Use of Nitrous Oxide in Neuroanesthesia: Why Bother?

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Nitrous oxide is one of the most frequently used anesthetic agents in clinical practice. Early studies indicate that it is pharmacologically inert and provides good analgesia, but by itself, it is insufficient to produce general anesthesia. Therefore it has become accepted as part of the background anesthetic for many forms of general anesthesia. In other words, unless there is a specific contraindication to its use, such as the need for a high inspired oxygen concentration to maintain normoxemia, its inclusion is seemingly automatic. Despite recent awareness that nitrous oxide can no longer be considered a pharmacologically inert agent (1), anesthesiologists continue to use nitrous oxide routinely because conventional wisdom and past experience suggest that its actions are minor and that the accrued benefits outweigh the disadvantages. We would argue that although this may well be true in most clinical situations, the use of nitrous oxide in the practice of neuroanesthesia is potentially inappropriate. Furthermore, its use should be treated as a conscious act, rather than a reflex (2).

This brief article will highlight the effects of nitrous oxide that are considered relevant to the central nervous system and neuroanesthesia. Other systemic effects without direct impact on the central nervous system are omitted. The readers are reminded that the arguments are meant to be provocative and the position taken is deliberate.

THEORETICAL CONSIDERATIONS

Effects of Nitrous Oxide on Cerebral Blood Flow and Metabolism

Animal Studies

Early studies in rats as well as in humans indicate that nitrous oxide has little effect on cerebral blood flow (CBF) and metabolism (3-6). However, recent studies have confirmed that nitrous oxide has a stimulatory effect on the brain and increases CBF in excess of its effect on metabolism. In other words, nitrous oxide is a direct cerebral vasodilator. Its vasodilatory effect has been documented in rats (7,8), rabbits (9-11), cats (12), dogs (13-15), and pigs (16). Increase in cerebral metabolism has also been found in various species, including rats (17), goats (18), and dogs (19). Its vasodilatory action is most evident during inhalation anesthesia, and Drummond et al. (10) reported that its action is greater during high-dose compared with low-dose anesthesia with volatile agents. Hansen et al. (7) also ascertained that nitrous oxide causes greater
cerebral vasodilation when compared with an equipotent dose of isoflurane. Roald et al. (20) investigated the cerebral stimulatory effect of nitrous oxide in dogs during deep isoflurane anesthesia sufficient to maintain an isoelectric EEG; they found that EEG activity returned when nitrous oxide was added.

**Human Studies**

Although Wollman et al. (6) did not observe any increase in CBF in their early studies, Sakabe et al. found an increase in CBF equivalent (cerebral blood flow/cerebral metabolic rate) when nitrous oxide was added during halothane anesthesia (21). A more recent investigation in humans by Deutsch and Samra indicates that nitrous oxide is indeed a cerebral vasodilator when given to awake volunteers in various concentrations (22). Lam et al. studied the cerebral effect of a 60% nitrous oxide–isoflurane mixture compared with an equipotent dose of isoflurane and demonstrated that nitrous oxide has a greater vasodilatory effect than isoflurane (23).

Thus there is no doubt that when an inhaled anesthetic is chosen and cerebrovascular dilatation is deemed undesirable, there is little advantage in adding nitrous oxide or substituting the inhaled anesthetic with nitrous oxide. The effect of nitrous oxide on CBF during intravenous anesthesia, however, does appear to be minimal. In addition, nitrous oxide does not seem to influence CO₂ reactivity when added to an intravenous agent, such as propofol (24).

**Effect of Nitrous Oxide on Intracranial Pressure**

As a result of its cerebral vasodilatory action, nitrous oxide has been reported to increase intracranial pressure (ICP) in patients with reduced compliance (25–28). Although this increase in CBF and therefore ICP can be treated effectively with hyperventilation, it may not be possible in patients with gas-exchange problems or in patients already maximally hyperventilated. And the increase in ICP may not be readily apparent or appreciated, particularly in patients with normal ICP but reduced compliance. Elimination of nitrous oxide from all neurosurgical cases will obviate such considerations.

**Effect of Nitrous Oxide on Experimental Cerebral Ischemia**

Nitrous oxide has potential cerebral stimulatory effects and may have a deleterious effect during cerebral ischemia by causing an increase in cerebral metabolism when there is an insufficient supply of energy substrates. The concomitant vasodilatory action is not necessarily beneficial, since vessels in the ischemic areas may already be maximally dilated. Dilation of vessels in unaffected areas could lead to intracerebral steal. This vascular consideration obviously would not apply during global hypoxia.

Nonetheless, Hartung and Cottrell have noted that in the hypoxemic hypoxia mouse model nitrous oxide counteracts the protective effect of barbiturates and decreases survival (29). Although their results were disputed by Milde (30), who could not duplicate the findings, the experimental conditions were dissimilar (31). Moreover, Hartung and Cottrell reviewed the literature and found that almost all previous studies that failed to show a cerebroprotective effect of barbiturates included nitrous oxide as the background anesthetic. They therefore argued convincingly that nitrous oxide can worsen the effects of cerebral ischemia and consequently counteract the protective effect of barbiturates (29).

**Outcome Studies**

We are not aware of any outcome studies comparing nitrous oxide anesthesia with other types of anesthesia. However, studies of experimental cerebral ischemia are strongly suggestive that nitrous oxide can contribute to poor outcome in patients at risk of cerebral ischemia.

