Xenon Provides Faster Emergence from Anesthesia than Does Nitrous Oxide-sevoflurane or Nitrous Oxide-isoflurane

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Background: Xenon, an inert gas with anesthetic properties (minimum alveolar concentration [MAC] = 71%), has an extremely low blood gas partition coefficient (0.14). Therefore, we predicted that xenon would provide more rapid emergence from anesthesiap than does N₂O-isoflurane or N₂O-sevoflurane of equivalent MAC.

Methods: Thirty American Society of Anesthesiologists class I or II patients undergoing total abdominal hysterectomy were randomly assigned to receive 60% xenon, 60% N₂O + 0.5% isoflurane, or 60% N₂O + 0.7% sevoflurane (all concentrations are end-tidal; n = 10 per group). After placement of an epidural catheter, anesthesia was induced with standardized doses of midazolam, thioental, and fentanyl. Thirty minutes later, xenon, N₂O+isoflurane, or N₂O+sevoflurane was started as previously assigned. These regimens were supplemented with epidural anesthesia with mepivacaine so that the mean arterial pressure and heart rate were controlled within 20% of the preoperative values. At the end of operation lasting approximately 2 h, all inhalational anesthetics were discontinued, and the patients were allowed to awaken while breathing spontaneously on an 8 l/min inflow of oxygen. A blinded investigator recorded the time until the patient opened her eyes on command (T1), was judged ready for extubation (T2), could correctly state her name, her date of birth, and the name of the hospital (T3), and could count backward from 10 to 1 in less than 15 s (T4).

Results: Emergence times from xenon anesthesia were: T1, 3.4 ± 0.9 min; T2, 3.6 ± 1 min; T3, 5.2 ± 1.4 min; and T4, 6.0 ± 1.6 min (mean ± SD). These were one half to one third of those from N₂O+sevoflurane (T1, 6.0 ± 1.7 min; T4, 10.5 ± 2.5 min) or N₂O+isoflurane (T1, 7.0 ± 1.9 min; T4, 14.3 ± 2.8 min) anesthesia. The three groups did not differ in terms of patient demographics, the duration of anesthesia, the amount of epidural mepivacaine administered, or the postoperative pain rating. No patient could recall intraoperative events.

Conclusions: Emergence from xenon anesthesia is two or three times faster than that from equal MAC N₂O-isoflurane or N₂O-sevoflurane anesthesia. (Key words: Anesthesia; general. Anesthetics, gases: nitrous oxide; xenon. Anesthetics, volatile: isoflurane; sevoflurane.)

XENON, an inert gas with anesthetic properties, has recently attracted renewed interest because it possesses many of the characteristics of an ideal anesthetic. Its minimum alveolar concentration (MAC) is 71% in humans, suggesting that it is more potent than nitrous oxide (N₂O: MAC = 104%). It is nonexplosive, nonpungent, and odorless; it produces only minimal cardiac depression; and it is extremely unreactive. Further, unlike other inhalational anesthetics, it is environment friendly because it is prepared by fractional distillation of the atmospheric air. Although high cost has hindered it from being accepted in anesthesia practice, this may be minimized by using a minimum fresh gas flow and a rebreathing system. Recently, the xenon-recycling system was developed in Europe, which might also contribute to cost reduction.

Xenon has a blood:gas partition coefficient of 0.14, which is significantly lower than those of other clinically used inhalational anesthetics, and even lower than that of N₂O (0.47), sevoflurane (0.65), or desflurane (0.42). This property predicts more rapid emergence from anesthesia with xenon relative to other inhalational agents. Therefore, we conducted a randomized, controlled study to compare emergence times in patients undergoing lower abdominal surgery with equal MAC xenon, N₂O+sevoflurane, or N₂O+isoflurane anesthesia supplemented with epidural anesthesia.
Materials and Methods

