Hazards of nitrous oxide exposure in healthcare personnel

DEBORAH ANN SMITH, CRNA, MSN
Rochester, Minnesota

Nitrous oxide, a commonly used agent in the dental and anesthesia practice, carries serious risks to healthcare providers. Complications from its exposure can range from hematological abnormalities and neurological deficits to increased risk of spontaneous abortions in women. A concentrated effort by all anesthesia personnel is necessary to prevent the adverse effects associated with the use of this agent.

Key words: Health risks, nitrous oxide, psychomotor performance, vitamin \(\text{B}_{12}\).

Introduction
Nitrous oxide is a commonly used agent in the dental and anesthesia arena. The adverse effects from its exposure can range from hematological and neurological abnormalities to spontaneous abortion. However, these adverse effects seem to be taken lightly by healthcare workers, especially anesthesia personnel. Although the risks of nitrous oxide delivery have been known for many years, the effort to limit its exposure to healthcare personnel has been inadequate.

History
Nitrous oxide gas was first discovered in 1776 by Joseph Priestley, a Unitarian minister who resided in England. He discovered this gas by "exposing nitrogen to the action of iron, thus depriving it of some oxygen." The effects of nitrous oxide were then noted by Sir Humphry Davy, a surgeon's assistant also from London. Although nitrous oxide possessed analgesic, anxiolytic, and sedative properties, these were not utilized until 1844 by Dr. Horace Wells. Dr. Wells, a well-known Boston dentist, discovered the therapeutic application after it was administered to several people who had attended a lecture of Gardner Quincy Colton, a chemist in New York City. A participant who had been exposed to nitrous oxide unintentionally ran into a bench and lacerated his leg. After awakening from the nitrous oxide, he discovered an ecchymotic area on his leg but had no recollection of any injury. Colton later administered nitrous oxide to Wells while he was having his tooth extracted by a fellow dentist. After the procedure, Wells stated that the procedure was painless.

Review of literature
Nitrous oxide administration poses significant risks to anesthesia providers. High levels of exposure have been associated with reduced fertility, increased risk of spontaneous abortion, and neurological disturbances. Historically, nitrous oxide was believed to be inert in the human body. Adverse effects were believed to be related to general anesthesia itself or inadequate administration of oxygen. It was not until a 1956 article in *Lancet* that prolonged administration of nitrous oxide was associated with complications including fatal aplastic anemia, thrombocytopenia, hematuria, retinal hemorrhage, and granulopenia in patients who were being treated with prolonged nitrous oxide administration in cases of severe tetanus. Thirteen patients were studied, and the only correlation between those in whom hematological complications developed and those without complications was nitrous oxide administration. In addition, bone marrow changes that occurred disappeared after the nitrous oxide was discontinued.
In the mid-20th century, anesthetists reported complaints of pruritis, headache, nausea, fatigue, and irritability. In addition, 31 participants in the study were pregnant. Of these, 58% (18) experienced spontaneous abortion and 1 infant had congenital abnormalities, and of the remaining pregnancies, only 7 were without complications. In 1968, Banks and coworkers discovered that nitrous oxide could nonenzymatically oxidize the cobalt atom in vitamin $B_{12}$. Only the reduced form of vitamin $B_{12}$ is active in vivo. Nitrous oxide administration has been correlated with a condition similar to pernicious anemia. In pernicious anemia there is not an inactivation of vitamin $B_{12}$, but rather a problem with the absorption due to an inadequate secretion of intrinsic factor.

In a 2-year prospective study, in patients who were exposed to 50% nitrous oxide and 50% oxygen for 6 to 24 hours, changes developed in bone marrow cells similar to changes seen in pernicious anemia. This occurred due to inactivation of vitamin $B_{12}$. These abnormalities were not associated with abnormal serum $B_{12}$ levels, but the deoxyuridine suppression test revealed a clinically relevant decrease in vitamin $B_{12}$ activity. In addition, Amess et al found that recovery occurred after nitrous oxide was stopped and believed that vitamin $B_{12}$ administration might partially offset the effects of nitrous oxide. Evidence reveals that prolonged exposure to nitrous oxide inhibits cellular proliferation of the elements in the blood and can lead to megaloblastic anemia, leukopenia, and thrombocytopenia. The biological effects occur with a continuous exposure of 100 ppm for 8 hours or 400 ppm for anesthetic administration.

Vitamin $B_{12}$ is necessary for the production of normal red blood cells and the function of the central nervous system. It is also essential for methionine synthase activity. The action of this enzyme is inhibited by nitrous oxide inactivating vitamin $B_{12}$. Methionine synthase is essential for DNA synthesis. The adverse effects of nitrous oxide are dependent on the following factors:

1. The duration, intensity, and pattern of exposure to nitrous oxide.
2. The amount of methionine synthase inactivation and the time needed to recover.
3. The extent to which body stores and dietary intake offset the biochemical block caused by nitrous oxide.
4. The sensitivity of important biochemical pathways to substrate decrements.
5. The sensitivity of tissues to alterations by the affected biochemical pathways.

