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Minimum Alveolar Concentration–Awake of Xenon Alone and in Combination with Isoflurane or Sevoflurane

Takahisa Goto, M.D., Yoshinori Nakata, M.D., M.B.A.,† Yoshiki Ishiguro, M.D.,‡ Yoshinari Niimi, M.D., Ph.D.,* Kunio Suwa, M.D.,§ Shigeho Morita, M.D.‖*

Background: **The minimum alveolar concentration (MAC)-awake is a traditional index of hypnotic potency of an inhalational anesthetic. The MAC-awake of xenon, an inert gas with anesthetic properties (MAC = 71%), has not been determined. It is also unknown how xenon interacts with isoflurane or sevoflurane on the MAC-awake.**

Methods: **In the first part of the study, 90 female patients received xenon, nitrous oxide (N_2O), isoflurane, or sevoflurane supplemented with epidural anesthesia (n = 36 for xenon and n = 18 per group for other anesthetics). In the second part, 72 additional patients received either xenon or N_2O combined with the 0.5 times MAC-awake concentration of isoflurane or sevoflurane (0.2% and 0.3%, respectively, based on the results of the first part; n = 18 per group). During emergence, the concentration of an assigned anesthetic (xenon or N_2O only in the second part) was decreased in 0.1 MAC decrements every 15 min from 0.8 MAC or from 70% in the case of N_2O until the patient followed the command to either open her eyes or to squeeze and release the investigator's hand. The concentration midway between the value permitting the first response to command and that just preventing it was defined as the MAC-awake.**

Results: **The MAC-awake were as follows: xenon, 32.6 ± 6.1% (mean ± SD) or 0.46 ± 0.09 MAC; N_2O, 63.3 ± 7.1% (0.61 ± 0.07 MAC); isoflurane, 0.40 ± 0.07% (0.35 ± 0.06 MAC); and sevoflurane, 0.59 ± 0.10% (0.35 ± 0.06 MAC). Addition of the 0.5 MAC-awake concentrations of isoflurane and sevoflurane reduced the MAC-awake of xenon to 0.50 ± 0.15 and 0.51 ± 0.16 times its MAC-awake as a sole agent, but that of N_2O to the values significantly greater than 0.5 times its MAC-awake as a sole agent (0.68 ± 0.12 and 0.66 ± 0.14 times MAC-awake; $P < 0.01$, analysis of variance and Dunnett's test).**

Conclusions: **The MAC-awake of xenon is 33% or 0.46 times its MAC. In terms of the MAC-fraction, this is smaller than that for N_2O but greater than those for isoflurane and sevoflurane. Unlike N_2O, xenon interacts additively with isoflurane and sevoflurane on MAC-awake. (Key words: Anesthetic interaction; general anesthesia, hypnosis.)**

XENON is a gaseous anesthetic that shares many characteristics with nitrous oxide (N_2O). For example, they are both gaseous, have low blood–gas partition coefficients (0.12[1] and 0.43 for xenon and N_2O, respectively), have minimal alveolar concentrations (MAC) at least one order higher than those of volatile anesthetics (71%[2] and 104%[3]), and have good analgesic properties.[4]

These similarities lead us to predict that xenon, like N_2O,[5] may be weak in its hypnotic potency. Accordingly, we determined the MAC-awake of xenon, a concentration associated with imminent arousal and a traditionally accepted index of the hypnotic potency of an inhalational anesthetic. Furthermore, because N_2O is known to interact infraadditively with isoflurane and sevoflurane on the MAC-awake,[6,7] we sought to determine if this is also the case with xenon.

Methods and Materials

Participants

After written informed consent was obtained, 162 women aged 30–65 yr with American Society of Anesthesiologists physical status I or II who were scheduled for elective total abdominal or vaginal hysterectomy were studied according to a protocol approved by the Institutional Human Studies Committee of Teikyo University. Exclusion criteria included the history or presence of neurologic diseases, ingestion of medications known to influence anesthetic or analgesic requirements, and contraindications to epidural anesthesia. All baseline laboratory values were normal.

