**Minimum Alveolar Concentration (MAC) of Xenon with Sevoflurane in Humans**

Yoshinori Nakata, M.D., M.B.A.,* Takahisa Goto, M.D.,* Yoshiki Ishiguro, M.D.,† Katsuo Terui, M.D.,† Hiromasa Kawakami, M.D.,‡ Masayuki Santo, M.D.,‡ Yoshinari Niimi, M.D., Ph.D.,* Shigeho Morita, M.D.§

**Background:** Although more than 30 yr ago the minimum alveolar concentration (MAC) of xenon was determined to be 71%, that previous study had technological limitations, and no other studies have confirmed the MAC value of xenon since. The current study was designed to confirm the MAC value of xenon in adult surgical patients using more modern techniques.

**Methods:** Sixty patients were anesthetized with sevoflurane with or without xenon. They were randomly allocated to one of four groups: patients in group 1 received no xenon, whereas those in groups 2, 3, and 4 received end-tidal concentrations of 20, 40, and 60%, respectively (n = 15 each group). Target end-tidal sevoflurane concentrations were chosen using the “up-and-down” method in each group. After steady state sevoflurane and xenon concentrations were maintained for at least 15 min, each patient was monitored for a somatic response at surgical incision. Somatic response was defined as any purposeful bodily movement. The MAC of sevoflurane and its reduction by xenon was evaluated using the multiple independent variable logistic regression model.

**Results:** The interaction coefficient of the multiple variable logistic regression was not significantly different from zero (P = 0.143). The MAC of xenon calculated as xenon concentration that would reduce MAC of sevoflurane to 0% was 63.1%.

**Conclusions:** The authors could not determine whether interaction in blocking somatic responses in 50% of patients is additive. The MAC of xenon is in the range of the values that were predicted in a previous study.

The minimum alveolar concentration (MAC) of xenon was found to be 71% 31 yr ago. Since that time, no other studies have confirmed the MAC value of xenon. Although the study by Cullen et al. was conducted very carefully, it has technological limitations of the 1960s. Cullen et al. were unable to measure xenon concentration directly, whereas it is now possible to do so. In addition, our previous clinical study cast doubt about the MAC value of xenon; the fentanyl requirement in xenon anesthesia is considerably smaller than that in nitrous oxide anesthesia at an equi-MAC concentration based on the MAC value of Cullen et al. Therefore, it is valuable to confirm the previous results using more modern techniques.

---

* Associate Professor of Anesthesiology. † Assistant Professor of Anesthesiology. ‡ Clinical Fellow in Anesthesiology. § Professor and Chairman.

Received from the Department of Anesthesiology, Teikyo University School of Medicine Ichihara Hospital, Chiba, Japan. Submitted for publication January 10, 2000. Accepted for publication November 17, 2000. Supported by a grant-in-aid for scientific research (No. 09877310) from the Ministry of Education, Culture and Science of the Japanese Government, Chiyoda-ku, Tokyo, Japan. Xenon was provided by Daido-Hoxan, Inc., Minato-ku, Tokyo, Japan.

Address reprint requests to Dr. Nakata: Department of Anesthesiology, Teikyo University School of Medicine Ichihara Hospital, 3426-3 Anesaki, Ichihara, Chiba 299-0111 Japan. Address electronic mail to ynakata@med.teikyo-u.ac.jp. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

