

## The Additive Contribution of Nitrous Oxide to Isoflurane MAC in Infants and Children

David J. Murray, M.D.,\* Mahesh P. Mehta, M.D.,† Robert B. Forbes, M.D.†

The purpose of this study was to determine the contribution of nitrous oxide to isoflurane MAC in pediatric patients. MAC was determined in 47 infants and small children (mean ages  $16.6 \pm 6.7$  months) during isoflurane and oxygen anesthesia ( $n = 11$ ) and isoflurane and nitrous oxide anesthesia (25% nitrous oxide [ $n = 12$ ], 50% nitrous oxide [ $n = 12$ ], and 75% nitrous oxide [ $n = 12$ ]). After assigning patients to one of four groups, anesthesia was induced with increasing inspired concentrations of isoflurane in oxygen. After anesthetic induction and tracheal intubation, ventilation was controlled (carbon dioxide partial pressure =  $32 \pm 5$  mmHg), and nitrous oxide was added to the inspired gas mixture to achieve end-expired nitrous oxide concentrations of 0, 25, 50, or 75%. Inspired and expired gas samples were obtained from a distal sampling port in the tracheal tube. The response to skin incision in each patient was assessed at a previously selected end-tidal concentration of isoflurane. The MAC of isoflurane was determined in each group using the up-and-down method described for evaluating quantal responses. The mean duration of constant end-tidal concentrations prior to skin incision was  $14 \pm 7$  min (range 6–46 min). The ratio of expired to inspired nitrous oxide and isoflurane concentrations during the period of constant end-tidal concentrations was  $0.96 \pm 0.01$  and  $0.93 \pm 0.03$  respectively. The MAC of isoflurane in oxygen was  $1.69 \pm 0.13$  vol % (mean  $\pm$  standard deviation). The MAC of isoflurane in the presence of 25, 50, and 75% nitrous oxide was  $1.26 \pm 0.10$ ,  $0.97 \pm 0.10$ , and  $0.58 \pm 0.09$  vol %, respectively. As the concentration of nitrous oxide increased, the MAC of isoflurane decreased linearly ( $r^2 = 0.93$ ). The predicted MAC of nitrous oxide in children was  $109 \pm 5$  vol %, a value similar to the predicted MAC of nitrous oxide in prior studies of adults. (Key words: Anesthesia; pediatric. Anesthetics, gases: nitrous oxide. Anesthetics, volatile: isoflurane. Interactions: additivity. Potency: age factors; MAC.)

NITROUS OXIDE frequently is combined with inhalation and intravenous anesthetics in pediatric anesthesia practice. The relatively low solubility of nitrous oxide enhances induction of anesthesia with halothane and isoflurane and reduces concentrations of volatile anesthetics required to produce anesthesia.<sup>1</sup> Volatile anesthetic requirements are greater in children than in adults.<sup>2–5</sup> In a recent study,<sup>2</sup> halothane MAC was greater in children than in prior studies of adults, but the predicted MAC of nitrous oxide in infants and children was similar to the measured and

predicted MAC of nitrous oxide in prior studies of adults.<sup>6–9</sup> In children,<sup>2</sup> nitrous oxide reduced halothane MAC in a linear manner when concentrations of 25, 50, and 75% nitrous oxide were added to halothane anesthesia. Recently, Cole *et al.* have suggested that the contribution of nitrous oxide to halothane, isoflurane, and enflurane MAC is nonlinear.<sup>10,11</sup>

The purpose of the current study was to determine the MAC of isoflurane in oxygen as well as the contribution of three different nitrous oxide concentrations to isoflurane MAC in infants and small children. Using the nitrous oxide–isoflurane MAC determinations, the MAC of nitrous oxide in infants and children was predicted, and the relationship between nitrous oxide and isoflurane MAC fractions was determined.

