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Analysis of the EEG bispectrum, auditory evoked potentials and the EEG power spectrum during repeated transitions from consciousness to unconsciousness

R. J. Gajraj, M. Doi, H. Mantzaridis and G. N. C. Kenny

Summary

We have compared the auditory evoked potential (AEP) index (a numerical index derived from the AEP), 95% spectral edge frequency (SEF), median frequency (MF) and the bispectral index (BIS) during alternating periods of consciousness and unconsciousness produced by target-controlled infusions of propofol. We studied 12 patients undergoing hip or knee replacement under spinal anaesthesia. During periods of consciousness and unconsciousness, respective mean values for the four measurements were: AEP index, 60.8 (SD 13.7) and 37.6 (6.5); BIS, 85.1 (8.2) and 66.8 (10.5); SEF, 24.2 (2.2) and 18.7 (2.1); and MF, 10.9 (3.3) and 8.8 (2.0). Threshold values with a specificity of 100% for a state of unconsciousness were: AEP index, 37 (sensitivity 52%); BIS, 55 (sensitivity 15%); and SEF, 16.0 (sensitivity 9%). There was no recorded value for MF that was 100% specific for unconsciousness. Of the four measurements, only AEP index demonstrated a significant difference ($P < 0.05$) between all mean values 1 min before recovery of consciousness and all mean values 1 min after recovery of consciousness. Our findings suggest that of the four electrophysiological variables, AEP index was best at distinguishing the transition from unconsciousness to consciousness. (*Br. J. Anaesth*. 1998; **80**: 46–52)

Keywords: brain, evoked potentials; monitoring, evoked potentials; monitoring, electoencephalography; monitoring, depth of anaesthesia; anaesthesia, depth

The ability to detect recovery of consciousness from a state of unconsciousness is an essential attribute for a monitor of depth of anaesthesia so that awareness during anaesthesia may be prevented. While an ideal method of assessment of anaesthetic depth remains an elusive goal, it has been suggested that monitoring of auditory evoked potentials (AEP)[1–3] or bispectral electroencephalographic (EEG) analysis[4–8] may be more reliable than other techniques. Recently, the AEP index (formerly known as the level of arousal score), a mathematical derivative which reflects AEP waveform morphology that is calculated from the amplitude difference between successive segments of the AEP curve,[9] has been investigated as a means of assessment of depth of anaesthesia.[10–12] Median frequency (MF)[13 14] and 95% spectral edge frequency (SEF)[7 15] of the EEG power spectrum have also been investigated for assessing anaesthetic depth and have been incorporated into commercially available monitors for this purpose.

In a recent study, our group observed that while the bispectral index (BIS) and to a lesser extent SEF correlated well with predicted blood concentrations of propofol during recovery from anaesthesia, AEP index was best at distinguishing consciousness from unconsciousness.[16] Therefore, this study was designed to investigate further the ability of AEP index, BIS, SEF and MF to identify awareness by their capacity to detect recovery of consciousness. We assessed changes in these electrophysiological measurements during alternating periods of unconsciousness and consciousness, the reproducibility of these changes in each patient and analysed the amount of inter-patient variability.

Patients and methods

After obtaining hospital Ethics Committee approval and informed consent, we studied 12 patients undergoing orthopaedic surgery (hip or knee replacement) under spinal anaesthesia. Two male patients and 10 female patients, mean age 73.8 (range 62–82) yr and mean weight 70.7 (55–84) kg completed the study. Patients with psychiatric or hearing abnormalities were excluded.

All patients were premedicated with temazepam 30 mg, 2 h before surgery. Spinal anaesthesia was produced with either 0.5% plain bupivacaine 3.0–3.5 ml or 0.75% plain bupivacaine 3 ml administered via a 26-gauge needle at the L2–3 interspace. An extradural catheter was also inserted for administration of top-up doses during surgery in prolonged cases.

