Relationship between calculated blood concentration of propofol and electrophysiological variables during emergence from anaesthesia: comparison of bispectral index, spectral edge frequency, median frequency and auditory evoked potential index

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Summary
We studied four electrophysiological variables (bispectral index (BIS), 95% spectral edge frequency (SEF), median frequency (MF) and auditory evoked potential index (AEP index)) in 10 patients during emergence from anaesthesia. We compared correlation of the signals with gradually decreasing calculated blood propofol concentrations, and evaluated the signal differences between preinduction and emergence from anaesthesia. Values of BIS, MF and SEF correlated with calculated blood concentrations of propofol during emergence from anaesthesia. The correlation was best with BIS, but was poor with MF and SEF at low calculated blood propofol concentrations. Although AEP index values did not correlate with calculated blood concentrations of propofol during emergence from anaesthesia, values after eye opening and before anaesthesia were well distinguished from those during emergence from anaesthesia. BIS correlated best with calculated blood concentrations of propofol. AEP index appeared to distinguish the awake from asleep state. (Br. J. Anaesth. 1997; 78: 180–184)

Key words

The major requirement of a monitor of anaesthetic depth is to distinguish consciousness from unconsciousness. Another desirable feature would be for the signal to provide an estimate of the effect of a given brain concentration of an anaesthetic agent to predict movement or awareness. Several processed EEG variables have been studied for use as a monitor of anaesthetic depth, including bispectral index, median frequency and 95% spectral edge frequency. Although middle latency auditory evoked potentials (MLAEP) have been reported to correlate well with anaesthetic depth and to be able to demonstrate potential awareness, MLAEP are usually obtained intermittently and the waveforms are difficult to use in the clinical situation. More recently, the auditory evoked potential index (formerly known as the level of arousal score), derived from auditory evoked potentials, has been proposed as a single numerical variable for monitoring depth of anaesthesia. The auditory evoked potential index reflects the morphology of the auditory evoked potential curves and is calculated from the amplitude difference between successive segments of the curve. A moving time average of the auditory evoked potential index is obtained at 3-s intervals.

The purpose of this study was to compare the four variables, bispectral index, median frequency, 95% spectral edge frequency and auditory evoked potential index, recorded simultaneously during emergence from propofol anaesthesia. In this situation, propofol concentrations in the brain would change in parallel with those in blood. We studied the correlation of the four variables with calculated blood concentrations of propofol, as a substitute for brain concentrations. The ability of the four variables to distinguish consciousness from unconsciousness was also investigated.

Patients and methods
After obtaining approval from the Ethics Committee and informed consent, we studied 10 female patients undergoing minor surgery: five for diagnostic laparoscopy, four for ligation of varicose veins and one for hysteroscopy. Mean age was 31.2 (range 17–49) yr and mean weight 60.9 (47–72) kg.

All patients were unpremedicated and had been fasted for at least 6 h. A single dose of fentanyl 50–75 μg was given immediately before induction of anaesthesia. Anaesthesia was induced and maintained with target-controlled infusions of propofol and a laryngeal mask was inserted. The target-controlled infusion system was operated by a three-compartment pharmacokinetic model “Diprifusor”. Mean

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values of minimum and maximum target blood concentrations of propofol during anaesthesia were 3.8 (range 2–5) and 9.6 (6–14) μg ml⁻¹, respectively. Anaesthesia was supplemented with 66% nitrous oxide in oxygen and ketorolac 10 mg i.v. Patients breathed spontaneously throughout the study. After discontinuation of propofol infusion and nitrous oxide inhalation, patients were prompted verbally to open their eyes. The observer was unaware of the values being measured. Consciousness was deemed to be present when patients opened their eyes to command.

SURFACE EEG ANALYSES

The EEG was obtained from four disposable silver–silver chloride electrodes (Zipprep, Aspect Medical Systems, MA, USA) placed on both sides of the outer malar bone (Atl and At2), with Fpz as the reference and Fpl as the ground. Impedance of the electrodes was confirmed to be less than 2000 Ω. Bispectral index, median frequency and 95% spectral edge frequency were measured using an EEG monitor (A-1000, BIS 3.0 algorithm, rev. 0.40 software, Aspect Medical Systems, MA, USA). Bispectral index, median frequency and 95% spectral edge frequency required at least 30 s to be fully updated. Data were stored automatically on a micro-computer (T1950CT, Toshiba, Japan) at 5-s intervals. The EEG before induction of anaesthesia was obtained when the patient's eyes were closed.