Anesthesiology, V 94, No 4, Apr 2001 611
No patient received premedication. After the patients were in the operating room, monitoring by an electrocardiograph, a pulse oximeter, and a noninvasive blood pressure cuff was started. Anesthesia was induced with single vital capacity inhalation of 5% sevoflurane in oxygen, and the tracheal intubation was first attempted without the use of muscle relaxants. If unsuccessful, 1 mg/kg succinylcholine was administered intravenously to facilitate intubation. The residual sevoflurane administered during inhalation induction was adjusted to the target concentration by high-flow oxygen (6 l/min) for at least 10 min. For the groups that received xenon, oxygen was then discontinued, and the upright ventilator bellows was deflated completely and refilled quickly with 100% xenon with sevoflurane. Xenon application was then started at 2 l/min. Two to 3 min later, when the end-tidal concentration reached the designated value, xenon flow was reduced, oxygen administration was resumed, and the anesthesia system was closed. Respiratory gases were sampled at the Y connector, and inspired and expired sevoflurane and carbon dioxide concentrations were continuously monitored using an infrared gas monitor (PM8050; Drägerwerk, Lübeck, Germany), calibrated just before each use according to the manufacturer’s instructions. The xenon concentration was continuously monitored using an AZ720 xenon monitor (Anzai Medical, Minato-ku, Tokyo, Japan), which used the absorption of a characteristic X-ray for the measurement. It was calibrated before each case with the use of an 80:20 xenon:oxygen mixture analyzed to ± 0.02% accuracy (Nihon-Sanso, Minato-ku, Tokyo, Japan). The effective working range for this monitor was 1–100%, with the error ± 1% and 90% response time less than 1 s. The sample gas was returned to the anesthesia circuit after analysis in the xenon groups. The lungs were mechanically ventilated to maintain the end-tidal carbon dioxide concentration between 30 and 35 mmHg, and body temperature was maintained above 35.5°C during the period of the study. No patient received medications or analgesics other than those stated. When the MAC of sevoflurane and its reduction by xenon was evaluated using the following multiple independent variable logistic regression model:

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

where \(X_1\) is the measured end-tidal sevoflurane concentration, \(X_2\) is the measured end-tidal xenon concentration, \(\beta_0\) is the regression intercept constant, \(\beta_1\) is the coefficient for sevoflurane, \(\beta_2\) is the coefficient for xenon, and \(\beta_{12}\) is the coefficient for the product of the end-tidal sevoflurane and xenon concentration (interaction coefficient). The MAC of xenon was determined by setting the probability of no response to be 0.5 \((P = 0.5)\) and sevoflurane concentration to be zero \((X_1 = 0)\) and solving for xenon concentration as follows:

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

The responses of patients to skin incision at each xenon concentration were subjected to probit analysis to determine the MAC values of sevoflurane in each group. The results were reported as mean ± SD. These statistical analyses were performed using StatView software (SAS Institute Inc., Cary, NC).

Results

Of these 60 patients, 13 were men and 47 were women. Average age was 45 ± 9 yr (range, 23–60 yr) with a weight of 58 ± 10 kg (range, 41–78 kg). Eight patients received succinylcholine for tracheal intubation. No patient responded to a verbal command before skin incision.

The logistic model was fitted to 60 data sets of observed responses, measured end-tidal sevoflurane concentrations, and measured end-tidal xenon concentrations. Coefficient estimates for the logistic regression model are presented in table 1. The interaction coefficient \(\beta_{12}\) was not significantly different from zero \((P = \ldots\)
0.143). The probability of no movement in response to skin incision versus measured end-tidal concentration in the absence or presence of xenon is presented in figure 1. The MAC values of sevoflurane in the presence of 20, 40, and 60% xenon were 1.39 ± 0.09, 0.88 ± 0.11, and 0.20 ± 0.16%, respectively. The MAC of sevoflurane in the absence of xenon was 1.74 ± 0.12%. The MAC of xenon calculated as xenon concentration that would reduce MAC of sevoflurane to 0% in this model was 63.1%.

**Discussion**

We found that the MAC values of xenon and sevoflurane are 63.1 and 1.74%, respectively. Although Cullen et al.\(^1\) reported that the MAC of xenon was 71%, they also predicted that the MAC of xenon would be as low as 63% by considering the scatter of their data. The current MAC value of xenon lies within the range of their prediction. Therefore, with more modern techniques, we confirmed the results of Cullen et al.\(^1\) The MAC value of sevoflurane in the current study is similar to that obtained in previous studies. The age-adjusted MAC value of sevoflurane using the Mapleson formula was 1.75%,\(^9\) which is very close to the current result (1.74%). This suggests that the current protocol was similar to those of a number of previous studies of MAC.

