Emergence times from xenon anaesthesia are independent of the duration of anaesthesia†

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Summary

Xenon (MAC = 71%) has an extremely low blood:gas partition coefficient (0.14). Therefore, we predicted that the rate of emergence from xenon anaesthesia would not be affected greatly by duration of anaesthesia. We studied 54 ASA I–II patients undergoing lower abdominal surgery who received equal MAC anaesthesia with 60% xenon, 60% nitrous oxide with 0.5% isoflurane or 60% nitrous oxide with 0.7% sevoflurane (n = 18 per group), each supplemented with extradural mepipvacaine anaesthesia. Duration of anaesthesia was 58–380 min. At the end of operation, all inhalation anaesthetics were discontinued and patients were allowed to wake up while breathing oxygen spontaneously. A blinded investigator recorded the time until patients opened their eyes on command (T1), were judged ready for tracheal extubation (T2), could correctly state their name, date of birth and name of the hospital (T3), and could count backwards from 10 to 1 in less than 15 s (T4). Emergence times after xenon and nitrous oxide–sevoflurane anaesthesia did not correlate with duration of anaesthesia, whereas those from nitrous oxide–isoflurane had positive correlations. Mean emergence times from xenon anaesthesia were: T1, 3.3 (SD 1.0) min; T2, 3.6 (1.0) min; T3, 5.0 (1.1) min; and T4, 6.2 (1.7) min. These values were approximately 50% of those after nitrous oxide–sevoflurane anaesthesia (T1, 5.6 (1.4) min; T4, 10.5 (2.0) min). We conclude that xenon provided fast emergence from anaesthesia, regardless of the duration of anaesthesia. (Br. J. Anaesth. 1997; 79: 595–599).

Key words


Xenon, an inert gas with a clinically relevant anaesthetic potency (MAC = 71%),1 is extremely insoluble in human body tissues. Its blood:gas partition coefficient is 0.14,2 significantly lower than those of other inhalation anaesthetics, including nitrous oxide (0.47), sevoflurane (0.65) and desflurane (0.42).3 This property predicts that emergence from xenon anaesthesia is faster than that from other inhalation anaesthetics (which we demonstrated previously to be the case4), and that it is influenced less by duration of anaesthesia.5 In order to test the latter prediction, we conducted a randomized, controlled study to examine the correlations between duration of anaesthesia and emergence times in patients anaesthetized with equal MAC xenon, nitrous oxide–sevoflurane or nitrous oxide–isoflurane for various lengths of time.

Patients and methods

The methods were similar to those of our previous investigation4 with slight modifications.

After written informed consent was obtained, we studied 54 ASA I or II patients of both sexes, aged 32–64 yr, undergoing elective lower abdominal surgery (mainly gynaecological procedures) according to a design approved by the Institutional Human Studies Committee of Teikyo University. Patients with pulmonary, cardiovascular, hepatic, renal or neurological diseases were excluded. Also excluded were patients receiving medications known to influence anaesthetic or analgesic requirements and those who had contraindications to extradural anaesthesia (e.g. coagulopathy, history of allergic reactions to local anaesthetics, patient’s refusal). Preanaesthetic laboratory values were within normal limits.

When the unpremedicated patient arrived in the operating theatre, midazolam 30 μg kg⁻¹ was administered i.v. An extradural catheter was placed at the L2–3 interspace, through which 1.5% mepipvacaine with adrenaline 1:200 000 were administered, 3 ml as a test dose, followed 3 min later by an additional 9–12 ml depending on the height of the patient. If a sensory level to pinprick of T10 or higher was not obtained within 15 min, the extradural catheter was judged to be functioning inadequately and the patient was excluded from the study. A well-functioning extradural catheter was provided fast emergence from anaesthesia, regardless of the duration of anaesthesia. (Br. J. Anaesth. 1997; 79: 595–599).

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regarded as an essential component of our anaesthetic technique because of the MAC value of xenon (71%) and our desire to avoid other systemic suppletions while assuring patient comfort.

Patients were allocated randomly to one of three anaesthetic treatment groups: xenon, nitrous oxide–sevoflurane or nitrous oxide–isoflurane (n = 18 per group). General anaesthesia was induced with fentanyl 2 μg kg⁻¹ and thiopentone 4 mg kg⁻¹ i.v., and the trachea was intubated with the aid of vecuronium 10 mg i.v. Patients were then denitrogenated for 30 min using an inflow of oxygen 8 litre min⁻¹ in order to suppress nitrogen accumulation within the system during subsequent closed-circuit anaesthesia.⁶ During this denitrogenation period, anaesthesia was maintained with 1% isoflurane (xenon and nitrous oxide–isoflurane groups) or 1.8% sevoflurane (nitrous oxide–sevoflurane group). The end-tidal concentration of carbon dioxide ($E_{\text{CO}_2}$) was maintained at 4.0–4.7 kPa with mechanical ventilation. If clinically indicated, adrenaline 4–8 mg or phenylephrine 50–100 μg were administered i.v. to maintain systemic arterial pressure at acceptable levels.

