Current Status of Nitrous Oxide

Release Date: March 2007 Expiration Date: March 31, 2008

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LEARNING OBJECTIVES

At the completion of this activity, participants should be able to:

1. List noxious effects of nitrous oxide (N₂O) anesthesia.
2. Discuss risks and benefits of N₂O compared with other inhaled anesthetics.
3. Review safety concerns, including effects of N₂O on vitamin B₁₂ and folate metabolism and the implications of these effects for selected patients.
4. Relate N₂O use patterns to the introduction of other inhaled anesthetics.
5. Identify clinical scenarios in which N₂O use is contraindicated.

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Introduction

Newer anesthetics can supply most of the desirable properties of nitrous oxide (N\textsubscript{2}O), properties previously considered to be unique. The availability of these newer anesthetics combined with the limitations and toxicities of N\textsubscript{2}O may indicate that the use of N\textsubscript{2}O should be curtailed or discontinued.

Several advantages of N\textsubscript{2}O prompted its continued use for more than a century and a half. These included an absence of pungency, minimal cardiorespiratory depression, low solubility and rapid kinetic changes, low cost, minimal metabolism, and apparent freedom from toxicity after routine clinical exposure. But several factors have decreased its use in clinical practice (Figure 1), particularly an understanding of its negative attributes and the capacity of newer potent inhaled anesthetics to provide its advantageous but not its deleterious effects. Some negative attributes have long been known: a limited potency and a potential for hypoxia at higher concentrations; untoward kinetics (expansion of internal gas spaces; diffusion hypoxia); and possible production of abortions.

Concern has heightened in the past decade regarding other diverse effects: toxicity consequent to inactivation of methionine synthase combined with genetic, age, and nutritional factors promoting a deficit of methionine synthase; a tendency to increase postoperative nausea; poor clinical effects; toxicity consequent to inactivation of methionine synthase contributing to greenhouse gases. Replacing methionine synthase; a tendency to increase postoperative nausea; poor effects: toxicity consequent to inactivation of methionine synthase contributes to greenhouse gases. Replacing methionine synthase is decreased equipment costs associated with anesthetics (desflurane, isoflurane) that supply most of the desirable attributes of N\textsubscript{2}O, may also decrease equipment costs associated with anesthetics—thus requiring the contribution of a potent anesthetic may decrease equipment costs associated with anesthetics—thus requiring the contribution of a potent anesthetic may decrease equipment costs associated with anesthetics—but will require additional delivery of more expensive potent inhaled anesthetics to compensate for the omission of the anesthetic contribution by N\textsubscript{2}O.

Neutral Properties of N\textsubscript{2}O

Metabolism. N\textsubscript{2}O is the least metabolized inhaled anesthetic. Intestinal bacteria degrade it trivially, and interaction of N\textsubscript{2}O with methionine synthase destroys an equally miniscule amount. However, although desflurane\textsuperscript{2} and sevoflurane\textsuperscript{3} undergo metabolic degradation (desflurane 0.02%; sevoflurane 5%), with one exception the metabolites (eg, inorganic fluoride, trifluoroacetic acid, and hexafluoropropionaldehyde) are not toxic. On rare occasions, trifluoroacetate from desflurane can produce an immune hepatotoxic response.\textsuperscript{4}

Degradation by Carbon Dioxide Absorbents. Carbon dioxide (CO\textsubscript{2}) absorbents do not degrade N\textsubscript{2}O. D esci d ed CO\textsubscript{2} absorbs can degrade potent inhaled anesthetics (particularly desflurane) to clinically relevant concentrations of carbon monoxide (CO).\textsuperscript{5} Sevoflurane degradation by moist or desiccated CO\textsubscript{2} absorbents produces a nephrotoxin, compound \textit{A}.	extsuperscript{6} Although this can cause renal injury in humans,\textsuperscript{7} such injury is minimal and exceedingly rare. New CO\textsubscript{2} absorbents that minimally degrade sevoflurane (or desflurane) eliminate this rare problem,\textsuperscript{8} even when the absorbents are desiccated.\textsuperscript{9}

Desirable Properties of N\textsubscript{2}O

Cost. N\textsubscript{2}O is inexpensive and decreases the need for more expensive anesthetics.\textsuperscript{10} Because MAC (the minimum alveolar concentration of anesthetic that produces immobility in response to noxious stimulation in 50% of subjects) decreases with increasing age,\textsuperscript{11} the contribution of a constant N\textsubscript{2}O concentration (eg, 50% to 60%) to the total required anesthetic increases with increasing patient age. For children, the contribution provides only a quarter of the anesthetic requirement but this rises to over half in the elderly.\textsuperscript{12}

