Bispectral analysis of the electroencephalogram does not predict responsiveness to verbal command in patients emerging from xenon anaesthesia

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The bispectral index (BIS) is derived empirically from the electroencephalogram database of patients receiving common anaesthetics, but it may not be valid for uncommon agents. Therefore, we investigated how xenon affects the BIS. Nine and 11 patients were anaesthetized with 0.8 of the minimal alveolar concentration (MAC) of isoflurane (0.92%) and xenon (56%), respectively. After the end of operation, these concentrations were decreased in decrements of 0.1 MAC (isoflurane 0.12% or xenon 7%) and each new concentration was maintained for 15 min. This was repeated until the patient first opened her eyes or squeezed the investigator’s hand on command. Isoflurane and xenon at 0.8 MAC reduced the BIS to a median of 40 (range 36–53) and 36 (30–61), respectively. With decreasing concentrations of isoflurane, the BIS increased progressively and it reached a median of 96 (90–98) when the patients awoke. In contrast, four patients receiving xenon responded to verbal command while the BIS was below 50 (median 45 (range 41–49)). The remaining seven patients in the xenon group awoke when their BIS was greater than 80 [median 96 (range 82–98)], but in four of them the BIS was no greater than 50 when the xenon concentration was only 0.1 MAC (7%) higher than that associated with awakening. We conclude that low BIS values (<50) do not guarantee adequate hypnosis during xenon anaesthesia.


Keywords: anaesthesia, general; anaesthetics, gases, xenon; anaesthetics, volatile, isoflurane; monitoring, electroencephalography; measurement techniques, spectroscopy

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The bispectral index (BIS) is an electroencephalogram (EEG)-derived univariate scale reflecting the level of hypnosis in anaesthetized patients.¹ Because the algorithm to compute the BIS was formulated empirically on the basis of the EEG data of patients receiving common anaesthetics such as isoflurane and propofol,¹ the BIS may not necessarily be valid for other agents. For example, ketamine does not affect the BIS value when administered at doses that produce unconsciousness.² ³

Xenon is an inert gas with many favourable characteristics as an anaesthetic,⁴ including a low blood/gas partition coefficient (0.12),⁵ a minimal alveolar concentration (MAC; 71%)⁶ that is lower than that of nitrous oxide but analgesic properties similar to those of nitrous oxide,⁷ ⁸ a lack of toxicity, and harmlessness to the environment. However, xenon was not considered when the algorithm for the BIS was formulated, and whether the BIS appropriately reflects the depth of anaesthesia produced by this gas has not been investigated. Therefore, we performed a randomized prospective study to characterize how the BIS changes as the concentration of xenon is decreased during emergence from anaesthesia until the patient awakens and regains responsiveness to verbal command.

Patients and methods
Written consent to participation in the study was obtained from 20 women of ASA physical status I or II, who were

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aged 38–56yr and were scheduled for elective total abdominal or vaginal hysterectomy. The women were studied according to a protocol approved by the Institutional Human Studies Committee of Teikyo University. Exclusion criteria included a history or the presence of neurological diseases, ingestion of medications known to influence anaesthetic or analgesic requirements, and contraindications to extradural anaesthesia.

The unpremedicated patients had an extradural catheter placed at the L2/3 interspace, and after a 3 ml test dose, 10 ml of mepivacaine 1.5% with 1:200,000 epinephrine was administered. If the sensory level of T10 or higher to pinpricks was not obtained within 15min, the extradural catheter was judged to be functioning inadequately and the patient was not included in the study.

In addition to routine monitoring devices, the EEG signal was acquired using four electrodes (ZipprepTM; Aspect Medical Systems, Natick, MA, USA) applied to the forehead, with one on each outer malar bone, one at the centre of the forehead and one (ground) on either side of the centre electrode. The BIS (version 3.22) value and the 95% spectral edge frequency (SEF95) were displayed using an Aspect EEG monitor (Model A-1050; Aspect Medical Systems) and were stored every 5s on a personal computer for later off-line analysis throughout the study.

