Special Article

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Nitrous oxide at 576 mm Hg

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Nitrous oxide possesses many characteristics of the ideal anesthetic[1,2]. It is nonflammable, produces excellent analgesia, and reduces anesthetic requirement. It costs little, particularly relative to the cost of potent inhaled anesthetics. Its low blood and tissue solubilities permit a rapid onset and elimination of effect. This tendency to a rapid recovery from anesthesia is enhanced by a relatively high MACawake relative to MAC: the ratio of these is approximately 0.68 whereas with potent anesthetics such as desflurane or isoflurane, the ratio is approximately 0.35[3]. Clinical measures of circulation and respiration are little affected by its use, implying a wide margin of safety, a safety also suggested by its long history without apparent untoward effect. Finally, metabolism, and hence organ toxicity, appear to be minimal or nonexistent.

Nitrous oxide does have limitations[4]; the most obvious of which is that to use it effectively limits the inspired concentration of oxygen. Even when used at sea level at concentrations of 70 to 80 percent, its potency is too low to produce anesthesia sufficient for surgery in the normal patient. An ambient pressure of 576 mmHg (three quarters of an atmosphere) as in Mexico City, further limits the concentration that may be applied without encroaching unduly on the partial pressure of oxygen. If we insist on delivering at least 25% of an atmosphere of oxygen in inspired gases, that restricts the delivered partial pressure of nitrous oxide to 50% of an atmosphere in Mexico City. That is, nitrous oxide might comprise two thirds of the delivered gas and oxygen one third.

The effectiveness of nitrous oxide at 50% of an atmosphere or less, depends on the age of the patient. For young patients, perhaps only 30-40% of MAC may be delivered with nitrous oxide, but with adults this increases to 40-60% of MAC, the highest values found for the elderly. This effect of age is of particular value because it is the elderly in whom awakening is most likely to be delayed and in whom circulatory stability is sometimes hardest to achieve.

The delivery of partial pressures of nitrous oxide of 50% of an atm or less may be helpful in some unexpected ways. Higher partial pressures of nitrous oxide can produce muscle rigidity[5]. Nitrous oxide can increase the incidence of emesis after anesthesia[6]. However, in volunteers we found that 45% of an atm of nitrous oxide infrequently causes nausea and vomiting whereas 65% usually causes nausea and vomiting[3]. Thus, the use of lower partial pressures of nitrous oxide may minimize the problem of nausea and vomiting.

We have learned that not all the uptake characteristics of nitrous oxide are desirable[7]. Gas spaces within the body are expanded, sometimes with untoward results. Nitrous oxide may be contraindicated in the presence of a tension pneumo-thorax or if air embolization occurs. Embolization to the myocardium may produce greater injury in the presence of nitrous oxide[8]. The gas spaces in endotracheal tube cuffs may be increased and thereby produce ischemia of tracheal mucosa[9]. This probably is of minimal concern in short procedures but may begin to be important when surgery lasts for more than one to three hours. Nitrous oxide may increase pressure in sinuses or the middle ear[10]. Abdominal distention and respiratory compromise from intestinal obstruction may be exaggerated by nitrous oxide. In patients without distention but undergoing intro-abdominal surgery, the use of nitrous oxide may delay recovery of function and prolong hospitalizations[11]. However,

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other studies do not support this finding[12].

Toxicity and death may result from the prolonged administration of nitrous oxides and abuse of nitrous oxide can cause neurological injury[14-15]. For operating personnel exposed to high concentrations of nitrous oxide (i.e., in unscavenged operating rooms), there may be an increased incidence of abortions and birth defects[16,17], such findings are particularly applicable to dental operatories[18-19]. These untoward findings may be explained by the discovery that nitrous oxide can inactivate methionine synthase[20-23], a vitamin B_{12} containing enzyme which converts homocysteine to methionine and, in the process, changes methyl tetrahydrofolate to tetrahydrofolate. Tetrahydrofolate is needed for the synthesis of DNA. A decreased capacity to synthesize DNA might be the mechanism whereby nitrous oxide produces the disorders listed above.

Concern regarding the potential for nitrous oxide to produce untoward effects on vital organs lad to the pursuit of several studies of outcome in patients given nitrous oxide. Lampe and his co- workers reported results from nearly 300 patients randomly assigned to receive isoflurane with or without nitrous oxide[24-30]. With only minor exceptions, nitrous oxide did not increase the incidence of untoward effects[24]. No evidence for neurologic injury was found[24], even in patients subjected to anesthesia of nine hr duration[25]. Postoperative hypoxemia was not increased [26], nor was hepatic injury found[28]. Hematologic effects in patients given nitrous oxide were not different from the effects in patients not given nitrous oxide[30]. The effect of nitrous oxide on folate and vitamin B_{12} metabolism was minimal or nonexistent and any effect seen was transient. Results of one study contradict the finding regarding the capacity of nitrous oxide to produce postoperative ischemia. Maroof et al. did find a decrease in saturation 48 hr after anesthesia in patients given nitrous oxide plus fentanyl and isoflurane as opposed to patients given fentanyl and isoflurane in oxygen -enriched air[31]. Possibly, Lampe et al. failed to find a difference because they used oxygen rather than air as the background gas in the control group.