Respiratory Irritation. Because N\textsubscript{2}O has no pungency, its use for induction of anesthesia minimizes coughing, breath holding, laryngospasm or increased secretions. Accordingly, it is used with pungent anesthetics (desflurane, isoflurane) to smooth anesthetic induction. But sevoflurane also is nonpungent,\textsuperscript{13} and anesthetizing concentrations produce minimal or no undesirable respiratory responses.\textsuperscript{13}

Solubility. Relative to the solubilities of potent inhaled anesthetics,\textsuperscript{14} the poor solubility of N\textsubscript{2}O in blood\textsuperscript{2} and tissues\textsuperscript{5} makes it useful for induction of and recovery from anesthesia. It enters and leaves the body faster than potent inhaled anesthetics, and the second gas effect from N\textsubscript{2}O enhances the entrance of anesthetics given concurrently.\textsuperscript{16} The concentration effect accelerates its own entrance into the body.\textsuperscript{16} However, where the rapid entrance and exit of N\textsubscript{2}O clearly exceeds that found with older anesthetics such as isoflurane, ingress and egress differ but slightly from that with desflurane\textsuperscript{15} and sevoflurane.

Cardiorespiratory Effects. Like potent inhaled anesthetics, N\textsubscript{2}O can profoundly decrease the ventilatory response to imposed increases in CO\textsubscript{2} and to hypoxia.\textsuperscript{18} Unlike potent inhaled anesthetics, N\textsubscript{2}O partial pressures of up to 1.5 MAC (approximately 1.6 atmospheres of N\textsubscript{2}O) do not increase the partial pressure (tension) of cerebral arterial carbon dioxide (PaCO\textsubscript{2}),\textsuperscript{19} nor does N\textsubscript{2}O appear to increase the depression produced by potent inhaled anesthetics.\textsuperscript{20} Substitution of, say, 50% N\textsubscript{2}O for a comparable MAC contribution of a potent anesthetic may decrease cardiovascular depression (one can argue whether depression is good or bad). N\textsubscript{2}O minimally affects blood pressure and heart rate.

Neuromuscular Effects. N\textsubscript{2}O minimally, if at all, triggers malignant hyperthermia.\textsuperscript{21} Thus, one indication for the use of N\textsubscript{2}O is a finding of a personal or familial history of the disorder.

Undesirable Properties of N\textsubscript{2}O

Potency. A drawback to N\textsubscript{2}O is its limited potency; its MAC in 30 to 60 year-old patients exceeds one atmosphere. Alone it cannot produce anesthesia, even in the elderly.\textsuperscript{11} Thus, it lacks the flexibility of potent inhaled anesthetics. Its use, perforce decreases the O\textsubscript{2} concentration presented to the patient and increases the risk of hypoxia. Impaired pulmonary function may further decrease the N\textsubscript{2}O contribution by requiring greater O\textsubscript{2} concentrations to secure adequate oxyhemoglobin saturation.

Kinetics Issues and Potency. N\textsubscript{2}O\textsuperscript{25} is a poorly soluble anesthetic compared to potent inhaled anesthetics such as isoflurane.\textsuperscript{26} But N\textsubscript{2}O is much more soluble than N\textsubscript{2} and O\textsubscript{2} (blood/gas partition coefficients of approximately 0.02). This solubility and the need to supply high concentrations of N\textsubscript{2}O lead to unique kinetic issues. Larger volumes of N\textsubscript{2}O than N\textsubscript{2} (and other poorly soluble gases) move to and from gas spaces enclosed within the body. The cause is the greater capacity of blood to hold N\textsubscript{2}O as opposed to N\textsubscript{2}: more N\textsubscript{2}O is available. N\textsubscript{2}O administration can expand bowel gases,\textsuperscript{27} the gas within a pneumothorax,\textsuperscript{28} an air embolism,\textsuperscript{29} and cuffs filled with air (tracheal tube or a laryngeal mask airway (LMA)]. Anesthetists often avoid using N\textsubscript{2}O in patients with abnormal closed gas spaces or devices that may create gas spaces (eg, cardiopulmonary bypass devices).