Anesthesia Protocols

This study consisted of two parts (table 1). The first part was intended for determination of the MAC-awake of two gaseous anesthetics, xenon and N_2O, and two volatile agents, isoflurane and sevoflurane. The second part was designed to characterize the interactions between the gaseous and the volatile agents by examining whether, as predicted from simple additivity, the 0.5 MAC-awake concentrations of volatile agents would reduce the MAC-awake of xenon or N_2O by half when administered together.

For both parts of the study, the unpremedicated patients had an epidural catheter placed at the L2–L3 interspace and received 10 ml of 1.5% mepivacaine with 1:200,000 epinephrine after a 3-ml test dose. If the sensory block level of T10 or higher to pin pricks was not obtained within 15 min, the epidural catheter was judged to be functioning inadequately, and the patient was not included in the study.

In the first part, 90 patients were randomly assigned to

* Associate Professor, ‡ Assistant Professor, § Professor, ‖ Professor and Chairman, Department of Anesthesia, Teikyo University School of Medicine, Ichihara Hospital. † Associate Professor, Departments of Health Economics and Anesthesia, Teikyo University School of Medicine, Tokyo.

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

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Table 1. Anesthesia Protocol

Anesthetic Treatment	n	Induction	Decrement of Anesthetic during MAC-awake Measurement
First part			
Xe 56%	36	Propofol 2.5 mg/kg intravenous	Xe 7%
Sevo 1.4%	18	Sevo 5% inhalation	Sevo 0.2%
Iso 0.92%	18	Propofol 2.5 mg/kg intravenous	Iso 0.12%
N_2O 70%	18	Sevo 5% inhalation	N_2O 10%
Second part			
Xe 56% + Sevo 0.3%	18	Propofol 2.5 mg/kg intravenous	Xe 7% (Sevo maintained at 0.3%)
Xe 56% + Iso 0.2%	18	Propofol 2.5 mg/kg intravenous	Xe 7% (Iso maintained at 0.2%)
N_2O 70% + Sevo 0.3%	18	Sevo 5% Inhalation	N_2O 10% (Sevo maintained at 0.3%)
N_2O 70% + Iso 0.2%	18	Propofol 2.5 mg/kg intravenous	N_2O 10% (Iso maintained at 0.2%)

MAC = minimum alveolar concentration, Xe = xenon; Iso = isoflurane; Sevo = sevoflurane; N_2O = nitrous oxide.

receive one of the four anesthetics (n = 36 for xenon and n = 18 for other anesthetics; table 1). The patients assigned to xenon or isoflurane were induced with propofol 2.5 mg/kg intravenously. After the larynx and upper trachea were topicalized by spraying 4% lidocaine 3 ml, the trachea was intubated with the aid of vecuronium 10 mg administered intravenously. Anesthesia was maintained using xenon 56% (0.8 MAC) in oxygen *via* a closed breathing system, or with 1.0–1.5% isoflurane (all concentrations of inhalational anesthetics are end-tidal unless otherwise specified). For those receiving sevoflurane or N_2O, anesthesia was induced with an inhalation of 5% inspired concentration of sevoflurane. After tracheal topicalization and intubation, they received 1.2–2.0% sevoflurane or 70% N_2O (plus approximately 0.5% sevoflurane to prevent intraoperative awareness) as assigned.

For at least 15 min before the end of surgery, the end-tidal concentrations of isoflurane and sevoflurane were maintained at 0.92% and 1.4%, respectively (both approximately 0.8 MAC).[8] The supplemental sevoflurane in the N_2O patients was discontinued at least 30 min before the end of surgery and was washed out using a 10-l/min fresh flow of 70% N_2O in oxygen so that no more than 0.01% residual sevoflurane was detected by the analyzer during the last 10 min.

