British Journal of Anaesthesia **91 (3)**: 336–40 (2003)
DOI: 10.1093/bja/aeg189

BJA

Comparison of Alaris AEP index and bispectral index during propofol-remifentanil anaesthesia†

S. Kreuer[1], J. Bruhn[2], R. Larsen[1], M. Hoepstein[1] and W. Wilhelm[1]*

[1]Department of Anaesthesiology and Intensive Care Medicine, University of Saarland, D-66421 Homburg/Saar, Germany. [2]Department of Anaesthesiology and Intensive Care Medicine, University of Bonn, D-53119 Bonn, Germany

**Corresponding author. E-mail: wolfram.wilhelm@uniklinik-saarland.de*

Background. The Alaris AEP monitor™ (Alaris, UK, version 1.4) is the first commercially available auditory evoked potential (AEP) monitor designed to estimate the depth of anaesthesia. It generates an 'Alaris AEP index' (AAI), which is a dimensionless number scaled from 100 (awake) to 0. This study was designed to compare AAI and BIS™ (Aspect, USA, version XP) values at different levels of anaesthesia.

Methods. Adult female patients were premedicated with diazepam 0.15 mg kg^{-1} orally on the morning of surgery. Electrodes for BIS and Alaris AEP monitoring and a headphone to give auditory stimuli were applied as recommended by the manufacturers. Anaesthesia was induced with remifentanil (0.4 μg kg^{-1} min^{-1}) and a propofol target-controlled infusion (Diprifusor™ TCI, AstraZeneca, Germany) to obtain a predicted concentration of initially 3.5 μg ml^{-1}. After loss of consciousness the patients were given 0.5 mg kg^{-1} of atracurium. After tracheal intubation, remifentanil was given at 0.2 μg kg^{-1} min^{-1} and the propofol infusion was adjusted to obtain BIS target values of 30, 40, 50, and 60. AAI and BIS values were recorded and matched with the predicted propofol effect-site concentrations. Prediction probability was calculated for consciousness *vs* unconsciousness. Values are mean (SD).

Results. Fifty female patients, 53 (15), range 18–78 yr, ASA I or II were studied. Mean values before induction of anaesthesia were 95 (4), range 99–82 for BIS and 85 (12), range 99–55 for AAI. With loss of eyelash reflex both values were significantly reduced to 64 (13), range 83–39 for BIS ($P<0.05$) and 61 (22), range 99–15 for AAI ($P<0.05$). The prediction probability P_K for consciousness *vs* unconsciousness (i.e. loss of eyelash reflex) was better for BIS ($P_K=0.99$) than for AAI ($P_K=0.79$). At a BIS of 30, 40, 50, and 60 the corresponding AAI values were 15 (6), 20 (8), 28 (11), and 40 (16), and these were significantly different.

Conclusions. During propofol-remifentanil anaesthesia a decrease of the depth of anaesthesia as indicated by BIS monitoring is accompanied by corresponding effects shown by the AAI. However, wide variation in the awake values and considerable overlap of AAI values between consciousness and unconsciousness, suggests further improvement of the AAI system is required.

Br J Anaesth 2003; **91**: 336–40

Keywords: anaesthetics i.v., propofol; analgesics opioid, remifentanil; equipment, AEP monitor; monitoring, bispectral index; monitoring, electroencephalogram

Accepted for publication: April 18, 2003

Estimation of 'depth of anaesthesia' is of great interest. Many investigations have used the raw EEG, but derived measures were not available until modern computing became available. Several monitor systems are now commercially available and have been introduced into clinical practice.

One of these is the bispectral index monitor (BIS, Aspect Medical Systems Inc., Newton, USA), which can quantify the pharmacodynamic action of anaesthetic drugs in the

†This study was presented in part at the American Society of Anesthesiologists meeting on October 16, 2002, Orlando, USA.

laboratory setting,[1] and has been used clinically to titrate the depth of anaesthesia.[2] Although the ability of the BIS to reduce the risk of intraoperative awareness is questioned,[3] less anaesthetic drug use and faster and improved recovery have been reported when using the BIS monitor.[4–10]

Middle-latency auditory evoked potentials (AEP) can also quantify action of anaesthetic drugs,[11–14] and may be better able to detect the transition from unconsciousness to consciousness than the BIS.[15] The Alaris AEP monitor (Alaris, Hampshire, UK, version 1.4) is the first commercially available AEP monitor designed to measure the depth of anaesthesia. It generates an index (AAI), which is a dimensionless number scaled from 100 (awake) to 0. Comparisons of AAI and BIS values in awake patients at loss of consciousness and during surgical anaesthesia are advisable before the AAI is introduced into clinical practice.

We compared measures of the depth of anaesthesia by the AAI with BIS values (version XP) during anaesthesia with propofol and remifentanil.

