*Lesson of the week***Toxicity after intermittent inhalation of nitrous oxide for analgesia**

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Nitrous oxide used for analgesia at home can cause neurological complications even with intermittent use

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A mixture of nitrous oxide and oxygen in equal proportions (Entonox or Equanox) is an effective analgesic and is considered safe with minimal side effects. The mixture is ideal for treating short term pain. We report a serious neurological problem in a patient using such a mixture to control pain from the daily packing of a large perineal cavity.

Case report

A 21 year old man presented with a short history of being unable to stand. He had had a series of serious operations for the treatment for inflammatory bowel disease over a four year period—colectomy, ileostomy, and laparotomy with the formation of an ileoanal pouch. He developed pelvic sepsis requiring the laying open of an extensive perineal abscess.

The provision of postoperative analgesia for a perineal abscess proved difficult, during daily changes of packs to the cavity. Doctors gave paracetamol, diclofenac, regular oral slow release opioids, morphine tablets, and a 50:50 mixture of nitrous oxide and oxygen for managing the incident pain while changing dressings.

The hospital gave the man a 300 litre cylinder of the mixture as a short term arrangement over the Christmas period to provide analgesia for dressing changes. The man was to be readmitted after two weeks for review. When he was not readmitted as planned, his family arranged for replacement with larger cylinders. The hospital issued increasing amounts during four months, resulting in the weekly consumption of 1280 litres of nitrous oxide mixture. The district nurses contacted the hospital's pain team to express concern about the amount of mixture that the patient was using.

The man had had progressive severe difficulty in walking for six weeks, so his general practitioner referred him to a neurologist with no reference to the use of nitrous oxide. The neurologist diagnosed him as having a spinal cord disorder and admitted him to hospital for more detailed investigation.

On admission, the patient weighed 60 kg; he had a drain in the rectal pouch and reported severe pain in his perineum. He was unable to hold a cup or put on his glasses owing to severe lack of coordination and was unable to stand independently owing to severe ataxia.

The patient reported that his only drugs at that time were the standard analgesics, vitamin and mineral supplements, iron sulphate, citalopram, zinc, and paracetamol. Neurological examination showed severe pseudo-athetosis of the fingers and arms, and motor examination of his arms and legs, brisk reflexes and bilateral flexor plantar responses was normal. Sensory examination found severe loss of joint position sense in the hands and feet and loss of vibration sense in all

four limbs with no spinothalamic sensory loss or trunkal sensory level.

He was diagnosed as having a dorsal column spinal syndrome (probably subacute combined degeneration), and doctors gave 1000 µg hydroxocobalamine (vitamin B-12) after taking blood for vitamin B-12 and other haematological and biochemical estimations.

Concentration of vitamin B-12 was slightly below the normal range (269 ng/l; normal >300 ng/l). Serum and red cell folate were normal. The patient denied having taken folate or vitamin B-12 antagonists.

A long lesion of the dorsal column, typical of subacute combined degeneration, was evident in a magnetic resonance imaging scan of the cervical spinal cord (figure).

Transverse myelitis was a possible differential radiological diagnosis in view of the normal vitamin B-12 concentration. Viral and atypical bacterial organism serological tests were negative. Because of pelvic sepsis and the man's evident rapid improvement, a lumbar puncture was not done.

After his discharge the neurological team learnt that the man had been taking nitrous oxide, explaining the paradoxical clinical picture of subacute combined degeneration with normal vitamin B-12 and folate concentrations. Appropriate aftercare was arranged with further injections of vitamin B-12 and to provide psychological support to manage his evident addiction.

On follow up at three months the man had no gait ataxia and normal hand function and was independent

Magnetic resonance image showing dorsal column lesion (arrow) of the spinal cord

in all activities of daily living. The case illustrates the need to be aware of adverse effects of all drugs—even those considered to be among the safest.

Discussion

Nitrous oxide can interfere with the metabolism of vitamin B-12 and can cause spinal cord degeneration.¹⁻² The mechanism of neuropathology with nitrous oxide is due to inactivation of vitamin B-12, which leads to impaired methionine synthesis. The cobalt atom in vitamin B-12 donates two electrons to nitrous oxide¹:

This is followed by the rapid reaction of Co^{3+} with Co^{4+} resulting in the failure of methylation of basic proteins in myelin sheaths³:

Polyneuropathy and spinal cord degeneration are the most common neurological manifestations of vitamin B-12 deficiency. The diagnosis is made clinically and by finding a decreased serum vitamin B-12 concentration. (Often there is no macrocytosis on the blood film, as in this case). The typical magnetic resonance imaging findings show a typical dorsal cervical cord lesion.⁴

Reports describing spinal cord degeneration of the cord after treatment with nitrous oxide have generally been attributed to prolonged exposure to the gas and poor nutrition.⁵⁻⁶ Toxicity related to the prolonged intermittent exposure of low concentrations of nitrous oxide has been described in experimental animals.⁷⁻⁸

In this case, nitrous oxide probably complicated longstanding malnutrition, causing neurological com-

plications with intermittent administration of small amounts of nitrous oxide. The good safety record and rapid action of 50:50 nitrous oxide-oxygen mixtures in pain management make it a desirable agent, particularly for pain during medical procedures. It is important, however, that health workers who prescribe nitrous oxide are aware of its potential long term adverse effects, particularly in patients with chronic illness. After this incident, our hospital has put in place appropriate procedures to guard against a repetition.

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Q&A

Cocaine and amphetamine combined

Question

What would happen if someone was to take a mixture of cocaine and amphetamine at the same time?

Elizabeth M Sobiech, *medical student, Birmingham*

Answer

It depends on dose, route of administration, and history of drug misuse.

Both cocaine and the amphetamines developed originally for clinical use (including methamphetamine (or "ice")) are psychomotor stimulants.¹ They have broadly similar actions at the synaptic level (such as blocking reuptake of dopamine released from the meso-limbic-cortical dopamine terminals), the level of mood and alertness, and the behavioural level. Some other amphetamines (such as phenylamphetamine (mescaline)) have slightly different actions, based, like ecstasy (MDA, MDMA), on a predominantly serotonergic effect.

All can be taken by different routes, including oral, intranasal, intravenous, or smoked (the freebase of cocaine "crack" or methamphetamine "crystal"). In a drug-naïve, low dose, intranasal or oral user the stimulant effect would probably be additive at the time of use, with the longer half life of amphetamines giving a much prolonged "high" compared with cocaine by itself. Tolerance in regular users builds up to a great degree, so naïve users are at immediate risk of overdose (such as with severe cardiovascular effects) if they take the dose of their more experienced friends, say at a party or club. Fatal overdoses are

particularly common if taken in combination with other substances, especially injected heroin (a "snowball" or "speedball") and abundant alcohol (cocaethylene is produced). A prolonged run of stimulant use, say continuously over a weekend, always produces an unpleasant emotional state very different from the initial euphoria—people who try desperately to prolong the "high" may end up feeling desperate and behave in a pretty wild or frightened way.

In my unpublished work on London stimulant users, dependent drug users significantly preferred cocaine to amphetamine (although it is more expensive)—the first stimulant drug used was predominantly amphetamine in early adolescence. One of the peculiar phenomena of these drugs is priming (early low dose exposure to either one increases the effect of later use of the other), a type of learning. Heavy users of intravenous stimulants show their proconvulsant action—over repeated use, seizures are kindled. This is one (of many) reasons why I would not recommend substitution of prescribed methamphetamine or methylphenidate for former illicit cocaine users.

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