One study finds that N\textsubscript{2}O administration delays recovery of bowel function after surgery on the colon,\textsuperscript{30} while other studies find no such effect.\textsuperscript{31,32} One study finds no clinically significant bowel gas expansion during bariatric surgery.\textsuperscript{33} This result is not surprising given the limited amount of bowel gas (ie, there is little gas to expand). The study also finds that any expansion of CO\textsubscript{2} instilled for laparoscopy does not

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**Figure 1. Operating usage of N\textsubscript{2}O in the past decade. Extrapolation of these results suggests that N\textsubscript{2}O use will approach zero in 2–3 years.**

Data were gathered by Hospital Research Associates for Baxter Healthcare Corp., and privately communicated to EIE.
N2O movement into closed gas spaces may increase pressure and compromise regional blood flows in the skull, sinuses, middle ear, or eye. Increased pressure in the eye can cause permanent blindness, and tympanic membrane rupture has been reported. Increased pressure in the middle ear correlates with increased postoperative nausea and vomiting. These effects may also be used to advantage. For example, N2O used to expand a joint space during arthroscopy is rapidly reabsorbed, and, unlike CO2, N2O does not produce pain from a local acidosis. Substitution of N2O for CO2 in laparoscopic procedures decreases end-tidal CO2, ventilatory demand, and postoperative pain. However, the respiratory acidosis from CO2 insufflation may better preserve blood pressure and cardiac output.

N2O may also transiently affect variable-bypass vaporizers because the solution (absorption) of N2O in the liquid anesthetic in the vaporizer sump decreases effective flow through the sump and thereby decreases potent anesthetic output from the vaporizer. The reverse, a greater than dialed output, occurs when the carrier gas change from N2O to O2.

**MACawake.** MACawake is the minimum alveolar concentration of inhaled anesthetic that prevents an appropriate response to command in 50% of subjects. A measure of the anesthetic concentration that suppresses awareness but not necessarily of the concentration that suppresses recall (ie, produces amnesia); that concentration may be smaller than MACawake. MACawake for N2O is approximately two-thirds of MAC, a value nearly twice that for desflurane, isoflurane, and sevoflurane. This higher fraction means that relatively less N2O must be eliminated to permit awakening and thus may expedite patient transit through the operating room and the post-anesthesia care unit. But MACawake correlates with what might be called MACamnesia. Thus patients primarily anesthetized with N2O may remember events during anesthesia, whereas those only given potent inhaled anesthetics may be less apt to remember.

**Analgesia.** The greater MACawake/MAC ratio for N2O may underlie part of its claim as an analgesic. MAC-fractions that allow a report of pain/no pain (because the patient is still awake) can be reached with N2O but not with potent inhaled anesthetics. Parenthetically, concentrations of approximately 0.1 MAC of both N2O and potent inhaled anesthetics have anti-analgesic (hyperalgesic) effects, and thereby can increase the perception of pain. Passing rapidly below these concentrations may be advantageous.

Unlike potent inhaled anesthetics, N2O may increase release of enkephalins, naturally occurring opioid-like substances, through actions on GABAAergic neurons, and spinal cord alpha1 adrenoceptors. GABAAergic interneurons at both supraspinal and spinal levels influence antinociception. This effect on naturally occurring opioids may underlie part of the greater postoperative nausea and vomiting seen with N2O. Naloxone antagonizes the analgesia produced by nitrous oxide. As with opioids, tolerance to analgesia with N2O develops rapidly. Acute tolerance may restore wakefulness and account for part of awareness during anesthesia that relies heavily on N2O.

**Respiratory Effects.** The liter or more per minute of N2O eliminated during the initial portion of recovery dilutes alveolar O2 and CO2. The smaller concentration of CO2 decreases respiratory drive, and that, along with the decrease in O2 can slightly decrease oxyhemoglobin saturation (diffusion hypoxia). Diffusion hypoxia is only of concern in patients who have compromised respiratory function, and even in these patients it may be minimized by administration of O2 during the first several minutes of recovery.

**Cardiovascular Effects.** N2O may not supply anesthetic preconditioning and therefore may not protect the heart against the ischemia that may occur during coronary artery bypass graft placement. In contrast, desflurane and sevoflurane provide protection. N2O may increase pulmonary vascular resistance.

**Neuromuscular Effects.** Potent inhaled anesthetics cause muscle relaxation, and augment the effects of neuromuscular blocking drugs. In contrast, N2O increases muscle tone when used alone, and increases the rigidity seen with opioid administration. Unlike potent inhaled anesthetics, N2O does not augment the effect of neuromuscular blocking drugs and can antagonize such effects.