In the second part, 72 patients were randomly assigned to receive either xenon or N_2O plus 0.2% isoflurane or 0.3% sevoflurane (n = 18 per group; table 1). The concentrations of isoflurane and sevoflurane were chosen to match 0.5 times their respective MAC-awake based on the results of the first part. Induction of anesthesia was achieved by an inhalation of 5% inspired concentration of sevoflurane for the N_2O-plus-sevoflurane group and intravenous propofol 2.5 mg/kg for the other three groups. Subsequently, xenon 56% or N_2O 70% with isoflurane 0.2% or sevoflurane 0.3% were administered until the end of surgery.

The end-tidal concentrations of carbon dioxide, N_2O, isoflurane, and sevoflurane were measured using an infrared analyzer (Capnomac Ultima; Datex, Helsinki, Finland). For those who received xenon as a sole agent, an in-line infrared capnogram (Hewlett Packard, Waltham, MA) was used instead. The end-tidal concentration of xenon was continuously monitored using a xenon analyzer (Anzai Medical, Tokyo, Japan), the effective working range of which was 1–100% with the error ± 1% and the 90% response time less than 1 s. These analyzers were calibrated before each use according to the manufacturers' instructions.

All patients also received a continuous epidural infusion of 1.5% mepivacaine with 1:200,000 epinephrine at 5–10 ml/h to maintain mean arterial pressure and heart rate within 20% of the preoperative values. The lungs were mechanically ventilated to maintain the end-tidal concentration of carbon dioxide at 30–35 mmHg, and additional doses of vecuronium were administered as necessary. The body temperature measured with an esophageal sensor was maintained with the use of a warming mattress placed on the operating table and by warming the intravenous fluids.

Determination of MAC-awake

Shortly before the end of surgery, all the patients received neostigmine 2.5 mg and atropine 1.0 mg intravenously to reverse residual neuromuscular blockade, and the recovery was verified by the train-of-four response to the ulnar nerve stimulation. When surgery was completed, a designated investigator blinded to the anesthetics administered asked the patient in a normal tone to open her eyes and then to squeeze and release the investigator's hand. If the patient failed to follow both commands, the end-tidal concentration of an anesthetic was reduced by the primary anesthetist in a decrement of approximately 0.1 MAC (7% for xenon, 10% for N_2O, 0.12% for isoflurane, and 0.2% for sevoflurane; table 1), and the new concentration was maintained for 15 min. During the second part of the study, the concentrations of isoflurane and sevoflurane were kept constant at 0.2% and 0.3%, respectively, whereas those of xenon and N_2O were reduced (table 1). In all patients, commands were given every 5 min and when clinical signs of impending arousal such as spontaneous movements or coughs were noted. This process was repeated until an alveolar con-

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centration was reached at which the patient first responded to either one of the commands (eye opening or hand squeezing and releasing). As in previous studies,[9,10] the concentration midway between the value permitting the first response to command and that just preventing it was defined as the MAC-awake. Mechanical ventilation was continued during the entire wake-up period. When coughing or bucking hindered effective ventilation with positive pressures, the ventilator was stopped to avoid excessive elevations in the airway pressure. Care was taken to minimize stimuli to the patients except that, in the last 15 patients in each anesthetic treatment group, we recorded the midlatency auditory evoked potentials (MLAEPs) immediately before each testing of the responsiveness to verbal commands (manuscript in preparation). For each recording, we applied 500 click stimuli of 0.1 ms at 80 dB at the frequency of 5 Hz binaurally using earphones.

The patients received no medication other than those previously stated until the end of the MAC-awake measurement. Fifteen minutes after extubation, the epidural block level to pin pricks was examined, and the patient was asked to rate her incisional pain using a 0–10 verbal rating scale, with 0 and 10 being no pain and the worst pain imaginable, respectively.

