British Journal of Anaesthesia **82 (5)**: 672–8 (1999)

Comparison of bispectral EEG analysis and auditory evoked potentials for monitoring depth of anaesthesia during propofol anaesthesia†

R. J. Gajraj[1], M. Doi[2], H. Mantzaridis[3] and G. N. C. Kenny[4]*

[1]Department of Anaesthesia, General Infirmary at Leeds, Great George Street, Leeds LS1 3EX, UK. [2]Department of Anaesthesiology and Intensive Care, Hamamatsu University School of Medicine, 3600 Handa, Hamamatsu 431–31, Japan. [3]Department of Anaesthetics, Law Hospital, Carluke, Lanarkshire ML8 5ER, UK. [4]Glasgow University Department of Anaesthesia, Royal Infirmary, 8–16 Alexandra Parade, Glasgow G31 2ER, UK

**Corresponding author*

We have compared the auditory evoked potential index (AEP_{Index}) and bispectral index (BIS) for monitoring depth of anaesthesia in spontaneously breathing surgical patients. Twenty patients (aged 17–49 yr) undergoing day surgery were anaesthetized with computer-controlled infusions of propofol. The mean (SD and range) of each measurement was determined during consciousness and unconsciousness and at specific times during the perioperative period. Mean values for AEP_{Index} during consciousness and unconsciousness were 74.5 (SD 14.7) and 36.7 (7.1), respectively. BIS had mean values of 89.5 (SD 4.6) during consciousness and 48.8 (16.4) during unconsciousness. AEP_{Index} and BIS were greater during consciousness compared with during unconsciousness. The average awake values of AEP_{Index} were significantly higher than all average values during unconsciousness but this was not the case for BIS. BIS increased gradually during emergence from anaesthesia and may therefore be able to predict recovery of consciousness at the end of anaesthesia. AEP_{Index} was more able to detect the transition from unconsciousness to consciousness.

Br J Anaesth 1999; **82**: 672–8

Keywords: monitoring, evoked potentials; monitoring, depth of anaesthesia; brain, evoked potentials; anaesthesia, depth; memory; anaesthetics i.v., propofol

Accepted for publication: November 27, 1998

The use of clinical signs for assessing 'depth of anaesthesia', although universally employed, is notoriously unreliable.[1 2] However, it may be possible to ensure adequate anaesthesia, if *spontaneous respiration* is maintained during surgery. If anaesthesia is inadequate, the patient moves reflexly in response to surgery and if the level of anaesthesia is excessive, respiration is depressed.

Changes in middle latency auditory evoked potentials (MLAEP) have been shown to reflect reliably the level of anaesthesia with a wide range of anaesthetic drugs[3–6] and to detect awareness.[7] However, auditory evoked potential (AEP) waves are difficult to analyse in the clinical situation. Recently, the AEP_{Index} (formerly known as the level of arousal score), a mathematical derivative that reflects the morphology of the AEP curves, has been investigated as a means of assessment of depth of anaesthesia.[8] It has also been used successfully as the input signal in a closed loop system for administration of total i.v. anaesthesia in patients undergoing various surgical procedures.[9] The AEP_{Index} is calculated from the amplitude difference between successive segments of the AEP curve.[8]

Unlike other electroencephalogram (EEG) processing techniques which ignore inter-frequency phase information, bispectral EEG analysis includes intra-component relationships (i.e. power coupling) in the EEG.[10] Bispectral index (BIS), derived from the EEG bispectrum, has been shown to predict movement in response to surgery[11–13] and to detect consciousness[14 15] when using a variety of anaesthetic drugs. In a previous study by our group that included a comparison of AEP_{Index} and BIS in patients undergoing surgery with regional anaesthesia, AEP_{Index} was shown to be capable of distinguishing consciousness from unconsciousness produced by propofol.[16] Our study was designed to compare measures of depth of anaesthesia with clinical assessment of the level of anaesthesia, in *spontaneously*

†This article is accompanied by Editorial I

breathing patients anaesthetized with propofol and undergoing surgery without regional anaesthesia.

Patients and methods

After obtaining approval from the Hospital Ethics Committee and informed consent, we studied 20 patients (19 females, mean age 32.8 (range 17–49) yr) undergoing day surgery under general anaesthesia.