The patients were assigned randomly to receive either xenon (n=11) or isoflurane (n=9) for maintenance of anaesthesia. After a stable baseline EEG had been obtained with the patients’ eyes closed, those who were to receive xenon and isoflurane received propofol 2.5 mg kg⁻¹ intravenously (i.v.) and an inhalation of 5% sevoflurane, respectively, for induction of anaesthesia. The larynx and upper trachea were sprayed with 4% lidocaine 3 ml, and the trachea was then intubated with the aid of vecuronium 10mg i.v. In the xenon group, anaesthesia was maintained with 56% xenon (0.8 MAC) in oxygen using a closed breathing system (all concentrations of inhalational anaesthetics are end-tidal). The isoflurane group received isoflurane 1.0–1.5% in a 6litre min⁻¹ flow of oxygen, which was reduced to 0.92% (0.8 MAC) at least 15 min before the end of surgery. All patients also received a continuous extradural infusion of 1.5% mepivacaine containing 1:200,000 epinephrine at 6–8 ml h⁻¹ to maintain the mean arterial pressure and heart rate within 20% of the preoperative values. The lungs were ventilated mechanically to maintain the end-tidal concentration of carbon dioxide (CO₂) at 30–35 mm Hg, and additional doses of vecuronium were administered if clinically indicated. The body temperature, measured with an oesophageal sensor, was maintained by the use of a warming mattress placed on the operating table. Intravenous fluids were also warmed.

The end-tidal concentration of xenon was monitored continuously using a xenon analyser (Anzai Medical, Tokyo, Japan), the effective working range of which was 1–100% with error <1% and 90% response time less than 1s. This device measures absorption by the gas mixture of a characteristic x-ray, which is proportional to the concentration of xenon in the gas mixture. The end-tidal concentrations of carbon dioxide and isoflurane were measured using an infrared analyser (Capnomac Ultima; Datex, Helsinki, Finland). In the xenon group, an in-line infrared capnogram (Hewlett-Packard, Waltham, MA, USA) was used instead. These analysers were calibrated before each use according to the manufacturers’ instructions.

Shortly before the end of surgery, residual neuromuscular blockade was reversed with neostigmine 2.5 mg and atropine 1.0 mg i.v. and recovery was verified by the train-of-four response to ulnar nerve stimulation. When surgery was complete, a designated investigator, blinded both to the anaesthetic administered and to the EEG data, asked the patient in a normal tone to open her eyes and to squeeze and release the investigator’s hand. If the patient failed to follow both of these commands, the end-tidal concentration of xenon or isoflurane was reduced by 7 or 0.12%, respectively (both approximately 0.1 MAC). The new concentration was maintained for 15 min. During this period, the patient’s ability to respond to verbal commands was checked every 5min and whenever clinical signs of imminent awakening, such as coughing, bucking and frowning, were noted. If no response was observed for the entire 15 min period, the concentration of anaesthetic was reduced again. This process was repeated until an alveolar concentration was reached at which the patient responded appropriately to either one of the commands. This concentration was termed the awakening concentration. Care was taken to minimize stimuli other than verbal commands during the entire wake-up period. Mechanical ventilation was continued during the entire period. When coughing or bucking hindered effective ventilation with positive pressure, the patient was allowed to breathe spontaneously.

The BIS and SEF95 values at each concentration at which no response to verbal command was observed during the entire 15-min equilibration period were calculated by averaging the values obtained over the last 3min of that period. At the awakening concentration, the values displayed at the time of the patient’s response were recorded. The data from right- and left-sided electrodes were averaged.

Fifteen minutes after tracheal extubation, the extradural block level to pinpricks was examined, and the patient was asked to rate her incisional pain using a verbal rating scale of 0–10, values of 0 and 10 representing no pain and the worst pain imaginable, respectively. All patients were asked 2h after the operation if they remembered being called by their name when they woke up.

The BIS values, the postoperative pain ratings and the extradural analgesia levels are reported as median (range) and were analysed using Mann-Whitney U-tests. Other data are presented as mean (SD) and were analysed using unpaired t-tests. A P value less than 0.05 was considered statistically significant.
Results

The two anaesthetic treatment groups were comparable with respect to the patients’ characteristics, the BIS and SEF\textsubscript{95} values recorded before induction of anaesthesia, and the postoperative data listed in Table 1.