### Materials and Methods

After obtaining approval of the protocol by the Committee for Human Studies and informed written parental consent, we studied 47 ASA physical status 1 infants and small children (7–30 months of age) who required elective surgery. The infants and small children received no pre-anesthetic medication and fasted for 4–6 h prior to anesthesia induction. Anesthesia was induced by mask with increasing inspired isoflurane concentrations and a  $5 \text{ l} \cdot \text{min}^{-1}$  flow of oxygen delivered *via* a pediatric circle system. Temperature, oxygen saturation, blood pressure, and heart rate by ECG were monitored during induction and maintenance of anesthesia. In 32 patients, the trachea was intubated under deep isoflurane anesthesia. If breath-holding or coughing occurred prior to the achievement of deep isoflurane anesthesia (an inspired isoflurane concentration of greater than 2.5 vol % for 5 min), tracheal intubation was facilitated using an intravenous dose of succinylcholine  $0.5\text{--}1.0 \text{ mg} \cdot \text{kg}^{-1}$  ( $n = 15$ ). The trachea of infants and children was intubated with a noncuffed tracheal tube that contained a secondary lumen to obtain gas samples from the trachea.

In the initial group ( $n = 11$ ), the MAC of isoflurane in oxygen was determined. In the three groups in whom the MAC of isoflurane in the presence of 25, 50, and 75% nitrous oxide concentrations was to be assessed, nitrous oxide was added to the inspired gas after tracheal intubation. End-tidal and inspired gas concentrations were measured using a Perkin-Elmer® mass spectrometer. After

\* Associate Professor, Departments of Anesthesia and Pediatrics.

† Associate Professor, Department of Anesthesia.

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Address reprint requests to Dr. Murray: Department of Anesthesia, University of Iowa College of Medicine, Iowa City, Iowa 52242.

tracheal intubation, isoflurane concentrations were adjusted to a previously selected end-tidal isoflurane concentration. When end-tidal isoflurane concentrations were within 0.05 vol % of the target concentration, expired isoflurane concentrations were held constant. During the period of constant end-tidal anesthetic concentrations, inspired and expired gas concentrations were recorded every 1 min until skin incision. The end-tidal anesthetic concentrations were maintained constant for a minimum of 6 min (range 6–46 min) prior to skin incision. Ventilation was controlled with tidal volumes of 10–12 ml · kg<sup>-1</sup> (measured in the pediatric circle system) and respiratory rates of between 14 and 20 breaths per min. In the children who received succinylcholine, return of neuromuscular function was confirmed by monitoring the adductor pollicis response to ulnar nerve stimulation.

The forty-seven patients were divided into four groups according to nitrous oxide concentration at the time of skin incision. The 0% nitrous oxide (n = 11) group was studied to determine the MAC of isoflurane in oxygen prior to determining the MAC of isoflurane during 25, 50, and 75% nitrous oxide. The remaining 36 patients were randomly assigned to either 25 (n = 12), 50 (n = 12), or 75% (n = 12) nitrous oxide. In all patients, the effect of a single isoflurane concentration was assessed to determine the child's response to skin incision (movement or no movement).

The technique used to determine MAC was adapted from prior MAC studies; the objective is to bracket an end-tidal concentration of isoflurane that is the MAC for the group being studied.<sup>2-9,12,13</sup> The study design is similar to a method described by Dixon for determining quantal responses.<sup>14</sup> Each patient was observed for purposeful movement, *i.e.*, movement of the head or upper or lower extremities in the 30-s period after skin incision. The initial isoflurane concentration assessed in the first patient receiving 25, 50, or 75 vol % nitrous oxide was 1.2, 0.9 and 0.45 vol % isoflurane, respectively. For each subsequent patient, the end-tidal isoflurane concentration was increased if the preceding subject in the group had moved after skin incision and was decreased if the preceding sub-

ject in the group had not moved. The incremental change in isoflurane concentration between patients, whether an increase or a decrease, was 0.2 vol %. The age, weight, end-tidal carbon dioxide partial pressure, duration of constant end-tidal values, and isoflurane MAC were analyzed by one-way analysis of variance to determine differences among the four groups. Follow-up comparisons were made using a Dunnett's test ( $P < 0.0125$ ). A regression analysis was applied to the isoflurane groups to determine the correlation between isoflurane MAC at the 0, 25, 50, and 75 vol % nitrous oxide concentrations.

