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Nitrous oxide: an ageing gentleman

[Editorial]

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In 1994 *Acta Anaesthesiologica Scandinavica* celebrated the 150th anniversary for the clinical use of nitrous oxide with a series of articles covering all important aspects related to this anaesthetic agent (1, 2). These were the benefits and adverse effects of clinical use of nitrous oxide, as well as the possible harm of nitrous oxide for operating room staff, and last, but not least, the environmental aspects of medical use of nitrous oxide. Since then the use of the old-timer has come under attack again (3, 4). In this editorial we will discuss briefly the status of nitrous oxide, and then focus on any new information that requires that the clinical use of nitrous oxide should be altered.

Clinical aspects

The benefits and adverse effects of nitrous oxide in patients are well known and easily controllable. Nitrous oxide has a unique safety record in the history of anaesthesia. It had been used more than a hundred years before the first serious side effect, bone marrow depression, was provoked by long-term sedation in the 1950s (5). Nitrous oxide can be administered in a very controllable manner due to its favourable kinetics (6), and a great advantage is that it can be monitored continuously on-line, which eliminates the need for calculation/estimation of pseudo drug concentrations, as done for some intravenous agents. The kinetics of intravenous anaesthetics are also significantly influenced by kidney and liver function, which makes it even more difficult to predict the concentration resulting from a given infusion rate.

Nitrous oxide is potent enough to provide analgesia corresponding to 10-15 mg of morphine without the cost of respiratory depression. It is also a good sedative agent. We know all about diffusion hypoxia and that volume or pressure of "closed" gas spaces, such as the bowel, gas emboli or the middle ear, may increase under nitrous oxide

administration. Nitrous oxide has also been considered to induce postoperative nausea and vomiting (PONV). We know that there are some relative or absolute contraindications related to neuro- and cardiac anaesthesia (7, 8). A significant change in clinical practice from short-term anaesthesia to long-term sedation disclosed irreversible toxic effect of nitrous oxide on bone marrow (9). However, this is easily preventable, also in patients at risk, by limiting the duration of nitrous oxide administration.

Have there been any significant new observations since 1994? Very few, indeed! PONV is probably the most common side effect of anaesthesia. To what extent PONV is caused by N_2O has long been debated and there is still no conclusive study in this field. In one study published in 1996 (10), it was found that omission of nitrous oxide reduced the risk for PONV. However, according to another 1996 meta-analysis (11), omitting nitrous oxide in patients with an anamnestically high risk of PONV could be justified, but it was also stated that "omitting N_2O had no effect on complete control of emesis or nausea". Finally, a significant increase in risk of awareness may follow omission of nitrous oxide; thus, any benefit on PONV may be compromised by the risk of a "major harm" caused by awareness.

Basically, no significant knowledge justifying a change in the clinical use of nitrous oxide has emerged when it comes to the drug itself. However, we have new technology that may be useful in monitoring anaesthetic depth, and we have the new opioid remifentanil with one unique characteristic: a duration of action similar to that of nitrous oxide, albeit without nitrous oxide's lack of respiratory depression. The problem with these is that their overall benefits when it comes to patient safety are unknown, and, for instance, completely replacing nitrous oxide with remifentanil infusions may put the patient at risk unless controlled studies prove that the new drug is equal or better than nitrous oxide when it comes to real outcomes such as morbidity and mortality.

Occupational aspects

In 1997 Boivin published a meta-analysis of 19 epidemiological studies from the "pre-scavenging era" on the risk of spontaneous abortion in women occupationally exposed to anaesthetic gases (12). The overall relative risk in hospital workers was 1.3 (95% confidence interval 1.21-1.41), in accordance with previous estimates (13). Like previous reviewers, Boivin emphasized that the associations found may be due as much to biases from confounding variables and response rates as to really harmful effects of anaesthetic gases, but that, on the other hand, a real risk may be present. It has been suggested (14) that an increase in spontaneous abortion among women working with anaesthesia might be due to the emotional and physical rigours of the profession, and not to exposure to the gases, but information on this is still lacking. In Swedish midwives, Axelsson et al. (15) observed that night work and high work load increased the risk of spontaneous abortion, whereas use of nitrous oxide (in >50% of the deliveries) did not. In a study of spontaneous abortion in female dental assistants, Rowland et al. (16) observed an increased risk among women who worked in clinics not using scavenging equipment, but not among those using scavenging equipment.

"Waste anesthetic gases: What's New? - Much Ado About Nothing". This was how, at the 1999 annual meeting of The American Society of Anesthesiologists, Diana B. McGregor reported on the work of the "ASA Task Force on Trace Anesthetic Gases" of the ASA Committee on Occupational Health of Operating Room Personnel (17). The report concluded that "Studies have not shown an association between trace levels of waste anesthetic gases found in scavenged anesthetizing locations and adverse health effects to personnel", and recommended that "Waste anesthetic gases should be scavenged" and "Appropriate work practices should be used to minimize exposure to waste anesthetic gases". Several recent studies in various clinical settings have demonstrated that by doing so, it is in fact possible to maintain very low concentrations of anaesthetic gases in the anaesthetists' breathing zones (18-21); in other words it is relatively easy to employ nitrous oxide in a manner that eliminates possible harm to personnel.

Environmental aspects

To the best of our knowledge no significant new information related to anaesthetic use of nitrous oxide and the environment has been published. What is then the significance of anaesthetic nitrous oxide for the greenhouse effect? Sherman and Cullen (22) estimated in 1988 that the world total anaesthetic nitrous oxide emissions were $0.5\text{-}1.0\times10^{9}$ mol/year, corresponding to 22-44 000 metric tons. This is considered to be less than 1% of the total amount of nitrous oxide conveyed to the atmosphere. As nitrous oxide only accounts for 5% of the greenhouse effect, the anaesthetic contribution to the greenhouse problem will be only about 0.05%. The anaesthetic fraction may be even lower today (estimated to 3% of total manmade nitrous oxide emissions by Ratcliffe et al. in 1992 (23)), as low-flow techniques are more widely used. Regardless, the medical use of nitrous oxide will have little impact on the global environment, and is probably too small to justify the replacement of nitrous oxide with drugs that have not proven to be better or safer than nitrous oxide.

Conclusion

Since the 150th anniversary of nitrous oxide in 1994 no new information has appeared that justifies a significant change in the place of nitrous oxide in clinical anaesthesia. The positive effects of rational anaesthetic use of nitrous oxide far outweigh the adverse effects, also in the occupational and global perspectives. However, in order to reduce occupational exposure and atmospheric emission, nitrous oxide should be limited to low-flow anaesthetic techniques.

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