AUDITORY EVOKED POTENTIALS ACQUISITION

Auditory evoked potentials (AEP) were obtained using a similar system to that described in our previous study⁹ from three electrodes (Zipprep) placed at the right mastoid (+), and middle forehead (−), with Fp2 as the reference. The amplifier was custom-built with a 5 kV medical grade isolation. It had a common mode rejection ratio of 170 dB with balanced source impedance, input voltage noise of 0.3 μV (10 Hz–1 kHz rms) and current input noise of 4 pA (0.05 Hz–1 kHz rms). A third-order Butterworth analogue band-pass filter with a band-width of 1–220 Hz was used. The clicks were 70 dB above the normal hearing level and had a duration of 1 ms. They were presented at a rate of 6.9 Hz to both ears. The amplified EEG was sampled at a frequency of 1778 Hz by a 12-bit analogue-to-digital converter (PCM-DAS08, Computer Boards Inc., MA, USA) and was processed in real-time by the micro-computer. Auditory evoked potentials were produced by averaging 256 sweeps of 144 ms duration. The time required for a full update of the signal was 36.9 s, but a moving time averaging technique allowed a faster response time to any change in the signal. The auditory evoked potentials were obtained at 3-s intervals. The auditory evoked potential index is a mathematical derivative reflecting morphology of the AEP. The value was calculated as the sum of the square root of the absolute difference between every two successive 0.56-ms segment of the AEP waveform.¹²

Each variable was recorded simultaneously and mean values were obtained at intervals of 15 s. Mean values of the four variables were analysed using linear regression analysis against the calculated blood propofol concentration simulated by the “Diprifusor” pharmacokinetic model¹³ during the emergence phase of anaesthesia, after discontinuation of propofol infusion and nitrous oxide inhalation until eye opening. The 95% prediction bands of the values were also obtained. Minitab for Windows was used for statistical analysis. Mean values obtained in the 15-s period just before induction of anaesthesia and those in the 15-s period just after eye opening to command were compared with the 95% prediction band. Values before induction and after eye opening were also compared with values just before eye opening using the Kruskal–Wallis and Tukey's tests. \( P<0.05 \) was considered statistically significant.

Results

Mean duration of surgery and anaesthesia was 13.3 (range 5.5–30.2) min and 28.6 (18.6–46.1) min, respectively. Mean time interval from discontinuation of propofol infusion and nitrous oxide inhalation until eye opening was 8.6 (6.6–12.5) min. Mean calculated propofol concentration in blood at the time of eye opening was 1.9 (1.3–2.2) μg ml⁻¹.

Bispectral index values before eye opening correlated well with the calculated blood concentration of propofol (fig. 1). All bispectral index values before induction of anaesthesia and all values after eye opening were distributed in the 95% prediction band of the values before eye opening. Mean bispectral index values before and after eye opening did not differ from each other, but were significantly smaller than before induction of anaesthesia (fig. 5).

The 95% spectral edge frequency values before eye opening also correlated well with the calculated blood concentration of propofol (fig. 2). Although

![Figure 1](image)

Figure 1: Calculated propofol blood concentration vs bispectral index (O = before eye opening; • = after eye opening; × = before induction of anaesthesia). The linear regression line with 95% prediction band was analysed between calculated propofol concentration and values before eye opening. Bispectral index before eye opening was linearly related to propofol blood concentration (bispectral index = −12.8 (propofol) + 93.6, \( r^2 = 0.734 \), \( n = 349 \)).
most of the values after eye opening were distributed within the 95% prediction band, those before induction of anaesthesia were spread widely below the band. The 95% spectral edge frequency values at a propofol blood concentration of zero had poor correlation with the regression line during anaesthesia. Mean 95% spectral edge frequency values just before and after eye opening were not different from each other, but significantly larger than before induction of anaesthesia (fig. 5).

