Oral Clonidine Premedication Reduces Minimum Alveolar Concentration of Sevoflurane for Tracheal Intubation in Children

Kahoru Nishina, M.D.,* Katsuya Mikawa, M.D.,† Makoto Shiga, M.D.,‡ Nobuhiro Maekawa, M.D.,§ Hidehumi Obara, M.D.,∥

Background: Sevoflurane is a useful anesthetic for inhalational induction in children because of its low solubility in blood and relatively nonpungent odor. Clonidine has sedative and anxiolytic properties and reduces the requirement for inhalation agents. Nitrous oxide (N₂O) also decreases the requirement of inhaled anesthetics, but the effect is variable. The minimum alveolar concentration for tracheal intubation (MAC₉₅) of sevoflurane was assessed with and without N₂O and clonidine premedication.

Methods: Seventy-two patients, aged 3–11 yr, were assigned to one of six groups (n = 12 each). They received one of three preanesthetic medications (two groups for each premedication): placebo (control), 2 µg/kg oral clonidine or 4 µg/kg oral clonidine. In one group of each premedication, anesthesia was induced with sevoflurane in oxygen; in the other group, anesthesia was induced with sevoflurane in the presence of 60% N₂O. Each concentration of sevoflurane at which tracheal intubation was attempted was predetermined according to Dixon’s up-and-down method and held constant for at least 20 min before the trial.

Results: The MAC₉₅ of sevoflurane in the absence of N₂O (mean ± SEM) was 3.2 ± 0.2%, 2.5 ± 0.1%, and 1.9 ± 0.2% in the control, 2 µg/kg clonidine, and 4 µg/kg clonidine groups, respectively. Nitrous oxide (60%) decreased the MAC₉₅ of sevoflurane by 26%, 24%, and 27% in the control, 2 µg/kg clonidine, and 4 µg/kg clonidine groups. Oral clonidine premedication decreased the MAC₉₅ of sevoflurane. Nitrous oxide also decreased the MAC₉₅.

Conclusions: Oral clonidine premedication decreased the MAC₉₅ of sevoflurane. Nitrous oxide also decreased the MAC₉₅. The combination of clonidine and N₂O lessened the MAC₉₅ of sevoflurane more than did either drug alone. (Key words: Anesthesia; pediatric; Anesthesiology; volatile; sevoflurane; Potency, anesthetic; MAC. Sympathetic nervous system, α₂-adrenoceptor agonist: clonidine.)

SEVOFLURANE has been shown to be suitable for inhalational anesthesia in children because of its beneficial pharmacologic and physiochemical characteristics, including relative nonpungency, less depressant for the cardiovascular system, rapid and smooth induction of anesthesia, and rapid emergence from anesthesia. It is reported that the minimum alveolar concentration (MAC) and the MAC for tracheal intubation (MAC₉₅) of sevoflurane in children are 2.03% and 2.69%, respectively. Clonidine, a useful preanesthetic medication for children, has been reported to decrease the MAC in animal experiments. In humans, the concentrations of volatile anesthetics required to blunt hemodynamic responses to noxious stimuli are decreased in patients who receive clonidine as a preanesthetic medication. After clonidine, the EEG shows increased slow-wave activity and decreased alpha activity in healthy young adults. Clonidine has been shown to deepen isoflurane anesthesia even at lower concentrations, as assessed by electroencephalogram power spectra and somatosensory- and auditory-evoked potentials. We also previously showed that oral clonidine decreased the induction dose of barbiturate and the concentration of halothane required to decrease fluctuations of perioperative hemodynamics in children. Thus we hypothesized that oral clonidine premedication may reduce the MAC₉₅ of sevoflurane in children. In addition, because nitrous oxide (N₂O), which is commonly used for the inhalational induction of anesthesia, decreases the MAC of volatile anesthetics, we suspected that N₂O may also decrease the MAC₉₅ of sevoflurane. We conducted the present study to test these hypotheses in children who were scheduled to undergo elective surgery.

* Postgraduate in Anesthesiology.
† Assistant Professor of Anesthesiology.
‡ Instructor in Anesthesiology.
§ Associate Professor of Anesthesiology and Intensive Care Unit.
∥ Professor and Chair of Anesthesiology and Intensive Care Unit.

Received from the Department of Anesthesiology, Kobe University School of Medicine, Kobe, Japan. Submitted for publication March 26, 1997. Accepted for publication July 8, 1997.

