Nitrous Oxide and Anaesthesia

In 1844, a dentist named Horace Wells attended a public demonstration of nitrous oxide (N₂O), after seeing an advertisement stating "Those who inhale the gas once, are always anxious to inhale the second time ... No language can describe the delightful sensation produced ...". Later, Wells had one of his own teeth extracted by a fellow dentist under N₂O and was so impressed that he experimented on many patients before demonstrating his new finding at Harvard University. Although this was a failure — "a humbug" — N₂O anaesthesia rapidly became popular throughout much of the world. Unlike the fate of other anaesthetic gases subsequently introduced, such as chloroform and ether, N₂O still has a central role in current anaesthetic practice. Despite some authoritative opinions to the contrary, a recent survey of anaesthetists in Great Britain found that 82% used N₂O frequently and 80% felt that it should remain freely available for use on anaesthetic machines. There are about two million anaesthetics given each year in Australia, about half of which can be expected to include N₂O. A re-appraisal of the potential risks and benefits of N₂O therefore is indicated.

N₂O has a number of known side-effects, yet it is a cheap, widely available and well-known adjunct to general anaesthesia. Most anaesthetists consider it has a very good safety profile, but its relative merits have yet to be tested in a large trial of effectiveness in anaesthetic practice.

N₂O has limited potency, with a minimum alveolar concentration of 104%. N₂O anaesthesia cannot prevent intraoperative recall reliably. Thus it is unable to provide anaesthesia as a sole agent. The usual practice is to administer 60% to 70% N₂O in oxygen along with an inhalational agent or propofol in order to produce a depth of anaesthesia sufficient for surgery. N₂O increases the speed of induction of anaesthesia by a "second gas effect". This is of theoretical benefit during inhalational anaesthesia, but in practice simple overpressure with volatile agent in the first few minutes of anaesthesia is used by most anaesthetists to achieve a similar result. Early studies clearly demonstrated that N₂O produces dose-related analgesia in humans, thereby ablating potentially harmful responses such as tachycardia and movement. Current anaesthetic practice usually includes N₂O, allowing a dose-reduction of other anaesthetic, opioid, and possibly muscle relaxant drugs, administered during surgery.

The prevailing view is that N₂O is a cheap, relatively "safe" drug that can reduce exposure to other anaesthetic drugs. However, in a recent commentary,
Stenquist and colleagues outlined the history of N₂O and explored its place in modern anaesthesia. They concluded, partly because of the availability and effectiveness of modern drugs, that N₂O should be "retired" from use. A similar opinion was expressed by Eger in 1983. The arguments for and against the continued use of N₂O are summarized (Figure 1).

**Adverse Effects of N₂O**

N₂O interferes with vitamin B₁₂ and folate metabolism, by oxidizing the cobalt atom and irreversibly inactivating the enzyme methionine synthetase. This impairs production of methionine (from homocysteine), a substrate for tetrahydrofolate and thymidine during DNA synthesis (Figure 2). These adverse effects are time-exposure dependent and are probably greater in elderly and unwell patients. A two-hour exposure to N₂O is associated with a 50% reduction in methionine synthetase activity, raising the possibility of adverse effects such as immunodeficiency and impaired wound healing. It is well-known that N₂O-induced vitamin B₁₂ and folate deficiency can lead to a clinical syndrome similar to pernicious anaemia, manifesting as megaloblastic anaemia and subacute combined degeneration of the spinal cord.

1. **Megaloblastic anaemia**

Unrecognised vitamin B₁₂ and folate deficiency are reasonably common in the community, particularly in the elderly and vegan populations. We therefore may be putting many patients at risk of post-operative megaloblastic anaemia by exposing them to N₂O. The inhibitory effect of N₂O on methionine synthetase and DNA synthesis can be assessed by the deoxyuridine (dU) suppression test. Amos and co-workers, in a prospective study of 70 seriously ill patients admitted to an intensive-care unit, identified megaloblastic bone-marrow change in 22 patients on admission, of whom 18 had been anaesthetized with N₂O for less than six hours during surgery. Sixteen of these 18 patients died, compared with seven of the 22 patients who were normoblastic despite receiving equivalent amounts of N₂O. An abnormal dU-suppression test only developed in patients who had received N₂O; and on admission an abnormal dU-suppression test was found in 39 of the 42 patients who had been exposed to N₂O. Similarly, Delee and co-workers randomized 69 elderly patients undergoing eye surgery to receive general anaesthesia with or without N₂O. They reported a significant decrease in serum folate and a significant increase in mean red cell volume. Three of the N₂O-exposed patients developed symptoms of folate deficiency.

