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Recreational use of Laughing Gas: What are the Health Risks?

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Abstract **Case Report**

The recreational use of nitrous oxide is a growing practice among young people. Nitrous oxide cartridges are easy to access and low cost. Generally inhaled, from steel bombs or balloons, Nitrous Oxide is today the 7th most popular drug in the world for its euphoric effects. We will present through a case report where psychiatric symptoms are significant, an overview of psychiatric complications, but also neurological and general of the recreational use of Nitrous Oxide. Indeed, this use, even recreational, can produce a series of neurological, psychiatric, hematological and respiratory symptoms. Its pathogenic mechanism remains largely unknown; there is no specific treatment apart from vitamin B12 supplementation. Therapeutic approaches are therefore based on motivational interviews and psychotherapies. Prevention campaigns among young people therefore seem necessary because they underestimate the dangers.

Keywords: Nitrous oxide, laughing gas, vitamin B12, Delirium, Hallucinations.

I. INTRODUCTION

In the current psychopharmacological panorama, the variety of substances capable of causing an acute psychotic episode, and which have become part of the habits of users of psychoactive substances, has rapidly increased [1]. Here we will take the example of Nitrous Oxide, which in addition to its medical use, has numerous applications in the food and automobile industries [2]. Its use as a recreational substance dates back to the 19th century where it was mainly used for entertainment at parties [3].

Nitrous oxide was first synthesized in 1772 by an English chemist named Joseph Prestley, who described it in his work "Experiments and observations on differences kinds of air" [4]. This chemical description will be followed, two decades later, by the discovery of its analgesic and euphoric properties by Humphrey Davy in 1799, from his personal experience during a toothache accompanied by migraine, he will be the first to use the term "laughing gas" and will thus promote nitrous oxide during public demonstrations [5].

Due to its euphoric and relaxing properties, the inhalation of nitrous oxide became a popular public entertainment at the end of the 18th century, but also a fashionable element in the social parties of British high society. Its misused recreational use is an integral part of its history from its discovery to the present day. This trend spread to different countries at the end of the 1990s, causing awareness of its harmful power when consumed as a drug [6].

These various findings lead us to ask ourselves certain questions: Can the recreational use of nitrous oxide seriously harm the health of its consumers?

To do this, we will present through a case report where psychiatric symptoms are significant, an overview of the psychiatric complications of the recreational use of Nitrous Oxide, we will first address its properties, its uses and its mechanisms of action in order to know its nature. We will then address the misuse of nitrous oxide by taking stock of its epidemiology around the world, before exploring its undesirable effects and its addictive potential. Finally, we will endeavor to demonstrate the need to inform consumers and health professionals about its misuse.

II. CASE REPORT

Our case report describes a French tourist, aged 25, a banker by profession, with no particular psychiatric or medical history, who was brought to the emergency room of the Ar-razi psychiatric hospital in Salé by the authorities, for treatment of psychomotor instability, verbalization of delusional remarks and insomnia evolving for approximately 02 days, following excessive and isolated use of nitrogen peroxide bombs, in a festive setting in Marrakech, according to the statements of his friends who accompanied him.

The psychiatric interview at admission revealed a dissociative syndrome, a delusional persecution and mystical-religious syndrome, a hallucinatory syndrome, with impaired judgment and insight.

A complete biological assessment, a brain CT as well as a drug test in the urine were requested, which returned without any particularities.

The patient was placed on Aripiprazole and Diazepam, with very good clinical progress and complete resolution of symptoms after 02 days.

III. DISCUSSION

1. Classification:

Nitrous oxide is classified among the group of "inhalants". It should be noted that this group is specific, because the substances which are part of it are classified by their mode of administration and not in relation to their mechanism of action in the Diagnostic and Statistical of Mental Disorders, fifth edition (DSM-5) [7].

In addition, a classification system proposes to separate inhalants into three categories, according to their pharmacological type and their mode of consumption: the first being consisting of volatile solvents (ether), the second comprising only nitrous oxide and the third being composed of volatile alkyl nitrites ("poppers"). Thus nitrous oxide constitutes a category in itself [3].

2. Action Mechanism

Nitrous oxide is a colorless, almost odorless, oxidizing gas that is heavier than air. It acts as a central nervous system depressant, with a dose-dependent effect [8]. Its anesthetic power, weak due to its low solubility coefficient in blood and in oil, explains that, for anesthesia, it must be used in combination with other volatile anesthetics or administered intravenously. Its onset of action is rapid, as is its elimination upon stopping administration [9].

Nitrous oxide has a mechanism of action which is not yet clearly known although numerous authors and studies evoke an interaction with the system opioid endogenous and NMDA receptors in particular [10]. Indeed, nitrous oxide can be a partial agonist of receptors mu, kappa, sigma and delta opioids; to which it binds and stimulates the release of beta-endorphins. Additionally, the administration of specific antagonists such as naloxone (an opioid antagonist specific) attenuates the effects of nitrous oxide, which clearly demonstrates a link between opiate receptors and the action of nitrous oxide [11].