Methods

We obtained institutional review board approval and written informed consent, and studied 50 adult female patients about to have gynaecological surgery. We excluded patients with disabling central nervous or cerebrovascular diseases, a history of hypersensitivity to opioids or substance abuse, or those receiving treatment with opioids or any psychoactive medication.

All patients were premedicated with diazepam 0.15 mg kg^{-1} orally on the morning of surgery. An i.v. catheter was inserted into a large forearm vein and standard monitors were applied. The EEG was recorded continuously using an Aspect A-2000 BIS monitor (version XP) and the Alaris AEP monitor (version 1.4). The skin of the forehead was degreased with isopropanol 70%, and the BIS (BIS sensor™), the Alaris AEP monitor electrodes (AEP electrodes; Danmeter A/S), and a headphone for auditory stimuli were applied as recommended by the manufacturers. The three AEP electrodes were placed at mid forehead, left forehead (reference) and left mastoid; both forehead electrodes were positioned cranially to the BIS sensor. Impedances were measured for each set of electrodes to be sure that electrode contact was optimal, and an averaging period of 30 s was chosen for BIS calculations.

Induction of anaesthesia was started with a remifentanil infusion at 0.4 μg kg^{-1} min^{-1}; 5 min later a propofol target-controlled infusion (TCI, Diprifusor™, AstraZeneca, Wedel, Germany), was started with a propofol target concentration set at 3.5 μg ml^{-1}. After loss of verbal response the eyelash reflex was continuously tested, and its loss was defined as the time of loss of consciousness. Oxygen was given by face mask, patients were given 0.5 mg kg^{-1} of atracurium, the trachea was intubated 3 min later, and the lungs ventilated to obtain an end-tidal carbon dioxide partial pressure of 35 mm Hg. AAI and BIS values were recorded immediately before and after intubation. After intubation the remifentanil infusion was reduced to 0.2 μg kg^{-1} min^{-1}. Fifteen minutes later the propofol TCI setting was adjusted to obtain a BIS target value of 30, and then to BIS values of 40, 50, and 60 while the patients received no surgical stimulation. After a stabilization period of 15 min at the respective BIS levels, AAI and BIS values, and the corresponding propofol effect-site concentration displayed by the TCI Diprifusor, were recorded. Mean arterial pressure and heart rate values were obtained at these times. Complete neuromuscular block during the investigation was ensured by further atracurium, 0.25 mg kg^{-1}.

After these measurements, anaesthesia was continued according to individual clinical needs, and the surgical procedure was started.

Statistics

Statistical comparisons used the Student's *t*-test or one-way analysis of variance (ANOVA) for repeated measures, with Student–Newman–Keuls test for multiple comparisons where appropriate. All tests were two-tailed with statistical significance defined as $P<0.05$; data are presented as mean and standard deviation (SD). In addition, linear and non-linear correlation between AAI and BIS values were calculated.

The ability of EEG measures to predict consciousness/unconsciousness was measured with prediction probability (P_K), which compares the performance of indicators. The mathematical basis of P_K is described by Smith and colleagues.[16] A P_K value of 1 means that the values of the predicting variable (e.g. anaesthetic depth indicator such as BIS or AAI) always correctly predicts the variable to be predicted (e.g. consciousness *vs* unconsciousness). A P_K value of 0.5 means that the prediction is no better than chance alone. Using a spreadsheet macro the P_K value was computed for the assessments made while awake but during remifentanil infusion, that is immediately before the propofol TCI was started, and immediately after loss of eyelash reflex.

Statistical analysis was done with SigmaStat 2.03 and SigmaPlot 2000 computer software (SPSS Inc., Erkrath, Germany).

Results

Fifty female patients with ASA physical status I or II were enrolled in this study. They had a mean age of 53 (15) [range 18–78] yr, weighed 68 (13) kg, and were 165 (6) cm tall.

The awake mean values for AAI were 85 (12) and for BIS 95 (4). Five minutes after the remifentanil infusion had been started at 0.4 μg kg^{-1} min^{-1} the AAI values decreased significantly to 79 (18) whereas BIS values remained unchanged at 92 (7). After the propofol TCI infusion was started the mean time to loss of eyelash reflex was 52 (22) s. Loss of eyelash reflex occurred at a mean propofol effect-

Table 1 Predicted propofol effect-site concentrations, AAI and BIS values, and circulatory measurements at the different stages of the study. Values are mean (SD). The asterisk (*) indicates that values are significantly different with $P<0.05$ (repeated measures ANOVA; Student–Newman–Keuls test) when compared with preceding values. Remifentanil+5 min, 5 min after start of remifentanil infusion; LOC, loss of consciousness; before NMB, immediately before injection of neuromuscular blocker