Address reprint requests to Dr. Nishina: Department of Anesthesiology, Kobe University School of Medicine, Kusunoki-cho 7, Chuo-ku, Kobe 650, Japan. Address electronic mail to: nishina@med.kobe-u.ac.jp

Anesthesiology, V 87, No 6, Dec 1997

Downloaded From: http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931275/ on 06/21/2017
CLONIDINE AND MAC OF SEVOFLURANE

Materials and Methods

This study was approved by the review board of the Kobe University School of Medicine. Written informed consent was obtained from a parent of each child. Eighty-six patients were enrolled in the study; 14 children were later excluded from the study before the first pair of opposite responses to intubation (described below), and the remaining 72 children were enrolled. The patients, aged 3–11 yr (classified as American Society of Anesthesiologists physical status I), were scheduled to undergo minor surgery and were assigned to one of six groups (n = 12 each). The patients in three of these groups were premedicated with a placebo, 2 μg/kg clonidine or 4 μg/kg clonidine with a small amount of water 105 min before anesthesia. The children and their parents were blinded to the nature of the premedication. Anesthesia was induced with sevoflurane up to 5% in an incremental manner in oxygen via a face mask with 5 l/min fresh gas flow through a vaporizer (Sevotec 5, Ohmeda, Madison, WI). After loss of consciousness, venous access was obtained for the injection of drugs and infusion. Atropine sulfate (0.01 mg/kg) was administered intravenously. Then the inspired concentration of sevoflurane was changed to the predetermined concentration. End-tidal sevoflurane and carbon dioxide concentrations were continuously monitored with infrared absorption spectroscopy (RGM5250, Ohmeda) through a tube inserted into a nostril. Anesthetic concentrations were maintained constant at the target level for 20 min before tracheal intubation in each child to ensure that the end-tidal sevoflurane concentration represented the sevoflurane concentration in the brain. Tracheal intubation was attempted with an uncuffed tracheal tube without neuromuscular relaxant by an anesthetist who was blinded to the nature of the premedication. Each patient’s response to tracheal intubation was evaluated as “no movement” or “movement.” “No movement” was defined as the absence of bucking or gross purposeful muscular movements during or immediately after tracheal intubation. “Movement” was recorded when mouth opening was difficult, or when bucking or gross purposeful muscular movement occurred during or after tracheal intubation. Children who moved during laryngoscopy and tracheal intubation were given 0.1 mg/kg vecuronium intravenously, and the inhaled concentration of sevoflurane was increased to 5%.

The MAC_TI was determined using a modification of Dixon’s up-and-down method\textsuperscript{14} (starting with 2.8%, with 0.2% as a step size). Each child contributed one datum point toward the measurement of the MAC_TI for the study group. The determination of the MAC_TI of each group began only after the first pair of opposite responses to tracheal intubation of the subjects within the group. Twelve children were used to determine the MAC_TI in each group. The MAC_TI was the mean of the concentrations of the 12 patients in each group. The standard error of the mean (SEM) was calculated using a method of Taylor and Lerman.\textsuperscript{15} The SEM of MAC_TI was the standard deviation of the mean concentrations of the three subgroups within each group. A subgroup was defined as four sequential children.

The remaining three groups of children (with three different premedications) were studied to evaluate the effect of N_2O on the MAC_TI. They were premedicated, anesthetized, and monitored as stated above except that anesthesia was induced with sevoflurane in 60% N_2O and oxygen instead of in 100% oxygen.

Parametric data were analyzed using analysis of variance. The significance of nonparametric data was determined using the chi-square test. For all comparisons, P < 0.05 was considered significant.

Results

The children in the six groups were comparable with respect to age, weight, height, and premedication time (table 1). As shown in figure 1A, clonidine reduced the MAC_TI of sevoflurane in the absence of N_2O. Figure 1B indicates that the inhalation of N_2O decreased the MAC_TI from 3.2% to 2.4% in the children who received the placebo. In the presence of N_2O, oral clonidine also decreased the sevoflurane MAC_TI. The reductive effects of 4 μg/kg clonidine and 60% N_2O on the MAC_TI was larger than that of either drug alone (40%, 26%, and 56% reduction by 4 μg/kg clonidine, 60% N_2O, and the combination of them, respectively).

Discussion

We have shown that the MAC_TI of sevoflurane was 3.2% in unpremedicated children aged 3–11 yr. Oral clonidine at 4 μg/kg successfully decreased the MAC_TI by 40% in the absence of N_2O, whereas the inhalation of 60% N_2O reduced the MAC_TI by 26% in the children who received a placebo. We have shown that the reduc-
### Table 1. Clinical Characteristics of the Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>( N_2O(-) )</th>
<th>( N_2O(+) )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Clonidine 2 ( \mu g/kg )</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>7.3 ± 2.5</td>
<td>6.3 ± 2.2</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>8/4</td>
<td>5/7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>24.8 ± 9.0</td>
<td>23.9 ± 8.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>121 ± 16</td>
<td>120 ± 15</td>
</tr>
<tr>
<td>Time from premedication to induction of anesthesia (min)</td>
<td>107 ± 10</td>
<td>111 ± 12</td>
</tr>
</tbody>
</table>

Data are mean ± SD where appropriate. All data were \( P > 0.05 \) between groups.

