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Review of Nitrous Oxide Intoxication

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Abstract

Inhalants for recreational use in the United States rise in the 1950s and is widespread among adolescents now. The main use of inhalants is for entertainment. After inhalation, nitrous oxide can be rapidly absorbed into the blood through the alveolar capillaries and act neurologic effect. Nitrous oxide related neurologic dysfunction was related to serum vitamin B12 levels decline. Acute and chronic nitrous oxide intoxication will lead to central nervous system(CNS), pulmonary and cardiovascular damages including confusion, pneumonitis, dyspnea and arrhythmia. The treatment of nitrous-oxide induced neuropathy can be alleviated by ceasing nitrous oxide use, vitamin B12 supplements. (J Intern Med Taiwan 2021; 32: 180-184)

Key Words: Nitrous oxide, Inhalants, Vitamin B12

Introduction

Inhalants for recreational use in the United States rise in the 1950s and is widespread among adolescents now. Inhalants include a variety of substances, such as nitrous oxide, amyl nitrite, cleaning fluids, gasoline, spray paint, aerosol sprays and glue. Inhalants are volatile substances can be inhaled and absorbed by pulmonary capillaries. Inhalants abuse caused a heavy burden on society and nearly 11 percent of adolecent reporting to have experience of inhalants use in the U.S.A [1] and rounds 0.5 million people and to the estimate of approximately 546,000 people aged 12 or older were current users of inhalant. The main purpose of inhalants was used for recreation. Nitrous oxide is common used inhal-

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ants and can be stored in different containers, such as medical grade gas canisters or gas contained in whipped cream aerosol containers [2,3]. The medical use of nitrous oxide inhalation included pain relief, depersonalisation, derealisation, dizziness, euphoria, and some sound distortion [4].

Epidemiology of nitrous oxide intoxication in Taiwan

In Taiwan, nitrous oxide has become the most drug abuser among teenagers. In the past, laughing gas is not listed as a drug and no drug prohibition law for regulation. The teenagers mistakenly believe that it is legal because of no obvious withdrawal symptoms. Nitrous oxide is also an important raw material in the industry, food processing industry and medical industry. Taiwan is a major semiconductor manufacturing country, and the semiconductor industry makes extensive use of this gas in the production of wafer integrated circuit boards. In 2018, Taiwan's use of nitrous oxide reached 12,922 metric tons; the number of imports also increased from 2,626 tons in 2016 to 4,857 tons in 2018, nearly doubled. The most likely way for illegally nitrous oxide is from industry. In 2020, Nitrous oxide is the first chemical substance of concern to be managed in the "Toxic and Chemical Substances Management Law" in Taiwan. It will be approved, labelled, recorded online, reported monthly, prohibited online transactions, and prohibited unlicensed operations[5]. The prevention of nitrous oxide abuse and health education need to be strengthened in the future.

Mechanism of action

Nitrous oxide is a highly lipid soluble, commonly known as laughing gas or nitrous, chemical compound that consists of an oxide of nitrogen with the formula N_2O. At room temperature, Nitrous oxide with a slight metallic taste, non flammable and colourless gas. Nitrous oxide is a powerful oxidizer once the molecules break apart into oxygen and nitrogen at 565^{o}F [6].

After inhalation, nitrous oxide can be rapidly absorbed into the blood through the aveolar capillaries with neurologic effects[7]. In animal study, the N_2O exposed rats had signifiant reduction in plasma glutathione and total antioxidant capacity as well as increased serum homocysteine (Hcy), glutamate and malonodialdehyde (MDA). Astrocyte activation was signifiantly altered in spinal cord as compared to cerebral cortex, which was associated with neurobehavioral changes through evoked oxidative stress and accumulated serum glutamate[8].

Nitrous oxide-related neurologic dysfunction was related to declined vitamin B12 levels. It is postulated that vitamin B12 is an essential cofactor, which converted homocysteine into methionine. Decreased serum B12 leads to an accumulation of homocysteine, which result in reactive oxygen species (ROS) accumulation and eventually lead to apoptosis.

Specifically, NMDA receptor was activated, then following calcium influx and ROS generation[9]. (Figure 1)

The downstream effect of this is that methionine synthase — which requires active B12 to function — is irreversibly blocked. This leads to depletion of methionine and tetrahydrofolate, which are required for DNA synthesis and myelin production. In turn, this depletion results in a clinical picture that resembles the characteristic findings of pernicious anemia (bone marrow depression and polyneuropathy). This demyelination can be seen on MRI and is diagnosed as Subacute Combined Degeneration (SDG) [10].

Clinical presentation

The clinical history can be broken down into acute intoxication, chronic toxicity, and withdrawal syndrome.

