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# *Additive Contribution of Nitrous Oxide to Sevoflurane Minimum Alveolar Concentration for Tracheal Intubation in Children*

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***Background:*** **To study the interaction between nitrous oxide and sevoflurane during trachea intubation, the authors determined the minimum alveolar concentration of sevoflurane for tracheal intubation ($MAC_{TI}$) with and without nitrous oxide in children.**

***Methods:*** **Seventy-two children aged 1–7 yr were assigned randomly to receive one of three end-tidal concentrations of nitrous oxide and one of four end-tidal concentrations of sevoflurane: 0% nitrous oxide with 2.0, 2.5, 3.0, or 3.5% sevoflurane; 33% nitrous oxide with 1.5, 2.0, 2.5, or 3.0% sevoflurane; or 66% nitrous oxide with 1.0, 1.5, 2.0, or 2.5% sevoflurane. After steady state end-tidal anesthetic concentrations were maintained for at least 10 min, laryngoscopy and intubation were attempted using a straight-blade laryngoscope and an uncuffed tracheal tube. The interaction between nitrous oxide and sevoflurane was investigated using logistic regression analysis of the responses to intubation.**

***Results:*** **Logistic regression curves of the probability of no movement in response to intubation in the presence of sevoflurane and 0, 33, and 66% nitrous oxide were parallel. The interaction coefficient between nitrous oxide and sevoflurane did not differ significantly from zero ($P = 0.89$) and was removed from the logistic model. The $MAC_{TI}$ (± SE) of sevoflurane was 2.66 ± 0.16%, and the concentration of sevoflurane required to prevent movement in 95% of children was 3.54 ± 0.25%. Thirty-three percent and 66% nitrous oxide decreased the $MAC_{TI}$ of sevoflurane by 18% and 40% ($P < 0.001$), respectively.**

***Conclusions:*** **We conclude that nitrous oxide and sevoflurane suppress the responses to tracheal intubation in a linear and additive fashion in children. (Key words: Anesthetic potency; drug interaction; tracheal intubation.)**

THE interaction between nitrous oxide and halogenated anesthetics has been studied extensively in the last four decades. Several studies have demonstrated that nitrous oxide decreases the minimum alveolar concentration (MAC) of the halogenated anesthetics halothane,[1,2] isoflurane,[3,4] and sevoflurane[5] in a linear additive manner. In contrast with these findings, other studies have reported that the contribution of nitrous oxide to the MAC of sevoflurane[6] and desflurane[7] is less than additive. Moreover, nitrous oxide has been reported to antagonize sevoflurane- and cyclopropane-induced hypnosis.[8,9] These findings raised doubt about the notion that the additivity principle always holds true for nitrous oxide and sevoflurane.

Several measures of potency have been used to study the interaction between anesthetic agents. One such measure is the MAC of anesthetic that prevents movement in response to tracheal intubation in 50% of subjects ($MAC_{TI}$). $MAC_{TI}$ has been determined for several halogenated anesthetics.[10–15] For sevoflurane, $MAC_{TI}$ is 2.7–3.2% in children.[13–15] Whether nitrous oxide and sevoflurane are additive or antagonistic if they are administered simultaneously to facilitate tracheal intubation is unclear. To study this drug interaction, we determined the $MAC_{TI}$ of sevoflurane with and without nitrous oxide in children.

## Materials and Methods

Approval from the hospital research ethics board and parental informed consent were obtained to study 72 children aged 1–7 yr with American Society of Anesthesiologists physical status 1 or 2 who were undergoing general anesthesia and tracheal intubation for elective

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surgery. Excluded from the study were children who requested sedative premedication; those with a history or clinical evidence of a difficult airway, acute respiratory tract illness, asthma, or gastroesophageal reflux; and those with a family or personal history of adverse reaction to inhaled anesthetics.