Several days may be needed for full return of methionine synthase activity after exposure to nitrous oxide. It is also plausible that repeated exposures to nitrous oxide may lead to a cumulative effect. In addition, recovery rates may be dependent on the health of the individual. For example, if the person already has a deficiency of vitamin $B_{12}$ (perhaps a subclinical case of pernicious anemia), the person may be more susceptible to the adverse effects of nitrous oxide.

A landmark epidemiological survey conducted by mail by Cohen, the American Dental Association, and the National Institute for Occupational Safety and Health (NIOSH) compared nitrous oxide–associated health problems of healthcare workers who administered anesthetic gases for dental surgery with a control group. The control group consisted of professionals who used local anesthetics and intravenous sedation and avoided inhalational agents. This study linked the relationship of nitrous oxide exposure to health problems, such as an increase in liver disease (1.7-fold), an increase in kidney disease (renal lighias and urinary tract infections, 1.2-fold), and an increase in general and nonspecific neurological dysfunction (numbness, tingling, and muscle weakness, 1.2- to 2.8-fold). Reproductive difficulties, such as increased incidence of spontaneous abortion and congenital abnormalities, were also reported. This study revealed that women exposed to nitrous oxide had twice the rate of spontaneous abortion along with an increase in congenital abnormalities (1.5-fold) compared with those not exposed to nitrous oxide. Another study by Cohen and Brown found that the rate of miscarriages in dental assistants was similar to the rate for female anesthetists.

Kugel et al believed that nitrous oxide might block the luteinizing hormone–releasing hormone from the hypothalamic-pituitary-gonadal axis, thus interfering with ovulation. Female rats exposed to 30% nitrous oxide for 8 hours had a disruption of ovulation related to a blockade in the luteinizing hormone–releasing hormone. After 3 weeks of breathing normal air, ovulation returned to normal.

The findings of a study of 459 women done by Rowland et al in 1987-1988 were consistent with part of Cohen's study, which stated that personnel with high levels of nitrous oxide exposures were less likely to be fertile than those who were not exposed to nitrous oxide. The study, using questionnaires sent to dental assistants between the ages of 18 and 39 years, revealed a linear correlation between infertility and exposure to unscavenged nitrous oxide. The study revealed a 6% reduction in the probability of conception with each hour of unscavenged nitrous oxide. It also revealed a 50% spontaneous abortion rate (5 women) when women
were exposed to 5 or more hours of unscavenged nitrous oxide. The study excluded 93 women who were pregnant at the time of data collection.\footnote{3}

Psychomotor performance and its relation to nitrous oxide were evaluated by Bruce and Bach in a study of 40 volunteers.\footnote{18} They found that as little as 50 ppm of nitrous oxide in a 2-hour period decreased psychomotor performance on visual perception, motor responses, immediate memory, and cognitive responses.\footnote{18} NIOSH recommends that a concentration of 25 ppm or less shall be maintained by all workers during anesthesia administration.\footnote{19} However, to date, the Occupational Safety and Health Administration has not set a recommended safe level. Therefore, in most parts of the United States, the use of nitrous oxide is unregulated.\footnote{5}

Immunological effects have also been studied. Twenty-one staff members employed in a department of anesthesia were tested before and after a summer vacation. They all worked in operating rooms where scavenging systems were not used. It was found that leukocyte counts were decreased before the vacation and increased after the vacation. Although the red blood cell count and the hemoglobin and hematocrit concentrations were not changed significantly during exposure, they increased markedly after the vacations. The white blood cell count decreased during exposure and significantly increased after the vacations. The percentage of lymphocytes and concentrations of B lymphocytes and natural killer cells did not improve for up to 4 weeks after the cessation of nitrous oxide exposure. There was a minimal effect on T lymphocytes.\footnote{20}

\section*{Discussion}

Anesthesia personnel must incorporate measures into their practice to safely deal with nitrous oxide exposure. Despite the fact that nitrous oxide has been used in anesthesia practice for decades, the recognition of its adverse effects has not brought about an appropriate response. Its administration carries with it numerous risks to the patient, the anesthesia provider, and other personnel in the room. If proper technique, properly functioning equipment, and careful patient selection are utilized, the risks can be diminished.

