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Anesthetic Doses of Sevoflurane To Block Cardiovascular Responses to Incision when Administered with Xenon or Nitrous Oxide

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Background: **The authors' previous study demonstrated that xenon (Xe) and nitrous oxide (N_2O) in combination with sevoflurane can attenuate cardiovascular responses to skin incision. To quantitatively evaluate their suppressive effects on cardiovascular responses, the authors compared the MAC-BAR (minimum alveolar concentration that blocks adrenergic or cardiovascular response to incision) values of sevoflurane when administered with Xe or N_2O.**

Methods: **Forty-three patients received sevoflurane with one of three anesthetics; 1 MAC Xe, 0.7 MAC Xe and 0.7 MAC N_2O. The MAC-BAR of sevoflurane was determined in each anesthetic using the "up and down" method. The response was considered positive if the heart rate or mean arterial pressure increased 15% or more. The end-tidal sevoflurane concentration given to the next patient was increased or decreased by 0.3 MAC if the response was positive or negative in the previous patient, respectively. The MAC-BAR was calculated as the mean of four independent cross-over responses.**

Results: **The MAC-BAR of sevoflurane, including the contribution of Xe or N_2O, was 2.1 ± 0.2 MAC and 2.7 ± 0.2 MAC when administered with 1 MAC and 0.7 MAC Xe, respectively, and 2.6 ± 0.4 MAC when administered with 0.7 MAC N_2O (mean ± SD).**

Conclusions: **Although 1 MAC Xe has a more potent suppressive effect on cardiovascular responses to incision than 0.7 MAC Xe or N_2O, Xe and N_2O have a similar suppressive effect at 0.7 MAC. (Key words: Hemodynamics; inhaled anesthetics; MAC-BAR; surgical incision.)**

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THERE has been increasing interest in xenon (Xe) anesthesia.[1-3] Xenon, a noble gas, possesses a clinically relevant anesthetic potency (minimum alveolar concentration [MAC] = 71%).[4,5] Its small blood-gas partition coefficient (0.115)[6] makes a rapid induction and emergence possible.[7,8]

In our previous study,[9] we have demonstrated that Xe and N_2O in combination with sevoflurane can attenuate cardiovascular responses to skin incision in surgical patients, whereas sevoflurane alone failed to. However, we found no differences in the cardiovascular responses between Xe and N_2O anesthesia because their suppressive effects on cardiovascular responses were not quantitatively determined. MAC-BAR (blockade of adrenergic or cardiovascular responses) is the dose of an anesthetic that blocks the adrenergic or cardiovascular response in 50% of individuals who have a skin incision.[10,11] By comparing the MAC-BAR values of sevoflurane when administered with Xe or N_2O, we can indirectly evaluate their suppressive effects on cardiovascular responses. Therefore, to quantitatively evaluate the suppressive effects of Xe and N_2O on cardiovascular responses, we conducted a randomized clinical study to determine the MAC-BAR values of sevoflurane when administered with Xe or N_2O.

Materials and Methods

After approval from the Institutional Human Studies Committee of Teikyo University, we obtained informed consent from 43 adult patients (American Society of Anesthesiologists physical status I or II) aged 28 to 60 yr, presenting for elective abdominal or breast surgery. They were to have at least 5-cm-long skin incisions on the abdomen or breast. The patients scheduled for laparoscopic surgery or breast biopsy were excluded because of its small initial skin incision. Other exclusion criteria were history of cardiac and pulmonary abnormal-

ities, hypertension, and use of medications (as well as alcoholism and drug abuse) that might affect blood pressure, heart rate, and MAC values of inhaled anesthetics. Preanesthetic laboratory values were within normal limits.