After ensuring adequate regional anaesthesia for surgery, a target-controlled infusion (TCI)[17] of propofol was commenced and oxygen administered via a nasal sponge. One anaesthetist was responsible for standard monitoring of the patient and for manipulating the TCI of propofol to produce alternating periods of consciousness and uncon-

R. J. Gajraj, DM, FRCA, G. N. C. Kenny, BSC (HONS), MD, FRCA, University Department of Anaesthesia, HCI International Medical Centre, Beardmore Street, Clydebank G81 4HX, Scotland. M. Doi, MD, Department of Anesthesiology and Intensive Care, Hamamatsu University School of Medicine, 3600 Handa, Hamamatsu 431–31, Japan. H. Mantzaridis, MB, CHB, PHD, Department of Anaesthetics, Law Hospital, Carluke, Lanarkshire ML8 5ER, Scotland. Accepted for publication: August 21, 1997.

Correspondence to G. N. C. K.

sciousness. Two investigators were present in addition to the anaesthetist responsible for conducting the anaesthetic. One investigator observed the AEP system and the EEG monitor, and recorded the timing of events such as onset of unconsciousness and consciousness. At intervals of 30 s, the second investigator established the presence or absence of an eyelash reflex and the patient's response to a verbal command to squeeze the investigator's hand. The transition from consciousness to unconsciousness was defined as the point at which loss of response to verbal command occurred, and the return of this response was considered the transition from unconsciousness to consciousness.

AUDITORY EVOKED POTENTIAL MONITORING

Auditory evoked potentials were monitored as described in our previous studies.[16 18] The EEG was obtained from three disposable silver–silver chloride electrodes (Zipprep, Aspect Medical Systems, USA) placed on the right mastoid (+), and middle forehead (−), with Fp_2 as the reference. The custom-built amplifier had a 5-kV medical grade isolation, common mode rejection ratio of 170 dB with balanced source impedance, input voltage noise of 0.3 μV and current input noise of 4 pA (0.05 Hz–1 kHz rms). A third-order Butterworth analogue band-pass filter with a bandwidth of 1–220 Hz was used. The auditory clicks were of 1 ms duration and 70 dB above the normal hearing threshold. They were presented to the right ear at a rate of 6.9 Hz. The amplified EEG was sampled at a frequency of 1778 Hz by a high accuracy, low distortion 12-bit analogue-to-digital converter (PCM-DAS08, Computer Boards Inc., USA) and processed in real-time by a microcomputer (T1950CT, Toshiba, Japan).

AEP 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. Averaged curves were obtained at 3-s intervals.

The AEP index, which reflects the morphology of the AEP curves, allowed on-line analysis of the AEP. It is calculated as the sum of the square root of the absolute difference between every two successive 0.56-ms segments of the AEP waveform.[9] The AEP and other data were stored automatically on the hard disk of the microcomputer every 3 s, enabling future retrieval for further analysis.

EEG BISPECTRAL AND POWER SPECTRAL ANALYSIS

The EEG was obtained from four Zipprep electrodes placed on both sides of the outer malar bone (At_1 and At_2) with Fpz as the reference and Fp_1 as the ground. The EEG bispectrum, SEF and MF were monitored using a commercially available EEG monitor (A-1000, BIS 3.0 algorithm, rev. 0.40 software, Aspect Medical Systems, USA). The update rate on the bispectral index monitor was set to 10 s with the bispectral smoothing function switched off. Data from the A-1000 EEG monitor were down loaded automatically and stored on the microcomputer every 5 s.

Both monitoring systems (AEP and EEG) had sophisticated artefact rejection algorithms and the amplifiers of both also had medical grade isolation. Furthermore, the auditory clicks that produced the AEP generate signals 100 times smaller than the remainder of the EEG. Therefore, although the AEP and EEG were monitored simultaneously, there would have been no interference between the two systems that could have affected the results.

DATA ANALYSIS

Periods of consciousness and unconsciousness extended between the time of recovery of consciousness (response to verbal command) and the time when consciousness was lost (loss of response to verbal command). However, the periods from 1 min before until 1 min after transitions from one state of consciousness to the next were excluded when conscious and unconscious values of each measurement were analysed. These periods were excluded because they were likely to contain values representative of both consciousness and unconsciousness, as 36.9 s were required to obtain a full update of the AEP index (and 30 s for the BIS), and patients were also most likely to be drifting in and out of consciousness during these periods. Therefore, conscious values were considered to be those recorded during periods from 1 min after regaining consciousness until 1 min before the next loss of consciousness (fig. 1). Unconscious values were those recorded during periods from 1 min after loss of consciousness until 1 min before the next recovery of consciousness (fig. 1).