Three investigators were involved in the study. One anaesthetist was responsible for the conduct of the anaesthetic and for monitoring depth of anaesthesia by normal clinical methods. The second investigator ensured proper functioning of the EEG monitors while the third recorded the exact time of specific events, such as skin incision and patient movement in response to stimuli. After attaching the EEG electrodes, patients were asked to close their eyes and relax. Anaesthesia was induced after ensuring artefact-free signals and initial recordings from the EEG monitors.

No patient received premedication. Target-controlled infusions (TCI)[17] of propofol were used for induction and maintenance of anaesthesia. The TCI pump used the same pharmacokinetic model as Zeneca's Diprifusor system. A target blood propofol concentration of 2 $\mu g\ ml^{-1}$ was selected initially. Target propofol concentrations were then titrated to effect to achieve the desired depth of anaesthesia (assessed clinically by the investigator responsible for the anaesthetic), comparable with the way in which vaporizers and volatile agent concentration monitors are used for inhalation anaesthesia. Patients also breathed 66% nitrous oxide in oxygen spontaneously via a laryngeal mask airway (LMA). Analgesia was supplemented, at the discretion of the anaesthetist, with i.v. ketorolac and fentanyl. Heart rate, arterial pressure, ventilatory frequency, pulse oximetry, electrocardiography and end-tidal carbon dioxide tension were monitored.

All anaesthetic drugs were discontinued simultaneously at the end of surgery. Patients were then asked verbally at 30-s intervals to open their eyes.

Auditory evoked potential monitoring

Auditory evoked potentials (AEP) were monitored as described in our previous study.[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 both ears 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).

The 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.

$AEP_{Index,}$ 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.[8] AEP and other data were stored automatically on the microcomputer's hard disk 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 was 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. The low-frequency filter was set to 2 Hz and the high-frequency setting was 30 Hz. Data from the A-1000 EEG monitor were downloaded automatically and stored on the microcomputer every *5 s*.

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

Data analysis

Mean (SD and range) values during consciousness and unconsciousness of both measurements were determined. 'Conscious' values were defined as those recorded from before induction of anaesthesia until 30 s before loss of the eyelash reflex. 'Unconscious' values were defined as those from 1 min after skin incision until 30 s before eye opening. These conscious and unconscious values were used to determine threshold values of each measurement with 100% specificity and threshold values with approximately 85% sensitivity for consciousness and unconsciousness.

Measurements were also compared at specific times in the perioperative period. As the AEP_{Index} was recorded every 3 s and BIS every 5 s, both measurements were averaged over successive 15-s intervals to produce comparable periods for analysis. The averaged values were then compared at the following times: (A) baseline (first recorded awake value); (B) before induction of anaesthesia (last recorded awake value); (C) 30 s before skin incision; (D) 30 s after skin incision; (E) 5 min after skin incision; (F) at the end of surgery and anaesthesia; (G) 3 min before

Table 1 Mean (range) conscious and unconscious values of the auditory evoked potential index (AEP_{Index}) and bispectral index (BIS)

Measurement	Mean (range)
AEP_{Index}	
Conscious	74.5 (51–110)
Unconscious	36.7 (19–66)
BIS	
Conscious	89.5 (70–97)
Unconscious	48.8 (1–94)

Table 2 Threshold values of the auditory evoked potential index (AEP_{Index}) and bispectral index (BIS) with 100% specificity (with corresponding sensitivity) and threshold values with approximately 85% sensitivity (with corresponding specificity) for consciousness and unconsciousness. Sensitivity (sens.) and specificity (spec.) in %

	Threshold	85% sens. (spec.)	100% spec. (sens.)
Unconscious			
AEP_{Index}	50		100 (96)
	44	86 (100)	
BIS	69		100 (88)
	67	84 (100)	
Conscious			
AEP_{Index}	67		100 (58)
	60	85 (99.6)	
BIS	95		100 (8)
	86	83 (98)	