Statistical Analysis

Because two of the 18 patients in the N_2O group responded to verbal command at the highest concentration tested (70%), the MAC-awake of N_2O was calculated as in a previous study[11] by assuming that these patients would not have responded at 80%. This assumption is based on the literature demonstrating that responses to verbal command occurred only occasionally with 80% inspired concentration of N_2O, and only 1 in 50 patients responded at 86%.[12] In addition, we performed a logistic regression analysis to calculate the concentration of N_2O to suppress responses to verbal command in 50% of the patients (ED_{50}). This was to confirm our MAC-awake value for N_2O with an analysis that required no assumption and therefore better accounted for the two patients who responded at 70% N_2O.

To express the MAC-awake as the fraction of MAC, the MAC values of isoflurane and sevoflurane were adjusted for age in each individual patient based on the following equation[8]:

$$\text{MAC} = 1.18 \text{ (isoflurane) or } 1.80 \text{ (sevoflurane)} \times 10^{-0.00269 (\text{age in years} - 40)} (\%).$$

The MAC of xenon was taken as 71% for all the patients because this is the only value reported in the literature and because the age of the subjects studied was similar (46 ± 6 in this study *vs.* 43 ± 17 in the study by Cullen *et al.*,[2] mean ± SD). Likewise, the MAC for N_2O was taken as 104%[3] because this is the only reported value determined by the direct measurement although the subjects studied were somewhat younger than our patients (21–35 yr).

Results are reported as mean ± SD, mean and 95% confidence interval, or median and range as appropriate. To test whether the MAC-awake of xenon and N_2O obtained in the presence of 0.5 times the MAC-awake of isoflurane or sevoflurane were different from 0.5 times their respective MAC-awake as a sole agent, the results for xenon and N_2O from the first part were halved and compared with the results of the second part using analysis of variance and Dunnett's test, with the former as a control. To test whether application of click stimuli for the recording of the MLAEPs affected the MAC-awake, the results of the patients in the xenon group who did and did not undergo the recording (n = 15 and 21, respectively) were compared using the unpaired *t* test. Other data were analyzed using single-factor factorial analysis of variance and the Student-Newman-Keuls tests or Kruskal-Wallis tests as appropriate. A *P* value less than 0.05 was considered statistically significant.

Results

The eight anesthetic treatment groups were comparable with respect to patient demographics and other postoperative data listed in table 2.

Table 2. Patient Demographics and Postoperative Data

	Xenon	Iso	Sevo	N_2O	Xe + Iso	Xe + Sevo	N_2O + Iso	N_2O + Sevo
Age (yr)	46 ± 8	43 ± 8	47 ± 9	47 ± 8	47 ± 5	45 ± 6	46 ± 8	43 ± 5
Height (cm)	155 ± 6	157 ± 5	156 ± 3	154 ± 5	154 ± 5	158 ± 6	158 ± 6	156 ± 4
Weight (kg)	56 ± 7	59 ± 7	59 ± 11	55 ± 7	54 ± 6	57 ± 10	54 ± 6	54 ± 6
Anesthesia time (min)	119 ± 39	148 ± 59	120 ± 30	130 ± 49	146 ± 48	135 ± 55	140 ± 46	127 ± 40
Body temperature (°C)	35.9 ± 0.1	35.9 ± 0.2	35.9 ± 0.1	35.9 ± 0.1	35.8 ± 0.1	35.9 ± 0.2	35.9 ± 0.2	36.0 ± 0.1
Epidural dose (ml)	31 ± 9	30 ± 7	27 ± 6	31 ± 9	31 ± 7	28 ± 6	30 ± 6	29 ± 9
Epidural level	T8 (T6–11)	T8 (T4–11)	T8 (T4–10)	T8 (T4–10)	T8 (T4–11)	T7 (T4–10)	T8 (T5–10)	T8 (T5–11)
Pain rating	2 (0–5)	2 (0–5)	2 (0–5)	2 (0–4)	2 (0–4)	2 (0–4)	2 (0–5)	2 (0–5)

The body temperature was recorded at the time of the first response to verbal command. The epidural dose is the total volume of 1.5% mepivacaine with 1:200,000 epinephrine administered until 15 min after extubation. The pain rating is the numerical quantification of incisional pain by the patient using a 0–10 verbal rating scale, with 0 and 10 being no pain and the worst pain imaginable, respectively. Data are mean ± SD, or median (range).