To investigate the ability of the electrophysiological variables to detect awareness, values recorded 1 min before recovery of consciousness were compared with values at 1 min after consciousness returned (fig. 1). All patients had at least three transitions from unconsciousness to consciousness. Therefore, the first three transitions were used to compare the ability of the different measurement systems to detect these transitions.

The mean (SD) and range of each measurement during all periods of consciousness and unconsciousness were determined by analysing all conscious and unconscious values, respectively, recorded over the course of the study. Measurements made during all periods of unconsciousness and consciousness were used to determine threshold values with 100% specificity and threshold values with approximately 85% sensitivity. Statistical analysis was with Minitab 10.5 for Windows, using ANOVA with Tukey's test. $P < 0.05$ was considered significant.

All patients were interviewed on the day after surgery for memory of intraoperative events. They were also questioned on their satisfaction with the auditory clicks and the technique of monitoring.

Results

Mean duration of surgery was 74 (range 58–121) min. There was a mean of 10 (6–20) periods of consciousness and unconsciousness.

AUDITORY EVOKED POTENTIAL INDEX

Table 1 shows the mean values for AEP index, BIS, SEF and MF recorded during all conscious or unconscious periods, as defined above. Table 2 shows

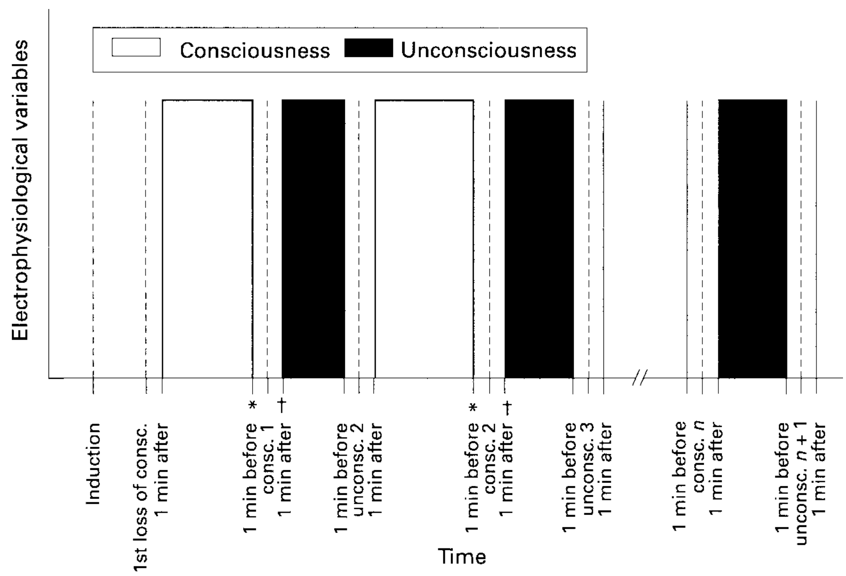

Figure 1 Periods when the four electrophysiological measurements (auditory evoked potential index (AEP index), bispectral index (BIS), spectral edge frequency (SEF) and median frequency (MF)) were analysed. All values recorded during periods of consciousness (consc.) and unconsciousness (unconsc.) were used to analyse the differences between the two states. Unconscious values of the four measurements at 1 min before regaining consciousness (*) were compared with conscious values at 1 min after regaining consciousness (†), at the first three transitions.

Table 1 Mean (range) values for the auditory evoked potential (AEP) index, bispectral index (BIS), 95% spectral edge frequency (SEF) and median frequency (MF) during consciousness (consc.) and unconsciousness (unconsc.)