Routine monitoring devices included an oesophageal stethoscope with a temperature sensor, ECG (lead II), automated arterial pressure cuff and pulse oximeter. End-tidal concentrations of nitrous oxide, carbon dioxide, sevoflurane and isoflurane were monitored continuously with an infrared gas analyser (PM 8050, Drägerwerk, Lübeck, Germany). The end-tidal concentration of xenon was monitored continuously using a xenon analyser (Anzai Medical, Tokyo, Japan), which was calibrated before each case with the use of an 80% xenon–20% oxygen mixture analysed to ±0.02% accuracy (Nihon-Sanso, Tokyo, Japan). The effective working range for this monitor was 1–100% with an error of ±1% and 90% response time of less than 1 s.

Thirty minutes after induction of anaesthesia when denitrogenation was complete, xenon, nitrous oxide–isoflurane or nitrous oxide–sevoflurane was started. For the xenon patients, oxygen was stopped and the upright ventilator bellows was deflated completely and refilled quickly with 100% xenon. Xenon was then started at 2 litre min⁻¹. Two to three minutes later when the end-tidal concentration reached 60%, xenon flow was reduced, oxygen was resumed and the anaesthesia system was closed in order to minimize subsequent expenditure of xenon. During closed-circuit anaesthesia, fresh inflow rates of xenon and oxygen were adjusted to maintain the end-tidal concentration of xenon at 60%. Xenon inflow was recorded every minute in seven patients for whom the anaesthesia system was made highly leak-free (leak <30 ml min⁻¹ at a constant circuit pressure of 20 cm H₂O). When the end-tidal oxygen concentration decreased to less than 20% because of accumulation of nitrogen, the system was flushed with a 60% xenon–40% oxygen mixture. Although no additional volatile anaesthetic was administered after xenon was started, our pilot study revealed that 0.1–0.2% isoflurane was always detected in the system, presumably because the isoflurane vapour contained within the patient’s lungs at the time of circuit closure was retained in the breathing system. Therefore, it was estimated that patients in the xenon group were receiving approximately 0.9 MAC of anaesthesia, assuming additivity of MAC, because xenon and isoflurane provided 60/71 = 0.84 and 0.1/1.15 = 0.085 MAC, respectively. In order to provide the same MAC fractions in the nitrous oxide–sevoflurane and nitrous oxide–isoflurane groups, end-tidal concentrations of nitrous oxide, sevoflurane and isoflurane were maintained at 60%, 0.7% and 0.5%, respectively.³⁷ The total inflow of 3 litre min⁻¹ was used in the nitrous oxide–volatile anaesthetic groups.

In addition, all patients received continuous extradural infusion of 1.5% mepivacaine containing adrenaline 1:200 000 at 6 ml h⁻¹, started immediately after induction of anaesthesia. When xenon or nitrous oxide was started, the extradural infusion rate was adjusted to maintain mean arterial pressure and heart rate within 20% of preoperative values. Additional doses of vecuronium or pancuronium were administered if indicated clinically. Body temperature was maintained with the use of a warming mattress placed on the operating table. I.v. fluids were also warmed.

Before skin closure, residual neuromuscular block was antagonized by neostigmine 2.5 mg and atropine 1.0 mg i.v., and spontaneous ventilation was allowed to return. At the end of operation, all inhalation anaesthetics were discontinued and oxygen 8 litre min⁻¹ was administered. $E_{\text{CO}_2}$, ventilatory frequency and oesophageal temperature were recorded at this time. An investigator who was blinded to the anaesthetic regimen administered recorded the times from discontinuation of the anaesthetics until patients opened their eyes on verbal command and were judged ready for extubation (i.e. in addition to opening eyes, they either squeezed the investigator’s hand or took a deep breath on command and showed a regular breathing pattern). Furthermore, times when patients regained orientation, that is when they were able to correctly state their name, date of birth and name of the hospital, were recorded. Finally, times when patients could count backwards from 10 to 1 in less than 15 s were recorded. These emergence times were assessed at either 30-s (eye opening and extubation) or 60-s (orientation and counting backward) intervals. Fifteen minutes after tracheal extubation when the continuous extradural infusion was stopped, extradural block level to pinprick was examined, and patients were asked to rate their incisional pain using a 0–10 verbal rating scale, with 0 and 10 being no pain and the worst pain imaginable, respectively. The incidence of nausea or vomiting during the first 1 h after extubation was also recorded, and antiemetics (e.g. metoclopramide 10 mg i.v.) were administered as necessary. All patients were asked 24 h after operation if they had recall of intraoperative events.

