Does nitrous oxide antagonize sevoflurane-induced hypnosis?

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Summary
We have studied 64 ASA I and II patients (aged 20–60 yr) to determine if nitrous oxide affects sevoflurane requirements for achieving 50% probability of no movement in response to verbal commands (MACawake). Patients were allocated randomly to one of four nitrous oxide concentration groups (0, 20, 40 and 60 vol.%). Patients in each group received sevoflurane at two different end-tidal concentrations according to a predetermined randomization table. After steady state sevoflurane and nitrous oxide concentrations had been maintained for at least 15 min, patients were assessed as being awake or asleep. The MACawake for sevoflurane was 0.63% and this was reduced significantly in a non-linear manner by increasing nitrous oxide concentration. A 50% reduction in MACawake was produced by a nitrous oxide concentration of 45%. The reduction in MACawake by nitrous oxide was non-linear; the interaction coefficient between nitrous oxide and sevoflurane being significantly less than zero (P = 0.0238), indicating that the reduction in MACawake by nitrous oxide was smaller than would be expected from simple additivity and that nitrous oxide antagonized the effects of sevoflurane in preventing response to verbal commands. (Br. J. Anaesth. 1997; 79: 465–468).

Key words
Anaesthetics volatile, sevoflurane. Anaesthetics gases, nitrous oxide. Potency, anaesthetic, MAC.

End-tidal anaesthetic concentration at the first response to command and the concentration just preventing the response is defined as MACawake.¹ In some studies,²,³ MACawake values for isoflurane and sevoflurane were reported to be approximately one-third of MAC values, being different from those of halothane.⁴ These MACawake values were determined when anaesthetics were administered in combination and no other inhaled anaesthetic was used. Nitrous oxide is frequently combined with inhalation anaesthetics and its MACawake value has been reported to be 0.64 MAC.⁵ The drug interaction between nitrous oxide and volatile anaesthetic on awakening concentration is not known well, while nitrous oxide reduced halothane, enfurane, isoflurane and sevoflurane MAC values in a linear manner when added to each respective anaesthetic.⁶⁻⁹ The purpose of this study was to determine the drug interaction between nitrous oxide and sevoflurane with regard to MACawake values. We determined which, if any, of three different nitrous oxide concentrations (20, 40 and 60 vol.%) changed the MACawake value in adult patients. Using the sevoflurane MACawake determinations in the presence of nitrous oxide, the relationship between nitrous oxide and these volatile anaesthetic MACawake fractions was determined.

Patients and methods
After obtaining approval from the departmental Ethics Committee and informed consent, we studied 64 patients of both sexes, ASA I and II, aged 20–60 yr, who were undergoing elective surgery. Exclusion criteria were a history of cardiac, pulmonary or renal disease; history of hearing disturbance or ear disease; history of oesophageal reflux or hiatus hernia; drug or alcohol abuse, or significant obesity (body mass index > 30); and contraindications to inhalation induction. Patients were fasted for at least 8 h before surgery, were monitored in a routine manner and received no premedication.

The 64 patients were allocated randomly to one of four groups. Patients in group 1 received no nitrous oxide, while those in groups 2, 3 and 4 received end-tidal concentrations of 20, 40 and 60 vol.%, respectively. End-tidal sevoflurane concentrations were chosen to provide both adequate and inadequate anaesthesia at each nitrous oxide concentration, and were based on data from our previous MACawake studies,²,³ and the study of Dwyer and colleagues.⁵ All patients received sevoflurane at two different concentrations. The inspired concentration of sevoflurane was adjusted to maintain the measured end-tidal concentration constant at the value predetermined according to a randomization scheme (fig. 1).

After an anaesthesia face mask was placed on the face of patients using a head strap, we confirmed that air leak from the margin of the mask was minimal when positive or negative airway pressure was applied to the inside of the mask. The mandible was displaced upward gently with two hands to avoid the
upper airway obstruction that may occur in unconscious patients. All patients breathed through the mask connected to a semi-closed anaesthetic system. To prevent contamination of end-tidal samples with inspired gas, the deadspace was augmented at the sampling port. Gas was withdrawn continuously from the sampling port, located between the face mask and deadspace, at a rate of 200 ml min⁻¹.

Concentrations of nitrous oxide, carbon dioxide, sevoflurane and oxygen were measured continuously using an infrared anaesthetic gas analyser (Capnomac Ultima, Helsinki, Finland) which was calibrated before anaesthesia for each patient using a standard gas mixture. Patients breathed spontaneously, and ventilation was assisted if tidal volume was too small to provide adequate end-tidal sampling for measurement of anaesthetic concentration. Staff in the operating theatre were instructed to be quiet and not to physically stimulate the patient. Patients were instructed not to open their eyes, talk or move before a verbal command.