The children were assigned randomly to receive one of three end-tidal concentrations of nitrous oxide and one of four end-tidal concentrations of sevoflurane: 0% nitrous oxide with 2.0, 2.5, 3.0, or 3.5% sevoflurane; 33% nitrous oxide with 1.5, 2.0, 2.5, or 3.0% sevoflurane; or 66% nitrous oxide with 1.0, 1.5, 2.0, or 2.5% sevoflurane. Randomization was achieved using a table of random numbers. Anesthesia was induced with up to 6% sevoflurane and the designated concentration of nitrous oxide in oxygen, administered *via* a face mask and a circuit (Jackson–Rees modification of Ayre's T-piece). The fresh gas flow rate was adjusted to the minimum required to prevent rebreathing. Upon loss of the eyelash reflex, ventilation was assisted manually to maintain the end-tidal carbon dioxide partial pressure at 32 to 36 mmHg.

Before tracheal intubation was attempted, the end-tidal concentration of sevoflurane was kept constant at the predetermined value for at least 10 min to allow equilibration between alveolar and brain concentrations. The face mask was then removed, and laryngoscopy and intubation were attempted using a straight-blade laryngoscope and an uncuffed tracheal tube. Throughout the experiment the inspired and end-tidal concentrations of sevoflurane, nitrous oxide, and carbon dioxide were measured using a gas analyzer (Capnomac Ultima, Datex, Helsinki, Finland) which was calibrated before each use. Before intubation, the end-tidal concentrations were measured at the naris *via* a cannula[16]; after intubation, they were measured from the distal end of the tracheal tube using a cannula that had been inserted through the elbow of the circuit such that its tip was within 1 cm of the tip of the tracheal tube.[17]

Successful intubation was defined as the absence of purposeful movement of the extremities, movement of the vocal cords preventing intubation, and coughing or bucking during or immediately after intubation. Movement of the vocal cords was assessed by the anesthesiologist who performed the intubation. All other responses to laryngoscopy and intubation were assessed by an observer who was unaware of the end-tidal anesthetic concentrations. The time from removal of the face mask to completion of tracheal intubation was recorded. If the intubation was unsuccessful, anesthesia was induced intravenously and the lungs were ventilated with oxygen before a second attempt. The incidence of laryngospasm among those who were not intubated on the first attempt was recorded.

*Statistical Analysis*

$MAC_{TI}$ was determined using a logistic regression model where $P$, the probability of no response, is:

$$P = \frac{1}{1 + e^{-z}}$$

$$\text{and, } Z = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 \quad (1)$$

where $X_1$ is the end-tidal $N_2O$ concentration, $X_2$ is the end-tidal sevoflurane concentration, $\beta_0$ is the regression intercept constant, $\beta_1$ is the coefficient for nitrous oxide, $\beta_2$ is the coefficient for sevoflurane, and $\beta_{12}$ is the coefficient for the product of the end-tidal nitrous oxide and sevoflurane concentrations (the interaction coefficient). The main effects components, $\beta_1$ and $\beta_2$, determined whether nitrous oxide and sevoflurane independently affected the response to intubation. The interaction coefficient, $\beta_{12}$, determined whether nitrous oxide and sevoflurane interacted to affect the response to intubation. The likelihood ratio test was used to determine which of the independent variables significantly affected the model. Age was not included in our logistic model because sevoflurane MAC remains constant in children 1–7 yr of age.[6]

To determine $MAC_{TI}$, the probability of no response was evaluated at $P = 0.5$. Solving equation 1 for $X_2$ yields:

$$X_2 = \frac{-(\beta_0 + \beta_1 X_1)}{\beta_2 + \beta_{12} X_1}$$

Likewise, to determine the concentration of sevoflurane required to prevent movement in 95% of children ($ED_{95}$), the probability of no movement was evaluated at $P = 0.95$ and the equation solved for $X_2$. One-way analysis of variance was used to compare the ages and weights of the children. $P < 0.05$ was considered statistically significant.