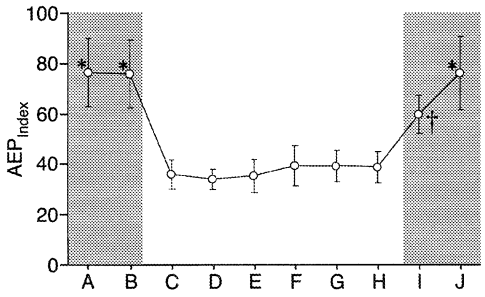

Fig 1 Mean (SD) auditory evoked potential index (AEP_{Index}) recorded at the following times: A=baseline (first recorded awake value); B=before induction of anaesthesia (last recorded awake value); C=30 s before skin incision; D=30 s after skin incision; E=5 min after skin incision; F=at the end of surgery and anaesthesia; G=3 min before eye opening; H=1 min before eye opening; I=at the time of eye opening and J=at the time of removal of the LMA. Shaded areas enclose the conscious periods (A, B, I and J). Mean conscious AEP_{Index} values at †(I) were significantly lower than mean conscious values at *(A, B and J).

Table 3 Mean (SD) auditory evoked potential index (AEP_{Index}) and bispectral index (BIS) before and after movement in response to stimuli. *P* values according to Wilcoxon's signed rank test

	Before movement	After movement	*P*
AEP_{Index}	37.2 (8.6)	43.2 (13.1)	<0.01
BIS	42.9 (15.6)	47.2 (18.8)	ns

eye opening; (H) 1 min before eye opening; (I) at the time of eye opening; and (J) at the time of removal of the LMA.

Both measurements were also compared before and after patient movement in response to noxious stimuli (LMA insertion or surgical stimuli). Values were again averaged over comparable intervals of 15 s. Pre-movement averaged values were 30 to 15 s before movement and post-movement averages were from 15 to 30 s after movement.

Data were analysed using ANOVA with Tukey's test and Wilcoxon's signed rank test as appropriate. $P<0.05$ was considered significant.

Results

Anaesthesia was supplemented with ketorolac 10 mg i.v. and a mean dose of fentanyl 1.4 μg kg^{-1} i.v. (range 0.8–2.0 μg kg^{-1}). Mean duration of anaesthesia (start of induction to discontinuation of anaesthetic drug administration) was 20.6 (range 12.2–40.0) min, surgery (skin incision to end of surgery) 13.0 (5.5–32.8) min and recovery (end of anaesthetic drug administration to eye opening on command) 6.6 (2.7–11.1) min. Mean duration from eye opening to LMA removal was 0.4 (0–1.3) min.

Ventilation was adequate in all patients. Mean minimum oxygen saturation (Sp_{O_2}) was 95.7% (89–99%) and the mean maximum end-tidal carbon dioxide concentration was 6.57 (5.1–8.7) kPa. Mean maximum changes in systolic arterial pressure and heart rate remained within 20% of baseline values. Eight patients moved in response to LMA insertion and four patients moved after surgical stimuli.

Auditory evoked potential index (AEP_{Index})

Table 1 shows the mean values for AEP_{Index} and BIS during consciousness and unconsciousness (as defined above). Table 2 shows the threshold values of these measurements with 100% specificity and threshold values with close to 85% sensitivity during consciousness and unconsciousness. Mean AEP_{Index} during consciousness was 74.5 (SD 14.7) compared with 36.7 (7.1) during unconsciousness. Although there was some overlap of conscious and unconscious values, the lowest conscious value was higher than the mean unconscious value, and the highest unconscious value was lower than the mean conscious value. An AEP_{Index} of 44 was 86% sensitive (and 100% specific) for unconsciousness. A threshold value of 67 was 100% specific (58% sensitive) for consciousness.

Figure 1 shows mean AEP_{Index} at the times of analysis. AEP_{Index} was greater and more variable when patients were awake compared with when anaesthetized. All mean awake AEP_{Index} values (times A, B, I and J) were significantly greater (Tukey's test, $P<0.001$) than all mean values recorded during unconsciousness (times C–H). There was no significant difference between mean AEP_{Index} values recorded during unconsciousness (times C–H). Mean awake values of AEP_{Index} at eye opening (Fig. 1, time I) were significantly lower ($P<0.001$) than awake values before anaesthesia or at removal of the LMA (times A, B and J). Values for AEP_{Index} 15 s after patient movement in response to stimuli were significantly higher (Wilcoxon's signed rank test, $P<0.01$) than values 15 s before movement (Table 3).