The inhibition of methionine synthetase by N₂O can be rapid and long-lasting. Exposure beyond a few hours will reduce methionine synthetase activity by 50% and 12 to 24 hours of exposure will result in marked megaloblastic changes. These effects have been reported in critically ill patients and those with sickle cell disease, and may be partly avoided with large doses of vitamin B₁₂ or folic acid. A propensity to anaemia may increase blood transfusion requirements, a risk factor for postoperative sepsis and other morbidity.

**FIGURE 1: Known and purported adverse effects and benefits of N₂O.**

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2. Immunosuppression

Surgery and anaesthesia compromise host defence mechanisms by depressing specific and non-specific components of the immune response. Those with pre-existing disease undergoing major surgery are most at risk. N₂O inhibits the lymphocytic response and cell-mediated cytotoxicity. The chemotactic migration of monocytes and neutrophils is more significantly depressed by N₂O than by other anaesthetic agents. The reversible leukopenic and granulocytopenic effects seen after long-term exposure to N₂O in both animal models and humans are consistent with the histological changes seen in bone marrow due to impairment of methionine production. DNA synthesis and mitosis. Cellular adenosine triphosphate levels fall after six hours of exposure to N₂O, leading to compromise of alveolar macrophage viability and function. Despite these laboratory studies, outcome studies have not been performed and so we are uncertain whether N₂O-induced immunosuppression is of clinical importance.

In a randomized controlled trial of 500 patients undergoing colorectal surgery, Greif and co-workers compared 80% oxygen (in nitrogen) with 30% oxygen (in nitrogen). They found a marked reduction in the incidence of wound infection (11% vs 5%; *P* = 0.01).

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suggesting that supplemental oxygen is antimicrobial. The use of N₂O prevents the administration of high oxygen concentrations (>80%) and therefore may further contribute to increased wound infection rates and a longer duration of hospital stay.

3. Homocysteine and myocardial ischaemia

N₂O-induced inactivation of methionine synthetase increases plasma homocysteine concentrations after surgery. A recent study has shown that plasma concentrations of homocysteine do not return to normal for at least one week after surgery and N₂O-based anaesthesia.

Long-term elevation of plasma concentrations of homocysteine is an independent risk factor for coronary artery and cerebrovascular disease and acute increases cause endothelial dysfunction and hypercoagulability. Thus, N₂O may be a risk factor for postoperative myocardial ischaemia. In a recent randomized trial, Badner and co-workers allocated 90 patients to anaesthesia with or without N₂O. The N₂O group had significantly increased plasma homocysteine concentrations and a higher incidence of myocardial ischaemia (46% vs. 25%; P<0.05), more ischaemic events in total (82 vs. 53; P<0.02), and more ischaemic events lasting 30 minutes (23 vs. 14; P<0.05). This is a particularly relevant finding, as the incidence of myocardial ischaemia is highest in the hours after surgery, and this is strongly associated with postoperative myocardial infarction.

4. Postoperative nausea and vomiting

Postoperative nausea and vomiting is the most common complication of surgery and anaesthesia, affecting up to 40% of patients. Postoperative nausea and vomiting is a major source of patient dissatisfaction, delays recovery after anaesthesia and surgery, and possibly hospital discharge. Level 1 evidence from a meta-analysis of 2478 patients in 24 randomized controlled trials found that avoidance of N₂O significantly reduced the incidence of PONV. The number-needed-to-treat (NNT) in a higher-risk group was 5 (95% CI: 4-10). Avoidance of N₂O also allows supplemental oxygen to be given, which of itself has been shown to reduce the incidence of postoperative nausea and vomiting. In a randomized controlled trial of 231 patients, use of 80% oxygen was associated with a 43% reduction in early (<24h) PONV (30% vs 17%; P=0.02). Thus, N₂O is a potent cause of PONV and may be associated with delayed ambulation after surgery, reduced food intake, increased postoperative complications and prolonged hospital stay.