The 0.8 MAC concentrations of isoflurane and xenon reduced the BIS to 40 (36–53) and 36 (30–61) and the SEF\textsubscript{95} to 13.6 (2.2) and 8.3 (4.2) Hz, respectively (Figs 1 and 2). The BIS did not differ between the groups, whereas the SEF\textsubscript{95} was significantly lower with xenon.

The patients who received isoflurane and xenon awoke at the end-tidal concentrations of 0.36 (0.06) and 31 (7%), respectively. Those who received isoflurane demonstrated progressively increasing BIS and SEF\textsubscript{95} as the anaesthetic concentration was decreased (Figs 1 and 2, upper panel). On awakening, these values were 96 (90–98) and 25.1 (2.3) Hz, respectively.

Xenon was markedly different from isoflurane in the BIS value on awakening. Four patients in the xenon group awoke while their BIS values were less than 50 (45 (41–49)) and had not appreciably increased from those observed at higher concentrations of xenon (Fig. 1, lower panel). The remaining seven patients awoke with the BIS greater than 80 (96 (82–98)), but in four of them the BIS value was no greater than 50 when the concentration of xenon was only 0.1 MAC (7%) higher than the awakening concentration (Fig. 1, lower panel).

The SEF\textsubscript{95} values of the xenon group changed similarly to the BIS (Fig. 2, lower panel). Thus, all four patients who awoke with their BIS below 50 and one who did so at a BIS of 82 showed relatively low SEF\textsubscript{95} values on awakening (11.1 (2.9) Hz, range 6.7–14.0 Hz). On the other hand, the remaining six patients awoke at a SEF\textsubscript{95} value of 25.0 (3.2) Hz, but in three of them the SEF\textsubscript{95} value was relatively low (<12 Hz) when the xenon concentration was only 0.1 MAC higher than that associated with awakening.

No subject experienced major anaesthesia-related adverse events. When interviewed postoperatively, none of the four patients who awoke with the BIS below 50 remembered that they were called by their name when they were waking up, while two of the seven patients who awoke with the BIS greater than 80 remembered it vaguely.

![Fig 1 Changes in the BIS values in each patient with decreasing concentrations of isoflurane (upper panel) or xenon (lower panel) until they demonstrated the first response to verbal command (awakening). The symbols X and O indicate the absence and presence of response to verbal command, respectively. Pairs of symbols connected by the broken lines were recorded at the same absolute concentration of xenon. This was because, depending on the awakening concentration for each individual, the 0.2 or 0.3 MAC higher concentrations of xenon were equal to 0.8 MAC.](image)

<table>
<thead>
<tr>
<th>Patient characteristics and postoperative data</th>
<th>Xenon</th>
<th>Isoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>47 (5)</td>
<td>46 (4)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156 (3)</td>
<td>156 (5)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>54 (6)</td>
<td>59 (7)</td>
</tr>
<tr>
<td>Preinduction BIS</td>
<td>98 (93–98)</td>
<td>98 (90–98)</td>
</tr>
<tr>
<td>Preinduction SEF\textsubscript{95} (Hz)</td>
<td>18.6 (5.0)</td>
<td>19.9 (3.9)</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>115 (39)</td>
<td>121 (34)</td>
</tr>
<tr>
<td>Oesophageal temperature (°C)</td>
<td>36.0 (0.1)</td>
<td>35.9 (0.2)</td>
</tr>
<tr>
<td>Extradural dose (ml)</td>
<td>28 (4)</td>
<td>29 (6)</td>
</tr>
<tr>
<td>Extradural level</td>
<td>T7 (T4–T11)</td>
<td>T9 (T6–T11)</td>
</tr>
<tr>
<td>Pain rating</td>
<td>2 (0–3)</td>
<td>2 (0–4)</td>
</tr>
</tbody>
</table>

Table 1 Patient characteristics and postoperative data. The extradural dose is the total volume of 1.5% mepivacaine with 1:200 000 epinephrine administered extradurally until 15 min after removal of the tracheal tube. The extradural level was checked using pinpricks 15 min after removal of the tracheal tube. The pain rating was the numerical quantification of incisional pain by the patient using a verbal rating scale of 0–10, 0 and 10 representing no pain and the worst pain imaginable, respectively. Data are mean (sd) except for the BIS values, the extradural level and the pain rating, which are median (range).
were observed rarely. This strongly suggests that a positive response to a simple verbal command is sufficient evidence that the subject is awake.