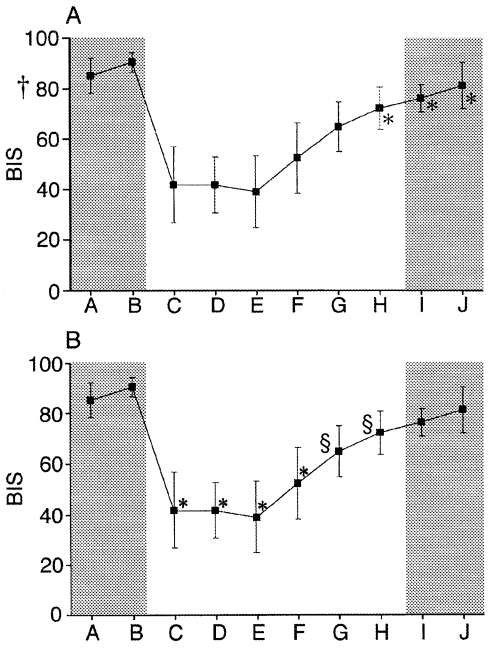

Fig 2 Mean (SD) bispectral index (BIS) during conscious (shaded areas) and unconscious periods (times A–J as for Fig. 1). In A, *****unconscious BIS values at H were not significantly different from conscious values at I and J; †conscious BIS values at B were significantly higher than conscious values at I. In B, unconscious BIS values at *(C–F) were significantly lower than unconscious values at §(G and H).

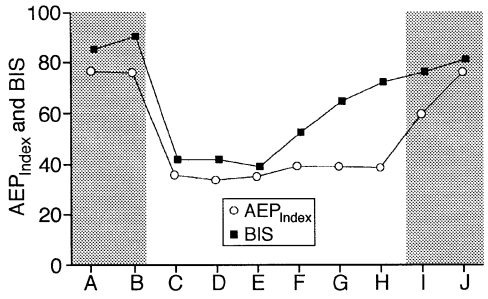

Fig 3 Mean auditory evoked potential index (AEP_{Index}) and bispectral index (BIS) during conscious (shaded areas) and unconscious periods (times A–J as for Fig. 1).

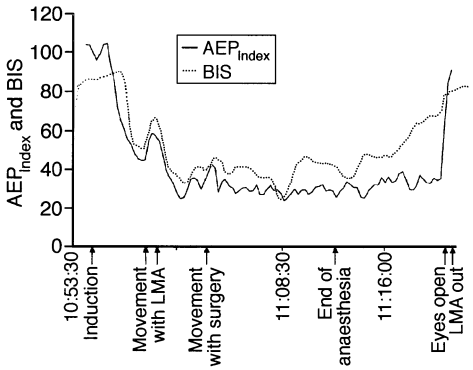

Fig 4 Changes in auditory evoked potential index (AEP_{Index}) and bispectral index (BIS) for one patient.

Bispectral index (BIS)

The mean conscious value for BIS was 89.5 (SD 4.6) and unconscious value, 48.8 (16.4) (Table 1). In common with $AEP_{Index,}$ the lowest conscious value for BIS was greater than the mean unconscious value, but unlike $AEP_{Index,}$ the greatest unconscious value (94) was higher than the mean conscious value. A BIS value of 67 was 84% sensitive (and 100% specific) for unconsciousness (Table 2). A high threshold value of 95 was required for 100% specificity (with only 8% sensitivity) for consciousness.

BIS also tended to be higher when patients were awake compared with during anaesthesia, but unlike $AEP_{Index,}$ BIS demonstrated more variability during unconsciousness (Fig. 2). Unlike $AEP_{Index,}$ mean awake BIS values were not significantly different from all mean values during unconsciousness; there was no significant difference between mean BIS values at 1 min before eye opening (Fig. 2A, time H) when patients were clinically unconscious, and mean awake values during recovery (times I and J). However, mean values during unconsciousness from 30 s before incision until the end of anaesthesia (times C–F, which included the entire duration of surgical anaesthesia) were significantly lower than all mean values during consciousness (times A, B, I and J). As with $AEP_{Index,}$, mean awake BIS values were not all similar (Fig. 2A) as mean values before anaesthesia (time B) were significantly higher than mean awake values at eye opening (time I). Unlike $AEP_{Index,}$ mean unconscious BIS values were not all similar (Fig. 2B), as values from 30 s before skin incision until the end of anaesthesia (times C–F) were significantly lower than values from 3 min to 1 min before eye opening (times G and H). Unlike AEP_{Index} which increased suddenly at the time of awakening, there was a gradual increase in BIS after discontinuation of anaesthetic drug (Figs 2–4). Unlike $AEP_{Index,}$ BIS values 15 s after patient movement in response to stimuli were not significantly greater than values 15 s before movement (Table 3).