Participants
After we obtained written informed consent, 30 women classified as American Society of Anesthesiologists physical status I or II who were aged 35–59 yr and scheduled for elective total abdominal hysterecom-omy were studied according to a protocol approved by the Institutional Human Studies Committee of Teikyo University. Patients with clinically significant pulmonary, cardiovascular, hepatic, renal, or neurological diseases were excluded. Also excluded were patients who were taking medications known to influence anesthetic or analgesic requirements, those who had contraindications to epidural anesthesia (e.g., coagulopathy, a history of allergic reactions to local anesthetics), and those who refused to have epidural anesthesia. Baseline laboratory values, including serum electrolytes, blood urea nitrogen, creatinine concentration, liver function tests, and complete blood count, and results of electrocardiograph were all within normal limits.

Anesthetics
No premedication was given on the ward. When the patient arrived in the operating suite, midazolam 30 μg/kg was administered intravenously. An epidural catheter was placed at the L2–L3 interspace, through which 3 ml 1.5% mepivacaine with 1,200,000 epinephrine was administered as a test dose. This was followed 3 min later by an additional 10 ml. If the sensory level of T10 or higher to pin pricks was not obtained within 15 min after this 10-ml dose, the epidural catheter was judged to be functioning inadequately and the patient was excluded from the study. A well-functioning epidural catheter was regarded as an essential component of our anesthesia protocol because of the MAC value of xenon (71%) and our desire to avoid other systemic supplementations while securing the patients’ comfort.

The patients were randomly assigned to three anesthetic treatment groups, i.e., xenon, N₂O+isoflurane, or N₂O+sevoflurane (n = 10 per group). General anesthesia was induced with intravenous doses of 2 μg/kg fentanyl and 4 mg/kg thiopental while the patients breathed a high flow of oxygen (8 l/min). Ventilation via mask was instituted with slowly increasing concentrations of isoflurane (xenon and N₂O+isoflurane groups) or sevoflurane (N₂O+sevoflurane group). After the trachea was intubated with the aid of 10 mg vecuronium, denitrogenation was continued for 30 min more using an 8 l/min inflow of oxygen so that accumulation of nitrogen during the subse-
quent closed-circuit anesthesia would be reduced. During this period, anesthesia was maintained with 1% isoflurane (xenon and N₂O+isoflurane groups) or 1.8% sevoflurane (N₂O+sevoflurane group). The end-tidal concentration of carbon dioxide was maintained at 30–35 mmHg. If clinically indicated, ephedrine (4–8 mg) or phenylephrine (50–100 μg) was administered intravenously to maintain the systemic blood pressure at acceptable levels.

Routine monitoring devices included an esophageal stethoscope with a temperature sensor, electrocardiograph (lead II), an automated blood pressure cuff, and a pulse oximeter. End-tidal concentrations of nitrous oxide, carbon dioxide, sevoflurane, and isoflurane were monitored continuously with an infrared gas analyzer (PM 8050; Drägerwerk, Lubeck, Germany), which was calibrated according to the manufacturer’s instructions. The end-tidal concentration of xenon was monitored continuously using a xenon analyzer (Anzai Medical, Tokyo, Japan), which was calibrated before each case using an 80% xenon–20% 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 the 90% response time less than 1 s.

After the 30-min denitrogenation period, xenon, N₂O+isoflurane, or N₂O+sevoflurane was started. First, the patient was transferred to a separate anesthesia machine (Vip-300; IMI, Saitama, Japan) with a breathing circuit that was prefilled with at least 70% of xenon or N₂O in a balance of oxygen. Then, for the patients in the xenon group, xenon was begun at 0.5 l/min without oxygen. Two or three minutes later, when the end-tidal concentration reached 60%, the breathing circuit was closed, the inflow of xenon reduced, and oxygen re-started. Thereafter, closed-circuit anesthesia was conducted. The fresh inflow rates of xenon and oxygen were adjusted to maintain the end-tidal concentration of xenon at 60%. No volatile anesthetic was administered once xenon was started. However, our pilot study revealed that 0.1–0.2% isoflurane was always detected in the circuit, presumably because the isoflurane vapor contained within the patient’s lungs at the time of circuit closure was retained in the closed breathing system. Therefore, it was estimated that the patients in the xenon group were under approximately 0.9 MAC anesthesia assuming additivity of MAC, because xenon and isoflurane provided 60/71 = 0.84 and 0.1/1.15 = 0.085 MAC, respectively. Although unproved, additivity of MACs between xenon and isoflurane appears to be a reasonable assumption because there is evidence that