Median frequency values before eye opening also correlated with blood concentrations of propofol (fig. 3). Values after eye opening were small and distributed below the regression line. Values before induction of anaesthesia were very small and spread mainly below 8 Hz, far below the prediction band. Median frequency values at a propofol blood concentration of zero showed poor correlation with the regression line during anaesthesia. There was no difference in mean median frequency values before induction of anaesthesia, before eye opening and after eye opening (fig. 5).

Figure 2  Calculated propofol blood concentration vs 95% spectral edge frequency (SEF) (○ = eye opening; ● = after eye opening; × = before induction of anaesthesia). The linear regression line with 95% prediction band was analysed between calculated propofol concentration and values before eye opening. The 95% SEF before eye opening was linearly related to propofol blood concentration (95% SEF = −3.44 (propofol) + 27.9; r = 0.686, n = 349).

Figure 3  Calculated propofol blood concentration vs median frequency (○ = before eye opening; ● = after eye opening; × = before induction of anaesthesia). The linear regression line with 95% prediction band was analysed between calculated propofol concentration and values before eye opening. Median frequency before eye opening was linearly related to propofol blood concentration (median frequency = −2.98 (propofol) + 16.5; r = 0.647, n = 349).

Figure 4  Calculated propofol blood concentration vs auditory evoked potential index (○ = before eye opening; ● = after eye opening; × = before induction of anaesthesia). The linear regression line with 95% prediction band was analysed between calculated propofol concentration and values before eye opening (n = 349). The auditory evoked potential index before eye opening was not related to propofol blood concentration. The values after eye opening and before induction of anaesthesia were distributed above the prediction band and were well distinguished from those before eye opening.

Figure 5  Mean (range) values of the four variables at three periods: before induction of anaesthesia (BI, ×), just before eye opening (BEO, ○) and just after eye opening (FEO, ●) (n = 10). *P < 0.05 between two values.
Although auditory evoked potential indexes did not correlate with blood propofol concentrations before eye opening, they were distributed closely around 40, between blood propofol concentrations of 1 and 5 µg ml$^{-1}$, before recovery of consciousness. Auditory evoked potential indexes after eye opening and those before induction of anaesthesia were clearly distinguished from those before eye opening (fig. 4). There was no difference between values just before induction of anaesthesia and those recorded just after eye opening. Mean auditory evoked potential index before eye opening was significantly smaller than that after eye opening and also significantly smaller than that before induction of anaesthesia (fig. 5).

Discussion
An appropriate performance measure is needed to evaluate and compare potential indicators of anaesthetic depth.\textsuperscript{14} In this study, we examined four EEG variables using two methods: first, comparing values just before and after eye opening, and before induction of anaesthesia; second, investigating the correlation with calculated blood propofol concentrations. Eye opening is considered one of the “gold standard” indicators of anaesthetic depth during recovery. Blood propofol concentrations would be controversial as a indicator of anaesthetic depth because blood concentrations do not always reflect brain concentrations. This study was limited to the period during emergence from anaesthesia after discontinuation of propofol infusion. Although it was not a steady state, propofol concentrations in the brain would change in parallel with those in blood, which minimizes the discrepancy of propofol concentrations between blood and effector sites.

Chassard and colleagues reported that although propofol had little effect on brainstem auditory evoked potentials, it markedly suppressed the MLAEP, even at low concentrations. They could not identify Pa or Nb at propofol concentrations of 1.6–2.44 µg ml$^{-1}.\textsuperscript{15}$ Thornton and colleagues also reported that propofol profoundly affected the MLAEP\textsuperscript{7} and speculated that the MLAEP reflected the hypnotic component of an anaesthetic agent. However, they did not study the transition from unconsciousness to consciousness. In this study we observed low auditory evoked potential indexes during sleep which increased suddenly just after eye opening. This suggested that the auditory evoked potential index reflected the level of consciousness rather than blood concentration of propofol. The auditory evoked potential index may therefore be a reliable monitor to detect awareness during anaesthesia.