**Effects on the Central Nervous System.** In association with concentration-related decreases in electrical activity, potent inhaled anesthetics decrease cerebral metabolic rate, and protect against periods of hypoxia. In contrast, N2O can increase cerebral metabolic rate, cerebral blood flow, and intracranial pressure. One study finds that desflurane and isoflurane, but not N2O, protect against cerebral hypoxia. However, another study finds that N2O provides protection. Studies comparing the relative protection provided by N2O versus potent inhaled anesthetics against cerebral hypoxia have not been conducted in primates, and such data would be helpful. N2O depresses sensory-evoked potentials, particularly in combination with potent inhaled anesthetics, and its use may be precluded if such potentials are needed to evaluate central nervous system function.

N2O increases postoperative nausea and vomiting more than potent inhaled anesthetics. An elevated middle ear pressure correlates with this increase in postoperative nausea and vomiting, and an enhanced release of naturally occurring opioids may add to the predisposition to postoperative nausea and vomiting. Concentrations of N2O (given alone) exceeding 50% are more likely to produce nausea and vomiting.

Potent inhaled anesthetics such as desflurane affect electroencephalographic activity more than does N2O. In some studies, N2O minimally affects the values obtained with the bispectral index (BIS) monitor, while others show the expected decrease in the value. In regard to these contrasting data, the BIS monitor is an empirically-based device with limitations. This difference may be important if the anesthetic community is pressed to routinely use the BIS as a measure of alveolar N2O.

**Contribution of N2O to the Greenhouse Effect.** Like CO2, N2O absorbs infrared light and contributes to the greenhouse effect. N2O also adds to depletion of the ozone layer. The atmospheric concentration of N2O is 0.3 ppm. This small concentration is important because the global warming potential from one molecule of N2O is 200 to 300 times that of CO2. However, most atmospheric N2O comes from microbial processes of nitrification (the oxidation of ammonia to nitrate) and denitrification (the reduction of nitrates or nitrites to gaseous nitrogen). The contribution of N2O from anesthetic sources is small to trivial.

**Support of Combustion.** Although N2O, itself, does not burn, it supports combustion. Therefore it can promote explosions during laparoscopy. Administration of O2 does not present a comparable hazard because tissue partial pressures of oxygen rarely exceed 40 mmHg to 50 mmHg (ie, 6%-7% atmospheres), even when a patient breathes 100% O2, whereas tissue partial pressures of N2O can equal those being respired (eg, 50%-70% atmospheres). While not specific to N2O, clinicians should remain current on the Joint Commission on Accreditation of Healthcare Organizations’ educational and competency standards related to staff training in fire prevention and management.

**Toxicity of N2O.** N2O can produce one specific toxicity in humans and a second toxicity in rats that may apply to humans. First is the long-known inactivation of methionine synthase and associated human pathology. Second, N2O antagonism of the N-methyl-D-aspartate (NMDA) receptor may produce neuronal death in developing, adult, and aged brains of rats—with presently unknown human implications. Advocates of N2O might argue that potent inhaled anesthetics such as isoflurane can also produce toxicities, particularly those affecting the central nervous system. N2O may share some of the bases (eg, NMDA blockade) underlying these capacities to produce injury, but N2O differs from anesthetics such as isoflurane in that it has an additional basis for its capacity to produce injury, inactivation of methionine synthase.

**Inactivation of Methionine Synthase**

**Mechanism of Inactivation.** Historically, investigators reported adverse outcomes in patients who received N2O for several days. Such prolonged use does not occur in contemporary practice. However, adverse hematologic, neurologic and cardiovascular outcomes have recently been observed after routine clinical exposure, and are discussed below. N2O irreversibly oxidizes the cobalt moiety of vitamin B12, consequently inactivating the cobalamin-dependent enzyme methionine synthase. Methionine synthase catalyzes remethylation of 5-methyltetrahydrofolate to tetrahydrofolate and homocysteine to methionine. S-adenosylmethionine (SAM), the activated form of methionine, is the universal donor for methylation in protein and nucleotide synthesis in proliferating tissues. In the methyl donor reaction, SAM is demethylated to S-adenosylhomocysteine, which is converted to

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homocysteine either to reenter the methionine cycle, or to be removed by conversion to cystathionine via vitamin-B-dependent cystathionine β-synthase. Steps in the folate-cobalamin-methylation pathway are enzymatically catalyzed, with the genes encoding each enzyme existing as multiple polymorphisms (e.g., multiple alleles, or DNA sequence variations of genes within a population). Some polymorphisms can alone be causal of disability and death, but these are rare. More prevalent polymorphisms in folate and cobalamins pathways contribute to more frequent but also potentially harmful phenotypes. Importantly, all bodily tissues except the liver and kidney rely solely on methionine synthase for methyl substitutions.

