

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

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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.¹ Since that time, no other studies have confirmed the MAC value of xenon. Although the study by Cullen *et al.*¹ was conducted very carefully, it has technological limitations of the 1960s. Cullen *et al.* were unable to measure xenon concentration directly,¹ 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.*² Therefore, it is valuable to confirm the previous results using more modern techniques.

If we assume that the MAC of xenon is approximately 71%, anesthesia with xenon must be supplemented with other anesthetic agents or techniques. Sevoflurane is one of the inhaled anesthetics that can be used with xenon.³ Moreover, more than 71% xenon must be administered to the patients to determine the MAC value of xenon, which may put the patients at a risk of hypoxia as a result of use of a closed-circuit technique. Therefore, it is necessary to administer sevoflurane with xenon to determine the MAC of xenon in the normobaric pressure. This study was conducted to determine the MAC value of xenon in adult surgical patients.

Materials and Methods

After approval from the Institutional Human Studies Committee of Teikyo University, we obtained informed consent from 60 patients of both sexes who were classified as American Society of Anesthesiologists physical status I or II, were aged 20–60 yr, and were undergoing elective surgery. They were to undergo at least 5-cm skin incisions on the abdomen or breast. The patients scheduled for laparoscopic surgery were excluded because of the small initial skin incision used for this type of surgery. Other exclusion criteria included history of cardiac and pulmonary abnormalities, neurologic disease, and use of medications that might affect MAC values of inhaled anesthetics.

Using a computer-generated random number table, the patients 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. The target end-tidal sevoflurane concentrations were chosen using the "up-and-down" method in each group.⁴ Each trial started with an arbitrary target sevoflurane concentration, representing approximately 1 MAC total, assuming that the MAC values of xenon and sevoflurane are 71 and 2.0%, respectively and that their interaction is additive. The outcome of each patient's response to skin incision determined the target sevoflurane concentration for the subsequent patient. When the patient responded to skin incision, the target sevoflurane concentration for the next patient was increased by 0.2%. Conversely, when the patient did not respond to incision, the target sevoflurane concentration for the next patient was decreased by 0.2%. This rule automatically concentrates testing in sevoflurane concentration, giving a 50% probability of blocking a somatic response, and makes for efficient estimation.⁵

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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,⁶ 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 $\pm 0.02\%$ accuracy (Nihon-Sanso, Minato-ku, Tokyo, Japan). The effective working range for this monitor was 1–100%, with the error $\pm 1\%$ 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.

For approximately 30 min after tracheal intubation the patients were left unstimulated except for positioning, preparation, and draping. The inhaled anesthetic concentrations remained stable at the target end-tidal concentration for at least 15 min before surgical incision. We confirmed that patients could not respond to the verbal command just before surgical incision. When a patient responded to a command, the response was treated as a positive somatic response to incision, and the patient received propofol immediately. During surgical incision, each patient was monitored for somatic responses. A somatic response was considered to be any purposeful bodily movement.⁷ The patients were monitored for a somatic response for 1 min after surgical incision by an observer who was blind to the inhaled anesthetic concentrations used; coughing, chewing, or

swallowing was not considered to be a positive purposeful movement. If patients who received succinylcholine did not move in response to incision, residual neuromuscular blockade was assessed by train-of-four stimulation of the ulnar nerve. We confirmed that the train-of-four ratio returned to almost 1.0 and first-twitch height at skin incision was not different from that recorded before administration of succinylcholine. All patients received approximately 10 ml \cdot kg⁻¹ \cdot h⁻¹ lactated Ringer's solution for the duration of this study. The total duration of these procedures was approximately 45 min.

Statistical Analysis

The measured concentrations, not the target concentrations, of inhaled anesthetics were used for statistical analysis. The MAC of sevoflurane and its reduction by xenon was evaluated using the following multiple independent variable logistic regression model⁸:

$$P(\text{no response}) = 1/(1 + e^{-Z})$$

$$Z = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2$$

where X_1 is the measured end-tidal sevoflurane concentration, X_2 is the measured end-tidal xenon concentration, β_0 is the regression intercept constant, β_1 is the coefficient for sevoflurane, β_2 is the coefficient for xenon, and β_{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:

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

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 \pm 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 \pm 9 yr (range, 23–60 yr) with a weight of 58 \pm 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 β_{12} was not significantly different from zero ($P =$

Table 1. Coefficient Estimates for Logistic Regression Model

Coefficient	Estimate	Standard Error	P
β_0	-13.509	3.896	0.0005
β_1	7.605	2.191	0.0005
β_2	0.214	0.062	0.0006
β_{12}	-0.045	0.031	0.1432

β_0 = regression intercept constant; β_1 = coefficient for sevoflurane; β_2 = coefficient for xenon; β_{12} = coefficient for the product of the end-tidal sevoflurane and xenon concentration (interaction coefficient).

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 $0.20 \pm 0.16\%$, respectively. The MAC of sevoflurane in the absence of xenon was $1.74 \pm 0.12\%$. The MAC of xenon calculated as xenon concentration that would reduce MAC of sevoflurane to 0% in this model was 63.1%.

Discussion

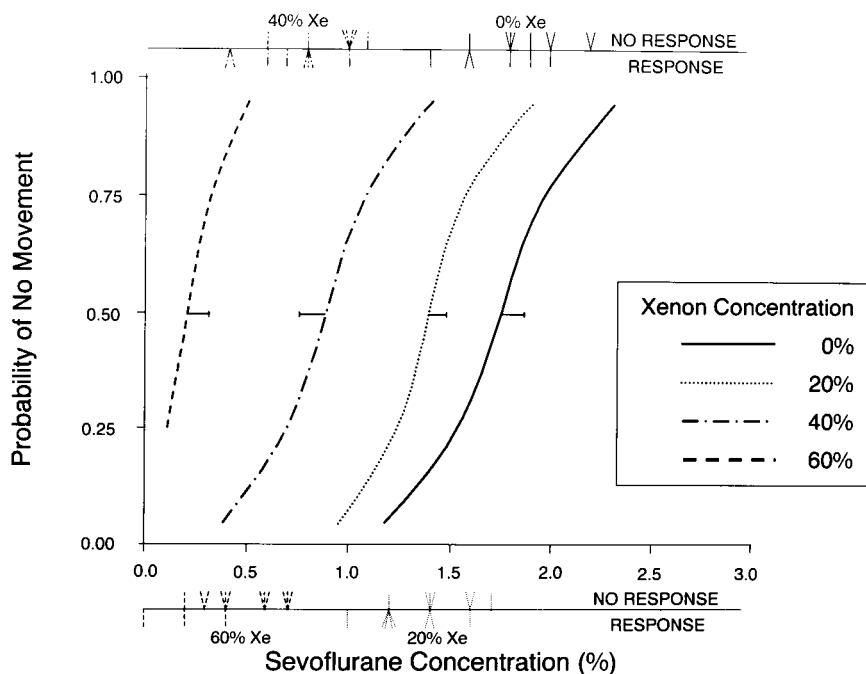
We found that the MAC values of xenon and sevoflurane are 63.1 and 1.74%, respectively. Although Cullen *et al.*¹ reported that the MAC of xenon was 71%, they also predicted that the MAC of xenon would be as low as 63% by considering the scatter of their data. The current MAC value of xenon lies within 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 previ-

ous 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 β_{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 coef-

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*).



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.¹² 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

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