5. Nerve and spinal cord toxicity

Subacute combined degeneration of the cord was first reported in critically ill patients chronically sedated with N₂O, a practice now obsolete. Nevertheless, there have been reports of serious nerve damage and paraplegia in humans with repeated exposure of N₂O<sup>19,21,23,26</sup>, including with a short period of only 65 minutes<sup>19</sup>. Subclinical folate and vitamin B₁₂ deficiency, common in elderly patients undergoing many types of surgery, may be a precipitating factor.

Recent evidence suggests that N₂O is an antagonist at N-methyl-D-aspartate (NMDA) receptors<sup>27</sup>, explaining at least some of its central effects. Another NMDA antagonist, scopolamine, has been shown to be neurotoxic in head injury patients<sup>28</sup>. This may be another mechanism by which N₂O can result in postoperative neuropathy<sup>29,30</sup>.

6. Carcinogenicity, teratogenicity, and occupational exposure

The inhibition of methionine synthetase by N₂O leads to deficiency in thymidine, impairing DNA production and possibly organogenesis. Other mechanisms may also be involved. N₂O is the only inhaled anaesthetic proven to be teratogenic in animals<sup>31</sup>, with increased rates of foetal reabsorptions and visceral and skeletal abnormalities. In 1978 Vessey<sup>32</sup>, in a review of the evidence, concluded that “there is ... reasonably convincing evidence of a moderate increase in the risk of spontaneous abortion among females, although it is possible that even this result is attributable to reporting bias”. A subsequent well-conducted large study by Rowland and co-workers found reduced fertility among dental assistants exposed to N₂O. Moreover, a recent meta-analysis found strong evidence of increased rates of spontaneous abortion in women occupationally exposed to N₂O<sup>33</sup>. The overall relative risk was 1.48 (95% CI: 1.4-1.6). The estimate of risk increased to 1.9 (95% CI: 1.7-2.1) when analysis was restricted to studies rated the most rigorous by the reviewers. Since then, a Swedish survey of midwives exposed to N₂O found a significant risk to them of low birthweight infants and infants small for gestational age (odds ratio: 1.8 [95% CI: 1.1-2.8]<sup>34</sup>).

Occupational exposure to trace anaesthetic gases, and in particular N₂O, is routine<sup>35</sup>. Leaks occur around the mask (40%), unconnected scavenging systems (19%), uncuffed endotracheal tubes (13%), equipment (12%) and other sites (16%). For example, Jernström and colleagues reported that during facemask anaesthesia, a concentration of

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N₂O above 100 ppm was found during 51% of the exposure time compared with 24% of the time during laryngeal mask anaesthesia. With occupational exposure to N₂O being common, and possibly harmful, the burden of proof of its safety should be set at a higher level than the traditional “statistically significant” 5% level.

7. Hypoxia

In the past, there were reports of oxygen delivery failure or inadvertent delivery of hypoxic gas mixtures in the setting of N₂O administration, resulting in severe hypoxic brain damage or death. Modern standards for the design of anaesthetic machines demand the inclusion of anti-hypoxic devices to flowmeter banks to prevent delivery of hypoxic mixtures, but this adds to the cost and complexity of this equipment. Cylinders, pipelines and valves require regular maintenance, and may malfunction. Thus, provision of high-pressure N₂O supply comes at substantial cost. Piped gas supplies may malfunction or be “crossed”, resulting in hypoxic mixtures being delivered throughout the hospital. These risks are partly mitigated by the routine use of oxygen analysers and pulse oximetry. Higher inspired fractions of oxygen (i.e. without N₂O) increase tissue oxygen tension, thereby increasing the time before hypoxia develops following a critical incident. At the end of surgery, when N₂O administration is ceased, there is a rapid movement of N₂O into the alveolar space. This reduces alveolar oxygen concentration, and may produce diffusion hypoxia.

8. Air spaces

The solubility of N₂O is 34 times that of nitrogen (the major component of air), with the blood gas partition coefficients being 0.46 and 0.015 respectively, so N₂O will diffuse rapidly into closed air spaces. If the air space is compliant (e.g. air embolus, pneumothorax, distended bowel, lung bullae) there will be a volume expansion, and if non-compliant (e.g. sinuses, middle ear post-typanic surgery, intracranial air) there will be an increase in pressure. The time course can be impressive, with an air space volume enlarging twofold in 10 minutes and threefold in 45 minutes. There have been many recent reports of patient blindness within weeks of vitreoretinal surgery that included intraocular perfluoropropane—the N₂O-induced expansion of air space led to retinal artery occlusion and optic atrophy. N₂O should not be given if a gas embolism or pneumothorax is suspected, and is contraindicated in bowel obstruction or within 30 days of vitrectomalous surgery.