## Results

The mean age, weight, expired nitrous oxide concentration and end-tidal carbon dioxide partial pressure in the four groups are presented in table 1. All study patients had normal hematocrits for age. Rectal temperatures during the study period were  $36.7 \pm 0.2^\circ \text{C}$ . The mean duration between the induction of anesthesia and the assessment of MAC was  $36 \pm 8$  min (22–64 min). In the children who received succinylcholine, the mean time between succinylcholine administration and the assessment of MAC was  $24 \pm 7$  min (range 14–52 min). Neuromuscular recovery was present at least 8 min prior to skin incision in patients who received succinylcholine. Tracheal intubation occurred a minimum of 12 min prior to the assessment of MAC at skin incision (range 12–56 min). The mean duration of constant end-expired isoflurane concentrations was  $14 \pm 7$  min (range 6–46 min). End-expired isoflurane concentrations varied by  $\pm 0.05$  vol % during the period in which end-expired isoflurane concentrations were maintained constant. The mean ratio between end-expired and inspired isoflurane was  $0.93 \pm 0.03$  during the period of constant end-tidal concentration (range 0.86–1.0). The mean ratio between end-expired and inspired isoflurane concentrations at the time of skin incision was  $0.94 \pm 0.02$ .

The response (movement or no movement) to skin incision of the infants and children at different nitrous oxide concentrations is presented in figure 1. The MAC value

TABLE 1. Results from Four Study Groups

N <sub>2</sub> O (%)	Age (months)	Weight (kg)	Movement		Expired N <sub>2</sub> O at Skin Incision (vol %)	Range of Expired Isoflurane Concentrations at Skin Incision (vol %)	Mean End-tidal CO <sub>2</sub> at Skin Incision (mmHg)	Isoflurane MAC (vol %)
			Yes	No				
0 (n = 11)	16.9 ± 6.3	10.4 ± 2.3	5	6	0	1.50–1.91	30.6 ± 4.3	1.69 ± 0.13
25 (n = 12)	15.2 ± 7.2	10.1 ± 1.7	6	6	25.1 ± 1.6	1.12–1.41	33.3 ± 4.1	1.26 ± 0.10
50 (n = 12)	16.6 ± 6.4	9.8 ± 3.0	6	6	50.1 ± 0.9	0.80–1.13	32.0 ± 6.8	0.97 ± 0.10
75 (n = 12)	18.8 ± 6.9	11.1 ± 1.7	6	6	73.9 ± 1.7	0.44–0.74	35.6 ± 3.3	0.58 ± 0.09

Results are expressed as mean ± SD.

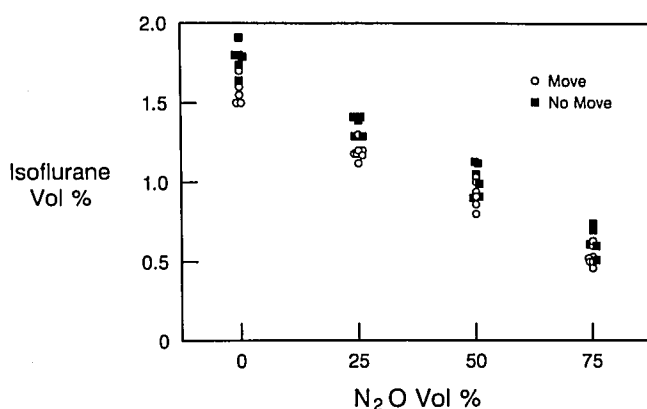


FIG. 1. Response to skin incision (movement or no movement) in the four groups of pediatric patients at different isoflurane concentrations. Each patient is represented by a circle (movement) or square (no movement).

for isoflurane in oxygen was  $1.69 \pm 0.13$  vol % (table 1). The addition of 25, 50, and 75% nitrous oxide reduced the isoflurane MAC to  $1.26 \pm 0.10$ ,  $0.97 \pm 0.10$ , and  $0.58 \pm 0.09$  vol %, respectively (table 1). The MAC of isoflurane was significantly different at each nitrous oxide concentration, and increasing nitrous oxide concentrations reduced anesthetic requirements for isoflurane.

