IAEM Clinical Guideline

Management of Nitrous Oxide Related Presentations in the Emergency Department

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DISCLAIMER

IAEM recognises that patients, their situations, Emergency Departments and staff all vary. These guidelines cannot cover all clinical scenarios. The ultimate responsibility for the interpretation and application of these guidelines, the use of current information and a patient's overall care and wellbeing resides with the treating clinician.

Revision History

Date	Version	Section	Summary of changes	Author
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GLOSSARY OF TERMS

CRP	C-reactive Protein
CT	Computer Tomography
ECG	Electrocardiogram
ED	Emergency Department
IM	Intramuscular Injection
MG	Milligram
MMA	Methylmalonic Acid
MMCoA	Methylmalonic Coenzyme A
MRI	Magnetic Resonance Imaging
N_2O	Nitrous Oxide
NMDA	N-methyl-D-aspartate
PND	Peripheral Neuropathy Disability
TFTs	Thyroid Function Tests

PARAMETERS

Target audience: Clinicians in the emergency department (ED) managing patients presenting with nitrous oxide related presentations

Patient population: Patients (aged > 16) presenting to the adult ED with symptoms related to the use of nitrous oxide

Exclusion criteria:

- Patients with no history of nitrous oxide use
- Children (< 16 years)
- Patients with known demyelinating disorders
- Patients with features suggestive of cauda equina syndrome
- Patients with sensorimotor neuropathy related to trauma
- Patient with history of malignancy

AIM

To provide an evidence-based guideline on the management of patients presenting to the ED with symptoms related to nitrous oxide use.

Management of Nitrous Oxide Related Presentations in the Emergency Department

INTRODUCTION

Nitrous oxide (N_2O) is an odourless, colourless, non-flammable inhalational anaesthetic agent which is used in the operating room and the emergency department[1].

The European monitoring centre for drug and drug addiction (Euro-DEN) has noted an increase in the reports of recreational use of nitrous oxide in multiple European countries including Ireland[2]. Nitrous oxide can be bought online in large canisters or in forms licensed for other uses, such as industrial whipped cream dispensers[3].

Nitrous oxide is recreationally used for its rapid onset brief feeling of euphoria and relaxation. Use of nitrous oxide is common due to its easy availability, affordability, and the perception that it is a safer and socially acceptable substance[4]. There have also been isolated cases of patients presenting frequently to EDs with self-inflicted injuries (for example, recurrent patellar dislocations) to be treated with N_2O in the ED and developing complications as a result. Acute adverse reactions include nausea, vomiting, dizziness and tingling[5].

Chronic use may lead to symptoms of ataxia, peripheral neuropathy, myelopathy (subacute combined degeneration of the cord) and psychosis. The neurological effects are due to its inhibition of vitamin B12[4].

PATHOPHYSIOLOGY

- N_2O leads to an irreversible inactivation of vitamin B12 by oxidising its cobalt-containing ring, causing a functional deficiency.
- The inactivation of cobalamin (vitamin B12) leads to a reduction in methionine synthase activity.

- Methionine synthase inactivation leads to methionine deficiency, preventing methylation of myelin proteins and causing both demyelination within the central and peripheral nervous systems and disruption in axonal regeneration.
- The gathering of metabolites causes hyperhomocysteinaemia which promotes mitochondrial dysfunction, oxidative stress, endothelial dysfunction, inflammation and NMDA excitotoxicity[6].

Biochemical Markers of Recent N_2O Consumption

Homocysteine increases rapidly, and it is a sensitive biomarker for recent N_2O consumption. Unfortunately, homocysteine lacks specificity. It can also be raised in vitamin B9 or B12 deficiency, renal or hepatic insufficiency, hypothyroidism, and other metabolic disorders[1].

Biochemical Markers of Clinical Severity of N_2O Abuse

Plasma methylmalonic acid (MMA) is a reliable marker of functional vitamin B12 deficiency. There is a lack in sensitivity of plasma MMA for N_2O intoxication due to the elevation not being consistent but can be associated with clinical severity. In comparison to homocysteine plasma MMA is more specific for vitamin B12 deficiency as it is independent of vitamin B6 and B9 levels but increases in renal insufficiency and in other metabolic diseases[1].

Nitrous Oxide Effects

There is no safe level of drug use. Nitrous oxide affects everyone differently based on:

- the amount taken
- the user's size, weight and health
- whether the person is used to taking it
- whether other drugs are taken around the same time.

SUSPECTED NITROUS OXIDE TOXICITY IN EMERGENCY DEPARTMENTS

Acute Toxicity

Acutely, the following have been reported:

- injuries secondary to intoxication or syncope
- hypoxia and asphyxiation (leading to arrhythmias, seizures, hypoxic brain injury, or death)
- barotrauma (pneumothorax, pneumomediastinum, tympanic membrane rupture)
- confusion, hallucinations
- vomiting with aspiration
- cold injuries to the lips or mucosa.

For these presentations, there is no specific toxicological management.

Chronic Toxicity

Presentations related to chronic harms are typically associated with long-term, high-frequency use, though some patients can present following use of high amounts of N_2O over a shorter period.

In patients developing N_2O-induced symptoms after modest doses or with significantly low B12 at baseline, one should consider the possibility of the N_2O unmasking a pre-existing B12 malabsorption state.

CLINICAL HISTORY

Obtaining a concise history from the patient is important.

Patients presenting with neurological abnormalities without obvious cause should have nitrous oxide toxicity considered as a potential cause for their symptoms. The typical presentation is with the combination of cervical myelopathy and length-dependent neuropathy (i.e. a myeloneuropathy)[7].