In humans, the mean half-life for hepatic methionine synthase inactivation by 1 atmosphere N₂O is approximately 1 hour (or 0.5 atmospheres for 2 hours), with less than 20% residual activity after 2 atmosphere-hours of exposure. Restoration of methionine synthase activity requires synthesis of new enzyme and may take several days. A second exposure during this interval may be especially harmful because it prolongs the period of diminished methionine synthase activity. Because methionine synthase integrates folate and cobalamin metabolism, inactivation by N₂O exaggerates the harmful effects of acquired conditions and inborn errors of metabolism in these pathways. In such settings, adverse outcomes after exposure may arise from methyl group deficiencies, from homocysteine accumulation to toxic levels, or from both.

**Methylation Deficiency**

**Bone Marrow Depression.** N₂O-mediated interference with cell division leads to megaloblastic anemia, leukopenia, thrombocytopenia and, ultimately, marrow failure. In healthy patients anesthetized with N₂O for 6 hours, stores of maturing cells maintain normal blood counts until methionine synthase is re-established. Although N₂O decreases proliferation of human peripheral blood mononuclear cells and depresses chemotactic migration of monocytes, exposure to 65% N₂O does not increase the incidence of surgical wound infections. No comparative safety data provide thresholds for effects from exposure to N₂O for more than 6 hours, or from N₂O administration to patients with acquired or inborn errors of folate and cobalamin metabolism, or with co-existing marrow failure from other causes. Few young patients have a cobalamin deficiency, but 10% or more of elderly patients do. In the absence of patient specific data (e.g., normal blood B₁₂, B₉, and folic acid levels), N₂O should rarely, if ever, be given to patients with pernicious anemia, malabsorption syndromes (e.g., secondary to alcohol dependency), and any synthetic folates. In patients with N₂O deficiency, methylcobalamin should be used.

**Myeloneuropathy in Adults.** The recreational popularity of N₂O (up to 10% of young adults), and recent reports of myeloneuropathy appear to be increasing. So are reports of neurotoxicity in adults after clinical use of N₂O for anesthesia and analgesia. In a randomized, prospective investigation, neurologic symptoms lasting up to 4 weeks after surgery followed one hour of N₂O anesthesia in elderly patients with abnormal pre-operative folate levels. In a patient with cobalamin deficiency, a single exposure to N₂O may have caused sub-acute combined degeneration of the spinal cord. A description with a common polymorphism (C677T) in the enzyme antecedent to methionine synthase in the folate cycle, i.e., methyltetrahydrofolate reductase (MTHFR), who developed diffuse myelopathy, paraplegia and neurogenic bladder after two exposures to N₂O anesthesia within an interval of two months. Between 5% and 15% of patients are homozygous for this mutation, the frequency varying among ethnic groups. The common incidence of such polymorphisms in folate and cobalamin pathways, plus the common frequency of B-vitamin deficiencies, suggests that many patients undergoing surgery are doubly vulnerable to the risks of N₂O exposure.

**Neurotoxicity in Childhood.** The incidence of specific disorders caused by mutations in the enzymes catalyzing folate and cobalamin metabolism that could cause syndromes in the absence of other acquired conditions or drug exposures are rare (perhaps 1/100,000 patients or fewer). Although each “single disorder” of folate and cobalamin metabolism may be rare, many have been recognized, and in aggregate may be an order of magnitude more common. In such patients, the contraindication to N₂O use is obvious, but it is less clear in apperently normal first-degree relatives who carry alleles underlying autosomal recessive traits. Early in the course of disease, no antecedent sign or symptom may denote the presence of an acquired or inborn disorder of single carbon pathways, except, possibly, hypotonia and developmental delay. Prevalent mutations (e.g., MTHFR C677T discussed above) may be expressed in otherwise normal children, dictating that potential risks of N₂O to the developing nervous system in fetuses and infants be balanced against potential benefits. Given the limited anesthetic contribution of N₂O in the young (i.e., its low potency), anesthetics should use it with caution.

