Large volume N2O uptake alone does not explain the second gas effect of N2O on sevoflurane during constant inspired ventilation

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Background. The second gas effect (SGE) is considered to be significant only during periods of large volume N2O uptake (VN2O); however, the SGE of small VN2O has not been studied. We hypothesized that the SGE of N2O on sevoflurane would become less pronounced when sevoflurane administration is started 60 min after the start of N2O administration when VN2O has decreased to 1/24 1.25 ml min/C0 and that the kinetics of sevoflurane under these circumstances would become indistinguishable from those when sevoflurane is administered in O2.

Methods. Seventy-two physical status ASA I–II patients were randomly assigned to one of six groups (n=12 each). In the first four groups, sevoflurane (1.8% vaporizer setting) administration was started 0, 2, 5 and 60 min after starting 2 litre min/C0 O2 and 4 litre min/C0 N2O, respectively. In the last two groups, sevoflurane (1.8 or 3.6% vaporizer setting) was administered in 6 litre min/C0 O2. The ratios of the alveolar fraction of sevoflurane (FA) over the inspired fraction (FI), or FA/FI, were compared between the groups.

Results. Sevoflurane FA/FI was larger in the N2O groups than in the O2 groups, and it was identical in all four N2O groups.

Conclusions. We confirmed the existence of a SGE of N2O. Surprisingly, when using an FA of 65% N2O, the magnitude of the SGE was the same with large or small VN2O. The classical model and the graphical representation of the SGE alone should not be used to explain the magnitude of the SGE. We speculate that changes in ventilation/perfusion inhomogeneity in the lungs during general anesthesia result in a SGE at levels of VN2O previously considered by most to be too small to exert a SGE.

Br J Anaesth 2006; 96: 391–5

Keywords: anaesthetics gases, nitrous oxide; anaesthetics volatile, sevoflurane; pharmacokinetics, uptake

Accepted for publication: December 20, 2005
sevoflurane administration would be started at the period of largest VN2O (2 min after circuit and alveolar wash-in); (ii) the SGE would become very small when sevoflurane administration would be started 60 min after the start of N2O administration when VN2O has decreased to ~125 ml min\(^{-1}\); and (iii) the FA/Fi of sevoflurane started 60 min after the start of N2O administration would not differ from that during administration of sevoflurane in O\(_2\) because the effect of small VN2O would not exert a significant SGE according to the classical model of the SGE.

Methods

The patients enrolled in this study were recruited in the Department of Anesthesiology, Intensive Care and Pain Therapy, Onze Lieve Vrouweziekenhuis, Aalst, Belgium. After obtaining IRB approval and informed consent, 72 ASA physical status I–II adult patients presenting for gynecologic, urologic, or plastic surgery were enrolled. Patients undergoing laparoscopic surgery or morbidly obese patients (BMI>35) were excluded. Patients were randomly assigned to one of six groups (n=12 each) depending on management of O\(_2\) and N2O fresh gas flows (FGF) and the delivered sevoflurane concentration. The patients’ age, height and weight were recorded. Premedication was titrated according to the patients’ needs. After preoxygenation (O\(_2\) FGF 8 litre min\(^{-1}\)) for 3 min, anaesthesia was induced with sufentanil (0.15 \(\mu g\) kg\(^{-1}\)) and propofol (3 \(mg\) kg\(^{-1}\)) and rocuronium was administered to facilitate tracheal intubation (0.7 \(mg\) kg\(^{-1}\)). Controlled mechanical ventilation (CMV) was started (ADU anaesthesia machine, Datex-Ohmeda, Helsinki, Finland) with a fixed inspired tidal volume (500 ml) and ventilatory frequency (10 min\(^{-1}\)) (constant inspired CMV). In the first four groups, sevoflurane (1.8\% vaporizer setting) administration was started 0, 2, 5 and 60 min after starting 2 litre min\(^{-1}\) O\(_2\) and 4 litre min\(^{-1}\) N2O (groups N2O 0 min, N2O 2 min, N2O 5 min and N2O 60 min, respectively). To ensure adequate anaesthesia in the N2O 60 min group where sevoflurane was started 60 min after tracheal intubation, anaesthesia was supplemented with a propofol infusion until sevoflurane was administered. In the last two groups, sevoflurane administration was started after the start of CMV with a 1.8 or 3.6\% vaporizer setting (1.8\% sevoflurane in O\(_2\) and 3.6\% sevoflurane in O\(_2\) groups, respectively) in 6 litre min\(^{-1}\) N2O (groups N2O 0 min, N2O 2 min, N2O 5 min and N2O 60 min, respectively). To ensure adequate anaesthesia in the N2O 60 min group where sevoflurane was started 60 min after tracheal intubation, anaesthesia was supplemented with a propofol infusion until sevoflurane was administered. Light anaesthesia was defined as tachycardia (heart rate (HR)>125\% of HR before anaesthesia induction or HR>110 beats min\(^{-1}\)) or hypertension (mean arterial pressure (MAP)>125\% of MAP before anaesthesia induction or MAP>100 mm Hg). Hypotension (MAP<75\% of MAP before anaesthesia induction or MAP<60 mm Hg) and bradycardia (HR<50 beats min\(^{-1}\)) were treated with ephedrine (5 mg) or atropine (0.5 mg), respectively.