The second issue involves a computational delay of the BIS monitor device. The BIS value reported by the monitor represents an average value derived from the previous 60 s of usable EEG data. Therefore, it is possible that the patients whose BIS values on awakening were less than 50 had experienced an increase in the BIS within the 60 s preceding awakening and that their BIS values at the exact moment of awakening were actually greater than 50. However, we believe this is unlikely because we provided a quasi-stable level of anaesthesia for 60 s preceding the moment of awakening by maintaining the end-tidal concentration of xenon constant, except for stepwise reductions at every 15 min, and by leaving the patients undisturbed as much as possible. Moreover, even if this increase actually occurred, this does not invalidate our conclusion that the low BIS may be associated with the near-awakening state during xenon anaesthesia, because the BIS stayed low until less than 60 s before awakening.

We can speculate how a level of xenon anaesthesia sufficiently light to permit a response to verbal command was associated with a BIS less than 50 in some patients, as the BIS computation algorithm has not been published. Our results demonstrated that, when the xenon patients awoke while their BIS were less than 50, their EEGs were always slowed, as indicated by the SEF<sub>95</sub> values of no greater than 14 Hz. In marked contrast, isoflurane permitted our patients to awaken only after their SEF<sub>95</sub> had increased to above 20 Hz. Because the BIS generally decreases as the power of the EEG high-frequency components declines, it is not surprising that the patients who awoke with low SEF<sub>95</sub> also had low BIS values.

This study has several limitations. First, we used extradural analgesia, which may affect the sensitivity of the brain to general anaesthetics. Whether it disturbs the relationship between the BIS and the clinical level of hypnosis is unknown. Secondly, we studied only females, although the relationship between the dose of anaesthetics and the BIS may be sex-dependent. Thirdly, we studied only one end-point of hypnosis, i.e., the presence or absence of responses to verbal command, although other endpoints, especially memory formation, are also clinically relevant. It is reassuring that the four patients of the xenon group who awoke with BIS below 50 did not recall that they had been called by their names when waking up. However, the number of the patients studied was too small to draw any firm conclusion about whether low BIS values guarantee loss of memory formation during xenon anaesthesia.

In summary, we have demonstrated that BIS values less than 50 do not guarantee adequate hypnosis during xenon anaesthesia. Therefore, other modalities for monitoring the hypnotic level are required if xenon is to be used in clinical practice.

**Discussion**

Our results for isoflurane are consistent with the well-documented reliability of the BIS as an indicator of the depth of anaesthesia. However, this is not the case for xenon. Most remarkably, 37% (4/11) of the patients responded to verbal command when their BIS value was lower than 50, which would normally indicate deep hypnosis.

In addition, among the remaining seven patients who awoke with their BIS greater than 80, four had BIS values no greater than 50 when the concentration of xenon was only 0.1 MAC (7%) higher than that associated with awakening. Therefore, we conclude that those who are anaesthetized with xenon can be awake or in the near-awakening state even when their BIS values are no greater than 50.

Two issues need to be addressed when considering the validity of our data. First, one may argue that the behaviours we used as the end-point of awakening (eye-opening and hand-squeezing) were too simple to distinguish a non-specific or reflexive reaction to hearing a voice from a conscious and deliberate response to the command. However, a recent investigation that evaluated the level of hypnosis using graded and varied stimuli and multiple verbal commands demonstrated that the participants either responded fully to all the stimuli and commands or showed no responses at all. Intermediate levels of responsiveness...
Acknowledgements
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