Xe = xenon; Iso = isoflurane; Sevo = sevoflurane; N_2O = nitrous oxide.

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Table 3. MAC-awake Values of Anesthetics Administered Alone

	Xenon	N_2O	Isoflurane	Sevoflurane
MAC-awake (%)	32.6 ± 6.1	63.3 ± 7.1	0.40 ± 0.07	0.59 ± 0.10
(95% Confidence interval)	(30.5–34.6)	(59.8–66.9)	(0.37–0.43)	(0.54–0.64)
MAC-awake/MAC	0.46 ± 0.09	0.61 ± 0.07	0.35 ± 0.06	0.35 ± 0.06
(95% Confidence interval)	(0.43–0.49)	(0.57–0.64)	(0.32–0.38)	(0.32–0.38)

The minimum alveolar concentration (MAC)-awake/MAC ratios were significantly different between anesthetic groups ($P < 0.001$, analysis of variance and Student–Newman–Keuls tests), except between isoflurane and sevoflurane.

N_2O = nitrous oxide.

Table 3 demonstrates the MAC-awake values and their MAC-fractions of four anesthetics studied. The MAC-awake expressed in fractions of MAC were significantly different between one another ($P < 0.001$) except between isoflurane and sevoflurane. The MAC-awake for xenon in the patients who did and did not undergo the recording of the MLAEPs were 31.3 ± 5.0% and 33.5 ± 6.7% (NS), respectively, suggesting that click stimuli used to elicit the MLAEPs did not affect the results. The MAC-awake for N_2O (63.3%) was almost identical to the ED_{50} derived using a logistic regression analysis (62.7%), confirming that our MAC-awake value for N_2O was close to the true value despite our assumption that the two patients who responded while breathing 70% N_2O would not have responded at 80%.

Table 4 demonstrates the MAC-awake values of xenon and N_2O when administered together with the 0.5 MAC-awake concentrations of isoflurane or sevoflurane. The values for N_2O were significantly greater than 0.5 times its MAC-awake determined when used as a sole agent in the first part ($P < 0.01$), suggesting infraadditive interactions between N_2O and these volatile anesthetics. In contrast, the values for xenon were equal to 0.5 times its MAC-awake as a sole agent, consistent with simple additivity.

Discussion

The MAC-awake of xenon was 33%. In terms of the MAC fraction, the MAC-awake for xenon (0.46 MAC) was smaller than that for N_2O (0.61 MAC) but greater than those for isoflurane and sevoflurane (both 0.35 MAC). We have also demonstrated that xenon interacted additively with both isoflurane and sevoflurane on MAC-awake, whereas N_2O was slightly infraadditive.

Several issues need to be addressed when considering the validity of our results. The first issue is the impacts of epidural analgesia on the MAC-awake. We used epidural analgesia from the intraoperative period because of our fear that, without it, the extremely low blood–gas partition coefficient of xenon (0.12)[1] would have allowed the patient to perceive pain immediately after the MAC-awake measurement was finished and xenon was discontinued. To our knowledge, only two previous studies conducted by the same group of investigators, have specifically examined the effect of epidural analgesia on MAC-awake.[13,14] Although both reported 30–40% reductions in the MAC-awake of isoflurane by epidural analgesia, the general applicability of these results may be questioned because the values determined without epidural analgesia (*i.e.*, regular MAC-awake, 0.30–0.32%) were markedly lower than those reported by others (*e.g.*, 0.36,[15] 0.41,[10] and 0.44[11]**). Furthermore, one of these studies[13] used nonverbal stimuli (music) to awaken the patients, which is atypical.