No patient had recall of events during anaesthesia. All patients were satisfied with the anaesthetic technique and none found the auditory clicks excessively loud or uncomfortable. They were all happy to have the same technique of monitoring for future anaesthesia.

Discussion

There may be a 1–2% frequency of awareness with spontaneous recall of intraoperative events.[19 20] The implications of potentially the worst experience of a patient's life are enormous and include psychological and psychiatric problems, morbid fear of surgery, substantial medico–legal implications and considerable adverse publicity for all concerned.[21–23] A reliable monitor that ensures unconsciousness is highly desirable. The use of neuromuscular blocking agents, in addition to providing the conditions in which inadequate anaesthesia is more likely, also make its detection more difficult by abolishing two of the most valuable indicators of depth of anaesthetic, respiration and

movement in response to surgery. Our study compared different measurements of depth of anaesthetic in *spontaneously breathing* anaesthetized patients.

AEP_{Index} and BIS appeared to be able to distinguish between awake and anaesthetized states (Figs 1, 2). Both measurements had greater awake values before anaesthesia and on recovery compared with values recorded during unconsciousness. However, AEP_{Index} appeared to distinguish the transition from unconsciousness to consciousness more accurately as *all* mean awake values (times A, B, I and J) were significantly higher than *all* mean values during unconsciousness until 1 min before eye opening (times C–H). Although other studies have shown BIS to be capable of detecting consciousness,[14 15] we found that BIS was unable to detect the transition from unconsciousness to consciousness. This was probably because of the gradual increase in BIS after discontinuing anaesthesia (Figs 2–4). This gradual increase in BIS during emergence is consistent with the findings of other studies[24] and suggests that BIS tracks the clearance of anaesthetic drugs and may be useful in predicting awakening at the end of surgery or as a monitor of sedation. Figure 3, showing the changes in mean values of AEP_{Index} and BIS at the analysed times, and Figure 4, illustrating changes in BIS and AEP_{Index} (at the actual time of occurrence, i.e. not averaged over 15 s) for a typical patient, demonstrate this gradual increase in BIS during recovery, contrasting with the sudden increase in AEP_{Index} at the time of awakening.

In a recent study, we found some differences in threshold and mean values of both measurements during repeated transitions between consciousness and unconsciousness.[16] Compared with the present study, there were lower threshold values of AEP_{Index} and BIS with 100% specificity for unconsciousness. In the previous study of repeated transitions, there were also lower threshold values of BIS and AEP_{Index} with 85% sensitivity for consciousness. There were also differences in mean conscious and unconscious values, with lower mean conscious AEP_{Index} and higher mean unconscious BIS values in the previous study. These differences were possibly because of a lack of premedicant drugs used in the present study, the greater influence that a lag between changes in the measurements and changes in anaesthetic concentration would have had in the previous study and the sedative effects of anaesthetic drugs on conscious values in the previous study. However, both studies demonstrated the superiority of AEP_{Index} over BIS in detecting the transition from unconsciousness to consciousness and the statistically significant difference between all mean conscious AEP_{Index} values and mean unconscious values.

When monitoring depth of anaesthesia, changes induced by light anaesthesia are partially reversed by surgical stimulation.[25–27] Previous studies have reported that stimulation produces an EEG arousal response that is detected by BIS.[28 29] However, we found that only AEP_{Index} was significantly higher after patient movement in response to stimuli compared with before movement (Table 3). This difference may be because of the longer period after stimulation (up to 3 min) used for detecting changes in BIS in the other studies,[28 29] compared with 15 s used in our study. Measurements were compared close to the exact time of movement to assess their ability to respond rapidly to changes. AEP_{Index} requires a marginally longer period (36.9 s) compared with BIS (30 s) for a fully updated signal. Therefore, the post-movement averaged values of AEP_{Index} would have contained more pre-movement data compared with BIS, making AEP_{Index} *less* likely to show statistically higher values after movement.