Other studies have examined the capacity of nitrous oxide to produce abortions and teratogenic changes. These have included both occupational exposure[32,33] and anesthesia to patients[34]. None have found a significant effect except for two studies of occupational exposure. In one it was found that a small subset exposed to the highest levels of nitrous oxide had a delay in the time to conception[35]. However, a change in the result for only two of the patients in this subset would have eliminated the significance of this finding. In another, it was concluded that frequent, high occupational exposure to nitrous oxide may have a negative influence on the ability of women to become pregnant[36].

Finally, we may ask if there are rare specific patients in whom nitrous oxide administration does present a toxic risk? Schilling suggested that vitamin B_{12} deficiency might have been the basis for two patients who developed neurologic deficiencies after receiving nitrous oxide[37]. Another case and a review of the literature by Rosener and Dichgans support Shilling's findings[33]. Further support for this position comes from the finding that inactivation of methionine synthase by nitrous oxide occurs more rapidly in patients with a pro-existing B_{12} deficiency[39].

Nitrous oxide is not a perfect anesthetic. It is less potent than we might wish, and it supports combustion. It has untoward uptake characteristics such as diffusion hypoxia and expansion of gas spaces within the body. It increases muscle tone - but only at higher partial pressures. It increases cerebral blood flow and intracranial pressure and does not decrease cerebral metabolic rate. It can predispose to nausea - but may do so to a much lesser extent if given at partial pressures less than 50% of an atm. A toxicity accrues to prolonged exposures - but does not appear to apply to patients provided briefer exposures, including those of a half day in length.

Despite some limitations, nitrous oxide continues to be a mainstay of our practice because of several desirable characteristics. These apply with greater or lesser force to its application at higher elevations such as found in Mexico City. It has little or no odor. Its low solubility and high MAC-awake/MAC ratio permit a more rapid recovery than can be obtained with potent anesthetics. Depression of respiration and circulation is less than that seen with potent anesthetics. It does not increase uterine bleeding nor does it trigger malignant hyperthermia.

And it is inexpensive. It continues to deserve a place in our management of patients, particularly adult patients, in Mexico City.

REFERENCES

1. Sandman L, Hamilton W. We Should Continue To Use Nitrous Oxide. *Nitrous Oxide/N_2O* 1985;345-53.
2. Hornbein T. Epilogue. *Nitrous Oxide/N_2O* 1985;355-7.
3. Dwyer R. Bennett HL, Eger EI, II, Helibron D. Effects of isoflurane and nitrous oxide in subanesthetic concentrations on

