Being awake intermittently during propofol-induced hypnosis: A study of BIS, explicit and implicit memory

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Background: Being awake during anaesthesia is a serious complication. An anaesthetic depth monitor must discriminate in real time between wakefulness and unconsciousness. The present study created a period of wakefulness during propofol-induced hypnosis. Bispectral index (BIS), explicit and implicit memories of the awake period were investigated.

Methods: Ten volunteers were studied. The calculated brain concentration of a target controlled infusion of propofol was increased until loss of response (LOR) to verbal command and then propofol was stopped. When fully awake, volunteers were presented with a picture, sound and smell. Propofol infusion was restarted until LOR and then ceased. BIS and the calculated brain concentration of propofol were recorded every minute. A structured interview was conducted for explicit memories after awakening and for explicit as well as implicit memories the day after.

Results: Median BIS-index for the transition between awake and asleep and vice versa differed significantly. It was not possible, however, to establish any threshold value or zone for discriminating between wakefulness and LOR due to the large interindividual variations in BIS-index. No volunteer could explicitly recall any of the stimuli presented during the period of wakefulness.

Conclusion: The BIS-index decreases with increasing sedation but because of the large individual variations, the real-time BIS-index for the individual subject cannot reliably discriminate wakefulness from unconsciousness during propofol infusion. Propofol causes such profound amnesia that lack of postoperative recall does not assure that episodes of awareness have not occurred during propofol-induced hypnosis.

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Key words: Propofol; bispectral index; loss of response; target controlled infusion; amnesia; awareness.

The bispectral index (BIS) of the electroencephalogram has been studied during propofol sedation in a number of studies looking at the relation between BIS and increasing depth of sedation (1–3). Nearly all these studies have shown that BIS decreases almost linearly with an increasing level of sedation. The aim of the present study was not to determine the BIS vs. sedation relationship, but rather to determine to what extent the real-time BIS-index is able to discriminate wakefulness from unconsciousness in the individual patient. One of the major indications for a monitoring modality like BIS is to guarantee an adequate level of hypnosis, while avoiding unnecessarily deep but also too light levels of anaesthesia/hypnosis with the risk for awareness and experiencing sensations during surgery. Awareness during anaesthesia with post-operative recall is an infrequent but serious complication (4). Correlations with average values are not sufficient for a depth of anaesthesia/hypnosis monitor that is to prevent awareness. Such a monitor must detect in real time the few individual patients for whom clinical signs of light anaesthesia are not sufficiently discriminating.

The present study was designed to mimic an episode of awareness, which is being awake during propofol hypnosis. The aim of the study was to determine whether BIS is able to discriminate wakefulness from unconsciousness in volunteers during propofol sedation and to study explicit and implicit recall of a visual, auditory and olfactory stimulus presented during that intentional period of wakefulness in the course of propofol hypnosis.

Methods

Ten healthy adult volunteers (age 32–48 years, male/female = 3/7, weight 57–98 kg) were studied after approval from the hospital ethics committee and informed consent. Four EEG electrodes were placed on the subject’s forehead for monitoring (Aspect Medical...
Systems; version 3.12, Natick, MA, USA) and the BIS-index was measured continuously. ECG and pulse oximetry were also monitored continuously.

**Study protocol**

The volunteers were pre-oxygenated (FiO\(_2\)=0.7) via a facemask for 3 min prior to induction. Propofol (10 mg/ml) was administered by a syringe pump. A target control infusion (TCI) system with a built-in algorithm for calculating brain “target” propofol concentration (Alaris Diprifusor®; Alaris Medical Systems Ltd, Hampshire, UK) was used. The TCI was initially set at a target concentration of 1 µg/ml. If the volunteer did not sleep within 1 min after the target concentration was reached, the target was increased by 0.5 µg/ml every other minute until loss of response to loud verbal command (LOR). The transition from awake, still responding to loud verbal command, to LOR to verbal commands was defined as when the subject no longer followed simple commands when addressed loudly by name and gently shaken on the shoulder. After LOR, the propofol infusion was stopped. When the subject was awake for at least 2 min and could converse alertly, he was presented with three stimuli: he was asked to smell and describe a smell, to look at and describe a picture, and to sing a song. The order of the stimuli was always the same and he was asked to recall the stimulus afterwards. The propofol infusion was restarted (as above) and the concentration increased until the subject again became unconscious, at which time the propofol infusion was stopped. BIS-index was measured throughout. When fully awake, approximately 30 min after the end of the experiment, the subjects were asked about any explicit recall. They were interviewed again 24 h later with a structured questionnaire including both explicit and implicit questions about the experiment. At the end of the second interview the volunteers were shown the three stimuli and asked if they seemed familiar.