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xenon and halothane are additive. To provide the same MAC fractions of inhalational anesthesia to the patients in the N₂O+sevoflurane and N₂O+isoflurane groups, the end-tidal concentrations of N₂O, sevoflurane, and isoflurane were maintained at 60%, 0.7%, and 0.5%, respectively. The total inflow of 3 l/min was used in the patients receiving N₂O+volatile anesthetic.

Table 1. Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Xenon</th>
<th>N₂O-Sevoflurane</th>
<th>N₂O-Isoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>44 ± 3</td>
<td>44 ± 7</td>
<td>43 ± 4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155 ± 6</td>
<td>155 ± 8</td>
<td>153 ± 6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>56 ± 6</td>
<td>55 ± 7</td>
<td>55 ± 5</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>122 ± 39</td>
<td>119 ± 41</td>
<td>121 ± 26</td>
</tr>
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</table>

All patients also received a continuous epidural infusion of 1.5% mepivacaine containing 1:200,000 epinephrine at 6 ml/h started immediately after induction of anesthesia; that is, after the analgesia level of T10 or higher was confirmed. Once xenon or N₂O was started, the epidural infusion rate was adjusted to maintain the mean arterial pressure and heart rate within 20% of the preoperative values. Additional doses of vecuronium were administered if clinically indicated. The body temperature was maintained using a warming mattress placed on the operating table. Intravenous fluids were also warmed.

Before skin closure, residual neuromuscular blockade was reversed with 2.5 mg neostigmine and 1 mg atropine given intravenously. Spontaneous ventilation was allowed to return, and adequacy of reversal was confirmed by stable respiration and a full recovery of the train-of-four response to the ulnar nerve stimulation. At the end of the operation, all inhalational anesthetics were discontinued, and oxygen was administered at 8 l/min. The end-tidal concentration of carbon dioxide, respiratory rate, and esophageal temperature were recorded at this time. An investigator who was blinded to the anesthetic regimen administered the times from discontinuation of the anesthetics until the patient opened her eyes on verbal command and was judged ready for extubation (i.e., in addition to opening her eyes, she either squeezed the investigator's hand or took a deep breath on command, and showed a regular breathing pattern). Further, the time when the patient could correctly state her name, her date of birth, and the name of the hospital (i.e., Teikyo University Ichihara Hospital) was recorded as the time the patient regained orientation. Finally, the time when the patient could count backward from 10 to 1 in less than 15 s was recorded. These emergence times were assessed either at 30 s (eye opening and extubation) or 60 s (orientation and counting backward) intervals. 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. Continuous epidural infusion was stopped, and the patient was transferred to the postanesthesia care unit. The incidence of nausea or vomiting during the first hour after extubation was also recorded, and antiemetics (e.g., 10 mg metoclopramide given intravenously) were administered as necessary. All patients were asked 24 h after operation if they could recall intraoperative events.

Statistical Analysis

Data other than the postoperative pain rating, the epidural analgesia level, and the incidence of nausea and vomiting are reported as means ± SD and were analyzed using analysis of variance followed by Dunnnett's t test with the xenon group as a control. The postoperative pain rating and the epidural level are expressed as medians (10–90 percentiles) and were analyzed using the Kruskal-Wallis with Mann-Whitney U tests to assess differences between the xenon group and the other groups. The incidence of postoperative nausea and vomiting was analyzed using a chi-square test. A probability value less than 0.05 was considered statistically significant.