## Results

The age and weight (mean ± SD) of the children were 4.7 ± 1.5 yr and 20.1 ± 5.4 kg, respectively; age and weight did not differ significantly among the groups. The proportion of successful intubations at each concentration of nitrous oxide and sevoflurane is shown (fig. 1).

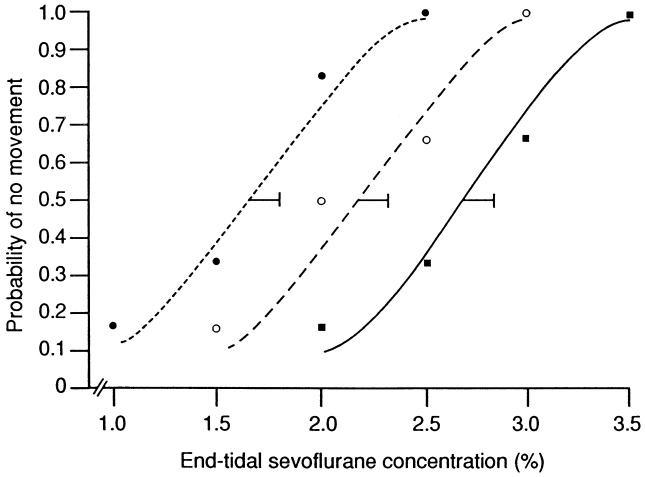


**Fig. 1. Logistic regression curves of the probability of no movement in response to intubation in the presence of sevoflurane and 0% (—), 33% (– –), and 66% (- - -) nitrous oxide. The symbols show the proportion of no-move responses at 0% (*closed squares*), 33% (*open circles*), and 66% (*closed circles*) nitrous oxide.**

The logistic regression curves of the probability of no movement in response to intubation in the presence of sevoflurane and 0, 33, and 66% nitrous oxide were parallel (fig. 1). Based on the likelihood ratio test, the interaction coefficient for nitrous oxide and sevoflurane, $\beta_{12}$, did not differ significantly from zero ($P = 0.89$) and was removed from the model.

The $MAC_{TI}$ (± SEM) of sevoflurane was 2.66 ± 0.16% and the $ED_{95}$ value was 3.54 ± 0.25% (table 1). The addition of 33% and 66% nitrous oxide decreased the $MAC_{TI}$ of sevoflurane by 18% and 40%, respectively ($P<0.001$) (table 1). Among the children who were intubated successfully, the time from removal of the face mask to completion of tracheal intubation did not differ among groups (7 ± 6 s). The ratio of the end-tidal sevoflurane concentration before intubation to that after intubation was 0.9 ± 0.03. Laryngospasm did not occur in any child in whom the end-tidal sevoflurane concentration was greater than 2.0%; it occurred in 4 of the 36 children in whom the end-tidal sevoflurane concentration was 2.0% or less. There were no other adverse events.

## Discussion

The purpose of the present study was to determine the nature of the interaction between nitrous oxide and sevoflurane if these anesthetics are coadministered to facilitate tracheal intubation in children. Using a logistic regression model, we determined that this relationship was linear and additive. The evidence for additivity is that the interaction coefficient did not differ significantly from zero. In addition, we found that nitrous oxide at end-tidal concentrations of 33 and 66% was associated with a linear dose-related reduction in sevoflurane $MAC_{TI}$ from 2.66% to 2.16% and 1.57%, corresponding to reductions of 18% and 40%, respectively. Our value for the $MAC_{TI}$ of sevoflurane is consistent with published data,[13, 14] although a value 20% greater (3.2%) has also been reported.[15] The present finding of linear additivity is consistent with the notion that nitrous oxide and sevoflurane share a common mechanism or site of action at which they suppress responses to tracheal intubation in children.