Symptoms of acute nitrous oxide intoxication, most resolved within 2 hours, may include euphoria, slurred speech, ataxia, dizziness, diplopia, con-

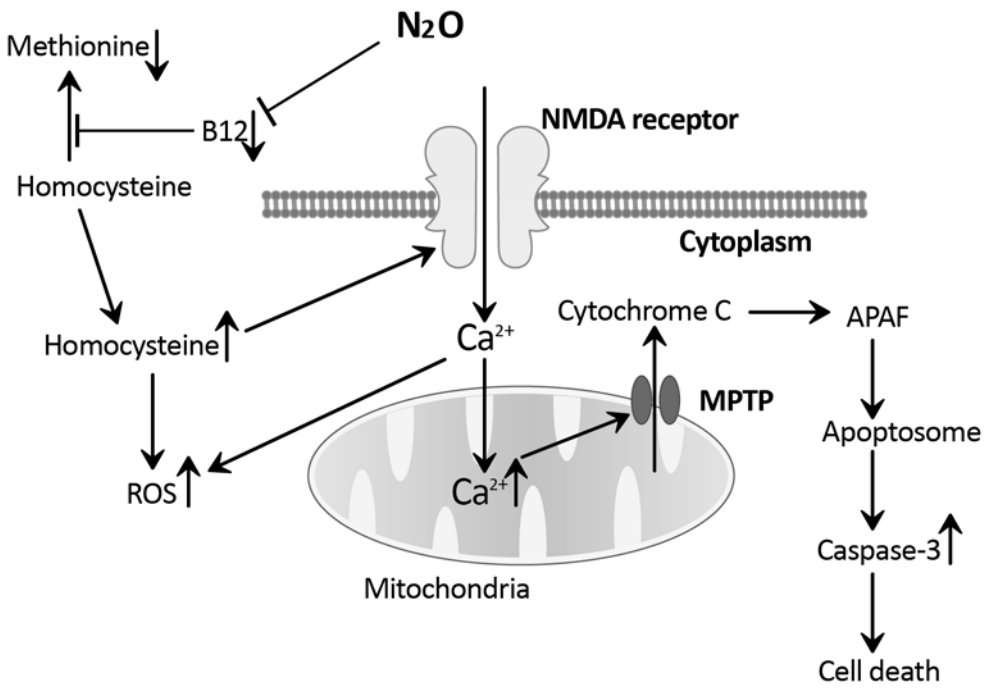

Figure 1. An mechanism of N_2O exposure induced the homocysteine-mediated pathway of cell death.

fusion, CNS depression, palpitation, tachycardia, and arrhythmia. Acute Nitrous oxide intoxication also induced acute lung damage, which is associated with the development of pneumonitis, dyspnea, wheezing, coughing and cyanosis[9].

In chronic inhalant abuser, vitamin B_{12} inactivation might induce neurological complications, including peripheral neuropathy, cerebral degeneration, cortex atrophy, cognitive dysfunction, dementia, gait disturbances, and coordination impairment[11]. Skin hyperpigmentation, a rare symptom in chronic abusers, can distribute locally in hands or diffusely throughout the body[12].

Diagnosis

Clinical signs

Diagnosis of N_2O intoxication is based on exposure history and clinical signs. The clinical signs of N_2O intoxication include the respiration disorder due to the compensation of hypoxia. In severe N_2O intoxication case, central respiratory system can be inhibited and finally lead to myocardial ischemia, apnea, and death.

In terms of the chronic poisoning effect caused by nitrous oxide, neurological abnormality will include peripheral paresthesia, muscle atrophy, and decreased or absent tendon reflexes[13].

1. Image studies or Laboratory tests:

(1) Serum examination revealed abnormal liver function, blood coagulation function and low vitamin B12 concentration.

(2) Electrocardiogram including T wave inversion / down ST segment indicated myocardial hypoxia and low amplitude response.

2. Differential diagnosis :

(1) If acute poisoning occurs, it must be distinguished from other asphyxiating gases, such as carbon monoxide, hemoglobinemia, cyanide, sulfide.

(2) If chronic poisoning occurs, it must be com-

bined with other diseases that may cause neurological diseases and blood system diseases

Treatment

The treatment for nitrous oxide-related myeloneuropathy can be alleviated by ceasing nitrous oxide use and vitamin B12 supplements. In emrgent and critical case, airway protection and maintain gas exchange with high-flow supplemental oxygen was mandatory. Chronic effects may resolve over 2–3 months after discontinuation of exposure[12]. Furethermore, Methionine supplement has also been reported as a strategy for nitrous oxide-induced myelopathy treatment.[13] Intramuscular vitamin B12 injection combined with additional plasmapheresis showed dramatic improvement, which indicated the possibility of nitrous oxide superimposed inflammatory polyneuropathy[14].

Conclusion

Nitrous oxide interacts with vitamin B12 resulting in selective inhibition of methionine synthase. Acute nitrous oxide intoxication may induce CNS depression or fetal arrhythmia. Chronic exposure to nitrous oxide may cause megaloblastic bone-marrow depression and neurological symptoms. The prevention of nitrous oxide abuse and health education need to be strengthened in the future.

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一氧化二氮中毒回顧

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摘 要

用於休閒娛樂的吸入劑在1950年代在美國興起，並在青少年中廣泛流行。其毒性已成為新的健康議題。吸入一氧化二氮(笑氣)後，可通過肺泡微血管迅速吸收散佈到全身，導致神經系統效用。一氧化二氮相關的神經功能障礙與維生素B12含量減少有關。急性和慢性一氧化二氮中毒，將引起中樞神經系統障礙，肺和心血管損害，包括肺炎，呼吸困難和心律不整。一氧化二氮引起的神經病變的治療包括停用一氧化二氮，補充維生素B12，蛋氨酸和接受血漿置換術。