Results

The three groups were comparable with respect to age, height, and weight (table 1). The duration of anesthesia after the start of xenon or N₂O was approximately 2 h and did not differ among groups. During operation, the three groups displayed similar blood pressure (fig. 1A) and heart rate (fig. 1B), although neither ephedrine nor phenylephrine was administered.

The times of emergence from xenon anesthesia were 3.4 ± 0.9 min to opening eyes; 3.6 ± 1.0 min to extubation; 5.2 ± 1.4 min to orientation; and 6.0 ± 1.6 min to counting backward. These were approximately one half the respective recovery times from N₂O+sevoflurane anesthesia (P < 0.01; fig. 2). Differences between xenon and N₂O+isoflurane were even greater (P < 0.01; fig. 2). Emergence from anesthesia was smooth in all groups. No partici-
pant experienced a major anesthesia-related adverse event. Similarly, there was no intraoperative awareness.

The final end-tidal concentration of isoflurane in the xenon group was 0.1%. There was no difference in the esophageal temperature, end-tidal concentration of carbon dioxide, or respiratory rate at the end of operation (table 2). Although the postoperative epidural analgesia level was slightly lower in the N₂O-isoflurane group compared with that of the xenon group ($P = 0.012$), neither the total amount of epidural mepivacaine administered nor postoperative pain rating was significantly different (table 2). The incidence of postoperative nausea or vomiting was also comparable among groups (table 2).

The expenditure of xenon from 0 to 60 min and 60 to 120 min after the start of xenon was $5,458 \pm 1,095$ ml ($n = 10$) and $2,564 \pm 1,140$ ml ($n = 7$), respectively, excluding the gas used to prime the anesthesia circuit.

**Discussion**

We have shown that xenon provides two or three times faster emergence from anesthesia than does equal-MAC N₂O+sevoflurane or N₂O-isoflurane to various end-points ranging from simple responses such as opening eyes to a verbal command to more complicated tasks such as counting backward quickly. The results
EMERGENCE FROM XENON ANESTHESIA

Table 2. Postoperative Data

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<tr>
<th></th>
<th>Xenon</th>
<th>N₂O-Sevoflurane</th>
<th>N₂O-Isoflurane</th>
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<tbody>
<tr>
<td>ET CO₂ (mmHg)</td>
<td>42 ± 4</td>
<td>41 ± 6</td>
<td>45 ± 4</td>
</tr>
<tr>
<td>Respiratory rate (min⁻¹)</td>
<td>21 ± 5</td>
<td>23 ± 3</td>
<td>21 ± 4</td>
</tr>
<tr>
<td>Esophageal temperature (°C)</td>
<td>36.0 ± 0.15</td>
<td>35.9 ± 0.14</td>
<td>35.9 ± 0.24</td>
</tr>
<tr>
<td>Epidural dose (ml)</td>
<td>28 ± 5</td>
<td>25 ± 7</td>
<td>27 ± 8</td>
</tr>
<tr>
<td>Epidural level</td>
<td>T8 (T7–10)</td>
<td>T9 (T7–10)</td>
<td>T10 (T7–11)</td>
</tr>
<tr>
<td>Pain rating</td>
<td>2.5 (0–5)</td>
<td>1.5 (0–3)</td>
<td>2.5 (0–5)</td>
</tr>
<tr>
<td>Nausea/vomiting (per 10 patients)</td>
<td>5</td>
<td>4</td>
<td>4</td>
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are consistent with the widely accepted concept that lower blood gas partition coefficients are associated with faster emergence. Other factors potentially influencing the rate of emergence such as age, body temperature, and pain were not significantly different among the three anesthetic treatment groups. The amounts of supplemental anesthetics and analgesics administered (including the epidural local anesthetic) were also similar, although xenon and other inhalational anesthetics might have interacted differentially with these supplemental agents on the speed of emergence. Minute ventilation again was probably comparable because the endtidal carbon dioxide concentration and respiratory rate at the end of operation were the same. However, because xenon’s lower solubility presumably allows its quicker elimination from the body, anesthetic-induced respiratory depression might have dissipated more rapidly with xenon compared with other inhalational agents. This could have enhanced ventilation and facilitated emergence.