memory and responsiveness in volunteers. *Anesthesiology* 1992;77:888-98.
4. Eger EI, II. Should we not continue to use nitrous oxide? *Nitrous Oxide/N_20* 1985; 339-43.
5. Freund FG, Martin WE, Wong KC, Hornbein TF. Abdominal-muscle rigidity induced by morphine and nitrous oxide. *Anesthesiology* 1973;38:358-62.
6. Hartung J. Twenty-four of twenty-seven studies show a greater incidence of emesis associated with nitrous oxide than with alternative anesthetics. *Anesth Analg* 1996;83:114-6.
7. Eger EI, II. Pharmacokinetics. In Nitrous Oxide/N_20 Edited by EI Eger, II. Elsevier, NY. 1985; 81-107.
8. Tuman KJ, McCarthy RJ, D SB, Overfield DM, Ivankovitch AD. Effects of nitrous oxide on coronary perfusion after coronary air embolism. *Anesthesiology* 1987;67:952-9.
9. Stanley TH, Kawamura R. Graves C. Effects of nitrous oxide on volume and pressure of endotracheal tube cuffs. *Anesthesiology* 1974;41:256-62.
10. Waun JE, Sweitzer RS, Hamilton WK. Effect of nitrous oxide on middle ear mechanics and hearing acuity. *Anesthesiology* 1987;28:846-50.
11. Scheinin B. Lindgren L, Scheinin TM. Perioperative nitrous oxide delays bowel function after colonic surgery. *Br J Anaesth* 1990;64:154-8.
12. Guiffre M, Gross JB. The effects of nitrous oxide on postoperative bowel motility. *Anesthesiology* 1986;65:699-700.
13. Lassen HCA, Henriksen E, Neukirch F. Kristensen HS. Treatment of tetanus. Severe bone-marrow depression after prolonged nitrous-oxide anaesthesia. *Lancet* 1956;1:527-30.
14. Layzer RB. Myeloneuropathy after prolonged exposure to nitrous oxide. *Lancet* 1978;2:1227-30.
15. Dinn JJ, Weir DG, McCann S. Reed B. Wilson P. Scott JM. Methyl group deficiency in nerve tissue: A hypothesis to explain the lesion of subacute combined degeneration. *Irish J Med Sci* 1980;149:1-4.
16. Knill-Jones RP, Moir DD, Rodriguez LV, Spence AA. Anaesthetic practice and pregnancy. Controlled survey of women anesthetists in the United Kingdom. *Lancet* 1972;1:1326-8.
17. Cohen EN, Brown BW, Bruce DL, et al. Occupational disease among operating personnel. A national study. *Anesthesiology* 1974;41:321-40.
18. Cohen EN, Brown BW, Wu ML, Whitcher CE, Brodsky JB, Gift HC, Greenfield W. Jones TW, Driscoll EJ. Occupational disease in dentistry and chronic exposure to trace anesthetic gases. *J Am Dent Assoc* 1980;101:21-31.
19. Brodsky JB. Toxicity of nitrous oxide. Nitrous Oxide/N_20. Ed. El Eger, II. Elsevier. NY. 1985; 259-79.
20. Koblin DD, Watson JE, Deady JE, Stokstad ELK, Eger E, II. Inactivation of methionine synthetase by nitrous oxide in mice. *Anesthesiology* 1981;54:318-24.
21. Koblin DD, Waskell L, Watson JE, Stokstad ELK, Eger EI, II. Nitrous oxide inactivates methionine synthetase in human liver. *Anesth Analg* 1982;61:75-8.
22. Deacon R. Lamb M, Perry J. Chanarin I, Minty B. Halsey MJ, Nunn JF. Selective inactivation of vitamine B_{12} by nitrous oxide. *Lancet 1978*;2:1023-4.
23. Royston BD, Nunn JF, Weinbren HK, Royston D, Cormack RS-Rate of inactivation of human and rodent hepatic methionine synthase by nitrous oxide. *Anesthesiology* 1988; 68: 213-6.
24. Eger EI, II, Lampe GH, Wauk LZ, Whitendale P. Cahalan MK, Donegan JH. Clinical Pharmacology of nitrous oxide: An argument for its continued use. *Anesth Analg* 1990;71:575-85.
25. Lampe GH, Wauk LZ, Donegan JH, Pitts LH, Jackler RK, Lift LL, Rampil IJ, Eger EI, II. Effect on outcome of prolonged exposure of patients to nitrous oxide. *Anesth Analg* 1990;71:586-90.
26. Lampe GH, Wauk LZ, Whitendale P. Way WL, Kozmary SV, Donegan JH, Eger EI, II. Postoperative hypoxemia after nonabdominal surgery: A frequent event not caused by nitrous oxide. *Anesth Analg* 1990;71:597-601.
27. Lampe GH, Donegan JH, Rupp SM, Wauk LZ, Whitendale P. Fouts KE, Rose BM, Litt LL, Rampil IJ, Wilson CB, Eger EI, II. Nitrous oxide and epinephrine-induced arrhythmias. *Anesth Analg* 1990;71:602-5.
28. Lampe GH, Wauk LZ, Whitendale P. Way WL, Murray W. Eger EI, II. Nitrous oxide does not impair hepatic function in young or old surgical patients. *Anesth Analg* 1990;71:606-9.
29. Koblin DD, Tomerson BW, Waldman FM, Lampe GH, Wauk LZ, Eger EI, II. Effect of nitrous oxide on folate and vitamin B12 metabolism in patients. *Anesth Analg* 1990;71:610-8.
30. Waldman FM, Koblin DD, Lampe G H. Wauk LZ, Eger EI, II. Hematologic effects of nitrous oxide in surgical patients. *Anesth Analg* 1990;71:618-24.
31. Maroof M, Khan RM, Siddique M. Ventilation with nitrous oxide during open cholecystectomy increases the incidence of postoperative hypoxemia. *Anesth Analg* 1992;76:1091-4.
32. Ericson HA, Kallen AJB. Hospitalization for miscarriage and delivery outcome among Swedish nurses working in operating rooms 1973-1978. *Anesth Analg* 1985;64:981-8.
33. Mazze RI, Kallen B: Reproductive outcome after anesthesia and operation during pregnancy: A registry study of 5405 cases. *Am J Obstet Gynecol* 1989;161:1178-85.
34. Aldridge LM, Tunstall ME. Nitrous oxide and the fetus: A review and the results of a retrospective study of 175 cases of anaesthesia for insertion of Shirodkar suture. *Br J Anaesth* 1986;58:1348-56.
35. Rowland AS, Baird DD, Weinberg CR, Shore DL, Shy CM, Wilcox AJ. Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide. *N Engl J Med* 1992;327:993-7.
36. Ahlborg G. Jr, Axelsson G. Bodin L. Shift work, nitrous oxide exposure and subfertility among Swedish midwives. *Int J Epidemiol* 1996;25:783-90.
37. Schilling RF. Is nitrous oxide a dangerous anesthetic for vitamin B_{12}-deficient subjects? *JAMA* 1986;255:1605-6.
38. Rosener M, Dichgans J. Severe combined degeneration of the spinal cord after nitrous oxide anaesthesia in a vegetarian. *J Neurol Neurosurg Psychiat* 1996;60:354.
39. Landon MJ, Creagh-Barry P. McArthus S. Charlett A. Influence of vitamin B_{12} status on the inactivation of methionine synthase by nitrous oxide. *Br J Anaesth* 1992; 69: 81-6.