foundation year doctor, Imperial College Healthcare NHS Trust, London, UK; [B]consultant physician, Imperial College Healthcare NHS Trust, London, UK

Table 1. Haematological parameters prior to, during and after hospital admission

	2 months prior	Admission	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	6 weeks
Haemoglobin (g/L)	113	101	96	88	87	92	92	85	90	94	100	110
MCV (fL)	82.1	86.7	86.3	86.6	87.3	86.3	86.5	86.9	88.2	88.6	89.3	92.6
White cell count (x 10^9/L)	5.8	2.0	2.0	1.8	2.7	2.8	2.6	3.3	3.5	3.6	4.7	5.7
Neutrophils (x 10^9/L)	1.98	0.7	0.3	0.2	0.4	0.5	0.4	0.5	0.6	0.5	0.9	2.94
Platelets (x 10^9/L)	241	83	65	93	87	111	112	138	172	268	360	307

MCV = mean corpuscular volume.

5-methyl-tetrahydrofolate to tetrahydrofolate (THF). THF is the precursor of thymidine monophosphate required for the synthesis of deoxyribonucleic acid and reduced THF accounts for its effects on haematopoiesis. In addition accumulation of methylmalonic acid leads to demyelination of neurons resulting in neurological damage. Most cases of N_2O toxicity reported in the literature present with neurological symptoms caused by myeloneuropathy and subacute combined degeneration of the cord.[5] In some cases haematological abnormalities were also documented[6] although in others they were not present.[7]

We could only find one report in which N_2O was linked to bone marrow failure without neurological symptoms, although the patient presented with altered mental status.[8] However there were other factors that could have contributed to the pancytopenia in this patient including pregnancy, use of other recreational drugs and possible viral infection. Our patient presented with non-specific symptoms including loss of consciousness and nausea that have been reported in N_2O users.[1] She was diagnosed with pyelonephritis and her pancytopenia presumed secondary to sepsis. However she had no clinical evidence of sepsis and subsequent laboratory and microbiological investigations did not support this diagnosis. The finding of a low B_{12} and the history of heavy N_2O use suggested the diagnosis of N_2O-induced B_{12} deficiency resulting in pancytopenia. This was supported by the previously normal blood count, the lack of an alternative cause for her pancytopenia, and the rapid response to cessation of N_2O use and B_{12} replacement. She had no neurological symptoms or signs during her hospital admission.

Conclusion

N_2O is increasingly used as a recreational drug particularly in young people. While the neurological toxicity related to N_2O misuse has been well documented, the haematological effects are less well recognised. In patients presenting with unexplained bone marrow failure a history of N_2O use should be sought even in the absence of neurological symptoms or signs. Recognition of N_2O toxicity as a potential cause of pancytopenia can result in early initiation of B_{12} treatment and the avoidance of invasive investigations such as bone marrow aspiration or biopsy. ■

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Address for correspondence: Dr Patrick Mallia, Imperial College Healthcare NHS Trust, Praed Street, London W2 1NY. Email: patrick.mallia@nhs.net