The protocol was similar to that of our previous investigation,[9] and was also designed to follow the protocol of the study by Daniel *et al.*[10] to make a comparison valid. No patient received any premedication. Once in the operating room, electrocardiogram, pulse oximetry, and noninvasive blood pressure cuff were installed. Anesthesia was induced with single vital capacity inhalation of 5% sevoflurane,[12] and tracheal intubation was facilitated with vecuronium 0.10–0.15 mg/kg given intravenously. Using a computer-generated random number table, the patients were assigned to one of three groups: (1) sevoflurane with 1 MAC Xe (1 MAC Xe group), (2) sevoflurane with 0.7 MAC Xe (0.7 MAC Xe group), or (3) sevoflurane with 0.7 MAC N_2O (N_2O group). The MAC values of sevoflurane, N_2O and Xe were adjusted to the patient's age using Mapleson's formula.[13] For the N_2O group, the target end-tidal concentration was achieved by the fresh gas flow of 3 l/min. For the Xe groups, 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. Then, oxygen was stopped, and the upright ventilator bellows was deflated completely and refilled quickly with 100% Xe with sevoflurane. Xenon was then started at 2 l/min. Two to three minutes later when the end-tidal concentration reached the designated value, Xe flow was reduced, oxygen was resumed, and the anesthesia system was closed. Respiratory gases were sampled at the Y-connector, and inspired and expired sevoflurane, N_2O, and carbon dioxide concentrations were continuously monitored with an infrared gas monitor (PM8050, Dräger-werk, Lübeck, Germany), calibrated just before each use according to the manufacturer's instructions. The Xe concentration was continuously monitored with AZ720 xenon monitor (Anzai Medical, Tokyo, Japan). It was calibrated before each case with the use of an 80:20 xenon:oxygen mixture analyzed to ±0.02% accuracy (Nihon-Sanso, 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 Xe groups. The lungs were mechanically ventilated to maintain the end-tidal carbon dioxide concentration between 30 and 35 mmHg. No patient received any medications or analgesics other than those stated.

For approximately 30 min after tracheal intubation the patients were left unstimulated except for positioning, prepping, and draping. The inhaled anesthetic concentrations remained stable at the target end-tidal concentration for at least 20 min before surgical incision. Heart rate (HR) and mean arterial pressure (MAP) were measured by a cuff with an automatic oscillographic method (Listmini BP-8800, Colin, Aichi, Japan) at the right arm before induction of anesthesia, 1 min before incision, at incision, and with "continuous" mode for 5 min thereafter. The Listmini BP-8800 can measure HR and MAP every 15–30 s with the "continuous" mode. The cardiovascular data were recorded on paper. The MAP and HR before induction were recorded as the baseline cardiovascular variables. The MAP and HR at 1 min before incision were recorded as the cardiovascular variables during anesthesia. If the MAP before incision decreased below 45 mmHg, the patient was excluded from the study and the treatment to restore blood pressure was immediately started. All patients received approximately 10 ml · kg^{-1} · h^{-1} of Ringer's lactate solution for the duration of this study. The duration of these procedures was about 45 min.

Similar to the investigation by Daniel *et al.*,[10] the "up and down" method was used to determine MAC-BAR.[14] We arbitrarily started the investigation with 0.3 MAC sevoflurane in each group. The response of the preceding patient determined the concentration of sevoflurane given to the succeeding patient in each group. If the response of the preceding patient in that group was positive (an increase in either HR or MAP ≥ 15% above the value 1 min before incision), the end-tidal concentration given to the next patient was increased by 0.3 MAC. If the response was negative (neither HR nor MAP increased by ≥ 15%), the end-tidal concentration given to the next patient was decreased by 0.3 MAC. This rule automatically concentrates testing in the neighborhood of the sevoflurane concentration giving 50% probability of blocking cardiovascular response and makes for efficient estimation.[15] The cardiovascular data recorded on paper were analyzed by a person blinded to the anesthetic concentration used. The mean of four independent response cross-overs, in which a positive response was followed by a negative response, provided the MAC-BAR for each group.[15] The data were also analyzed using a logistic model to calculate the effective sevoflurane concentration needed for blockade of cardiovascular responses in 50% and 95% (ED_{50} and ED_{95}, respectively) of patients.[16] Data for MAC-BAR are expressed with the

Table 1. Demographic Data

	N	Age (yr)	Gender (male/female)	Type of Surgery (breast/abdominal)
1 MAC Xe	11	43 ± 6	3/8	2/9
0.7 MAC Xe	15	49 ± 4	4/11	3/12
0.7 MAC N_2O	15	47 ± 10	4/11	2/13

Values are mean ± SD. Variables did not differ among the groups.