All data were collected using a single ADU anaesthesia workstation with a single vaporizing (Aladin\(^{8}\)) cassette in the same operating room with the same agent analyser. The Datex-Ohmeda Compact Block was used, a patented part of the circle system containing inspiratory and expiratory valves, FGF connection and a small disposable canister containing soda lime. Because the volume of this circle system is only 3.4 litre, the wash-in time constant of the system (circle system+functional residual capacity of 2.0 litre) is <1 min when using a FGF of 6 litre min\(^{-1}\). By electronically compensating for compression volume and circuit compliance and by using FGF compensation, the actual inspired tidal volume matches the set tidal volume. Inspired and expired gases were sampled between the tracheal tube and heat and moisture exchanger and analysed by a multi-gas analyser (Datex-Engstrom Compact Airway Module M-CAiOV, Datex-Engstrom, Helsinki, Finland; accuracy for sevoflurane ±0.2\%) that was calibrated each morning. Gases sampled by the agent analyser were not redirected to the anaesthesia circuit. Inspired and expired gas concentrations were automatically downloaded in a spreadsheet every 10 s.

FA/Fi was directly calculated from the data every 10 s, and the area under the curve (AUC) (from 0 to 15 min) was calculated to compare the groups (SigmaPlot 2002 for Windows Version 8.02, SPSS Inc., Chicago, IL). This methodology is similar to that described by Taheri and Eger,\(^7\) except that they used the area above the curve (1−FA/Fi) and ignored the first minute because they assumed that this mainly represents lung wash-in. Patient characteristics, MAP, HR and the AUCs of FA/Fi in the six groups were compared using ANOVA followed by Student Newman–Keuls test. P<0.05 was considered statistically significant. Data are presented as mean (SD) and the incidence of observations unless indicated otherwise.

Results

Patient characteristics (Table 1) were identical in all groups. One patient in the 2 min N2O O\(_2\) group was deleted because the hyperdynamic response after intranasal epinephrine injection led to an entirely different FA/Fi over time curve. The 1.8\% sevoflurane in O\(_2\) group needed more additional sufentanil boluses. MAP and HR (Table 2) were not different except for a lower HR at 0 min in the N2O 60 min group (P<0.05).

The sevoflurane FA/Fi patterns were similar in all the groups except between 0 and 4 min in the 1.8\% sevoflurane in O\(_2\) group. The sevoflurane FA/Fi was larger in the N2O groups than in the O\(_2\) groups, and was identical in all four N2O groups and in both O\(_2\) groups (Table 1 and Figs 1 and 2). Figure 1 shows only the mean data for clarity, and Figure 2 shows the results of only the N2O 5 min, N2O
60 min, and 3.6% sevoflurane in O₂ groups, with the 95% confidence intervals (± standard error of the mean×1.96).

**Discussion**

We found that N₂O clearly exerts a SGE on sevoflurane: \( F_A/F_I \) of sevoflurane was larger in the N₂O groups than in the O₂ groups. At first sight, these observations are compatible with the classical model of the SGE. According to this model, large amounts of VN₂O result in a concentrating effect and augmented inspired ventilation. These mechanisms have been didactically presented by a graphical ‘box’ approach, which also allows the calculation of the expected SGE. In our study, only the concentrating effect could have contributed to a SGE because CMV was used without any attempt at keeping the end-expired carbon
dioxide constant (‘constant inspired ventilation’). Augmented inspired ventilation can only occur during spontaneous ventilation (‘constant outflow’), because during CMV no additional gases can be drawn into the lungs during inspiration, and $V_{\text{N}_2\text{O}}$ will therefore cause a decrease in expired ventilation and consequently an increase in $F_a\text{CO}_2$. We now could calculate the expected magnitude of the SGE in, for example, the 5 min $\text{N}_2\text{O}$ group using the classical graphical representation. In this group $V_{\text{N}_2\text{O}}$ is very large at the moment sevoflurane is started and therefore would be expected to result in a large SGE. At the time the sevoflurane vaporizer is set at 1.8%, $V_{\text{N}_2\text{O}}$ is $\sim 450$ ml min$^{-1}$ according to the Severinghaus formula ($V_{\text{N}_2\text{O}}$ at an $F_A$ of 65% is $1000/\sqrt{t}$ ml min$^{-1}$, with $t =$ anesthesia duration). With a TV of 500 ml and a ventilatory frequency of 10, there is 45 ml uptake of $\text{N}_2\text{O}$ per breath. If FRC is 2000 ml, the FRC would be expected to be reduced by $\sim 2.25\%$. However, with the same $F_I$, we found that the $F_A/F_I$ of sevoflurane was 10 and 12% larger than in the 1.8% sevoflurane in $\text{O}_2$ and 3.6% sevoflurane in all the $\text{N}_2\text{O}$ groups (where sevoflurane was administered 0, 2, 5 and 60 min after the start of $\text{N}_2\text{O}$ administration). In addition, the $F_A/F_I$ in the 60 min $\text{N}_2\text{O}$ group was larger than that in the $\text{O}_2$ groups, indicating that small $V_{\text{N}_2\text{O}}$ ($\sim 125$ ml min$^{-1}$) still has a clearly measurable SGE. The demonstration of a SGE when $V_{\text{N}_2\text{O}}$ is small ($\sim 100$ ml min$^{-1}$) is a new finding. It is obvious that the classical model of the SGE fails to explain these two observations. We cannot exclude that with the use of spontaneous respiration (allowing augmented inspired ventilation) and a more precise determination method of the concentration of the gases using gas chromatography a difference could be demonstrated between the early and late $\text{N}_2\text{O}$ groups. Nevertheless, we showed a difference between the late $\text{N}_2\text{O}$ group (small $V_{\text{N}_2\text{O}}$) and the $\text{O}_2$ groups, indicating that even small $V_{\text{N}_2\text{O}}$ has a significant SGE.