Emergence from xenon anesthesia was not only fast but also smooth; none exhibited agitation or restlessness. Although these characteristics are favorable for early discharge from the postanesthesia care unit, whether or not the use of xenon actually leads to earlier “ward-readiness” remains to be determined.

None of our patients could recall intraoperative events when interviewed 24 h after operation, although the MAC value (71%) and electroencephalographic findings suggest that xenon produces relatively light anesthesia under normobaric conditions if it is the sole anesthetic. The observed lack of recall might be due, at least in part, to the use of supplemental injections such as intravenous fentanyl, midazolam, and epidural anesthesia. To date, three additional studies of xenon anesthesia involving a total of 53 patients have tested for patient intraoperative awareness, but none has been reported. Although this is reassuring, the number of the patients studied so far is too small to draw any firm conclusion regarding the risk of awareness associated with xenon anesthesia.

Because xenon is expensive, we used a closed rebreathing circuit to minimize its consumption. During closed-circuit anesthesia, nitrogen released from the patient’s body stores accumulates within the circuit, limiting the inspired concentration of oxygen. Therefore, we performed a prolonged denitrogenation before starting xenon to reduce the risk of hypoxia.

Another technical problem lies in the transition from denitrogenation to closed-circuit xenon anesthesia, because increasing the end-tidal concentration of xenon rapidly by simply using a high flow would be too expensive. Alternately, xenon could have been administered sufficiently fast to simply replace the amount of oxygen consumed by the patient. Although this would be the least costly, the concentration of xenon would rise far too slowly because the oxygen consumption by an average adult is only 200–250 ml/min, or only a small percentage of the total volume of the breathing system (i.e., the anesthesia circuit plus the patient’s lungs). Therefore, we transferred the patient to a separate anesthesia machine with its circuit primed with xenon. Our priming method has been described in another publication. Briefly, using a large (3 l) syringe, xenon was pushed into the circuit prefilled with oxygen. The expelled gas would be predominantly oxygen because the design of the anesthesia machine allows a unidirectional flow inside the circuit and because we had created a gas exit most distally along the flow from the site of xenon administration. The ventilator bellows was then inflated with xenon. In this way, the circuit was primed with approximately 3.5–4 l xenon with a minimal loss. When the patient was connected to this circuit, the concentration of xenon settled around 50% within several breaths.

Despite these efforts, approximately 10 l xenon was required for 2 h of anesthesia. This expenditure is comparable to that reported by others. Although this could be re-
duced further by rendering the anesthesia circuit free of leaks, xenon anesthesia is nonetheless expensive. When the acquisition costs of inhalational anesthetics alone are considered, 2h closed-circuit anesthesia with xenon costs approximately 170 dollars (xenon costs 17 dollars per liter in Japan), whereas the costs of N₂O+isoflurane and N₂O+sevoflurane anesthesia with the total inflow of 3 l/min are 57 and 60 dollars, respectively. (The prices of isoflurane and sevoflurane in Japan are the same at 1 dollar per milliliter of liquid agent. Nitrous oxide costs 0.20 dollar per liter of gas.) These differences in cost would be progressively smaller with longer duration of anesthesia because, when a closed rebreathing circuit is used, the rate of xenon consumption declines exponentially with time as the patient's body tissues become saturated. In any case, whether or not the potential benefits of xenon, such as the rapid recovery as demonstrated in this study, are sufficient to merit the increased costs remains to be determined.

In summary, we have shown that xenon leads to more rapid emergence from anesthesia than does equal-MAC N₂O+isoflurane or N₂O+sevoflurane. This is consistent with its low blood-gas partition coefficient. In this regard, xenon may have significant clinical potential when rapid, clear emergence is of paramount importance. However, because xenon is expensive, a careful evaluation of the cost/benefit ratio and the development of strategies for cost reduction are warranted before it is adopted in the anesthesia practice.

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