**STATISTICAL ANALYSIS**

To evaluate the correlations between duration of anaesthesia and each emergence time, a regression
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line was constructed by the least squares method for each anaesthetic regimen. Because no significant correlation was found for the xenon and nitrous oxide–sevoflurane groups, they were compared with respect to each emergence time using an unpaired \( t \) test. Data (except duration of anaesthesia, pain rating, extradural analgesia level and incidence of nausea/vomiting) are reported as mean (SD) and were analysed using analysis of variance (ANOVA) followed by Dunnett’s \( t \) tests with the xenon group as a control. The incidence of postoperative nausea/vomiting was analysed using a chi-square test. The remainder are expressed as median (range) and were analysed using the Kruskal–Wallis test with Mann–Whitney \( U \) tests used to assess differences between the xenon and other groups. \( P<0.05 \) was considered statistically significant.

**Results**

The three groups were comparable in age, height and weight (table 1). Duration of anaesthesia after the start of xenon or nitrous oxide anaesthesia was 58–380 min and did not differ between groups (table 1).

The rates of recovery from xenon and nitrous oxide–sevoflurane anaesthesia to four different end-points did not correlate with duration of anaesthesia, whereas those from nitrous oxide–isoflurane anaesthesia did (fig. 1A–D). Mean emergence times from xenon vs nitrous oxide–sevoflurane were: 3.3 (1.0) vs 5.6 (1.4) min to opening eyes; 3.6 (1.0) vs 6.3 (1.0)

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**Table 1** Patient data (mean (SD or range) or median [range])

<table>
<thead>
<tr>
<th></th>
<th>Xenon</th>
<th>N(_2)O–sevoflurane</th>
<th>N(_2)O–sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>44 (33–58)</td>
<td>45 (32–64)</td>
<td>43 (34–56)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158 (7)</td>
<td>156 (7)</td>
<td>157 (8)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58 (7)</td>
<td>56 (8)</td>
<td>56 (10)</td>
</tr>
<tr>
<td>No. of males</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>162 [58–380]</td>
<td>144 [58–303]</td>
<td>127 [61–296]</td>
</tr>
</tbody>
</table>

**Table 2** Postoperative data. End-tidal carbon dioxide concentrations (\( \mathrm{CO}_2 \)), ventilatory frequency and oesophageal temperature (temp.) were measured at the end of operation. Extraludal dose = total volume of 1.5% mepivacaine with adrenaline 1:200 000 administered extradurally until 15 min after extubation. Pain rating = numerical quantification of incisonal pain by the patient using a 0–10 verbal rating scale, with 0 and 10 being no pain and worst pain imaginable, respectively. Data are reported as mean (SD) or median [range]

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>( \mathrm{CO}_2 ) (kPa)</td>
<td>5.6 (0.5)</td>
<td>5.6 (0.7)</td>
<td>5.9 (0.5)</td>
</tr>
<tr>
<td>Ventilatory frequency (bpm)</td>
<td>21 (4)</td>
<td>23 (5)</td>
<td>20 (5)</td>
</tr>
<tr>
<td>Oesophageal temp. (°C)</td>
<td>36.0 (0.2)</td>
<td>35.8 (0.2)</td>
<td>35.9 (0.3)</td>
</tr>
<tr>
<td>Extraludal mepivacaine dose (ml)</td>
<td>36 (16)</td>
<td>32 (13)</td>
<td>31 (14)</td>
</tr>
<tr>
<td>Pain rating</td>
<td>3 [0–5]</td>
<td>2 [0–4]</td>
<td>2 [0–5]</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>9</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

**Figure 1** Correlations between duration of anaesthesia and emergence times from anaesthesia after xenon (●), nitrous oxide–sevoflurane (○) or nitrous oxide–isoflurane anaesthesia (●●) to four different end-points: from discontinuation of anaesthetic until patients could (A) open their eyes, (B) had their tracheas extubated, (C) state their name, date of birth and name of the hospital correctly (orientation), and (D) count backwards from 10 to 1 in less than 15 s. Each regression line was constructed by the least squares method. Whereas emergence times from nitrous oxide–isoflurane were correlated linearly with duration of anaesthesia \( (P<0.001) \), there was no significant correlation for xenon and nitrous oxide–sevoflurane, indicated by the broken regression lines.
Figure 2  Inflow rate of xenon during closed-circuit anaesthesia. Data are mean (SD) for the number of patients indicated (parentheses). The least squares method revealed that (xenon inflow in ml min\(^{-1}\)) \(n\) \(=\) 0.005((time on xenon in min)\(^{1/2}\) -1), \(r^2\) = 0.75 (P<0.001).