Regression analysis was applied to determine the correlation coefficient and slope of the line extrapolated through the data sets. The  $r^2$  value for this line was 0.93 (fig. 2), and the predicted MAC of nitrous oxide by extension of the linear regression line was  $109 \pm 6$  vol % (fig. 2).

### Discussion

The MAC of isoflurane in this study of infants and children ( $1.69 \pm 0.10$  vol %) is similar to the MAC reported by Cameron *et al.* in infants (6–12 months old) and children (1–3 yr old), for whom MAC was 1.8 and 1.6 vol %, respectively.<sup>15</sup> Similar to previous studies, the MAC of isoflurane was 140–150% greater in infants than reported in adult volunteers (1.15 vol %).<sup>8,15</sup> Based on a linear contribution of nitrous oxide to isoflurane MAC, the predicted MAC of nitrous oxide in infants and children was  $109 \pm 5\%$ , a value similar to the predicted MAC of nitrous oxide during halothane anesthesia in children<sup>4</sup> and similar to the measured MAC in adults determined in a pressure chamber and the predicted MAC of nitrous oxide in adults during 70% nitrous oxide and halothane or isoflurane anesthesia.<sup>6–9</sup>

Why MAC for nitrous oxide is similar in infants and adults, whereas volatile anesthetic MAC is greater in infants than in adults, requires further investigation.<sup>2–5,15</sup>

Nitrous oxide appears to have sympathetic-stimulating effects in adults<sup>16</sup> but not in infants.<sup>17,18</sup> If sympathetic stimulation increases MAC, then MAC for nitrous oxide might be greater in adults than in infants. For this reason, age-related differences in MAC may be less apparent with nitrous oxide than with volatile anesthetics. Alternatively, nitrous oxide may have pharmacodynamic effects in the central nervous system that differ from those of volatile anesthetics, and with nitrous oxide comparable age-related changes in anesthetic requirements may not occur. A similar study predicting the MAC of nitrous oxide at the extremes of age would be required to confirm or refute this hypothesis.

In this study we found that increasing nitrous oxide concentrations, when added to isoflurane anesthesia, reduced isoflurane MAC in infants and small children. The fractional MAC of nitrous oxide and isoflurane were additive in producing 1.0 MAC in children. This result is similar to that of our previous study assessing the contribution of nitrous oxide to halothane MAC in infants and children.<sup>2</sup> Unlike the findings of Cole *et al.* in rats,<sup>10,11</sup> increasing nitrous oxide concentrations led to a predictable reduction in the MAC of halothane and isoflurane in infants and children.<sup>2</sup>

The addition of 75% nitrous oxide to isoflurane reduced the MAC of isoflurane from  $1.69 \pm 0.13$  to  $0.58 \pm 0.09$  vol % in infants and children. The reduction in isoflurane MAC achieved by adding nitrous oxide in infants and children is compared (fig. 3) to previously determined reductions in isoflurane MAC when 70% nitrous oxide is added to isoflurane anesthesia in adults of various ages.<sup>8</sup> In middle-aged adults, 70% nitrous oxide reduced isoflurane concentrations from  $1.15 \pm 0.07$  to  $0.50 \pm 0.07$  vol %.<sup>8</sup> In young adults and elderly adults, isoflurane MAC was reduced from 1.28 and 1.05 to 0.56 and 0.37 vol %, respectively, by the addition of 70% nitrous oxide (fig.

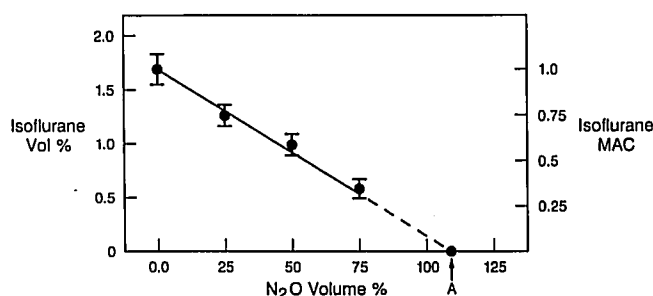


FIG. 2. Regression analysis of four data points. The isoflurane MAC determined at 0, 25, 50, and 75% are plotted, and the line represents the regression analysis through all four data points ( $r^2 = 0.93$ ). The dotted extension of the line to the x-axis represents the predicted MAC of N<sub>2</sub>O (109 vol %).