---

Fig. 1. (A) Response to tracheal intubation in children anesthetized with sevoflurane in the absence of nitrous oxide (\( n = 12 \) each). (B) Response to tracheal intubation in children anesthetized with sevoflurane and 60% nitrous oxide (\( n = 12 \) each). The horizontal bar indicates the end-tidal concentration of sevoflurane. The minimum alveolar concentration for tracheal intubation (MAC\textsubscript{TI}) is expressed as mean ± SEM at the right side of each line. Open circles indicate no movement, and closed circles indicate movement.

---


The MAC\textsubscript{TI} of sevoflurane has been reported as 2.69\textsuperscript{4} and 2.83\textsuperscript{10} in children. The calculation using a value of sevoflurane MAC (2%) reported in one of the previous studies\textsuperscript{4} revealed that the MAC\textsubscript{TI}/MAC ratio of the anesthetic is 1.33. The MAC\textsubscript{TI}/MAC ratio of other volatile anesthetics, halothane\textsuperscript{17} and enflurane,\textsuperscript{18} has been shown to be approximately 1.3. Sevoflurane seems to meet this formula. The MAC\textsubscript{TI} in the present study (3.2%) was higher compared with the previously reported values. Several studies have determined that the MAC of sevoflurane is approximately 2.5% in children (2.49\textsuperscript{15} and 2.5\textsuperscript{16}). In our investigation, the MAC\textsubscript{TI}/MAC of sevoflurane was estimated to be 1.28 using a MAC of 2.5% and 1.6 using a MAC of 2%. The MAC\textsubscript{TI}/MAC ratio remains to be determined in our clinical setting.

The degree to which \( N_2O \) reduces the MAC of inhalation anesthetics has been shown to vary among agents and with the age of the patients. The use of 64% \( N_2O \) decreases the sevoflurane MAC by 61% in adults,\textsuperscript{10} whereas 60% \( N_2O \) decreases it by only 20% in children.\textsuperscript{20,21} In the present study using children, the inhalation of 60% \( N_2O \) reduced the MAC\textsubscript{TI} of sevoflurane to a similar degree regardless of the clonidine dose (26%, 24%, and 27% reductions in the placebo, 2-\( \mu g/kg \) clonidine, and 4-\( \mu g/kg \) clonidine groups, respectively). This finding indicates that oral clonidine does not change the sevoflurane-sparing effect of \( N_2O \).

Clonidine has been reported to decrease the requirement of volatile anesthetics in animal experiments and human clinical studies. In the present study, 4 \( \mu g/kg \)
CLONIDINE AND MAC OF SEVOFLURANE

clonidine reduced the MAC\textsubscript{T1} of sevoflurane by approximately 40% in the presence and absence of N\textsubscript{2}O. In rabbits that received 50 \mu g/kg clonidine daily for 3 days, the MAC for halothane decreased from 1.29% to 1.09% (16% reduction).\textsuperscript{5} Intraperitoneal clonidine (10–1000 \mu g/kg) reduced the MAC for halothane by 32–42% in rats.\textsuperscript{22} We recently showed that 4 \mu g/kg clonidine decreased the halothane requirement to attenuate fluctuation of blood pressure and heart rate from 1.1% to 0.6% in children (45% reduction).\textsuperscript{13} Ghignone \textit{et al.}\textsuperscript{2} reported that the isoflurane requirement was reduced by 40% in hypertensive patients receiving 5 \mu g/kg oral clonidine. Further, the analyses of electroencephalograph power spectra and somatosensory- and auditory-evoked potentials revealed that the depth of anesthesia was sufficient despite a reduction in end-expiratory isoflurane concentrations after two consecutive injections of clonidine at 5 \mu g/kg.\textsuperscript{11} These findings suggest that clonidine reduces the MAC of volatile anesthetics or their requirements to depress hemodynamic changes to surgical stimuli by not more than 45%.

In conclusion, oral clonidine premedication reduced the MAC\textsubscript{T1} of sevoflurane in children. The inhalation of 60% N\textsubscript{2}O decreased the MAC\textsubscript{T1} in children who were not premedicated. The reduction of the MAC\textsubscript{T1} by the combination of oral clonidine and inhaled N\textsubscript{2}O was greater than that by either drug alone.

References

3. Inomata S, Watanabe S, Taguchi M, Okada M. End-tidal sevoflurane concentration for tracheal intubation and minimum alveolar concentration in pediatric patients. \textit{Anesthesiology} 1994; 80:93–6