Nitrous oxide has also an inhibitory effect on the enzyme methionine synthetase at the hepatic and cortical level by inactivation of vitamin B12. This inhibitory effect causes a methionine deficiency and a capture of the tetrahydrofolate molecule which leads to a vitamin B12 deficiency but also to a drop in the intracellular concentration of folates and finally to a reduction in nucleotide synthesis [12].

Its analgesic power is observed at low doses. In fact, it acts by increasing the pain threshold. It depresses the synaptic transmission of nociceptive messages and activates the sympathetic nervous system, the noradrenergic neurons of which play a role in nociception. It has a weak amnestic effect and provides very little muscle relaxation. At the respiratory level, we observe an increase in rhythm with a decrease in tidal volume without hypercapnia. At the cardiac level, it is responsible for myocardial depression, with a moderate decrease in contractility, a minor effect on left ventricular load conditions. This moderate circulatory depression is, to a large extent, compensated by the increase in sympathetic tone [9].

Furthermore, nitrous oxide appears to affect different regions preferably cerebral. Inhalation has been shown to activate the anterior cingulate cortex and deactivate regions of the posterior cingulate cortex, hippocampus, para-hippocampus and association cortex (= pre -striate cortex) in both hemispheres. This potentially explains the cognitive alterations observed, as well as the memory deficits which will be discussed later [13].

3. Misuse of Nitrous Oxide:

Recreational use of nitrous oxide appeared in conjunction with the discovery of the latter and its euphoric effects at the end of the 18th century. Nitrous oxide was therefore used for recreational purposes long before its medical potential was demonstrated.

It was initially used by high society in London during galas or "social parties", but also during funfairs where the population could try its effects during the 19th century. Since the discovery of its properties and the relative difficulty in obtaining it over time, nitrous oxide has been for a long time diverted from its use by the various health professionals to whom it has access was facilitated: dentists, anesthesiologists and medical students.

Recreational use has developed and experienced significant variations over time until today it has become a full -fledged public health problem in many countries around the world [3].

Figure I: Bombes de Protoxyde d'azote [8]

It is obtained most often from small gas cartridges called cream chargers whipped. These are small pressurized metal cartridges containing 8 grams of liquid nitrous oxide which release approximately 4 liters of gas when opened. They are intended to be used with whipped cream dispensers at home and by the food industry to make whipped cream, desserts, mousses, as well as infuse flavors into drinks [14].

Recreational use, the cartridges are opened using an empty whipped cream dispenser. This has a holder for the cartridge, and screwing the holder into the distributor causes a sharp pin to pierce the aluminum cap at the narrow end of the cartridge, releasing the gas into the distributor (causing a hissing sound).

A balloon is placed on the end of the dispenser nozzle (Figure I). By pressing the distributor lever, the gas is released into the balloon. The gas is then inhaled through the balloon and then exhaled directly into the air or rebreathed into the balloon for additional effect [15].

4. Epidemiology of recreational use of nitrous oxide:

Recreational use has been known for a long time, this phenomenon has exploded for several years, and even more so in the context of the health crisis linked to the Covid-19 pandemic. Frequencies and quantities consumed can be very variable, from a few cartridges to several hundred per day of use, with certain cases of daily consumption.

According to international studies from the Global Drug Survey (GDS), we find an increase in the prevalence of recreational consumption of nitrous oxide in the general population. In 2012 it stood at 18.8%, with higher figures in the United Kingdom (38.6%) and the United States (29.4%). In 2019 the prevalence increased to 23.5% [23]. The annual prevalence is also increasing since it went from 6.7% (GDS 2015) to 13.1% (GDS 2020) [16].

At the same time, this change in consumption was accompanied by an increase in the number of reports of serious health effects. In France, ANSES and ANSM published data in 2019, which showed a trend towards increasing cases of poisoning, with more than forty severe cases. In 2021, they are publishing new figures on these misuse reported to the Poison Control Center [17]. The figures confirm the very clear increase in cases of poisoning in 2020 among a young population (mainly young adults, particularly students, but also adolescents with more than a hundred severe cases [18].

From these various reports, it appears that the majority of consumers are middle- aged men median of 20-22 years, with an increase in the proportion of minors seems to be increasing, the doses described seem increasingly high, up to fifteen bottles per occasion, consumption is often associated with other psychoactive substances (alcohol, cannabis etc.) in 19.4% of cases [19].

