Nitrous Oxide is an Effective and Safe Anesthetic

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Nitrous oxide has been used for more than a century and given to about two billion patients. Its low tissue solubility (and therefore rapid kinetics), low cost, and minimal cardiorespiratory complications have made nitrous oxide by far the most commonly used general anesthetic in history.

The difficulty is that even brief exposure to nitrous oxide produces prolonged inactivation of vitamin B12 which is the cobalamin or methylcobalamin component of the enzyme methionine synthetase (1). Nitrous oxide thus inhibits methionine synthetase (2), the enzyme responsible for both conversion of homocysteine to methionine and methyltetrahydrofolate to tetrahydrofolate. Both are critical pathways for thymidine formation, an essential base in DNA formation and, therefore, protein production. Nitrous oxide also depresses chemotactic migration by neutrophils and monocytes, apparently by interfering with microtubules (3, 4). And finally, nitrous oxide increases plasma homocysteine concentration which stiffens arterial vessel walls and promotes coagulation (5). There are thus theoretical biochemical reasons to believe that nitrous oxide may reduce resistance to surgical wound infections and promote myocardial infarctions.

Concerns about potential complications due to nitrous oxide have markedly reduced use of the drug. Thus an anesthetic that was used for nearly every general anesthetic three decades ago is now used in perhaps 20% of cases in the United States, and even a smaller fraction in Europe. The difficulty is that this transition was based on no compelling human data; in fact very large randomized trials clearly show that nitrous oxide is nearly perfectly safe.

Well over 9,000 patients have been randomized to nitrous oxide or not, most recently in the ENIGMA-2 trial (6). The results are clear: nitrous oxide does not increase the risk of myocardial infarction after non-cardiac surgery overall, or in any sub-group of patients. Similarly, nitrous oxide does not increase the risk of surgical site infection or mortality (6) which is consistent with a previous trial (7). Randomized trials also show that nitrous oxide does not increase the risk of cancer recurrence (8). Nitrous oxide is a weak NMDA antagonist. As might thus be expected, nitrous oxide reduces the risk of persistent surgical pain (9).

In fact, there appear to be only two minor adverse effects of nitrous oxide. The first is a slight increase in nausea and vomiting, an increase that is considerably smaller than that provoked by volatile anesthesia (10). Clinicians concerned about nausea and vomiting should thus avoid volatile anesthetics rather than avoiding nitrous oxide. The second is bowel distension. But in unobstructed patients, the effect is modest and blinded surgeons in fact have difficulty determining whether nitrous oxide was used (11, 12).

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That nitrous oxide is a greenhouse gas, about 300 times more potent than carbon dioxide, is sometime proposed as a reason to avoid the anesthetic. However, medical use of nitrous oxide is trivial compared to use of the gas for propellant for foam products in cans (such as shaving cream), its use in the production of nylon, and its use in racing and rocket engines. And more importantly, only 30% of nitrous oxide released into the atmosphere is from human activity, with the bulk being made naturally in soil. Thus while global warming is a serious concern, anesthetic use of nitrous oxide does not contribute meaningfully and is not a substantive reason to avoid this otherwise useful drug.

Of course it is easy to provide general anesthesia without nitrous oxide. My point is not that clinicians should use nitrous oxide, only that they should not avoid it on the basis of theoretical concerns about biochemical toxicity which have clearly been shown to be untrue. This position is supported by a Task Force report from the European Society of Anesthesiologists which concluded: "There is no clinically relevant evidence for the withdrawal of N_2O from anaesthesia practice or procedural sedation… There is no evidence indicating that the use of N_2O increases health risk in patients or providers" (13).

In summary, nitrous oxide is inexpensive and has favorable kinetics; it does not increase the risk of surgical site infection, postoperative myocardial infarction, or cancer recurrence. The gas may be protective against persistent incisional pain. And the two complications resulting from nitrous oxide administration, nausea and bowel distension, are minor and no worse than complications caused by alternative anesthetics.

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