MAC = minimum alveolar concentration; Xe = xenon; N_2O = nitrous oxide.

contribution of Xe or N_2O. The data are reported as mean ± SD.

Statistical Analysis

Data were analyzed using Minitab Release 8 for Macintosh (Minitab, State College, PA). All the numeric data were first analyzed with normal probability plots to examine the validity of the assumption that the populations are normally distributed. Because the normality assumption was not rejected, the data were analyzed with parametric tests. The gender and type of surgery were analyzed using chi-square tests. The other demographic data and the MAC-BAR values obtained from independent cross-overs were compared using one-way analysis of variance (ANOVA). The cardiovascular data were analyzed using one-way ANOVA (between groups) and repeated-measures ANOVA (within the group). Multiple comparisons were performed using Tukey honestly significant difference test.[17] The MAC-BAR values were compared with ED_{50} obtained from logistic analysis using *t* tests. A *P* value of < 0.05 was considered statistically significant.

Results

Forty-one patients completed the investigation; one patient in the 0.7 MAC Xe group and another in the N_2O group were excluded from the investigation because their MAP before incision decreased below 45 mmHg. The groups did not differ significantly in age, gender, type of surgery, baseline cardiovascular variables, or cardiovascular variables under anesthesia (tables 1 and 2). HR and MAP decreased significantly during anesthesia from the baseline values in each group (table 2).

The MAC-BAR values of sevoflurane with the contribution of Xe or N_2O were 2.58 ± 0.38 MAC with N_2O, 2.65 ± 0.24 MAC with 0.7 MAC Xe, and 2.05 ± 0.24 MAC with 1 MAC Xe (fig. 1). The MAC-BAR with 1 MAC Xe was significantly smaller than that with 0.7 MAC Xe or N_2O ($P < 0.01$). However, the MAC-BAR with 0.7 MAC Xe was not significantly different from that with N_2O. The ED_{50} and ED_{95} for blockade of cardiovascular responses to incision obtained from logistic analyses were 2.50 and 3.78 MAC with N_2O, 2.65 and 3.06 MAC with 0.7 MAC Xe, and 2.08 and 2.58 MAC with 1 MAC Xe, respectively (values include the contribution of Xe or N_2O). The ED_{50} values did not differ significantly from the MAC-BAR values obtained by cross-over points in each group.

Table 2. Baseline and Preincisional Heart Rate and Mean Arterial Pressure

	Baseline		1 min before Incision	
	HR (bpm)	MAP (mmHg)	HR (bpm)	MAP (mmHg)
1 MAC Xe	71 ± 12	91 ± 4	61 ± 10*	70 ± 10*
0.7 MAC Xe	81 ± 14	103 ± 12	64 ± 12*	73 ± 12*
0.7 MAC N_2O	76 ± 13	106 ± 20	65 ± 14*	74 ± 20*

Values are mean ± SD. Variables did not differ among the groups.

HR = heart rate; MAP = mean arterial pressure; MAC = minimum alveolar concentration; Xe = xenon; N_2O = nitrous oxide.

* Significantly different ($P < 0.05$) from baseline value in each group.

Discussion

A previous study reported the MAC-BAR values of other volatile anesthetics in 60% (0.55 MAC) N_2O.[10] For example, the MAC-BAR values are 1.85 ± 0.18 MAC for isoflurane and 1.85 ± 0.34 MAC for desflurane with the contribution of N_2O.[10] As the MAC-BAR of sevoflurane in our study is found to be 2.58 ± 0.38 MAC with 0.7 MAC

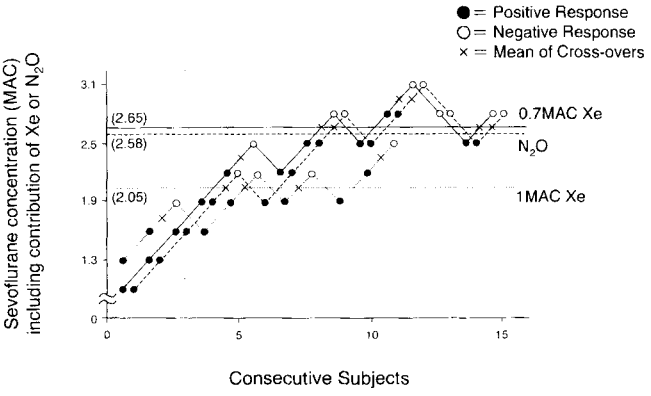

Fig. 1. The end-tidal sevoflurane concentration for consecutive subjects in each group is displayed. The solid line indicates the 0.7 MAC Xe group, the broken line the N_2O group, and the dotted line the 1 MAC Xe group. The determination of MAC-BAR is defined in the text. The MAC-BAR values of each group are represented by horizontal lines. The vertical axis MAC values include the contribution of Xe or N_2O.