After steady state nitrous oxide and sevoflurane concentrations had been maintained for at least 15 min, patients were assessed as being awake or asleep by having their name called out in a normal tone and by being instructed to open their eyes. The patient’s response to the verbal command was recorded as positive or negative, with slight movement of the eyelids considered a negative response.

STATISTICAL ANALYSIS

The MACawake of sevoflurane and its reduction by nitrous oxide was evaluated using the following multiple independent variable logistic regression model:

\[ P(\text{no response}) = \frac{1}{1 + e^{-Z}} \]

where \( X_1 = \text{end-tidal sevoflurane concentration} \), \( X_2 = \text{end-tidal nitrous oxide concentration} \), \( \beta_0 = \text{regression intercept constant} \), \( \beta_1 = \text{coefficient for sevoflurane} \), \( \beta_2 = \text{coefficient for nitrous oxide and} \)

\( \beta_{12} = \text{coefficient for the product of the end-tidal sevoflurane and nitrous oxide concentrations (interaction coefficient). The likelihood ratio test was applied to determine the independent variables to be removed from the model. The MACawake for a given end-tidal nitrous oxide concentration was determined by setting the probability of no response to 0.5 and solving for sevoflurane concentration as a function of end-tidal nitrous oxide concentration as follows:} \]

\[ X_1 = \frac{-(\beta_0 + \beta_1 X_2)}{\beta_1 + \beta_{12} X_2} \]

(1)

The concentration of sevoflurane required to prevent response in 95% of patients (MACawake95) was also determined from each model by setting the probability of no movement to 0.95 and solving for sevoflurane concentration. The responses of patients to verbal command at each nitrous oxide concentration were subjected to probit analysis, in order to determine MACawake and its 95% confidence limits. These statistical analysis was performed using SPSS software (SPSS, Inc., Chicago, IL, USA).

Results

Although a total of 64 patients were enrolled in the study, we could not assess eight responses in six patients because of pronounced excitatory phenomena and vomiting. Thus the results for 120 assessments in 58 patients are presented. This group included 27 men and 31 women with a mean age of
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47.5 yr (range 20–60 yr) and a mean body weight of 54.2 kg (40–81 kg).

The logistic model was fitted to 120 data sets of observed responses, end-tidal sevoflurane concentrations and end-tidal nitrous oxide concentrations. Coefficient estimates for the logistic regression model are presented in table 1. None of the three independent variables was removed from the model based on the likelihood ratio test. The interaction coefficient \( \beta_{1.2} \) was significantly less than zero (\( P=0.0238 \)). The MAC\textsubscript{awake} and MAC\textsubscript{awake95} of sevoflurane in the absence of nitrous oxide were 0.63 and 0.93\%, respectively. The probability of no movement in response to verbal command \( vs \) end-tidal sevoflurane concentration in the absence or presence of nitrous oxide is presented in figure 2. Reduction in the MAC\textsubscript{awake} of sevoflurane by nitrous oxide is presented in figure 3. MAC\textsubscript{awake} of nitrous oxide calculated as nitrous oxide concentration which would reduce MAC\textsubscript{awake} of sevoflurane to 0\% was 66\%. A 50\% reduction in MAC\textsubscript{awake} of sevoflurane was produced by a nitrous oxide concentration of 45\%.

Discussion

The effect of nitrous oxide on the MAC\textsubscript{awake} value of sevoflurane has not been documented previously. Nitrous oxide, however, has been shown to reduce the MAC\textsubscript{awake} for isoflurane in a dose-dependent manner, with the MAC\textsubscript{awake} reported as 67\%. Thus 20, 40 and 60\% nitrous oxide should correspond to MAC\textsubscript{awake} fractions of 0.3, 0.6 and 0.9, respectively. Chortkoff, Bennett and Eger examined the ED\textsubscript{50} for suppression of learning and ability to respond appropriately to verbal commands using the combination of isoflurane with 40\% nitrous oxide. For both ED\textsubscript{50} values, a slightly higher value was reported than predicted by the assumption of additivity. This indicates that the two anesthetics are antagonistic with regard to this hypnotic effect. We found that nitrous oxide reduced the MAC\textsubscript{awake} of sevoflurane in a dose-related manner. The interaction coefficient between sevoflurane and nitrous oxide was significantly less than zero, indicating that nitrous oxide had a non-linear effect on reducing sevoflurane requirements and that sevoflurane requirements were greater than would be expected from simple additivity.