If the classical model cannot explain our observations, are there alternative explanations? Nunn documented a SGE of $\text{N}_2\text{O}$ on $P_{\text{aCO}_2}$, but according to Peyton this went unnoticed by Nunn himself ‘because of the assumption that, at the expected rates of $V_{\text{N}_2\text{O}}$, this would be trivial’. When re-analysing Nunn’s data, Peyton found $P_{\text{aO}_2}$ in spontaneously

![Fig 2 Sevoflurane $F_A/F_I$ in the $\text{N}_2\text{O}$ 5 min, $\text{N}_2\text{O}$ 60 min, and 3.6% sevoflurane in $\text{O}_2$ groups. Mean values and 95% confidence interval are presented at 1 min intervals.]
The second gas effect of $N_2O$ on sevoflurane

breathing patients to be larger when using 30% $O_2$ with 70% $N_2O$ than with 70% $N_2$.\textsuperscript{10–12} Using a physiological model of gas exchange, Peyton calculated that in the presence of ventilation/perfusion ($V/Q$) inhomogeneity typically present during general anaesthesia, so-called ‘steady-state levels of $VN_2O$’ (100 ml min$^{-1}$) increase $PaO_2$ (10). This effect is opposite to absorption atelectasis, where alveolar collapse in lung units with very low $V/Q$ results in a decrease in $PaO_2$. The reduction in $PaO_2$ caused by absorption atelectasis is attenuated by nitrogen but worsened by $N_2O$ and the use of 100% $O_2$. However, in Peyton’s model, the concentrating effects of small $VN_2O$ on alveolar $PO_2$ in moderately low $V/Q$ compartments consistently outweighed the effect of $N_2O$ on desflurane than of 65%, but did not include an $O_2$ only control group, presumably because the SGE of small $VN_2O$ still exerts an important SGE. There are no clinical data in the literature to compare our results with; nobody has studied the SGE of $N_2O$ after administration. The SGE on $PaO_2$ has been documented to last for at least 30 min after the start of $N_2O$ administration.\textsuperscript{13,14} Data comparing the SGE of different concentrations of $N_2O$ are limited and are difficult to interpret. Taheri and Eger\textsuperscript{7} observed a much smaller SGE of 5% $N_2O$ on desflurane than of 65%, but did not include an $O_2$ only control group, presumably because the SGE of small $VN_2O$ was considered to be too small to exert any SGE. While peak $VN_2O$ with 5% $N_2O$ (77 ml min$^{-1}$) is still of the order of magnitude that according to Peyton could change $V/Q$ inhomogeneity, and therefore could cause a SGE, the SGE in Taheri’s 5% and 65% $N_2O$ groups did differ. It is possible that different combinations of alveolar $N_2O$ concentrations and $VN_2O$ cause different changes in $V/Q$ inhomogeneity, and that the SGE becomes minimal below a certain alveolar $N_2O$ concentration.

Could $N_2O$ increase $FA/FI$ by lowering the blood solubility of sevoflurane? Even though a plausible explanation, studies examining the effect of $N_2O$ on blood solubility of potent inhaled anaesthetics are conflicting. $N_2O$ has been reported to increase blood solubility of isoflurane by $\sim5\%$.\textsuperscript{15} However, a more recent study found no effect of $N_2O$ on the blood solubility of neither isoflurane nor sevoflurane.\textsuperscript{16}

In conclusion, our observations suggest that during constant inspired ventilation the classical model of the SGE alone, including the graphical representation, cannot be used to explain all aspects of the SGE nor quantify its effects. The main value of the graphical representation of the SGE is to illustrate its concept and to make it intuitively acceptable. We speculate that changes in lung ventilation/perfusion inhomogeneity caused by general anaesthesia result in a concentrating and thus a SGE of $N_2O$ on sevoflurane, and this at $VN_2O$ levels previously considered by most to be too small to exert a second gas effect.

References