9. Adverse circulatory effects

N₂O can increase pulmonary artery pressure, and is relatively contraindicated for patients with pulmonary hypertension. N₂O also activates the sympathetatic nervous system and can sensitize the myocardium to the arrhythmogenic effects of adrenaline. Increased sympathetic activity may support right ventricular function in the setting of increased pulmonary vascular resistance, but such an effect is probably mitigated by high-dose opioids.

10. Adverse cerebral effects

N₂O is associated with a mismatch between cerebral metabolism and blood flow, and can increase intracranial pressure. It is contraindicated for patients with severe head injury or expanding cerebral tumour, and many neuroanaesthetists no longer use N₂O.

11. Lung atelectasis

Some anaesthetists are hesitant to remove N₂O from the inspired gas mixture because a resultant high inspired oxygen fraction is thought to lead to atelectasis. But there is theoretical evidence that co-administered N₂O may promote collapse of poorly ventilated lung regions by gas absorption as effectively as does pure oxygen. These effects may be prevented if some nitrogen is included in the inspired gas mixture. Nevertheless, the clinical importance of absorption atelectasis in the pathogenesis of postoperative pulmonary collapse is unclear. There does not appear to be a significant increase in arterial oxygen desaturation attributable to atelectasis in the postoperative period among patients receiving high inspired oxygen concentrations during surgery.

12. Other

N₂O is manufactured by the heating of ammonium nitrate, a potentially explosive process that has resulted on rare occasions in catastrophic industrial accidents. Impurities include such toxic compounds as ammonia, nitrogen dioxide, carbon monoxide and chlorine. N₂O supports combustion. During laparoscopic surgery N₂O can diffuse into the peritoneal cavity and, when mixed with bowel gas containing methane or hydrogen, attain sufficient concentration to create an explosion hazard. Similar circumstances could occur during thoracoscopic surgery and throracostomy. N₂O depletes ozone, absorbs infrared
radiation and so is a greenhouse gas\textsuperscript{3,4}. Despite anaesthesia being a minor source of greenhouse gas emissions, estimated to be less than 1% of global N\textsubscript{2}O production, the environmental consequences of continued worldwide use of N\textsubscript{2}O may not be negligible.

**Beneficial Effects of N\textsubscript{2}O**

N\textsubscript{2}O has been given to millions of patients since 1844 and the side-effects and safety profile are thought to be well-known. N\textsubscript{2}O was the first anaesthetic discovered and despite the introduction of many others, remains a mainstay of anaesthesia throughout the world\textsuperscript{1}. The most notable advantage of N\textsubscript{2}O is that it allows a dose-reduction (in the order of 30-60%) of other more expensive and (possibly) more toxic anaesthetic drugs.

1. **Long-standing safety record**

When compared with other inhaled anaesthetics, N\textsubscript{2}O causes less cardiovascular and respiratory depression and may be associated with a lower incidence of intraoperative hypotension. It has less effect than some inhalational agents on cerebral haemodynamics. In addition, N\textsubscript{2}O is not associated with hepatotoxicity, nephrotoxicity or malignant hyperthermia. But because N\textsubscript{2}O is not a replacement for such agents (as it is only dose-sparing), it is unlikely that such rare events are prevented if N\textsubscript{2}O is used.

2. **Analgistic**

N\textsubscript{2}O produces dose-related analgesia in humans\textsuperscript{1}, partly explaining its “MAC-sparing” properties of minimizing patient movement in response to pain. This effect may be mediated by the NMDA receptor\textsuperscript{4,5}. Intraoperative opioid doses therefore can be decreased, although its effect on postoperative opioid requirements is less clear.