Leslie and colleagues\textsuperscript{3} reported that the bispectral index was monotonically related to blood concentrations of propofol; this finding is compatible with our study. This suggests that the bispectral index reflects the effect of given blood concentration of propofol. However, bispectral index values at the time of recovery of consciousness vary among studies. Howell and colleagues\textsuperscript{16} reported that bispectral index values at the time of recovery of consciousness were 79.7 (SEM 3) during emergence from propofol anaesthesia and 82.1 (2) during emergence from propofol and alfentanil anaesthesia. Flaishon, Sebel and Sigl\textsuperscript{17} reported that unconsciousness was not observed above a bispectral index of 70 and no consciousness was observed below a value of 65. We observed the transition from unconsciousness to consciousness at bispectral index values of 64–80. Kearse and colleagues\textsuperscript{18} also reported that the bispectral index value that predicts 95% probability of unconsciousness was 52. The results of these studies suggest that a patient may recover consciousness at a bispectral index value of 50–85, but with an increasing probability at a higher value of the index. Our study revealed that bispectral index values before and after eye opening were not different. This suggested that the bispectral index could not detect the transition from unconsciousness to consciousness, where consciousness was defined as response to command.

Although 95% spectral edge frequency has been used widely to assess depth of anaesthesia, it showed large variability at low blood propofol concentrations. The variability was larger than that reported by Schwender and colleagues,\textsuperscript{19} however our finding was comparable with that of Leslie and colleagues.\textsuperscript{3} In our study and that of Leslie and colleagues, some subjects had low 95% spectral edge frequency values of less than 10 Hz. This might result from measurement when the eyes were closed. Median frequency also showed large variability, especially at low blood propofol concentrations. The large variability when awake may make assessment of anaesthetic depth difficult. This study demonstrated that the bispectral index was superior to 95% spectral edge frequency and median frequency in this respect.

These three variables, bispectral index, 95% spectral edge frequency and median frequency, demonstrated different characteristics from the auditory evoked potential index. The former three variables were derived from the same two-channel surface EEG signals. They are considered to reflect mainly cerebral cortex activity. Therefore, they correlated with blood propofol concentrations during emergence from anaesthesia. In contrast, the auditory evoked potential index was calculated from 144 ms of auditory evoked potentials. It reflects overall responses to auditory stimuli from the brainstem to the cerebral cortex. Although we have not identified the components of the waveforms, the overall responses demonstrated the transition from unconsciousness to consciousness very sharply, which mirrors the clinical state.

Blood concentrations of propofol were not measured but were calculated using a pharmacokinetic model.\textsuperscript{20} However, in a previous study using a target control infusion system with the pharmacokinetic model,\textsuperscript{21} discrepancies between calculated and actual blood concentrations were small after discontinuation of propofol infusion. The bias (mean prediction error) was $-2\%$, and precision (mean of individual absolute prediction errors) was 15.1%.

This study was performed after the end of surgery. Therefore, the relationship between blood propofol
concentration and the variables was not affected by the variable levels of surgical stimulation.\textsuperscript{22}

Inhalation of nitrous oxide was discontinued at the same time as cessation of propofol infusion. Although the effects of nitrous oxide on auditory evoked potentials are weak,\textsuperscript{23} a simultaneous decrease in nitrous oxide tension could influence the results. This study, therefore, could not determine the absolute relationship between propofol blood concentrations and the four variables; auditory evoked potential index or bispectral index required 36.9 s or 30 s, respectively, to be fully updated. Values measured 15 s after eye opening, therefore, included some components of values obtained before eye opening.

Within these limitations, we found different characteristics of the four variables for monitoring depth of anaesthesia. The variables processed from the surface EEG (bispectral index, 95\% spectral edge frequency) generally reflected blood concentrations of propofol. Of the three variables, bispectral index changed most linearly with propofol concentrations in blood. Therefore, bispectral index may provide the best prediction of recovery of consciousness during emergence from anaesthesia at the end of surgery.

Median frequency and 95\% spectral edge frequency changed linearly when patients were unconscious, but lost the linearity during conscious- ness. Bispectral index was superior to median frequency and 95\% spectral edge frequency. The auditory evoked potential index was different from the surface EEG derivatives and was the best variable to distinguish the transition from unconsciousness to consciousness.

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References