	Unconsc.	Consc.
AEP index	37.6 (21–55)	60.8 (38–98)
BIS	66.8 (40–94)	85.1 (56–98)
SEF	18.7 (12.5–26.5)	24.2 (16.1–29.1)
MF	8.8 (1.7–13.7)	10.9 (1.5–18.9)

the threshold values of the four measurements with 100% specificity and threshold values with close to 85% sensitivity for states of consciousness and unconsciousness. In total, 4823 unconscious and 2055 conscious values of the AEP index, and 2885 unconscious and 1322 conscious values of BIS, SEF and MF were analysed. A threshold value of the AEP index of 37 had a specificity of 100% and a sensitivity of 52% for a state of unconsciousness. A threshold value of 56 was 60% sensitive and 100% specific for consciousness. Figure 2 shows the mean AEP index and BIS before and after the first three transitions from unconsciousness to consciousness. All mean awake values 1 min after return of consciousness were significantly higher than all mean unconscious values 1 min before ($P < 0.05$). AEP index values during periods of consciousness were more variable than values during unconsciousness (fig. 2, table 1).

Table 2 Values of the auditory evoked potential (AEP) index, bispectral index (BIS), 95% spectral edge frequency (SEF) and median frequency (MF) with 100% specificity and values with approximately 85% sensitivity for consciousness and unconsciousness

	Threshold	Sensitivity (%)	Specificity (%)
Unconscious			
AEP index	37	52	100
	44	85	57
BIS	55	15	100
	76	86	83
SEF	16.0	9	100
	21.0	85	92
MF	1.4	0	100
	10.7	85	55
Conscious			
AEP index	56	60	100
	45	87	85
BIS	95	14	100
	75	88	80
SEF	26.6	15	100
	21.9	84	92
MF	13.8	18	100
	7.9	85	25

BISPECTRAL INDEX

Table 1 shows that, unlike AEP index, some BIS values during unconsciousness were higher than the *mean* value during consciousness, and some conscious values were also lower than the *mean* value during unconsciousness. A BIS of 55 had a specificity of 100% but was only 15% sensitive for a state of unconsciousness (table 2). A very high value of 95 was required for 100% specificity for consciousness and was only 14% sensitive. Figure 2 shows the mean BIS at 1 min before and after the first three transitions from unconsciousness to consciousness. Unlike the AEP index, mean awake values 1 min after return of consciousness were not *all* significantly different from mean unconscious values 1 min before regaining consciousness ($P < 0.05$). BIS also contrasted with AEP index in that values recorded during unconsciousness demonstrated more interpatient variability than values during periods of consciousness (table 1).

SPECTRAL EDGE FREQUENCY

Comparable with BIS but unlike AEP index, some SEF values during unconsciousness were higher than the *mean* value during consciousness, and some conscious values were lower than the *mean* value during unconsciousness (table 1). An SEF value of 16.0 Hz had a specificity of 100% but only 9% sensitivity for a state of unconsciousness (table 2). A value of 26.6 Hz was 100% specific but only 15% sensitive for

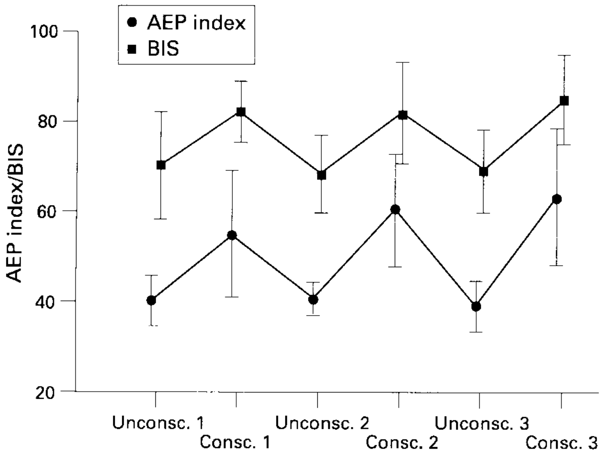

Figure 2 Mean (SD) auditory evoked potential (AEP) index and bispectral index (BIS) at 1 min before and after the first three transitions from unconsciousness (unconsc.) to consciousness (consc.). There was no significant difference between BIS at unconsc. 1 and consc. 2.