Measurements for BIS, level of consciousness, and TCI concentration were recorded on 9 occasions:

1. Awake – base line.
2. Last awake value while still responding to verbal command.
3. First value when no longer responding to verbal command.
4. Last value before awakening and responding to verbal command.
5. First value when awake – responding to verbal command.
6. Last value while still responding to verbal command before becoming unconscious a second time.
7. First value when no longer responding to verbal command a second time, LOR 2.
8. Last value while still not responding to verbal command before awakening.
9. First value when awake and responding to verbal command second time.

The stimulus, the picture, the sound and the smell, were presented 2 min after time point 5 when awake and responding promptly to command.

**Statistics**

All values are given as median and range unless otherwise stated. Differences were studied (Macintosh StatView) by means of non-parametric test, Kruskal-Wallis test and Mann-Whitney U-test and a \( P<0.05 \) was considered statistically significant. Sensitivity was calculated by dividing the number of subjects fulfilling the defined clinical criteria with the number of subjects with a defined monitor value \( >70 \). Specificity was calculated by dividing the number of subjects fulfilling the defined clinical criteria of unconsciousness with the number of subjects with BIS \( <70 \) or \( <50 \).

**Results**

The overall duration of the experiment was 26 min (range 21–33). All subjects became unresponsive at a calculated target propofol concentration of 1.4 µg/ml or more (median 2.4, range 1.4–3.3 µg/ml). Median BIS at LOR was 58 (range 24–75). After stopping the infusion all volunteers became awake at a calculated target propofol concentration of 2.3 µg/ml (range 1.3–3.5), and a BIS-index of 67 (range 51–85). During the awake period, with an average duration 8 (5–10) min, the volunteers became alert and responded promptly to the 3 stimuli.

Table 1 shows the median BIS-index and corresponding calculated propofol target concentrations at

<table>
<thead>
<tr>
<th>Event</th>
<th>BIS</th>
<th>Target concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Awake before propofol</td>
<td>97 (94–98)</td>
<td>0</td>
</tr>
<tr>
<td>2. Last awake value</td>
<td>68 (34–80)</td>
<td>2.1 (1.1–3.2)</td>
</tr>
<tr>
<td>3. First LOR</td>
<td>58 (24–75)</td>
<td>2.4 (1.4–3.3)</td>
</tr>
<tr>
<td>4. Last unconscious</td>
<td>51 (24–69)</td>
<td>2.5 (1.6–3.5)</td>
</tr>
<tr>
<td>5. First awake</td>
<td>67 (51–85)</td>
<td>2.3 (1.3–3.5)</td>
</tr>
<tr>
<td>6. Last awake</td>
<td>74 (63–88)</td>
<td>2.5 (1.5–3.1)</td>
</tr>
<tr>
<td>7. Second LOR</td>
<td>62 (43–78)</td>
<td>2.7 (1.9–3.3)</td>
</tr>
<tr>
<td>8. Second last unconscious</td>
<td>52 (27–66)</td>
<td>2.7 (1.7–3.2)</td>
</tr>
<tr>
<td>9. Second awake</td>
<td>60 (44–71)</td>
<td>2.5 (1.4–3.2)</td>
</tr>
</tbody>
</table>
the various time points. By including all four transition values between awake and LOR (or vice versa), a significant difference was seen in BIS-index ($P<0.01$), but not in calculated propofol target concentration. Huge inter-individual differences were seen both in BIS-index and calculated target concentrations. The sensitivity for BIS to discriminate awake from LOR with BIS $>70$ was 79%. The specificity for a BIS $<70$ to detect LOR was found to be 62% and for BIS $<50$ 71% (Table 2).

None of the 10 volunteers had any memories from the experiment when interviewed shortly after the end of the procedure. During the structured interview the day after the experiment, none of them could recall any clear, explicit memories of any of the stimuli presented. Even after having been given associations, no one could remember what stimuli had been presented. Three persons had vague sensations, one of a colour, one of a smell and one of a sound. Even after having been presented with the actual stimuli, none of the volunteers had a clear memory or experience of the stimuli during anaesthesia.

**Discussion**

The present study was designed to mimic a brief period of wakefulness during hypnosis with propofol and to evaluate the ability of BIS to detect such an episode and those patients who might recall it. We found that the average BIS-index, but not the calculated target concentration of propofol, was able to discriminate between wakefulness, defined as sedated but still responding to loud verbal command, and loss of response, defined as no longer responding to loud verbal command. However, the sensitivity and specificity for BIS to discriminate responders and non-responders were less than 80% regardless of the chosen threshold value for discrimination. None of the 10 volunteers had any explicit or implicit recollection either of the stimulus presented while awake or of having been awake during propofol infusion.

