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Nitrous oxide does not produce a clinically important sparing effect during closed-loop delivered propofol–remifentanil anaesthesia guided by the bispectral index: a randomized multicentre study†‡

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Editor's key points

- The hypothesis that N_2O administration decreases the amount of propofol and remifentanil required to maintain a specific bispectral index (BIS) was tested.
- N_2O did not reduce propofol and remifentanil requirements in men during BIS-guided anaesthesia.
- N_2O has a non-clinically significant sparing effect on propofol and remifentanil in women.

Background. Nitrous oxide (N_2O) offers both hypnotic and analgesic characteristics. We therefore tested the hypothesis that N_2O administration decreases the amount of propofol and remifentanil given by a closed-loop automated controller to maintain a similar bispectral index (BIS).

Methods. In a randomized multicentre double-blind study, patients undergoing elective surgery were randomly assigned to breathe 60% inspired N_2O (N_2O group) or 40% oxygen (AIR group). Anaesthesia depth was evaluated by the proportion of time where BIS was within the range of 40–60 (BIS_{40-60}). The primary outcomes were propofol and remifentanil consumption, with reductions of 20% in either being considered clinically important.

Results. A total of 302 patients were randomized to the N_2O group and 299 to the AIR group. At similar BIS_{40-60} [79 (67–86)% *vs* 76 (65–85)%], N_2O slightly decreased propofol consumption [4.5 (3.7–5.5) *vs* 4.8 (4.0–5.9) mg kg^{-1} h^{-1}, $P=0.032$], but not remifentanil consumption [0.17 (0.12–0.23) *vs* 0.18 (0.14–0.24) μg kg^{-1} min^{-1}]. For the subgroups of men, at similar BIS_{40-60} [80 (72–88)% *vs* 80 (70–87)%], propofol [4.2 (3.4–5.3) *vs* 4.4 (3.6–5.4) mg kg^{-1} h^{-1}] and remifentanil [0.19 (0.13–0.25) *vs* 0.18 (0.15–0.23) μg kg^{-1} min^{-1}] consumptions were similar in the N_2O *vs* AIR group, respectively. For the subgroups of women, at similar BIS_{40-60} [76 (64–84)% *vs* 72 (62–82)%], propofol [4.7 (4.0–5.8) *vs* 5.3 (4.5–6.6) mg kg^{-1} h^{-1}, $P=0.004$] and remifentanil [0.18 (0.13–0.25) *vs* 0.20 (0.15–0.27) μg kg^{-1} min^{-1}, $P=0.029$] consumptions decreased with the co-administration of N_2O.

Conclusions. With automated drug administration titrated to comparable BIS, N_2O only slightly reduced propofol consumption and did not reduce remifentanil consumption. There was a minor gender dependence, but not by a clinically important amount.

Clinical trial registration. This study was registered at ClinicalTrials.gov, number NCT00547209.

Keywords: bispectral index monitor; closed-loop; nitrous oxide; propofol; remifentanil

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Nitrous oxide (N_2O) is a reliable short-acting, well-tolerated, and inexpensive anaesthetic gas. N_2O is not potent enough to be used as a sole agent, but is commonly used as an adjunct to balance volatile or i.v. general anaesthesia; it has a hypnotic action mediated by the *N*-methyl-D-aspartate subtype of glutamate receptors. Moreover, N_2O has an analgesic effect because it acts as a supraspinal opioid agonist in the periaqueductal grey matter and activates noradrenergic neurones in the locus coeruleus which project to α_1 and α_2 adrenoreceptors within the dorsal horn of the spinal cord.[1]

The most obvious advantage of adding N_2O to an anaesthetic regimen is a reduction in hypnotic and opioid consumption. For example, the use of N_2O reduced propofol induction dose by 44%,[2] reduced the propofol concentration required to avoid a response to a surgical stimuli by 30%,[3] and reduced propofol consumption during general anaesthesia maintenance by 15–25%.[4 5] Other studies report that adding N_2O produces a clinical benefit similar to a remifentanil infusion of 0.085 $\mu g\,kg^{-1}\,min^{-1}$ during desflurane anaesthesia guided by the BIS[6] or 0.17 $\mu g\,kg^{-1}\,min^{-1}$ during isoflurane inhalation.[7] A limitation of these studies is that propofol administration was adjusted manually by unblinded investigators in accordance with haemodynamic and clinical criteria.[3–7]