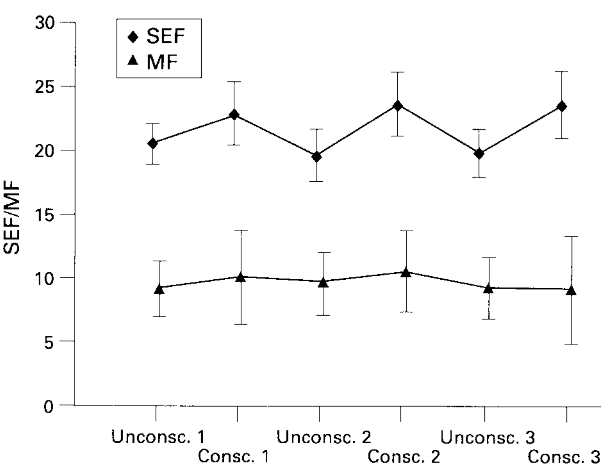

Figure 3 Mean (SD) spectral edge frequency (SEF) and median frequency (MF) at 1 min before and after the first three transitions from unconsciousness (unconsc.) to consciousness (consc.). There was no significant difference between SEF at unconsc. 1 and consc. 1.

consciousness. Figure 3 shows mean SEF and MF values at 1 min before and after the first three transitions from unconsciousness to consciousness. In common with BIS but unlike AEP index, mean awake values of SEF 1 min after return of consciousness were not *all* significantly different from mean unconscious values 1 min before regaining consciousness ($P < 0.05$). Similar to AEP index but unlike BIS, awake values of SEF were generally more variable than values recorded during periods of unconsciousness (fig. 3).

MEDIAN FREQUENCY

Similar to BIS and SEF, some values of MF during unconsciousness were higher than the *mean* value during consciousness, and some conscious values were lower than the *mean* value during unconsciousness (table 1). The lowest recorded awake value of MF was lower than the minimum MF value during unconsciousness (table 1) so that a value of 1.4 Hz, which was never attained, would have been 100% specific for unconsciousness (table 2). An MF value of 13.8 Hz was 100% specific but only 18% sensitive for consciousness. Figure 3 shows mean MF values at 1 min before and after the first three transitions from unconsciousness to consciousness. Although mean awake values of MF tended to be numerically greater than mean values during unconsciousness, all mean conscious and unconscious values were not significantly different. There was relatively large inter-patient variability for MF values during both consciousness and unconsciousness, and in common with AEP index and SEF but unlike BIS, this variability was greater during periods of consciousness (fig. 3).

No patient had recall of any event in theatre, including application of earphones and auditory clicks. All patients were satisfied with the anaesthetic technique and were happy to have the same technique of monitoring for any future anaesthetic.

Discussion

Although consistent changes (increased latency and decreased amplitude) in middle latency auditory evoked potential (AEP) waves occur as anaesthesia is deepened, it is difficult to analyse AEP waves in real time and to quantify changes in the clinical situation. The AEP index, a mathematical derivative that reflects AEP waveform morphology,[9] allows on-line assessment of the AEP during anaesthesia and surgery. Conventional EEG processing techniques such as those used to measure spectral edge frequency (SEF) and median frequency (MF) ignore the inter-frequency phase information in the EEG and may be unreliable for monitoring the level of anaesthesia because of the variable effects produced by different anaesthetic agents and the large inter-patient variability.[19] Unlike power spectrum analysis, bispectral EEG analysis also quantifies the phase coupling between component EEG frequencies.[20] The bispectral index (BIS), a numerical value derived from the EEG bispectrum, has been shown to have characteristics desirable in an anaesthetic depth monitor, such as the capacity to predict movement in response to surgery[4 21] and to detect consciousness[22–24] when using a variety of anaesthetic drugs.

The ability to distinguish consciousness from unconsciousness is an essential feature of a monitor of depth of anaesthesia, and was the clinical end-point used in this study, circumventing the problem of the absence of a universally accepted standard by which to compare such monitors under investigation.