**Occupational Exposure.** The American Society of Anesthesiologists Task Force on Trace Anesthetic Gases of the Committee on Occupational Health of Operating Room Personnel found no evidence that waste anesthetic gases pose a risk to pregnant women (or those contemplating pregnancy) working in a scavenged environment. [Waste Anesthetic Gases Information for Management in Anesthetizing Areas and the Postanesthesia Care Unit (PACU). http://www.ASAhq.org/publication-3AndServices/wasteanes.pdf] However, occupational exposures above the regulatory maximum occur with mask leaks, uncuffed endotracheal tubes and laryngeal mask airways, and scavenging system defects. Moreover, N₂O use outside the operating room is expanding. Dental assistants occupationally exposed to N₂O may have more spontaneous abortions and decreased fertility. Occupational exposure also may increase the incidence of low birth-weight infants. Carcinogenesis. Regulation of DNA methylation in the promoter sequences of genes is a key mechanism of coordinated gene expression, and altered DNA methylation is documented in tumorigenesis. Genome-wide hypermethylation correlates with malignancy, and may cause chromosomal translocations and altered expression of proto-oncogenes and tumor suppressor genes. Presently, data in adults do not reveal an increased risk of developing cancer after exposure to N₂O. Studies are needed to determine whether exposure to N₂O in early life affects methylation status, and the occurrence of chronic disease later in life.

**Homocysteine Accumulation.** N₂O increases homocysteine levels through its effect on methionine synthase. Increased homocysteine levels can produce various pathologies. It is tempting to complete this syllogism and argue that N₂O can produce various pathologies, but the direct evidence for or against the safety of N₂O in these settings is limited at present.

**Homocysteine Vascular Toxicity.** Plasma homocysteine levels can increase after N₂O exposures routinely encountered in anesthesia, and may not return to normal for a week or more. Short-term elevation of plasma homocysteine does not cause thrombosis, but increases platelet aggregation, activate procoagulant factor V, and inhibit anticoagulant protein C. Homocysteine is cytotoxic to endothelial cells, oxidizes low-density lipoproteins, and inhibits flow-mediated vasodilation of vascular smooth muscle. Modestly elevated homocysteine levels (>15 mmol/l) are an independent risk factor for myocardial infarction, stroke and peripheral vascular disease. The MTHFR C677T mutation and others in the folate and cobalamin pathways contribute to hyperhomocysteinemia in some but not all studies. Patients randomized to receive N₂O for carotid endarterectomy may have a higher incidence and duration of postoperative myocardial ischemic events. Randomized trials with genotyping and dose dependencies remain to be conducted. For now, concern about the vascular consequences of N₂O appears warranted, with particular attention to disorders associated with preoperative hyperhomocysteinemia (e.g., renal failure), and conditions intolerant of a super-imposed lesion (e.g., thrombophilia from other causes, peripheral vascular, cardiovascular or cerebrovascular disease).

**Homocysteine Neuronal Toxicity.** Acute and chronic hyperhomocysteinemia may contribute to Alzheimer’s disease, Parkinson’s disease, and stroke. Homocysteine damages neurons by impairing DNA synthesis and triggering apoptosis. Two models of adult traumatic injury provide evidence that folate is needed to promote neuronal regeneration, suggesting the avoidance of N₂O in settings of neural trauma.

**Drug Interactions**

N₂O inactivation of methionine synthase can underlie adverse drug interactions. For example, severe toxicity with mucositis and myelosup-
pression may accompany the combined use of N₂O and adjuvant chemotherapy. Methotrexate inhibits dihydrofolate reductase and blocks regeneration of tetrahydrofolate from dihydrofolate. Through depletion of 5-methyl-THF, methotrexate reduces methionine synthase activity, augmenting the effect of N₂O. Hyperhomocysteinemia, the latter methotrexate is marked in patients who are also MTHFR C677T homozygotes. Methotrexate induces leukoencephalopathy in patients treated intrathecally, intravenously and even orally, which may be particularly vulnerable to the harmful effects of N₂O. Lipid-lowering drugs, oral hypoglycemics, anticoagulants, diuretics, omepazole, cimetidine, esomeprazole and levodopa are associated with hyperhomocysteinemia. For example, methylation of levopopa and dopamine by catechol-O-methyltransferase uses SAM as a methyl donor, and yields S-adenosylhomocysteine, which is rapidly converted to homocysteine. Patients taking levodopa have approximately twice the concentration of plasma homocysteine as controls and untreated Parkinsonian patients.