The NIOSH standards set a goal of maintaining the nitrous oxide level at no more than 25 ppm. Note that 100% of a gas equals 1 million ppm, 1% of a gas equals 10,000 ppm, and 1 ppm equals 0.00001% of a gas (so 25 ppm equals 0.00025%).\footnote{21} The NIOSH set these recommendations after reviewing the research reported by Bruce and Bach in 1976,\footnote{18} which showed that at nitrous oxide concentrations as low as 50 ppm decreased behavioral performance occurred. They evaluated performance by looking at tests that examined visual acuity, the ability to recognize changes in a sequence, hand-eye coordination, vigilance, and immediate memory. When 50 ppm of nitrous oxide was administered alone without halothane, the auditory visual test was most affected. Testing began after the patient was exposed to 50 ppm of nitrous oxide for 2 hours. It looked at subjects' responses to differences in sound frequency and visual patterns. The auditory component was the clicking of a metronome, and the visual signals were patterns recorded from an electrocardiographic simulator. The subjects responded by pressing a button, and the lag time was then recorded. They also found that nitrous oxide levels of 25 ppm even with 0.5 ppm of halothane produced no adverse effects.\footnote{18}

It is the anesthesia provider’s responsibility to be cognizant of the importance of minimizing ambient anesthesia pollution. The aforementioned studies suggest that nitrous oxide may pose risk to the health of anesthesia personnel, other healthcare workers, and patients. That exposure of greater than 50 ppm of nitrous oxide decreases global performance suggests that we should reduce the environmental contamination of nitrous oxide.

Some ways in which occupational exposure to nitrous oxide can be decreased include:

1. Use of scavenging equipment,\footnote{22}
2. When checking the anesthesia gas machine, ensure that all scavenging systems are securely fastened.\footnote{21}
3. Use low flows whenever possible, as this can significantly decrease the discharge to the ambient air.\footnote{23}
4. Monitor levels of nitrous oxide regularly by using nitrous oxide analyzers or dosimeters,\footnote{22,24}
5. Utilize the minimum effective dose.
6. Assure that the room air exchange rate is at least 10 per hour.
7. Have scavenging systems tested at regular intervals for leaks, and document attempts at compliance.\footnote{25}
8. Maintain the 25 ppm for dentists and not the 50 ppm that was arbitrarily chosen for dentists by the American Dental Association.\footnote{24}
9. Maintain 25 ppm nitrous oxide for operating rooms as recommended by the NIOSH.\footnote{18}
10. Personnel who work in areas of high exposure, such as pediatric and dental sedation with nitrous oxide, should be rotated on a regular basis.\footnote{5}

In addition, certain personnel should avoid exposure; these personnel include:  
1. Women in their first trimester of pregnancy.
3. Any persons with known neurological complaints.
4. Severely immunocompromised persons.

Pediatric anesthesia care carries a high risk of leakage of nitrous oxide during cases. This can occur for numerous reasons. Children tend to be uncooperative initially and thus increase the risk of leakage of nitrous oxide into the environment. During cases in which a mask is used, a poor mask seal may lead to additional leakage of nitrous oxide. Even if intubation is chosen over the mask, the endotracheal tube is not 100% safe. In children younger than 9 years, uncuffed endotracheal tubes must be used, thus allowing some gases to escape while ventilating the patient. The gases that escape are released into the operating room despite adequate scavenging equipment. This can be minimized by the use of throat packs. Use of a laryngeal mask airway, when appropriate, will help decrease the leakage of anesthesia gas as well. In addition, choosing an endotracheal tube that is the proper size will minimize leakage of anesthetic gas into the operating room.

The choice of the delivery system of nitrous oxide also has a role in how much nitrous oxide is released into the environment. It is imperative to choose the best fitting mask for every patient in order to minimize our exposure to nitrous oxide. Under the choice of anesthetic techniques also falls the use of a nasal mask. This technique is often chosen for dental cases for patients of all ages; it must be understood that exposure to nitrous oxide is increased whenever the patient talks or even exhales.

Measurement of nitrous oxide exposure

Nitrous oxide exposure can be evaluated by the utilization of nitrous oxide dosimeters that are worn as lapel badges throughout the work day. After a determined period, the capsule is sealed and returned to the manufacturer. Analysis is performed on a time-weighted basis. The results are expressed in parts per million exposure to nitrous oxide.

Summary

By following the recommended precautionary measures, exposure to nitrous oxide can be decreased. According to the American Dental Association, a level of 50 ppm was chosen as the acceptable exposure since it was an easier level to attain. The association believed that not only was 25 ppm too difficult to attain, but also current studies were not conclusive enough to strive for the standards set by the NIOSH. Despite the difficulty of the endeavor, dental personnel should strive to meet the 25 ppm guideline as they face the same toxicity issues as other anesthesia providers. Effects are dose- and time-related problems. Therefore, even small changes in exposure can be very beneficial.

REFERENCES

(2) Keyes TE. The History of Surgical Anesthesia. New York: Schuman's. 1945.
(20) Peric M, Vranes Z, Marusic M. Immunological disturbances in anaesthetic personnel chronically exposed to high occupational concentrations of nitrous oxide and halothane. Anesthesiology. 1991;44:531-537.

AUTHOR

Deborah Ann Smith, CRNA, MSN, is currently employed at the Mayo Clinic, Rochester, Minnesota.