Prys-Roberts suggests that loss of consciousness is a threshold event.[30] Therefore, the rapid increase in AEP_{Index} at the time of awakening may be expected of a monitor that distinguishes consciousness from unconsciousness. The ability of BIS to predict movement[11–13] and major haemodynamic changes[31] in response to surgical incision implies that it may be used as a monitor of anaesthetic effect. However, its ability to predict response to incision was limited in the presence of effective opioid analgesia.[32] This suggests that BIS may be measuring the amount of anaesthetic drug-induced suppression of the EEG, and not reflecting changes in the state of arousal of the brain determined by the balance between hypnosis (provided by anaesthetic drugs) and the opposing effects of analgesia and surgical stimulation. In a study of a revised version of BIS, Howell and colleagues concluded that BIS was a useful monitor of the level of consciousness irrespective of profound analgesia with alfentanil.[33] However, Howell and colleagues studied volunteers who were not undergoing surgery.

In another study of volunteers undergoing anaesthesia without surgery, Alkire demonstrated that BIS correlated with changes in brain metabolism induced by anaesthesia, measured using positron emission tomography (PET).[34] Alkire's study necessitated measurements during steady-state conditions in volunteers not subjected to surgical stimuli, a situation that almost never occurs during normal clinical practice. We may speculate that there is a specific CNS arousal centre in the brainstem reticular formation that determines whether consciousness is present. The arousal centre may be 'switched on' during consciousness and 'switched off' during unconsciousness from any cause. If BIS reflects the global EEG (as opposed to arousal centre activity), then it would correlate with anaesthetic-induced changes in brain metabolism during steady-state conditions (Alkire's study), and increase gradually at the end of anaesthesia when anaesthetic drugs are discontinued (the present study). During recovery from anaesthesia, global EEG activity may increase progressively when anaesthetic drug administration ceases, while the arousal centre may *remain* switched off until return of consciousness. A monitor of global cortical EEG activity would therefore show a gradual increase in measurements at the end of anaesthesia, while a monitor that measures activity of the arousal centre

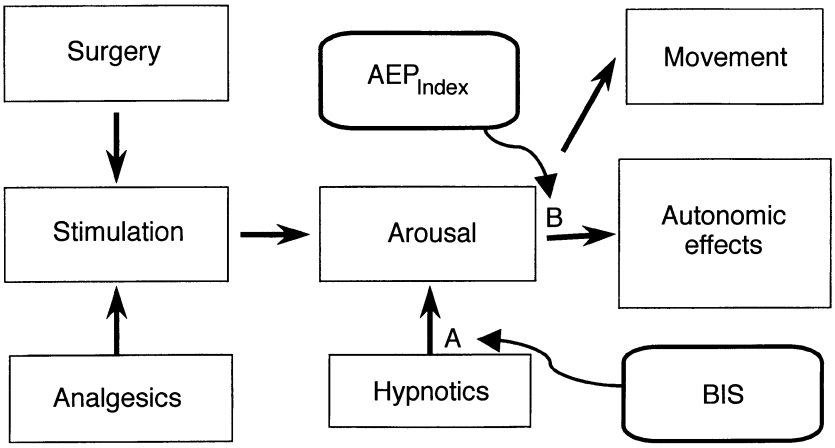

Fig 5 Schematic diagram of the interaction between surgical stimulation, analgesia and hypnosis. Analgesic agents decrease the stimulating effects of surgery and reduce the requirements for hypnotic agents. BIS appears to measure the effect of the hypnotic agent at time A while AEP_{Index} provides a measure of the overall balance between surgery, analgesia and hypnosis at time B.

may demonstrate a more sudden change at the point of recovery of consciousness. The present study and previous studies by our group demonstrated this sudden increase in AEP_{Index} on regaining consciousness, and a gradual increase in BIS during recovery from anaesthesia. AEP_{Index} was also found to be superior to BIS in detecting the transition from unconsciousness to consciousness in these studies.