Discussion

We have demonstrated that xenon was associated with fast emergence from anaesthesia, regardless of duration. This was also the case with nitrous oxide–sevoflurane, although emergence times were approximately twice as long as those after xenon. In contrast, duration of anaesthesia had a significant impact on recovery from nitrous oxide–isoflurane. It was prolonged markedly after a long anaesthetic but was only slightly slower than that after xenon with a brief anaesthetic. The results are consistent with the widely accepted concept that lower blood:gas partition coefficients render emergence less dependent on duration of anaesthesia because of less accumulation of anaesthetic in body tissues.5 This concept, however, assumes that the MAC fractions required to achieve each end-point of emergence are similar for different anaesthetics, although this assumption has been questioned recently8 and xenon has never been compared with other agents in this regard. Other factors potentially influencing the rate of emergence such as age, sex, body temperature, pain and amount of supplementary anaesthetics and analgesics administered (including extradural local anaesthetic) did not differ between the three anaesthetic groups. Minute ventilation was also probably comparable because the end-tidal carbon dioxide concentration and ventilatory frequency at the end of operation were similar.

Our results also suggest that the quality of emergence after prolonged anaesthetics might be different between xenon and other inhalation agents, especially nitrous oxide–isoflurane. For example, when anaesthetics lasting more than 3 h are considered, all six patients who received xenon were oriented and able to count backwards by 5 and 8 min, respectively, whereas four of six patients anaesthetized with nitrous oxide–isoflurane were unable to open their eyes by 8 min. In accordance with this, patients in the xenon group in general appeared less sedated and more clear-headed in the post-anaesthesia period. Although it remains to be determined whether or not these characteristics lead to earlier “ward-readiness”, xenon appears to have significant clinical potential in the setting where rapid, clear emergence is important.

The inflow rate of xenon required to conduct closed-circuit anaesthesia, which theoretically equals uptake by a patient, declined exponentially with time and followed a similar temporal pattern as those of other inhalation anaesthetics.9 This has profound economical implications when expensive agents such as xenon are used, because the mean hourly expenditure, and hence cost, would be progressively lower with more prolonged anaesthetics. In this study, 2-, 3- and 4-h anaesthetics required approximately 10, 11.4, and 12.3 litre of xenon, including that used to initially increase the end-tidal concentration to 60%. The respective acquisition costs were approximately UK£80.00, £91.20 and £98.4, respectively (xenon costs UK£8.00 per litre in Japan). In comparison, nitrous oxide–isoflurane and nitrous oxide–sevoflurane anaesthesia with a total inflow of 3 litre min\(^{-1}\) cost UK£28.50 and £30.00 for 2 h, £42.75 and £45.00 for 3 h, and £57.00 and £60.00 for 4 h, respectively. (The prices of isoflurane and sevoflurane in Japan are the same, UK£0.50 per ml of liquid agent. Nitrous oxide costs UK£0.10 per litre of gas.) Thus the differences in cost between xenon and nitrous oxide–volatile anaesthetic combinations become smaller with a longer duration of administration. It could be reduced further by using the circuit priming method described elsewhere10 instead of using high flow for the first 3 min as we did in this study. At the current price, however, xenon anaesthesia is still expensive. Whether or not the potential benefits of xenon, such as rapid recovery as demonstrated in this study, are sufficient to merit the increased costs remains to be determined.

In summary, we have demonstrated that xenon was associated with rapid emergence from anaesthesia, regardless of duration, which is consistent with its low blood:gas partition coefficient. In addition, uptake rate declined exponentially over time to less than 30 ml min\(^{-1}\) after 2 h of anaesthesia. These properties, together with its inert nature predicting
low toxicity, would make xenon a favourable choice for prolonged anaesthesia. Further evaluation of its clinical characteristics and a cost–benefit ratio are warranted to determine if this “close-to-ideal” anaesthetic gas\textsuperscript{11} can be adopted in clinical practice.

References