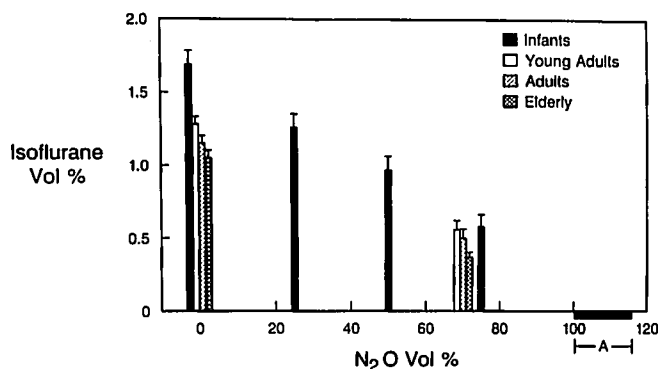


FIG. 3. The MAC of isoflurane at various N<sub>2</sub>O concentrations in different age groups. The range of predicted MAC for N<sub>2</sub>O in various age groups is represented by "A" (100–116 vol %). MAC values for young adults (26 ± 3 yr), adults (44 ± 5 yr) and elderly (65 ± 4 yr of age) are from Stevens *et al.*<sup>8</sup>

3).<sup>8</sup> Because isoflurane concentrations required for MAC are greater in children, adding nitrous oxide reduced end-tidal isoflurane concentrations more in infants and children than reported in prior studies of adults (fig. 3). The greater reduction in inhalation anesthetic concentration achieved in children when nitrous oxide is added suggests that nitrous oxide may be of greater benefit in the pediatric than in the adult patient during inhalation anesthesia.<sup>2</sup>

We used end-expired isoflurane concentrations as a measure of central nervous system partial pressures of isoflurane.<sup>13,18,19</sup> End-expired isoflurane concentrations are assumed to approximate alveolar concentrations. When respiratory rates are rapid and tidal volumes are small, entrainment of inspired gas may limit the accuracy of alveolar concentration measurements. Controlled ventilation using a pediatric circle system in combination with distal tracheal gas sampling was used to obtain end-expired gas samples for measurement.<sup>20</sup> This method provides end-expired carbon dioxide measurements that approximate alveolar carbon dioxide concentrations.<sup>20</sup> In addition, end-expired and inspired isoflurane and nitrous oxide concentration differences were small, and for this reason, mixing of expired with inspired gas would have less impact on alveolar isoflurane and nitrous oxide concentration measurements. Alveolar anesthetic concentrations reach equilibrium with anesthetic partial pressures in the brain over a period of time. In infants, the predicted time constant of equilibrium between end-tidal halothane concentrations and partial pressures in the central nervous system is 2.2 min.<sup>21</sup> Brandom *et al.*'s predicted halothane time constant assumed that the tissue solubility of halothane was similar in infants and adults.<sup>21</sup> Halothane's solubility in tissues is lower in infants and children than in

adults, and the actual time constant of vessel-rich equilibrium for halothane may be shorter than predicted<sup>22</sup> by Brandom. Isoflurane, a less soluble anesthetic than halothane, would have a shorter time constant of vessel-rich equilibrium than halothane.<sup>18,19</sup> A 6-min period of stable end-tidal isoflurane concentrations would represent more than three predicted time constants in infants and children. Three time constants would ensure that central nervous system partial pressures were 95% of alveolar isoflurane concentrations at the time of skin incision.

In summary, in infants and children, increasing nitrous oxide concentrations decreases isoflurane concentrations required for MAC in a predictable linear manner. The predicted MAC of nitrous oxide during isoflurane anesthesia in infants and children was 109 ± 5 vol %, similar to the MAC predicted in adults.<sup>8</sup>

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