It is also possible that a monitor of CNS arousal centre activity would give the same information during unconsciousness of any cause (e.g. natural sleep, trauma or general anaesthesia). Studies comparing AEP_{Index} and BIS during unconsciousness from causes other than general anaesthesia may be helpful in determining which measurement is a more reliable measure of consciousness or unconsciousness. Figure 5 is a schematic diagram of the combined effects of surgery and analgesia on stimulation of the patient's level of arousal. BIS could be considered to act at time A in Figure 5 while AEP_{Index} would seem to act at time B which represents the overall effects of analgesia and hypnosis.

In summary, we found that both BIS and AEP_{Index} had high values before anaesthesia, which decreased during anaesthesia, and increased towards pre-anaesthetic values on awakening. However, only AEP_{Index} demonstrated statistically significant differences between all awake values and all values during unconsciousness. AEP_{Index} was also the only measurement that partially recovered towards awake values after patient movement in response to stimuli. BIS increased gradually after discontinuation of anaesthetic drug administration and was therefore unable to detect the transition from unconsciousness to consciousness. In summary, therefore, both AEP_{Index} and BIS appear to be capable of distinguishing between the awake and the anaesthetized state during propofol–nitrous oxide–opioid anaesthesia. BIS may be able to predict recovery of consciousness during emergence from anaesthesia at the end of surgery. AEP_{Index} appeared to indicate more accurately the transition from the unconscious to the conscious state.

Acknowledgements

We thank Dr D. Russell for assistance, and Aspect Medical Systems for lending us the A-1000 EEG monitor.

References

1 Schultetus RR, Hill CR, Dharamraj CM, Banner TE, Berman LS. Wakefulness during cesarean section after anesthetic induction with ketamine, thiopental, or ketamine and thiopental combined. *Anesth Analg* 1986; **65**: 723–8
2 Russell IF. Midazolam–alfentanil: an anaesthetic? An investigation using the isolated forearm technique. *Br J Anaesth* 1993; **70**: 42–6
3 Thornton C, Heneghan CP, James MF, Jones JG. Effects of halothane or enflurane with controlled ventilation on auditory evoked potentials. *Br J Anaesth* 1984; **56**: 315–23
4 Thornton C, Heneghan CP, Navaratnarajah M, Bateman PE, Jones JG. Effect of etomidate on the auditory evoked response in man. *Br J Anaesth* 1985; **57**: 554–61
5 Heneghan CP, Thornton C, Navaratnarajah M, Jones JG. Effect of isoflurane on the auditory evoked response in man. *Br J Anaesth* 1987; **59**: 277–82
6 Thornton C, Konieczko KM, Knight AB, *et al.* Effect of propofol on the auditory evoked response and oesophageal contractility. *Br J Anaesth* 1989; **63**: 411–17
7 Newton DE, Thornton C, Konieczko KM, *et al.* Auditory evoked response and awareness: a study in volunteers at sub-MAC concentrations of isoflurane. *Br J Anaesth* 1992; **69**: 122–9
8 Mantzaridis H, Kenny GNC. Auditory evoked potential index: a quantitative measure of changes in auditory evoked potentials during general anaesthesia. *Anaesthesia* 1997; **52**: 1030–6
9 Kenny GN, Mantzaridis H, Fisher AC. Validation of anesthetic depth by closed-loop control. In: Sebel P, Bonke B, Winograd E, eds. *Memory and Awareness in Anesthesia*. Englewood Cliffs: Prentice Hall, 1993; 225–64
10 Sigl JC, Chamoun NG. An introduction to bispectral analysis for the electroencephalogram. *J Clin Monit* 1994; **10**: 392–404
11 Kearse LA jr, Manberg P, Chamoun N, DeBros F, Zaslavsky A. Bispectral analysis of the electroencephalogram correlates with patient movement to skin incision during propofol/nitrous oxide anesthesia. *Anesthesiology* 1994; **81**: 1365–70
12 Vernon JM, Lang E, Sebel PS, Manberg P. Prediction of movement using bispectral electroencephalographic analysis during propofol/

alfentanil or isoflurane/alfentanil anesthesia. *Anesth Analg* 1995; **80**: 780–5