Abroad, the data are consistent and show an almost exponential increase in the use of nitrous oxide and the resulting complications. For example, Australia, China, Denmark, the United States, the Netherlands and the United Kingdom have reported an increase in health incidents linked to its use. For example, an observational study carried out from 2010 to 2020 in the Netherlands showed that the incidence of poisoning increased rapidly, from 0.12% in 2010 to 11% in 2020 [20]. Data on the prevalence of its use in Morocco remains limited.

5. Side effects of using nitrous oxide:

Chronic or acute misuse of nitrous oxide is not without risks for the consumer. Indeed, numerous adverse effects of different types have been described in the literature. These risks incurred can be very diverse and varied, ranging from neurological, psychiatric or even hematological risks to cardiovascular risks.

5.1. Acute installation side effects:

Let it be used in a manner medical or recreational, nitrous oxide can cause undesirable effects which generally disappear fifteen minutes after stopping inhalation. We mainly find:

***Psychiatric disorders:**

Psychiatric disorders have been reported following N2O consumption. The clinical presentation is very varied: depression, hypomania, agitation, hallucinations, paranoia, even suicide; the most common clinical picture described in the literature is the constitution of ideas delusional. Biologically, there is also a deficiency in B12 and increased levels of its precursors. The addition of intramuscular B12 also improves psychiatric symptoms in patients [21].

The exact physiopathological mechanism is not yet recognized, but a study on rats hypothesizes that an effect on the system mesolimbic (neuronal lesions in the cingulate and retrosplenial cortices posterior) and an increase in dopamine concentration could provide an explanation for psychotic symptoms [22].

These psychiatric symptoms are most often preceded by prodromes, in particular a confusional state, agitation, asthenia or even memory disorders, which can guide the diagnosis, and can be reversible upon cessation of exposure to nitrous oxide and are treated with vitamin B12 supplementation as the symptoms neurological. However, these psychotic behaviors must not be left unsupervised and must most of the time be treated with anti-psychotic treatment [23].

***Cold burns:**

Inhalation directly from the cartridge, without using a container such as a balloon, due to the fact that this propellant gas is cold and packaged under high pressure, exposes to serious risks of burning the nose, lips and vocal cords [24].

***Respiratory disorders:**

Risks of hypoxia with loss of consciousness and resulting complications (risk of falling with head trauma, fracture, etc.). When used using a balloon, users, through repeated breathing cycles, will gradually deplete the contents of the balloon in oxygen. Such maneuvers can easily lead to hypoxia and even asphyxia, since nitrous oxide, in high concentrations (>50%), inhibits the normal physiological response to hypoxia. During this prolonged inhalation, nitrous oxide can also cause loss of consciousness with loss of the cough reflex and protection of the larynx, pneumothorax, and/or acute lung edema [25].

***General Signs:**

Nausea, vomiting, abdominal pain, diarrhea, headache, tinnitus, confusion, drowsiness, loss of consciousness [26].

5.2. Chronic complications:

Prolonged and/or repeated administrations of Nitrous Oxide expose one to several types of complications and in particular to the inactivation of vitamin B12, essential for good hematological and neurological functioning.

- **Abnormalities in vitamin B12 metabolism:**

Nitrous oxide irreversibly oxidizes the cobalt atom present in vitamin B12 and partially inactivates methionine synthetase, leading to a neuroanemic syndrome as described in Biermer's disease [27].

***Neurological disorders:**

Due to the previously mentioned functional vitamin B12 deficiency, some patients may present neurological damage, both in the peripheral nervous system (neuropathy) and the central nervous system (sclerosis combined marrow). Serious cases, with sometimes irreversible consequences requiring long stays in rehabilitation have been reported [28].

According to the addictovigilance report, neurological complications remain the most reported complications in 2020 (present in nearly 70% of cases), with an increasing proportion compared to the last study period. The number of disorders diagnosed as central (spinal cord) or peripheral (neuropathy) doubled in 2020 compared to 2018-2019, and in nearly 20% of cases of neurological complications it is an attack on the both central and peripheral, considered to have a poorer prognosis [29].

A rapid diagnosis is necessary to quickly initiate nitrous oxide withdrawal. Recovery would be all the more complete if replacement treatment with vitamin B12 was administered early. However, there is no validated treatment or proof of its effectiveness on recovery [30].

Hematological disorders:

In addition to anemia megaloblastic and some cases of pancytopenia, cases of venous thrombosis have been described. Since 2018, a total of four cases published in the literature report the occurrence of venous thromboembolism following recreational consumption of nitrous oxide [31].

IV. CONCLUSION

Attention paid to the use of nitrous oxide continues to increase, however, this awareness does not seem general and the misuse of nitrous oxide has been on the rise since the early 2000s, affecting many new audiences, increasingly younger. Prevention campaigns among young people therefore seem necessary because they underestimate the dangers.

There is no specific treatment apart from vitamin B12 supplementation. Therapeutic approaches

are therefore based on motivational interviews and psychotherapies.

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