The assumption that awareness, and therefore consciousness, is indicated by a response to command has been made in previous studies.[25 26] However, intraoperative awareness may occur without postoperative recall,[27] as occurred in all of our patients. Nevertheless, prevention of the dreaded consequence of intraoperative awareness without amnesia, especially in the presence of inadequate analgesia, is one of the most important functions of anaesthetic depth monitors. Amnesia for intraoperative events may have occurred in our patients because of the use of benzodiazepine premedication[28] or general anaesthetic drugs.[29 30]

Our study demonstrated the potential of the AEP index to detect recovery of consciousness. Of the four electrophysiological variables studied, only AEP

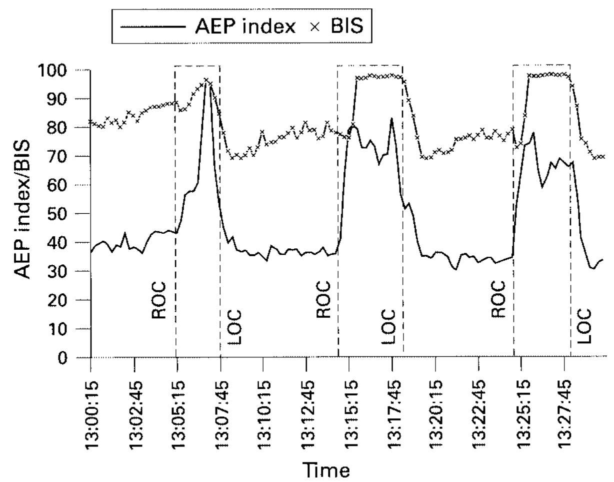

Figure 4 Changes in auditory evoked potential index (AEP index) and bispectral index (BIS) at recovery of consciousness (ROC) and loss of consciousness (LOC) for one patient in this study.

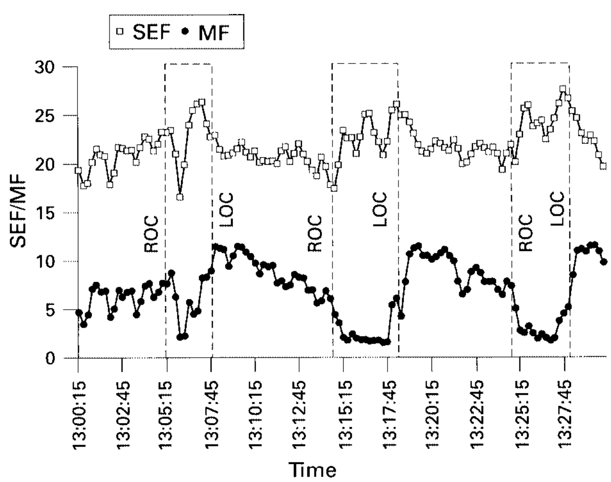

Figure 5 Changes in spectral edge frequency (SEF) and median frequency (MF) at recovery of consciousness (ROC) and loss of consciousness (LOC) for one patient in this study.

index demonstrated a significant difference ($P < 0.05$) between all mean values 1 min before recovery of consciousness and all mean values 1 min after recovery of consciousness (fig. 2). The clear distinction between conscious and unconscious values of the AEP index was also demonstrated by the fact that it was the only measurement in this study whose lowest recorded conscious value was higher than the mean unconscious value, and whose highest unconscious value was lower than the mean conscious score.

Although other studies[22–24] have shown BIS to be capable of detecting consciousness, in this study BIS was not significantly different when values 1 min before and after recovery of consciousness were compared. This could be explained by the gradual increase in BIS which frequently occurs during emergence from anaesthesia.[31 32] Values recorded 2 min apart (1 min before and after recovery) would therefore be more similar to each other than corresponding AEP index values, which increase suddenly at the time of awakening.[16] Figure 4, which shows changes in AEP index and BIS for one of the patients in our study, demonstrates this gradual increase in BIS during the first transition from unconsciousness to consciousness. In contrast, the AEP index increased sharply at all three transitions in this patient.

