Nitrous oxide

Introduction

Although an integral part of anaesthesia history since 1844, nitrous oxide (N₂O) is far from ready to be consigned to the history books. Current evidence supports the fact that this is a safe and versatile anaesthetic agent.

Mechanism of action

Nitrous oxide has both sedative/amnestic and analgesic properties. These are mechanistically clearly differentiated, but functionally contribute to its versatility and unique effect profile. Central to its mechanism of action is inhibition of the NMDA-receptor. It also has effects on AMPA, kainite, nicotinic and nociceptin receptors, as well as two-pore domain potassium channels. It therefore shares more similarities with ketamine and xenon than the predominantly GABAergic agents, such as propofol, barbiturates and volatiles.

Clinical applications and benefits

Clinically, nitrous oxide has applications ranging from procedural sedation/analgesia to an adjunctive amnestic/analgesic during general anaesthesia. Its use allows a reduction in the primary anaesthetic agent, reducing potentially harmful intraoperative hypotension, especially in the elderly and infirm. It may also help maintain vasoreactivity in shock states, reduces awareness, has salutary effects on induction and emergence, and is anaesthetic sparing and cost effective. In addition, it is readily available and easy to use.

Critique of claimed adverse effects

However, nitrous oxide is not a simple, inert carrier gas and must be used with the skill, knowledge and due diligence required for the safe use of any powerful drug. Although both novice and experienced users alike have become fearful of a litany of claimed side-effects, scientific literature dispels most of these concerns.

Nitrous oxide inhibits vitamin B₁₂ and thereby methionine synthase, inhibiting folate metabolism and methylation reactions. It has been claimed that this is responsible for a range of adverse effects, ranging from haematological and immunological to neurological. The clinical significance of these effects has been grossly overplayed. This possibly stems from an era in which scientific reporting standards were lax, or simply from the psychology of new trainees being thrilled by the promise of nitrous oxide causing subacute combined degeneration of the cord. Current evidence confirms the safety of the use of nitrous oxide-based anaesthesia in this regard in all but a subset of patients with rare inborn errors of folate metabolism or vitamin B₁₂/folate deficiency. In addition, it appears that any deleterious effect of nitrous oxide on this metabolic pathway is offset by perioperative vitamin B₁₂/folate supplementation.

The effect of nitrous oxide on intracranial dynamics is complex and its use in neurologically-vulnerable patients, and in neurosurgery in particular, has been much debated. The literature suggests that, in this context, when used appropriately, the effects of N₂O are neutral at worst, and possibly even beneficial when other factors such as its haemodynamic stability are taken into account.

There are still some instances where conventional teaching holds true. Nitrous oxide should be avoided in patients with air-filled spaces, such as a pneumothorax, lung bullae, or a pneumocephalus;
and should be used with caution in patients with pulmonary hypertension, although the increase in pulmonary artery pressures is mild.

The ENIGMA trial raised concerns regarding possible adverse postoperative effects, for example on wound healing, but these were rather dubious secondary analyses in the context of a poorly conducted trial and must be interpreted with great caution. The ENIGMA II trial is currently recruiting and is focusing on the influence of nitrous oxide on death and major adverse cardiac events in patients at high cardiac risk. The results, when available in 2012 or beyond, will add to our knowledge of the effects of nitrous oxide on this high-risk, but specific group.

Conclusion

Despite this being arguably the best studied of our current anaesthetic agents, there remains considerably more to learn about this venerable gentleman of the anaesthetic world and this offers many research opportunities. Readers wishing to ascertain more about this agent are referred to the series of articles listed below. Nitrous oxide remains a useful tool in the armamentarium of the modern anaesthetist.

Bibliography