Experimental Neurotoxicity, interference with cobalamin metabolism does not appear to underlie a second specific neurotoxicity due to N₂O. NMDA receptor blockade by N₂O causes neurotoxicity in 7 day-old developing rats, and adding N₂O to isoflurane, or to isoflurane with midazolam, worsens pro-apoptotic effects during brain growth. The aging brain is significantly more sensitive to the neurotoxic effects of N₂O in combination with ketamine (another blocker of NMDA receptors) than the young adult brain, although both are equally sensitive to N₂O alone. The mechanisms of these effects are not fully understood, nor are the analogous clinical investigations in humans likely to be forthcoming. Homocysteine promotes oxidative stress in neurons and may directly activate NMDA glutamate receptors rendering neurons vulnerable to excitotoxicity. N₂O readily crosses the placenta to produce a maternal-fetal concentration ratio of 0.6 within 15 minutes of continuous inhalation. Prospective investigations addressing possible neurotoxic effects of N₂O during surgical procedures in pregnant women are lacking.

However, experimental data may argue against fetal exposure in light of evidence pointing to harmful consequences of N₂O exposure.

Summary

The authors propose that eliminating N₂O use would lead to simpler and safer anesthetic delivery devices and installations that could decrease the potential for hypoxia and decrease cost. The decreased costs would particularly apply to new hospital construction. Use of N₂O versus oxygen and air requires equipment that must be calibrated, daily-checked and maintained—hidden but real costs. Pipes, valves, regulators, flowmeters, and scavenging devices all can and do break; all require periodic testing. On the other hand, the newer, potent inhaled anesthetics of reduced solubility (ie, desflurane and sevoflurane) that might substitute for N₂O will add to the cost of anesthesia.

A half-century ago, most anesthetists believed that, except for its limited potency, N₂O was the perfect anesthetic. Several facts obscured the untoward consequences of its use. Many noxious effects of N₂O were subtle (eg, expansion of gas-containing spaces) and only slowly recognized. Many (eg, bone marrow and central nervous system toxicity) were delayed in detection, and thus usually were not immediately connected to its administration. Some others (eg, homocysteine toxicity; NMDA receptor interference with DNA methylation) await further appraisal. Regarding toxicity, although N₂O is a relatively impotent anesthetic, it affects single carbon metabolism in concentrations and durations routinely employed in practice. These harmful and potentially harmful effects combined with competitive contemporary alternatives make N₂O a less attractive option. No absolute indication, and few relative indications (eg, malignant hyperthermia) justify its continued widespread application. To the contrary, the number of patients with absolute and relative contraindications to N₂O administration by procedure, genetic predisposition, or acquired susceptibility is larger than previously appreciated.
1. Which of the following is not a desirable attribute of N₂O? 
   a. Low cost
   b. A decreased density relative to air, and thus a decreased respiratory resistance
   c. No pungency
   d. Low solubility
   e. Minimal cardiovascular depressant effects

2. Which of the following is a desirable attribute of N₂O? 
   a. It does not cause a local or respiratory acidosis
   b. The ability to enhance the volume or pressure of therapeutic gases placed in the body
   c. Its solubility relative to nitrogen
   d. Potency sufficient to allow the application of high O₂ concentrations
   e. During induction of anesthesia, it increases the output of variable bypass vaporizers

3. Why does administration of N₂O increase the volume of internal gas spaces? 
   a. N₂O diffuses faster than N₂ in blood
   b. N₂O diffuses faster than N₂ in gas spaces
   c. The solubility of N₂O in blood is much greater than the solubility of N₂ in blood, and thus much more N₂O can be brought to the space relative to the amount of N₂ that can be removed.
   d. The solubility of N₂ in blood is much greater than the solubility of N₂O in blood, and thus much more N₂O can be brought to the space relative to the amount of N₂ that can be removed.
   e. The specific heat of N₂O is less than that of N₂ and thus warming of the space and consequent expansion occurs.

4. N₂O transiently alters the output of variable bypass vaporizers by 
   a. altering the temperature of the bimetallic control strip
   b. decreasing flow through the sump holding liquid anesthetic by dissolving in the anesthetic during a change from N₂O administration to O₂ administration.
   c. decreasing flow through the sump holding liquid anesthetic by dissolving in the anesthetic during a change from O₂ administration to N₂O administration.
   d. the difference in density of N₂O versus O₂.
   e. the difference in viscosity of N₂O versus O₂.