MF was least capable of distinguishing consciousness from unconsciousness, as all mean conscious and unconscious values were similar to each other (fig. 3). Studies by Schwilden and colleagues have suggested that MF values less than approximately 5 Hz indicate unconsciousness and that values of 2–3 Hz indicate a satisfactory depth of anaesthesia.[13 33–35] The difference between our findings and those of Schwilden and co-workers may be explained by differences in methodology and by the effects of EEG burst suppression which lead to misinterpretation of the EEG power spectrum.[36] In addition, there is possibly a lag between changes in MF and changes in anaesthetic concentration during recovery which could explain the *lower* values during conscious periods and *higher* unconscious values demonstrated in one of the patients in the present study (fig. 5).

The already low frequency of awareness during anaesthesia of 0.1%,[2 37] and the potentially disastrous consequences of its occurrence suggest that we should be attempting to develop monitors that will almost guarantee its elimination by reliably detecting unconsciousness. Such a monitor should be capable of providing information that is specific for unconsciousness at a level of anaesthesia that is not excessive. A BIS value of 55 was 100% specific but only 15% sensitive for unconsciousness (table 2). Additionally, a threshold value of 95 was necessary for 100% specificity for consciousness, as there were very high values of BIS recorded during periods of unconsciousness. These findings suggest that BIS could not be used to direct anaesthetic administration to *ensure* unconsciousness without the risk of excessive anaesthesia. Values of BIS which are specific for unconsciousness are not sensitive enough, and some adequately anaesthetized (clinically unconscious) patients have BIS values of fully awake subjects.

A similar problem of excessive anaesthesia may occur if SEF is used to ensure unconsciousness, as a value of 16.0 Hz was 100% specific but only 9% sensitive for unconsciousness. Very high SEF values were also recorded during unconsciousness so that a value of 26.6 Hz was necessary for 100% specificity for consciousness.

In contrast, an AEP index of 37 was 100% specific for unconsciousness, with a much greater level of sensitivity (52%) than corresponding SEF and BIS values. There was also no problem for unconscious patients with a very high AEP index, and a value of 56 was 100% specific and 60% sensitive for consciousness. These findings suggest that it may be possible to aim for an AEP index value that ensures unconsciousness while avoiding excessive anaesthesia.

The range of BIS values during periods of consciousness in this study varied between 68 and 98. Other studies have reported variable BIS values of approximately 50–85 at the time of recovery of consciousness.[8 16 22–24] Flaishon, Sebel and Sigl[23] reported that no unconsciousness was observed when BIS was greater than 70 and no consciousness occurred at values less than 65. In contrast, no consciousness was observed in this study at scores less than 55, while 36% of BIS values during unconsciousness (1048 of 2885 values) were greater than 70. The wide variation in BIS values between these studies may be a result of the use of different anaesthetic agents and different clinical end-points used to define consciousness.

Other studies have reported different results for SEF and MF during consciousness and unconsciousness. Median SEF was 20.4 Hz on recovery and 10.1 Hz during anaesthesia in one of the studies in Schwilden's series[33] compared with corresponding mean values of 24.2 and 18.7 Hz in this study. However, there was large variability in SEF values in both studies. Arndt, Hofmockel and Benad reported that adequate anaesthesia could be expected when SEF ranged from 14 to 16 Hz.[38] While an SEF value of 16 Hz was 100% specific for unconsciousness in our study (table 2), it was only 9% sensitive. Schwilden and colleagues also reported that no response to verbal command occurred at an MF value of less than 5 Hz for a variety of drugs.[33–35] In contrast, consciousness was present in the range 2–19 Hz in our study and, while 5 Hz was 94% specific for unconsciousness, it was only 7% sensitive.

This study demonstrated the potential of the AEP index to detect recovery of consciousness from propofol anaesthesia. Unconsciousness caused by different anaesthetic agents may produce dissimilar effects on the EEG[19 39 40] and on BIS,[21 41–44] although consistent changes have been demonstrated in MLAEP waves.[5 45–47] Further studies are therefore necessary to investigate the ability of these measurements to detect recovery of consciousness from anaesthesia produced by different drugs. Another limitation of this study was the lack of influence of surgical stimuli, effectively abolished by spinal anaesthesia, on the four measurements. Surgical stimulation is known to affect the EEG[48] and AEP.[48–50] However, it would be morally and ethically challenging to design a study in which consciousness was repeatedly induced in the presence of a painful surgical wound.

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