3. **Short-acting**

N\textsubscript{2}O is relatively insoluble in body tissues, especially fat stores, compared with other inhalational agents, and so induction and recovery from anaesthesia theoretically may be achieved more rapidly. Interestingly, however, a recent large randomized controlled trial could not find a beneficial reduction in recovery times with N\textsubscript{2}O\textsuperscript{6}. In this study, 1590 patients having gynaecological surgery under propofol anaesthesia were randomly allocated to N\textsubscript{2}O or N\textsubscript{2}O-free anaesthesia, and both groups had equivalent home readiness times\textsuperscript{6}. Unfortunately this trial did not report rates of serious complications, and in view of the low-risk population, was unlikely to have sufficient power to detect an important clinical difference.

4. **Reduced risk of awareness**

Consciousness is lost at an end-tidal concentration of N\textsubscript{2}O of about 70% (“MAC-aware”), which is the usual concentration of N\textsubscript{2}O administered routinely. Even though N\textsubscript{2}O cannot be used as a sole agent, the addition of N\textsubscript{2}O to other agents is thought to protect against awareness. Tramer and co-workers\textsuperscript{7}, in a systematic review of randomized trials including 2478 patients, reported a decreased risk of awareness with N\textsubscript{2}O. This finding may be challenged for its relevance to contemporary practice, as there is now widespread use of inhaled agent monitoring, better training and greater experience in total intravenous techniques, and the availability of monitors of hypnotic depth.

**Conclusion**

There are some compelling reasons to question the routine use of N\textsubscript{2}O. Despite the fact that N\textsubscript{2}O was the first anaesthetic to be introduced, and is still widely used\textsuperscript{8}, there is sufficient doubt as to its risk-benefit profile to justify a re-evaluation in contemporary anaesthetic practice. Level I evidence identifies exposure to N\textsubscript{2}O as a major risk factor in postoperative nausea and vomiting. It is clear that even brief exposure to N\textsubscript{2}O impairs methionine synthetase, DNA production, and red and white blood cell formation. This is most likely to be a problem with longer exposure. With increased potential for transient episodes of hypoxia, and a reduction in Fi\textsubscript{O2} and P\textsubscript{a}O\textsubscript{2}, tissue hypoxia may be more common. These adverse effects are enhanced in high-risk patients and the elderly (i.e. those at highest risk for increased hospital length of stay and healthcare expenditure). The incidence of wound infection and cardiac morbidity attributable to N\textsubscript{2}O is not known. Large outcome trial data are lacking.

A major supporting argument for continued use of N\textsubscript{2}O is that it has been a key component of general anaesthesia throughout the modern era. Nearly all anaesthetists around the world have based their practice on including N\textsubscript{2}O as part of the inhaled gas mixture. To change practice would entail some retraining and additional experience, and may lead to a greater risk of awareness (if the resultant anaesthesia is too light) or delayed recovery (if the resultant anaesthesia is too deep). For those anaesthetists who are familiar with an N\textsubscript{2}O-free anaesthetic, such as those providing services for cardiac and neurosurgery, there may be little adjustment required. But
for many, particularly those who have had a long time practice based on the inclusion of N₂O, there will need to be a "recalibration" of how much additional volatile or intravenous hypnotic agent is needed. Such a change adds new demands to our practice. Another issue relates to cost. Exclusion of N₂O from anaesthetic practice demands replacement with other agents, and drug acquisition costs can be expected to increase. However, if avoidance of N₂O is associated with a reduction in complications and/or length of stay in the recovery room or hospital, then there would be a reduction in indirect costs. A formal cost-effectiveness analysis is required, and this needs good quality outcome data.

When considering the widespread use of N₂O during anaesthesia in Australia and around the world, small differences in outcome would have major implications for healthcare delivery. A large randomized controlled trial is necessary to answer this question. With the support of the Australian National Health and Medical Research Council, and the Australian and New Zealand College of Anaesthetists, our group has commenced a trial in 2,000 surgical patients: the ENIGMA Trial (Evaluation of Nitrous oxide In the Gas Mixture for Anaesthesia). Our primary endpoint is hospital length of stay; the major outcomes of the trial include wound infection, myocardial infarction, severe vomiting, quality of recovery, and thromboembolism. Results are expected to become available in 2006.

REFERENCES


52. Acker O, Podolsky A, Eisenhuthe E et al. Comparable postoperative pulmonary atelectasis in patients given 30% or 80% oxygen during and 2 hours after colon resection. Anesthesiology 1999; 91:991-998.