Patients may present with any of:

- sensory deficits (either in a classic peripheral neuropathy pattern, or with isolated areas of numbness or paraesthesia)
- motor deficits (classically described as predominantly lower limb, or with issues relating to fine motor control)
- ataxia
- urinary retention
- erectile dysfunction
- non-specific symptoms such as confusion
- personality change (including low mood or irritability).

Patients presenting with haematological abnormalities (anaemia, macrocytosis, agranulocytosis or pancytopaenia) consistent with vitamin B12 deficiency should have nitrous oxide toxicity considered as a potential cause for their symptoms. Note that these are typically normal in most patients with N_2O induced myeloneuropathy.

EXAMINATION

Patients presenting to the ED should be examined by the clinician as per the “ABCDE” approach. Subsequently, a complete neurological examination must be done which includes cranial and peripheral nerves as well as a cerebellar examination.

INVESTIGATIONS

Blood tests that should be performed on patient presenting with suspected nitrous oxide related presentations include:

- Full blood count (FBC)
- Renal profile
- Calcium
- Magnesium
- Phosphate
- C-reactive protein (CRP)
- Liver function tests (LFTs)
- Folic acid♦
- Vitamin B12♦

Blood test that ideally should be completed prior to vitamin B12 treatment:

- Methylmalonic acid (MMA) ♦
- Homocysteine♦

♦ Note these tests should be sent from the ED, as tests undertaken after treatment has commenced may have normalised. However, if the patient is not being admitted to hospital, there should be a clear local protocol for specialty ownership of results. It is suggested that the biochemistry laboratory be consulted prior to obtaining these, as sampling procedures may vary between providers.

An electrocardiogram (ECG) should be done.

Hyperhomocysteinaemia causes a hypercoagulable state which can cause PE/DVT in people who have reduced mobility due to myeloneuropathy.

Available immediately	FBC** Renal function, electrolytes, LFTs Thyroid function tests Vitamin B12** Folic acid** ECG **While these tests may demonstrate features of folate/B12 deficiency (anaemia, macrocytosis), they may be falsely reassuring.
Need to be taken prior to treatment with vitamin B12 (but result may take several days)	Homocysteine Methylmalonic acid Consider intrinsic factor antibody and parietal cell antibody

Table 1. Investigations for Suspected Nitrous Oxide Toxicity in the Emergency Department

There is no indication for CT brain (or MRI brain) in these patients unless there is a suspicion of an alternative aetiology such as trauma. MRI of the whole spine is the imaging modality of choice in assessing spinal cord changes related to nitrous oxide induced subacute combined degeneration of the spinal cord. It does not need to be done during the emergency department assessment[8].

TREATMENT

Intramuscular hydroxocobalamin 1 mg should be given as soon as possible following assessment (prior to the return of diagnostic test results).

A suggested regimen is to give intramuscular hydroxocobalamin 1 mg daily for one week and then review in a follow up medical clinic if the patient is fit for discharge.

Check local protocols for guidance on duration of treatment as there have been few studies comparing different lengths of treatment. The Association of British Neurologists clinical practice guide suggests alternative days for at least 2 weeks and continue until no further clinical improvement.

Folic acid 5mg orally daily is recommended by the Royal College of Emergency Medicine (RCEM). Note that this is not included in the Association of British Neurologists (ABN) clinical practice guidance for nitrous oxide-induced subacute combined degeneration of the cord. Clinicians should refer to local protocols.

All patients should be explicitly warned that B12 injections and supplementation will likely not be successful if they continue to use nitrous oxide[8].

Consider referring patients to the local drug and alcohol service to aid abstinence from nitrous oxide.

DISPOSITION

This patient group may be candidates for acute neurology, or similar ambulatory pathways, if available. The patient should be discussed with the relevant medical team on call if there is a concerning differential, or red flag symptoms.

If a suitable ambulatory pathway is not available, consideration should be made to refer to the medical team on call.

FOLLOW-UP

If the patients are safe for discharge as per local guidelines, the ED team should consider the following before discharge:

- Appropriate follow-up clinic within 7 days for review of baseline, investigation results, treatment and consideration of another diagnosis if not improving.
- Access to contact follow-up clinic if patient has not received an appointment.
- Patients must be advised to stop using nitrous oxide immediately and to return to the ED if there is any deterioration.
- Patient education regarding intramuscular (IM) administration of vitamin B12

SPECIAL CONSIDERATIONS

Frostbite Injuries

Frostbite injury can occur due to direct spraying or spilling of the liquified gas on to the skin, with temperature on contact of approximately -55°C to -88°C. Alternatively, as nitrous oxide is discharged from the highly pressurised container (for direct inhalation or to fill a balloon), the metal canister briefly decreases its temperature to approximately -40 C due to the physical property of adiabatic cooling. If the container is mishandled, this may result in significant contact frostbite injury. There has been a recent case series published in the IMJ detailing frostbite injuries to seven paediatric patients from nitrous oxide. Patients may have delayed presentations due to the nitrous oxide analgesic and anaesthetic effects[9].

Injuries to the inner thighs can be sustained from prolonged positioning of a large canister of nitrous oxide between the thighs while filling balloons with the gas. The resulting injuries can involve full-thickness necrosis of skin and underlying fat, which may necessitate deep debridement and reconstruction with split-thickness skin grafting.

EM clinicians can refer to the IAEM Clinical Guideline Management of Thermal, Chemical and Electrical Burns in the Emergency Department for guidance on assessment, management and disposition.

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APPENDIX 1: GUIDELINE STAKEHOLDERS

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