(> 0.55 MAC) N_2O contribution and because our protocol and end-point are similar to those of Daniel *el al.*,[10] it is reasonable to conclude that sevoflurane has a less potent cardiovascular suppressive effect compared with isoflurane and desflurane. This conclusion is confirmed by Yamada *el al.*,[18] who demonstrate that the suppressive action of sevoflurane on the cardiovascular response to noxious stimuli is weaker than that of isoflurane.

The MAC-BAR for sevoflurane in 1 MAC Xe is smaller than that in 0.7 MAC Xe or N_2O. As the MAC values of Xe and N_2O are 72% and 104% at age 40 yr,[13] both 0.7 MAC N_2O and 1 MAC Xe represent the similar concentration at 1 atmosphere. This provides Xe with a clinical advantage over N_2O, because Xe can reduce sevoflurane requirements, leaving similar room for oxygen.

The similar requirement of Xe and N_2O for sevoflurane to suppress cardiovascular responses may be attributed to their similar analgesic actions at 0.7 MAC, assuming that the suppressive effects on cardiovascular responses to incision are due to analgesic actions.[9] The opioid-like analgesic action of N_2O is demonstrated by the previous studies, which reveal cross tolerance between N_2O and morphine[19] and partial reversal of N_2O-induced antinociception by naloxane.[19-21] N_2O increases the brain tissue concentrations of opioid peptides such as β-endorphine[22] although it does not interact directly with opioid receptors.[23] The analgesic properties of Xe have been suggested in humans as well as animals. Yagi *el al.*[24] reported decreased incidence of pain under subanesthetic concentration of Xe in human volunteers. Lachmann *el al.*[1] studied fentanyl requirements during 1 MAC Xe anesthesia and found that 80% of the patients required no fentanyl at skin incision to maintain the blood pressure within 20% of the baseline value. The mechanism of analgesic effects of Xe is described to be *via* suppression of spinal dorsal horn neurons[25] independent of α_2-adrenergic or opioid receptors[26] in the experimental settings. Recent evidence demonstrates that Xe potentially inhibits excitatory NMDA (*N*-methyl-D-aspartate) receptors, which supports its analgesic actions.[27] These findings, in addition to ours, suggest the hypothesis that Xe has the same degree of analgesia as does N_2O at 0.7 MAC.

Both 1.1 MAC sevoflurane with 1 MAC Xe (total 2.1 MAC) and 2.0 MAC sevoflurane with 0.7 MAC Xe (total 2.7 MAC) represent MAC-BAR, which implies that a 0.9 MAC increase of sevoflurane is necessary to compensate for a 0.3 MAC decrease of Xe. The interaction between Xe and halothane in their effect on MAC has been demonstrated to be additive.[5] If we assume the similar additivity between Xe and sevoflurane, this suggests that Xe is three times as potent a suppressor of cardiovascular responses as sevoflurane. In other words, Xe is suggested to have a sevoflurane-sparing effect in blocking cardiovascular responses.

In conclusion, we found MAC-BAR values of sevoflurane, including the contribution of Xe or N_2O, of 2.1 MAC and 2.7 MAC when administered with 1 MAC and 0.7 MAC Xe, respectively, and 2.6 MAC when administered with 0.7 MAC N_2O. Although 1 MAC Xe has more potent suppressive effects on cardiovascular responses to incision than 0.7 MAC Xe or N_2O, Xe and N_2O have similar suppressive effects at 0.7 MAC. Compared with the results obtained in a previous study,[10] sevoflurane has a less suppressive action on cardiovascular response to noxious stimuli than isoflurane or desflurane.

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