In previous studies it has been shown that the BIS-index does not sensitively measure the effects of nitrous oxide, opioids or ketamine (5–8). The capacity for BIS to discriminate various stages of sedation/hypnosis with propofol has been studied in a number of earlier studies. Our results are very much in agreement with these studies. Glass et al. showed in volunteers that BIS predicted the level of sedation better than drug concentration, and that a BIS of 50 or less had a “high probability” for loss of consciousness and recall. They also found that propofol at even subhypnotic doses produced profound memory impairment (1). Lui et al. found large individual variations in BIS in patients during propofol sedation, similar to results shown in the present study. Interestingly, in their study, a picture was recalled in about 50% of the subjects at BIS values around 90 (2). Kearse et al. also studied BIS during propofol sedation in volunteers and found that mean BIS predicted the degree of clinical sedation better than propofol target concentration, but with huge individual variations in BIS (3). Our findings are also in agreement with the studies of both Gajraj et al. in patients undergoing day surgery (9) and Baker et al. during anaesthesia for cardioversion (10). BIS did change with increasing sedation and LOR, but there were very large individual differences in BIS values at all time points. When drug combinations are given, interpretation of BIS seems even more complicated and hypnotic end-point is usually reached at higher BIS values (3, 11). Doi et al. studied a number of electrophysiological techniques during propofol hypnosis and found no difference in BIS just before and after eye opening whereas auditory evoked potential index did show a difference (12). Struys et al. found BIS to be superior to spectral edge frequency and median frequency for assessing the hypnotic effects of propofol (13).

The existence of outliers is crucial in the evaluation of a monitor of anaesthetic depth that is to guarantee that no patient will be awake or able to recall information. Correlations between average BIS values and level of consciousness are not of major clinical interest, where the outliers are more important than average values. More than a fourth of the BIS measurements in the present study which were less than 50 occurred when volunteers were awake, and one was as low as 34. The fourth who were non-responding with BIS greater than 70 are also outliers, but of less clinical significance. It seems reasonable to conclude that BIS indeed decreases with increasing sedation, but because of the huge individual variations even when a hypnotic is used its accuracy to discriminate between wakefulness/awareness and unconsciousness is not encouragingly high.

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**Table 2**

Number of bispectral (BIS) index values registered during the propofol sedation/hypnosis (n=10) for 3 different BIS threshold values for loss of response (LOR).

<table>
<thead>
<tr>
<th>BIS-index</th>
<th>&gt;70</th>
<th>70–50</th>
<th>&lt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake</td>
<td>19</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>LOR</td>
<td>5</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>All</td>
<td>24</td>
<td>42</td>
<td>14</td>
</tr>
</tbody>
</table>
There are a number of limitations in the present study. Only the hypnotic effects of propofol were studied without any concomitant analgesia or anaesthesia, and therefore what was mimicked was wakefulness or awareness during propofol hypnosis and not during general anaesthesia. It is important to emphasise that this is an experimental study in volunteers becoming intermittently awake. During that awake period they were receiving three different stimuli; however, during this study no painful stimuli were applied and the only drug used was a continuous infusion of propofol.

Propofol target concentration was increased rather rapidly, as often is the case in clinical practice. The TCI algorithm is designed to allow for equilibration between the central compartment and the brain, but one may argue that the time interval between increases in target concentration was too short.

As BIS algorithms are continually being revised, comparisons between studies must take into account which update is being used. In the present study the BIS 1000 monitor with the 3.12 software was used and the real-time BIS values were recorded. A potential limitation of this study is that the BIS monitor has a delay of about 1 min. The BIS-index as observed on the monitor is, however, what the clinician is intended to respond to. The delay in signal processing may make the real-time values less credible. We wanted to simulate the clinical setting in which drugs are titrated according to the needs for each individual patient and relying on the real-time clinical parameters, movements, heart rate, blood pressure and optionally the BIS value.

In the present study we used a continuous infusion of propofol for sedation and hypnosis. The calculated target concentration at which the volunteers became unconscious differed by a factor of more than 2. The large inter-individual variation in dose–response to propofol has been reported earlier (14). The algorithm for calculation of propofol concentration will also introduce some errors, as shown by Hoymork et al. (15). TCI-systems should therefore be seen as a device that can facilitate drug delivery and emergence/recovery, but the calculated target concentration does not allow the determination of hypnotic depth in an individual patient. The amnesic effects of benzodiazepines are well recognised (16). The amnesic effects of propofol are less well described but a number of studies have shown similar results to ours. Veselis et al. showed profound effects on memory functions from propofol in volunteers (16, 17). Chortkoff et al. have shown that propofol suppresses recall of emotionally charged information during light propofol anaesthesia (14).

Nordstrom and Sandin showed that only 35% of patients undergoing incontinence surgery with propofol recalled having been awakened and being asked to cough (18).

In conclusion, while BIS-index correlated with increasing levels of sedation, it could not sensitively detect for the individual in real time fast changes in wakefulness during propofol infusion. Furthermore, propofol’s profound amnesia prevented recall of a period of being fully awake and actively participating in three distinct stimuli.

References

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