The concept of linear additivity of the potencies of inhaled anesthetics emanates from studies in adults in which nitrous oxide decreased the MAC of halothane by approximately 1% for each percent of nitrous oxide in the inspired mixture.[1] Subsequent studies in children have demonstrated a similar additive relationship between nitrous oxide and halothane[2] or isoflurane.[3,4] In contrast, studies of the interaction between nitrous oxide and sevoflurane have demonstrated both additivity[5] and antagonism.[8] Additivity was demonstrated in studies of the effect of nitrous oxide on sevoflurane MAC for skin incision, whereas antagonism was demonstrated in studies of its effect on the minimum anesthetic concentration of sevoflurane at which suppression of response to verbal command occurs in 50% of subjects ($MAC_{awake}$). Thus, the interaction between these two anesthetics seems to depend upon the paradigm used. Consistent with this notion, 60% nitrous oxide decreased the MAC for skin incision of sevoflurane by only 24% in children,[6] compared with the 40% reduction in $MAC_{TI}$ in the present study.

An age-related difference in nitrous oxide–mediated increase in central sympathetic outflow might also explain why the interaction found in the present study differed from that in adults.[8] Nitrous oxide augments central and systemic sympathetic nervous system activ-

**Table 1. Sevoflurane $MAC_{TI}$ and $ED_{95}$ Values with and without Nitrous Oxide in Children**

| | End-tidal Sevoflurane Concentration | | |
|---|---|---|---|
| | 0% $N_2O$ | 33% $N_2O$ | 66% $N_2O$ |
| $MAC_{TI}$ | 2.66 ± 0.16 | 2.16 ± 0.16 | 1.57 ± 0.16 |
| $ED_{95}$ | 3.54 ± 0.25 | 3.04 ± 0.25 | 2.46 ± 0.24 |

Values are mean ± SE.

ity.[18] The magnitude of this effect is greater in adults than in infants and children.[19] Centrally acting drugs that increase sympathetic activity increase anesthetic requirements and could antagonize the effects of inhaled anesthetics on the brain.[20] If nitrous oxide–induced stimulation of sympathetic activity increases with age, then antagonism of other inhaled anesthetics by nitrous oxide might be present in adults but not in children. Consistent with this notion, the addition of nitrous oxide decreased the MAC of isoflurane more in infants and children than in adults[4,21]; however, the same does not hold true for sevoflurane.[5,6]

That the results of the present study are consistent with those of the MAC study in adults[5] (and not the $MAC_{awake}$ study[8]) argues in favor of a common mechanism or site of action at which anesthetics suppress responses to tracheal intubation and skin incision.[22] In support of this argument, the ratio of $MAC_{TI}$:MAC for halothane,[10] enflurane,[12] and sevoflurane[13,14] is relatively constant (approximately 1.35), whereas the ratio $MAC_{awake}$:MAC differs for halothane, enflurane, isoflurane, and desflurane.[23,24]

Several aspects of study design can influence the validity of estimates of anesthetic potency. First, the stimulus applied should be clinically reproducible. The coefficient of variation of our data is similar in magnitude to that obtained in studies of MAC for skin incision,[1–7] which suggests that tracheal intubation is as reproducible a stimulus as is skin incision. Second, the technique used to sample respiratory gases should provide a reliable estimate of the end-tidal anesthetic concentration as the latter, at equilibrium, is taken to represent the concentration of anesthetic in the blood and brain. The measurement techniques used in the present study have been validated previously.[16,17] Finally, appropriate mathematic methods should be applied to the dose–response data. We used logistic regression analysis, which has been shown in previous studies[7] to yield MAC values that are similar to those determined by the method described by Dixon.[25] In contrast to Dixon's approach, our study design permitted prospective randomization of all patients and yielded information about the interaction between independent variables.

In conclusion, we studied the interaction between nitrous oxide and sevoflurane during tracheal intubation in children. We found that nitrous oxide and sevoflurane suppress the responses to tracheal intubation in a linear and additive fashion. Sixty-six percent nitrous oxide decreased the $MAC_{TI}$ of sevoflurane by 40%, demonstrating that nitrous oxide produces a clinically significant reduction in the concentration of sevoflurane needed to facilitate tracheal intubation in children.

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