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A gas causing laughter and harm

EDITORIAL

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Misuse of nitrous oxide among partying young people has remained under the radar for several years. Good old pathophysiology can explain the dangers of this misuse.

The recreational drug market is creative and constantly evolving. The latest drug on the scene is nitrous oxide – both an anaesthetic that is being phased out and a domestic gas used to whip up cream quickly. It can also 'whip up' your mood and is therefore being increasingly misused. Nitrous oxide as a recreational drug is not illegal, and there is no age limit in Norway. The combination of an uncontrolled increase in use *and* a lack of knowledge about adverse effects has now resulted in several cases of classic neurological sequelae as previously seen with pernicious anaemia. What is the connection?

Dinitrogen oxide (N_2O) is tasteless and odourless and has a weak analgesic, sedative and euphoric effect, which accounts for its medical use and the nickname *laughing gas* (1). When misused, nitrous oxide can have an acute toxic effect due to displacement of oxygen, which can intensify the high while at the same time causing ischaemic complications in the heart and brain, although these are rare. Oxygen is added to medical nitrous oxide to counteract such hypoxia (1). Due to its rapid elimination, nitrous oxide is difficult to detect in practice – particularly in post-mortem examinations. Therefore, although the use of nitrous oxide for recreational purposes is increasing, it is difficult to draw any conclusions about the frequency of the harmful effects (1, 2).

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During the autumn meeting of the Baltic-Nordic Poisons Information Centres, it became evident that there was a major problem in Denmark and Sweden, which had apparently been 'imported' from raves in the Mediterranean. Therefore, an age limit of 18 years has been set for the purchase of nitrous oxide in Denmark, and in New York an age limit of 21 years has been set for the purchase of nitrous oxide cartridges for whipped cream (3). In Norway, the number of enquiries to the Poisons Information Centre has increased from less than 10 last year to almost 40 so far this year (own unpublished figures).

Neurological sequelae with more chronic use have been reported in the literature (1, 4, 5). In the case report now being published in the Journal of the Norwegian Medical Association, we follow a young man who clearly must have posed a diagnostic challenge with paresis and numbness in his legs as in polyneuropathy (4). By means of thorough and systematic investigation by the neurologists and advanced diagnostic imaging in the neuroradiology department, the correct diagnosis was reached. The problems with taking the patient's history of recreational drug use are also interesting and typical, with the patient denying drug misuse for a long time (to quote Dr House: 'Everybody lies!') – which is understandable to some extent based on what is legal and illegal. The diagnosis was only confirmed on direct questioning based on typical findings in good MRI images. The article also illustrates how easy it is to obtain nitrous oxide cartridges being sold online and supplied on social media.

At medical school in the 1970s, we were taught that vitamin B_{12} deficiency could cause demyelination and polyneuropathy with paresis. The cause then was deficiency of intrinsic factor following a Billroth II operation or atrophic gastritis. Old pathophysiological concepts came back to me when I read the following in this case report: 'Nitrous oxide oxidises the cobalt ion in vitamin B_{12} and impairs conversion of homocysteine to methionine. Without methionine, there is no methylation of myelin, the insulating layer around nerve cells' (4). The result will be demyelination, with typical presentation at C3 on an axial section in Figure 2 of the case report (4). I may not have enough imagination to see the 'rabbit ears' here, but the 'inverted V' is easy to see.

For years, the recreational drug scene has played cat and mouse with lawmakers around the world, and the narrative surrounding the growing use of nitrous oxide is *yet another* example of this. In the United States, the actual route of synthesis of a recreational drug was previously illegal, but not its use if it was produced via another route of synthesis. So new methods of synthesis were constantly emerging and 'legalising' the use. When the new oral recreational drugs appeared a few years ago (*Novel Psychoactive Substances* (NPS) or 'party drugs'), it was difficult to stop online sales because the substances were labelled as 'bath salts' or 'not meant for human consumption'. But all buyers knew what these codes meant. Banning the sale of nitrous oxide for recreational purposes is of little help when getting high on it is not illegal.

So what's the situation with these patients, and how can we prevent more people developing neurological sequelae? The condition of the patient in the case report has improved, and the same applies to several of the approximately ten patients treated in the Department of Neurology (private communication from My Hermansen) – also recently reported in the Norwegian *Dagbladet* newspaper (3). However, irreversible injury has been reported (4, 5), and therefore awareness of this misuse must be raised in both youth circles and the health service, without stimulating more misuse. Treatment is straightforward, but making a diagnosis can be more difficult, as in this case. The provision of factual drug information to young people must be one of the key steps – to keep them on their dancing feet.

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