An alternative to haemodynamic and clinical criteria for drug administration during general anaesthesia is titration to electrocortical activity measured by the bispectral index (BIS) monitor (Covidien, Dublin, Ireland).[8] There are reports showing that, in the absence of noxious stimuli, BIS is not affected by N_2O inhalation in volunteers[9] or patients.[10–13] Moreover, several studies showed a poor relationship between clinical sedation scales and the BIS during sedation of volunteers[14] and adult[15 16] or paediatric[17] patients. However, N_2O as an anaesthetic adjuvant modifies electrocortical activation during surgery[18] and the response to noxious stimuli such as laryngoscopy during volatile anaesthesia.[19] Furthermore, electrocortical activity is a function of anaesthetic depth during surgery[20] and in response to noxious stimuli.[19 21 22] There is only slight evidence that N_2O does not affect BIS values during maintenance of general anaesthesia. Studies related to the influence of N_2O on BIS values were performed on volunteers[9] during induction[10] and the number of patients studied during surgery was limited.[11–13] The extent to which N_2O spares i.v. anaesthetics or modifies BIS values during maintenance of general anaesthesia thus remains unclear.

We have developed a closed-loop controller allowing automated titration of propofol and remifentanil solely guided by the BIS. An automated controller of drug delivery is an unbiased assessment of anaesthetic requirements when an adjunct is used.[23] We used this objective system in a randomized controlled multicentre trial to determine the sparing effect of 60% N_2O on propofol or remifentanil consumption during maintenance of general anaesthesia. Specifically, we tested the primary hypothesis that N_2O administration decreases the amount of propofol and remifentanil given by our closed-loop controller to maintain a similar BIS index. Our secondary hypothesis, added at the request of the German Ethics Committee, was that there is an interaction between gender and the drug-sparing effect of N_2O.

Methods

Study population

Our prospective multicentre randomized double-blind clinical trial was approved by the Ethics Committees of the participating French (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Hôpital A. Paré, Boulogne Billancourt, France), Belgian (Comité d'Ethique hospitalo-facultaire Erasme-ULB, Brussels, Belgium), and German universities (Ethikkommission der Charité-Universitätsmedizin, Berlin, Germany). It was also approved by the French national regulatory office (Agence Française de Sécurité Sanitaire des Produits de Santé). This study was registered at ClinicalTrials.gov, number NCT00547209.

Written informed consent was obtained during the preoperative visit performed by the investigators. Patients undergoing elective surgery (vascular, general, orthopaedic, gynaecological, urological, otolaryngological) requiring general anaesthesia without combined regional/general anaesthesia expected to last more than 60 min and requiring tracheal intubation were enrolled at 10 university, general, or private hospitals: Hôpital Foch (Suresnes), Centre Hospitalier Victor Dupouy (Argenteuil), Centre Hospitalo-Universitaire of Besançon and Tours, Clinique Saint Augustin (Bordeaux), La Baie des Citrons (Nouméa) New Caledonia, ULB-Erasme (Brussels) Belgium, and Charité-Universitaetsmedizin Berlin (Berlin) Germany. Patients were aged 18–80 yr and ASA physical status I–IV. Exclusion criteria included cranial procedures, psychiatric illness, supraspinal neurological disorders, and patients equipped with a pacemaker. Moreover, patients undergoing thoracic or cardiac surgery were excluded due to possible occurrence of hypoxaemia or gas embolism, respectively.

Procedures

All patients received a propofol and remifentanil infusion controlled by our automated closed-loop system during induction and maintenance of general anaesthesia.[8] All investigators received a full day of training in the use of the automated controller at the Hôpital Foch, Suresnes, France.

On arrival in the theatre, a dedicated i.v. cannula was inserted, routine monitoring commenced including temperature. Neuromuscular function at the adductor pollicis was monitored after loss of consciousness. A BIS electrode (Zipprep, Covidien) was positioned on the patient's forehead and connected to either an A-2000 XP (version 3.11) BIS monitor or a BIS M-Module (GE-Healthcare S/5™, Helsinki, Finland).

The controller[8] was implemented using Infusion Toolbox 95® version 4.11 software[24] which served as a platform: (i) to calculate effect-site concentrations of propofol and remifentanil using the pharmacokinetic population of Schnider and colleagues[25] and Minto and colleagues[26] for propofol and remifentanil, respectively; (ii) to display these calculated effect-site concentration estimates in real time; (iii) to provide a user