In contrast, close proximity of our MAC-awake values (0.40% for isoflurane and 0.59% for sevoflurane) to those determined previously without using epidural analgesia (0.36–0.44% for isoflurane[10,11,15] and 0.62–0.67% for sevoflurane[7,10,15,17,18]) strongly suggests that epidural analgesia only minimally affects the MAC-awake. However, because this is based on indirect comparisons, the true magnitude of the effect remains to be elucidated.

The second issue is whether the different anesthetic induction techniques we used (propofol *vs.* sevoflurane) affected our results. We used inhalational induction in the sevoflurane group, as was used in previous studies,[7,10,15,17,18] because, as previously described, we wished to estimate the effect of epidural analgesia on the MAC-awake by comparing our results with those of the previous investigators.

We believe that propofol used for induction only minimally affected our results. The pharmacokinetic calculation†† using the parameters by Schnider *et al.*[19] predicts that, in a patient who is 155 cm tall and weighs 55 kg (close to the average values of our patients), a 2.5-mg/kg bolus administration of propofol would produce a plasma concentration of 0.06 μg/ml in 2 h. Because the plasma concentration associated with a 50% chance of awakening is approximately 3 μg/ml,[20,21] 0.06 μg/ml is equivalent to 0.02 (= 0.06/3) times MAC-awake. Assuming additivity between propofol and xenon or isoflurane, the true MAC-awake values are estimated to be 33.3% [= 32.6/(1 − 0.02)] for xenon and

** Because this investigation[11] studied young humans (age, 22–30 yr) whereas others (including the present study) investigated older subjects (age ≈ 40 yr), the value was age-adjusted by multiplying the reported MAC-awake/MAC by the MAC of isoflurane for the latter age range (1.15%).[16]

†† The computer software used for this calculation was obtained courtesy of Dr. Steven L. Shafer, Department of Anesthesia, Stanford University, Stanford, California.

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Table 4. MAC-awake of Xenon and N_2O Administered in Combination with the 0.5-MAC-awake Concentrations of Isoflurane or Sevoflurane

	+Isoflurane	+Sevoflurane	Value Predicted Assuming Additivity
Xenon (%)	16.3 ± 4.9	16.7 ± 5.3	16.3 ± 3.0
(Fraction of MAC-awake as a sole agent)	(0.50 ± 0.15)	(0.51 ± 0.16)	(0.5)
N_2O (%)	43.0 ± 7.7*	41.7 ± 9.1*	31.7 ± 3.5
(Fraction of MAC-awake as a sole agent)	(0.68 ± 0.12)	(0.66 ± 0.14)	(0.5)

The values predicted assuming additivity were calculated by multiplying the minimum alveolar concentration (MAC)-awake of xenon and nitrous oxide (N_2O) presented in table 3 by 0.5 because the assumption of additivity between xenon or N_2O and isoflurane or sevoflurane predicts that the addition of the 0.5 MAC-awake concentrations of these volatile anesthetics would halve the MAC-awake of xenon and N_2O. These predicted values were then compared to those determined in the presence of isoflurane or sevoflurane.

* $P < 0.01$ *versus* the value predicted assuming additivity, analysis of variance and Dunnett test, indicating infraadditivity between N_2O and isoflurane or sevoflurane.

0.41% [= 0.40/(1 − 0.02)] for isoflurane. Importantly, adopting these estimated MAC-awake values does not change the results of our statistical analyses regarding either the MAC-awake/MAC ratios or the interactions. Furthermore, the error for xenon (33.3 − 32.6 = 0.7%) is smaller than the measurement error of our xenon monitor (< 1%).

The third issue concerns the potential error in the MAC-awake of N_2O caused by residual sevoflurane. Although we washed out supplemental sevoflurane using a high flow of fresh gas before the MAC-awake measurement, up to 0.05% sevoflurane might have remained in the brain.[22] This is equivalent to 0.08 times MAC-awake (0.05/0.6). Because N_2O and sevoflurane interact slightly infraadditively on the MAC-awake, the value we obtained (63.3 ± 7.1%) might have been slightly more than 0.92 (= 1 − 0.08) times the true MAC-awake of N_2O. Then, the true MAC-awake for N_2O would be 68.8 ± 7.7% (= 63.3/0.92) or less. Again, adoption of this value does not alter the result of our statistical analysis regarding the interactions between N_2O and isoflurane or sevoflurane.