13 Sebel PS, Lang E, Rampil IJ, *et al.* A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. *Anesth Analg* 1997; **84**: 891–9

14 Flaishon R, Windsor A, Sigl J, Sebel PS. Recovery of consciousness after thiopental or propofol. Bispectral index and isolated forearm technique. *Anesthesiology* 1997; **86**: 613–19

15 Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology* 1997; **86**: 836–47

16 Gajraj RJ, Doi M, Mantzaridis H, Kenny GNC. Analysis of the EEG bispectrum, auditory evoked potentials and the EEG power spectrum during repeated transitions from consciousness to unconsciousness. *Br J Anaesth* 1998; **80**: 46–52

17 Kenny GN, White M. A portable target controlled propofol infusion system. *Int J Clin Monit Comput* 1992; **9**: 179–82

18 Davies FW, Mantzaridis H, Kenny GNC, Fisher AC. Middle latency auditory evoked potentials during repeated transitions from consciousness to unconsciousness. *Anaesthesia* 1996; **51**: 107–13

19 Breckenridge JL, Aitkenhead AR. Awareness during anaesthesia: a review. *Ann R Coll Surg Engl* 1983; **65**: 93–6

20 Jones JG. Memory of intraoperative events. *BMJ* 1994; **309**: 967–8

21 Blacher RS. On awakening paralyzed during surgery. A syndrome of traumatic neurosis. *JAMA* 1975; **234**: 67–8

22 Moerman N, Bonke B, Oosting J. Awareness and recall during general anesthesia. Facts and feelings. *Anesthesiology* 1993; **79**: 454–64

23 Payne JP. Awareness and its medicolegal implications. *Br J Anaesth* 1994; **73**: 38–45

24 Doi M, Gajraj RJ, Mantzaridis H, Kenny GNC. Relationship between calculated blood concentration of propofol and electrophysiological variables during emergence from anaesthesia: a comparison of bispectral index, spectral edge frequency, median frequency and auditory evoked potential index. *Br J Anaesth* 1997; **78**: 180–4

25 Thornton C, Konieczko K, Jones JG, Jordan C, Dore CJ, Heneghan CP. Effect of surgical stimulation on the auditory evoked response. *Br J Anaesth* 1988; **60**: 372–8

26 Schwender D, Golling W, Klasing S, Faber Zullig E, Poppel E, Peter K. Effects of surgical stimulation on midlatency auditory evoked potentials during general anaesthesia with propofol/fentanyl, isoflurane/fentanyl and flunitrazepam/fentanyl. *Anaesthesia* 1994; **49**: 572–8

27 de Beer NA, van Hooff JC, Cluitmans PJ, Korsten HH, Grouls RJ. Haemodynamic responses to incision and sternotomy in relation to the auditory evoked potential and spontaneous EEG. *Br J Anaesth* 1996; **76**: 685–93

28 Jopling M, Cork R, Greenwald S. Changes in the bispectral index (BIS) in the presence of surgical stimulation reflect the level of analgesia. *Anesthesiology* 1996; **85**: A478

29 Bloom M, Greenwald S, Day R. Analgesics decrease arousal response to stimulation as measured by changes in bispectral index (BIS). *Anesthesiology* 1996; **85**: A481

30 Prys-Roberts C. Anaesthesia: a practical or impractical construct? *Br J Anaesth* 1987; **59**: 1341–5

31 Kearse LA jr, Manberg P, DeBros F, Chamoun N, Sinai V. Bispectral analysis of the electroencephalogram during induction of anesthesia may predict hemodynamic responses to laryngoscopy and intubation. *Electroencephalogr Clin Neurophysiol* 1994; **90**: 194–200

32 Sebel PS, Lang E, Rampil IJ, *et al.* A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. *Anesth Analg* 1997; **84**: 891–9

33 Howell S, Gan TJ, Martel D, Glass PSA. Defining the CP_{50} and BIS_{50} for propofol alone and propofol with alfentanil. *Anesthesiology* 1995; **83**: A367

34 Alkire M. Quantitative EEG correlations with brain glucose metabolic rate during anesthesia in volunteers. *Anesthesiology* 1998; **89**: 323–35