The results of this study showed that 33\% nitrous oxide would reduce the MAC\textsubscript{awake} of sevoflurane to 68.1\%, and that the sevoflurane MAC\textsubscript{awake} value is 18\% greater than the value expected from simple additivity of the two agents. These findings correspond to those reported with isoflurane. Nitrous oxide appears to antagonize the effect of sevoflurane to prevent responses to verbal commands. Nitrous oxide has some characteristics of a central nervous system stimulant. It fails to supplement isoflurane-induced depression of cerebral metabolic rate and may antagonize the electroencephalographic effects of volatile agents. A study by Yli-Hankala and colleagues showed that the addition of nitrous oxide to isoflurane decreased the frequency and duration of isoflurane-induced burst suppressions in the electroencephalogram in an apparently non-additive interaction. Although we did not monitor the EEG in this study, this activating mechanism may explain our findings.

We reported that nitrous oxide produced a non-linear reduction in thiopentone requirements for preventing response to verbal commands. The findings of this study agree with those of our previous study. The observed deviation from linearity of the interaction between nitrous oxide and sevoflurane was rather small, so that clinical relevance may be questioned.

It has been shown that the interaction between nitrous oxide and volatile agents such as halothane, enflurane or isoflurane is additive in the sense that the linear combination of two MAC fractions of nitrous oxide and the volatile agent equating to 1.0 MAC also prevents response to skin incision in 50\% of patients. We reported that the MAC of sevoflurane was also reduced by nitrous oxide in an additive manner. Recent studies by Cole and colleagues claimed to have shown a non-linear contribution to the interaction of nitrous oxide with halothane, enflurane and isoflurane in rats. Gauman, Mustaki and Tassonyi demonstrated that ratios of MAC\textsubscript{awake} to MAC differed for the anesthetics halothane, enflurane and isoflurane in humans. Their findings do not support a unitary mechanism of anaesthetic action. Instead, response to noxious stimuli such as skin incision and response to verbal command seem to be depressed by different mechanisms. Although nitrous oxide has an additive effect with these volatile agents in preventing movement in response to surgical incision, this may not translate to additivity for suppression of responsiveness to a verbal command.

In our study we demonstrated that nitrous oxide had a non-linear effect on reducing sevoflurane, and the shape of the reduction curves in MAC\textsubscript{awake} by nitrous oxide differed from that in MAC. In rats, acute decerebration (removal of part of the central nervous system—cortex and thalamus) did not affect the concentration of isoflurane required to prevent...
movement in response to tail-clamping.²⁰ In goats with the brain preferentially anaesthetized, higher anaesthetic concentrations were required to prevent movement in response to a clamp; this supports the importance of subcortical structures, such as the spinal cord, in the generation of purposeful movement in response to a painful stimulus under general anaesthesia.²¹ These observations suggest that motor responses in response to a noxious stimulus may be mediated primarily by subcortical structures, including the spinal cord, at least in lower animals. In contrast, purposeful responsiveness to a verbal command apparently requires intact cortex function.

Contrast, purposeful responsiveness to a verbal command vs no response to noxious stimulus may be associated with different sites of anaesthetic action.²² Therefore, the type and degree of interaction between any two anaesthetics may depend on the clinical end-point used.

We calculated the MAC<sub>awake</sub> of nitrous oxide as the concentration of nitrous oxide which would reduce the MAC<sub>awake</sub> of sevoflurane to 0% by extrapolating equation (1). The predicted MAC<sub>awake</sub> value (66%) was almost equal to that determined by Dwyer and colleagues.³ Nitrous oxide alone did not reliably prevent conscious awareness during anaesthesia. The probability of no movement in response to verbal command vs end-tidal sevoflurane concentration in the presence of 60% nitrous oxide revealed that nitrous oxide would prevent 20% of patients from responding to verbal commands at this nitrous oxide concentration in the absence of sevoflurane (fig. 2). Dwyer and colleagues reported that the percentage of volunteers not responding purposefully to verbal commands at 0.6 MAC of nitrous oxide was 20%.³

In conclusion, we have studied the interaction between nitrous oxide and sevoflurane on loss of consciousness. The MAC<sub>awake</sub> of sevoflurane was 0.63% and this was reduced significantly in a non-linear manner by increasing nitrous oxide concentration. A 50% reduction in the MAC<sub>awake</sub> value was produced by a nitrous oxide concentration of 45%. The reduction in MAC<sub>awake</sub> by nitrous oxide was less than would be expected from simple additivity at low concentrations.

References

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