We could not determine the interaction between xenon and sevoflurane in the current study. Although we did not find a significant difference between \(\beta_{12}\) and zero, this lack of difference may result from a type II error. The power analysis shows that the sample size (\(n = 60\)) in the current study could detect the true difference with only 30% probability; a sample size of 300 would be necessary to achieve a power of 90%.\(^10\) Our results from the probit analysis also support the speculation that the lack of significant difference is a result of a type II error. The combined MAC values obtained from probit analysis exceed the value 1 and range from 1.07 to 1.14 in each xenon group. This result suggests that there is a small antagonistic interaction between xenon and sevoflurane. The small antagonistic interaction between xenon and halothane was also suggested by Cullen et al.\(^1\) Therefore, whether the interaction between xenon and sevoflurane is additive cannot be determined until a larger scale clinical investigation is completed.

There are some limitations to the current study. First, we did not directly measure the MAC of xenon, but estimated it from the data of the combination with sevoflurane. One may be concerned about a potential error resulting from extrapolation beyond the range of data.\(^11\) However, we did not use the assumptions of additivity of MAC, nor did we make an unwarranted linear extrapolation. Instead, we calculated the MAC value from the model and included an interaction coeffi-

---

### Table 1. Coefficient Estimates for Logistic Regression Model

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\beta_0)</td>
<td>-13.509</td>
<td>3.896</td>
<td>0.0005</td>
</tr>
<tr>
<td>(\beta_1)</td>
<td>7.605</td>
<td>2.191</td>
<td>0.0005</td>
</tr>
<tr>
<td>(\beta_2)</td>
<td>0.214</td>
<td>0.062</td>
<td>0.0005</td>
</tr>
<tr>
<td>(\beta_{12})</td>
<td>-0.045</td>
<td>0.031</td>
<td>0.1432</td>
</tr>
</tbody>
</table>

\(\beta_0\) = regression intercept constant; \(\beta_1\) = coefficient for sevoflurane; \(\beta_2\) = coefficient for xenon; \(\beta_{12}\) = coefficient for the product of the end-tidal sevoflurane and xenon concentration (interaction coefficient).

---

Anesthesiology, V 94, No 4, Apr 2001

---

![Fig. 1. Probability of no movement in response to skin incision during sevoflurane anesthesia in combination with 0, 20, 40, or 60% xenon. Error bars in the horizontal direction represent the 95% confidence limits around the minimum alveolar concentration (MAC) value. The tick mark plots show the response–no response (movement) versus measured end-tidal sevoflurane concentrations. Each mark indicates the measured end-tidal sevoflurane concentration and response to surgical incision. The upper tick mark plots show a 40% xenon group (left) and a 0% xenon group (right). The lower tick mark plots show a 60% xenon group (left) and a 20% xenon group (right).](image-url)
ficient. Thus, the MAC value of xenon of 63.1% is expected to be accurate. Second, we anesthetized patients with xenon in combination with sevoflurane. It is difficult to administer more than 70% xenon to the patients to determine the MAC value because it would put the patients at risk of hypoxia as a result of use of a closed-circuit anesthesia technique because of the accumulation of foreign gases in the system. Our extensive clinical experience with xenon anesthesia has confirmed this concern. Therefore, we measured MAC for the combination of xenon and sevoflurane.

In conclusion, we found that the MAC values of xenon and sevoflurane are 63.1 and 1.74%, respectively. We could not determine whether their interaction in blocking somatic responses in 50% of patients is additive. The MAC of xenon is in the range of the values that were predicted in the previous study.1

The authors thank Mieko Saito, M.S., Teikyo University School of Medicine, Ichihara Hospital, Ichihara, Chiba, Japan, for preparing the figure, and Takasumi Kato, M.D., Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan, for his statistical assistance.

References