**CLINICAL CONSIDERATIONS**

**Limitation of Inspired Oxygen Concentrations**

Since nitrous oxide is a weak anesthetic, it has to be used at a minimum of 50% to make any significant contribution to overall anesthesia. This limits the concentration of inspired oxygen that can be administered to the patient. Consequently, any patient requiring >50% inspired oxygen should not be given nitrous oxide anesthesia. Many traumatized
patients may have concurrent head and chest injuries and have compromised gas exchange requiring a high inspired oxygen concentration. Thus the anesthesiologist needs to develop experience with anesthetic techniques where nitrous oxide is omitted.

**Expansion of Air Embolus**

The incidence of venous air embolism in intracranial surgery procedures ranges from 12% (supine) to 45% (sitting) (32) and therefore should be considered a constant threat in any craniotomy procedure. Patients with ventriculoatrial shunts are particularly at risk of air embolus. Although some consider the use of nitrous oxide an advantage since it may provide early warning signals in the event of an air embolus and allows treatment by its withdrawal, this argument is based on faulty logic. Nitrous oxide expands the air embolus and may transform a hemodynamically insignificant air embolus into a significant one. Moreover, its withdrawal does not represent effective treatment, since it can reduce the size of the air embolus only to what it would have been had nitrous oxide been omitted in the first place. Furthermore, in the event of paradoxical air embolus, the presence of nitrous oxide no doubt will exacerbate the situation.

**Expansion of Pneumocephalus**

Since nitrous oxide can diffuse into an air-containing cavity quicker than nitrogen can exit, it can expand the volume of this cavity. Nowhere in the body is this consideration more important than within the cranium. This rigid structure does not permit any room for expansion, and the intracranial pressure will consequently rise. Nitrous oxide is therefore clearly contraindicated in any patient with pneumocephalus, either from trauma or recent intracranial surgery. Fortunately, pneumoencephalography is no longer used.

Debate also continues on the merit of discontinuing nitrous oxide before or after dural closure (33–35). Early discontinuation eliminates the possibility of expansion of the aerocele, whereas late discontinuation allows resorption of the aerocele. The determining factor is the nitrous oxide content within the aerocele at the time of complete dural closure. This concentration has never been documented. The lack of consensus suggests that this concentration may be variable, and therefore no conclusive statement can be made.

Indeed, a recent clinical study comparing two groups of patients emerging from craniotomy with or without discontinuation of nitrous oxide at the time of dural closure found no significant difference in ICP between the two groups (35). Omission of nitrous oxide in the first place would obviate such debate. It should be mentioned that the practice of administering nitrous oxide after complete dural closure to reduce the inhaled or intravenous anesthetic requirement should be condemned, since it can definitely lead to expansion of the aerocele. The benefit from such practice is minimal; early awakening can also be achieved with careful titration of a low-solubility inhaled agent, such as isoflurane. When desflurane, with a blood-gas solubility lower than that of nitrous oxide, becomes readily available, even this marginal benefit will become nonexistent.

**Intraoperative Monitoring of Evoked Responses**

Nitrous oxide depresses the amplitude of somatosensory evoked potentials (SSEPs), whether it is added on to a narcotic/muscle relaxant (36) or to an inhalation anesthetic (37,38). Moreover, in a clinical study, its depressant effect on median nerve SEP cortical amplitude was found to exceed that of an equipotent dose of isoflurane (Lam et al., unpublished data). Thus, in neurosurgical procedures where SEP monitoring is contemplated, omission of nitrous oxide is preferred.

**RISK-BENEFIT ANALYSIS**

We have clearly established that if an inhaled anesthetic is used, there is virtually no advantage with nitrous oxide. What about its use in a narcotic relaxant–based technique? While it is true that for this purpose nitrous oxide does not cause cerebral vasodilation, this technique is not universally applicable, and blood pressure may be difficult to control. Moreover, in patients who require 50% inspired oxygen or more, the potential of awareness is ever present. To our knowledge, there are no outcome studies to substantiate the contention that nitrous oxide can contribute to poor outcome in clinical use. Nevertheless, considering the many possible risks and the minimal benefits that can accrue from
the use of nitrous oxide, it may be prudent to omit it in the practice of neuroanesthesia.

CONCLUSION

We believe it is time to reevaluate the use of nitrous oxide in neuroanesthesia. Clear indications should exist before it becomes part of the anesthetic regimen. Patients for whom it might be used include those without significant neurologic disease, e.g., a patient with epilepsy being treated with subdural electrode placement; those having extracranial surgery, e.g., carotid endarterectomy; those with very high intracranial compliance, e.g., cerebral atrophy or absent bone flap; those who have normal ICP and no evidence of ischemia, e.g., Grade I intracranial aneurysm; and those with no cerebral metabolic activity, e.g., a patient placed in therapeutic barbiturate coma (use of nitrous oxide would nevertheless be superfluous in this case). It is clear that the use of nitrous oxide in neuroanesthesia must now be considered a conscious choice; it must not be used merely by default.

REFERENCES

23. Lam AM, See TA, Cooper JO, Bashenholm KL, Mathisen TL. Nitrous oxide is a more potent cerebrovasodilator than isoflurane in humans. Anesthesiology 1991;75:473.
30. Milde LN. The hypoxic mouse model for screening cerebral
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32. Black S, Ockert DB, Oliver WC, Cucchiara RF. Outcome following posterior fossa craniectomy in patients in the sitting or horizontal positions. Anesthesiology 1988;69:49-56.