5. Nitrous oxide decreases which of the following 
   a. Cerebral metabolic rate.
   b. Cerebral blood flow.
   c. Intracranial pressure.
   d. Sensory-evoked potentials.
   e. Postoperative nausea and vomiting (PONV).

6. MACawake is ________ . 
   a. the concentration of inhaled anesthetic at which 50% of subjects do not remember 
   b. greater (as a fraction of MAC) for potent inhaled anesthetics than for N₂O 
   c. has no relationship to the concentration of anesthetic that produces amnesia 
   d. smaller (as a fraction of MAC) for potent inhaled anesthetics than for N₂O 
   e. None of the above

7. The analgesia produced by N₂O is ________ . 
   a. transient 
   b. produced, at least in part, by the release of enkephalins 
   c. antagonized by naloxone 
   d. subject to rapidly developing tolerance 
   e. all of the above

8. Which correctly describes the toxic potential of N₂O? 
   a. Although metabolism is small, the metabolites (e.g., nitrous acid) can injure several organs.
   b. Degradation by desiccated CO₂ absorbents can produce volatile products (nitrous dioxide) capable of causing severe lung injury.
   c. Although N₂O is minimally degraded, it augments the metabolism of potent inhaled anesthetics to toxic byproducts.
   d. N₂O inactivates methionine synthase and thereby lessens the availability of methionine and folic acid.
   e. None of the above

9. Which answer most accurately describes the time course of N₂O inactivation of methionine synthase in humans? 
   a. Inactivation requires exposure over several days.
   b. Recovery after inactivation from several hours of N₂O exposure may take several days.
   c. Recovery requires several minutes after N₂O administration is discontinued.
   d. Tolerance to N₂O inactivation explains rapid recovery after repeated exposures.

10. All of the following are correct except: 
    a. N₂O is a neurotoxin.
    b. N₂O is a bone marrow toxin.
    c. N₂O is an effective contraceptive.
    d. N₂O is an occupational hazard.
    e. N₂O is a drug of abuse.
Answer Sheet & Evaluation Form
Current Status of Nitrous Oxide

Release Date: March 2007
Expiration Date: March 31, 2008

Directions: Select one answer for each question in the exam and circle the appropriate letter. A minimum score of 80% is required to earn credit. Retakes are not permitted for CRNAs. Other participants are allowed 2 attempts. Please submit your answers only once through one of the methods listed below. Allow 4 weeks for processing.

Participant online at: or mail to: or fax to:
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❑ Pharmacist ❑ Other (specify): _____________________________________________________________________________
❑ Nurse Anesthetist--AANA number (required): _____________________________________________________________________

CE/CME/CPE Post-test Answers
Current Status of Nitrous Oxide
Select the single-letter response that best answers the question or completes the sentence.

1. a b c d e
2. a b c d e
3. a b c d e
4. a b c d e
5. a b c d e
6. a b c d e
7. a b c d e
8. a b c d e
9. a b c d e
10. a b c d e

Evaluation Questions
Please answer the following questions by circling the appropriate rating.
4 = Strongly Agree 3 = Agree 2 = Disagree 1 = Strongly Disagree

1. After participating in this activity, I am better prepared to:
   a. List noxious effects of nitrous oxide (N2O) anesthesia.
   b. Discuss risks and benefits of N2O compared with other inhaled anesthetics.
   c. Review safety concerns, including effects of N2O on vitamin B12 and folate metabolism and the implications of these effects for selected patients.
   d. Relate N2O use patterns to the introduction of other inhaled anesthetics.
   e. Identify clinical scenarios in which N2O use is contraindicated.

2. The information was relevant to my professional needs and practice.

3. The educational level of this activity was appropriate.

4. The faculty was knowledgeable and effective in presentation of content.

5. The teaching method(s) and learning materials were effective.

6. Overall, I was satisfied with this educational activity.

7. The content was objective, current, scientifically based, and free of commercial bias. ❑ Yes ❑ No (please explain): _____________________________________________________________________________

Based on information presented in this activity, I will:
❑ do nothing as the content was not convincing.
❑ seek additional information on this topic.
❑ change my practice.
❑ do nothing as current practice reflects program’s recommendations.

The most important concept learned during this activity that may effect a change in patient care is:

What issue(s) related to the therapeutic area discussed in this activity, or other topics, would you like addressed in future continuing education?

Comments:

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