The fourth issue concerns the presence of an endotracheal tube that might have confounded the MAC-awake measurements by stimulating the trachea, especially in those who coughed during emergence. We left endotracheal tubes during the MAC-awake measurements, as was done in the original[9] and many other studies on MAC-awake,[17,18,23] because they would provide more accurate measurements of the end-tidal anesthetic concentrations. We believe it unlikely that our results were overly affected by stimulation from the endotracheal tube. First, there is evidence in the literature that the MAC-awake values of sevoflurane measured by the same investigators are similar regardless of whether the endotracheal tubes or less stimulating airway devices are used; it is 0.62%[18] or 0.67%[17] with the endotracheal tube, 0.63% with the face mask[7], and 0.62%[10] or 0.63%[15] with the laryngeal mask airway. Second, we sprayed the tracheal mucosa with lidocaine before intubation, as has been done by many other investigators.[9,17,18,23]

We calculated the MAC-awake for xenon as 0.46 MAC based on the reported MAC for xenon (71%).[2] Recently, however, this MAC value has been questioned[24] because it is based on a single study published more than 30 yr ago without the use of a xenon concentration monitor. We have estimated the MAC of xenon as 63.1% in patients of similar age as those in this study (Nakata *et al.*, submitted). If this value is correct, the MAC-awake for xenon would be 0.52 MAC (95% confidence interval, 0.48–0.55 MAC). This is again significantly smaller than that of N_2O and is greater than those for isoflurane and sevoflurane ($P < 0.001$). Interestingly, this is equal to those reported for halothane or methoxyflurane (both, 0.52 MAC).[9]

Our results regarding the interaction between xenon and the volatile anesthetics isoflurane and sevoflurane on MAC-awake are consistent with simple additivity. In contrast, N_2O was infraadditive with these volatile anesthetics, confirming the results of other investigators.[6,7] Because an eye-opening on verbal command is a supraspinally mediated response, these findings lead us to speculate that xenon and N_2O might differ in their effects on the supraspinal neural activities. Several lines of evidence indirectly support this notion. For example, xenon slows the electroencephalogram,[25] whereas N_2O increases the fast-wave components[26] and opposes the isoflurane-induced burst suppression.[27] Moreover, xenon reduces the cerebral metabolic rate,[28] whereas N_2O increases it in specific regions of the brain.[29]

A clinical implication of the MAC-awake value of xenon (33%) is that xenon may be more likely to produce hypnosis at clinically used concentrations than would N_2O, the MAC-awake of which is 63%. In fact, 49% xenon prevented responses to verbal command in all of our 36 patients. This predicts that, at the confidence limit of 95%, less than 8% of the population would respond at the end-tidal concentration of 49% xenon. However, many clinicians would find an 8% risk unacceptable, and the number of the patients we studied is too small to draw any firm conclusion as to what concentration of xenon is needed to ensure adequate hypnosis in a majority of patients.

Finally, the hypnotic potency of xenon we demonstrated may offer a potentially valuable clinical utility for

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this gas; it may be useful in patients who are hemodynamically too unstable to tolerate other anesthetics and are therefore at high risk of intraoperative awareness. There is evidence that xenon only minimally depresses the cardiovascular system in healthy humans[30,31] and in animals with cardiac dysfunction.[32] Furthermore, xenon does not alter the function of the isolated heart or major cation currents in the cardiac myocyte.[33] The combination of hypnotic actions and a lack of significant hemodynamic depression in one agent may make xenon a unique choice in our armamentarium of anesthetics because most currently available hypnotics are potent cardiovascular depressants.

Xenon was provided by Daido Hoxan, Inc., Tokyo, Japan.

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