	Propofol effect-site concentration (μg ml^{-1})	AAI	BIS	Heart rate (beats min^{-1})	Mean arterial pressure (mm Hg)
Baseline	0	85 (12)	95 (4)	80 (15)	96 (16)
Remifentanil+5 min	0	79 (18)*	92 (7)	76 (14)	93 (21)
LOC	1.1 (0.4)*	61 (22)*	64 (13)*	68 (19)*	72 (28)*
Before NMB	1.8 (0.8)*	45 (23)*	55 (13)*	65 (13)	66 (26)
After intubation	2.5 (0.4)*	23 (15)*	44 (10)*	67 (13)	66 (17)
BIS 30	3.1 (0.4)*	15 (6)*	31 (1)*	60 (9)*	64 (20)
BIS 40	2.6 (0.8)*	20 (8)*	40 (1)*	59 (9)	64 (11)
BIS 50	2.1 (0.8)*	28 (11)*	50 (1)*	59 (10)	65 (11)
BIS 60	1.8 (0.7)*	40 (16)*	60 (1)*	60 (9)	62 (20)

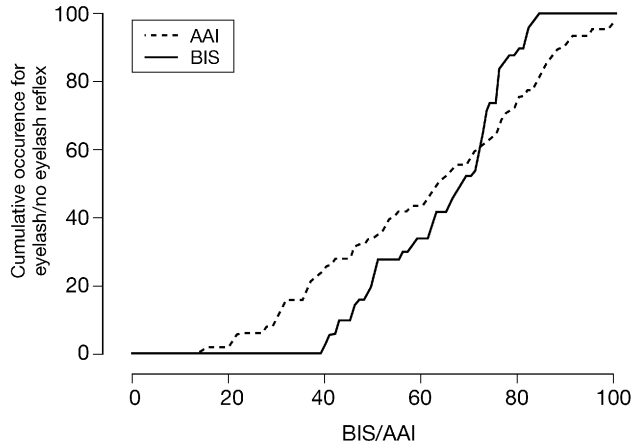

Fig 1 Cumulative onset of unconsciousness indicated by loss of eyelash reflex as a function of AAI (dotted line) and BIS (solid line) values.

site concentration of 1.1 (0.4) μg ml^{-1} (Table 1) and was accompanied with a significant reduction of mean AAI to 61 (22) and BIS to 64 (13). However, the range of values obtained at the time of loss of eyelash reflex was 15–99 for the AAI and 39–83 for the BIS monitor (Fig. 1). The prediction probability P_K for consciousness *vs* unconsciousness defined as the loss of eyelash reflex was greater for BIS (P_K=0.99) than for AAI (P_K=0.79). Mean AAI values just before intubation were 23 (12) and remained unchanged just after intubation at 23 (15). The same was true for the BIS values with 44 (11) before and 44 (10) after intubation. The circulatory values at the different times are given in Table 1.

Propofol effect-site concentrations at the different times and the respective AAI and BIS values are shown as a scatter diagram in Figure 2A and B, and as mean values in Table 1. With induction of anaesthesia and increasing propofol effect-site concentrations we observed a significant reduction of the mean AAI and BIS values. As the propofol TCI was reduced to obtain BIS values of 40, 50, and 60, this was accompanied by a significant decrease in the effect-site concentrations and a significant increase of mean AAI values: at a BIS of 30, 40, 50, and 60 the corresponding AAI values were 15 (6), 20 (8), 28 (11), and 40 (16), and these were significantly different. Linear correlation for these values between AAI and BIS was calculated as AAI=0.82×BIS – 11.1 with a correlation coefficient of r=0.63 (Fig. 3). The relationship of all the BIS and AAI data was best described by a sigmoidal model ($AAI=15.5+70.1/(1+e^{((BIS-64.3)/8.5)})$; r=0.92) (Fig. 3).

Discussion

Middle-latency AEPs have been used to measure the effects of anaesthetics.[11–14] We compared the depth of anaesthesia indicated by the AAI with BIS values.

Awake state

The awake values for AAI were less than BIS values with a mean value of 85 and showed substantially more variation between subjects than the BIS values. This supports previous investigations which reported mean awake values for AAI of 70,[17] 74.9,[18] 79,[19] or 86.[20] The reported ranges for individual awake AAI values were 51–99[17] and 61–99[20] compared with our observed range of 55–99.

A small variation in baseline values is needed to allow definition of anaesthesia and the quantification of depth of sedation or anaesthesia.[21] Technical aspects such as high electrode impedances, contamination with electrical noise and electrical activity from the temporalis or postauricular muscles may explain the wide interindividual variation of the AAI.[19] Alpiger and colleagues[19] used a preliminary version of the device that did not monitor impedance and EMG, and suggested that a revised version of the Alaris AEP monitor with impedance and EMG meters might solve these problems. The present results suggest that this problem remains unsolved.

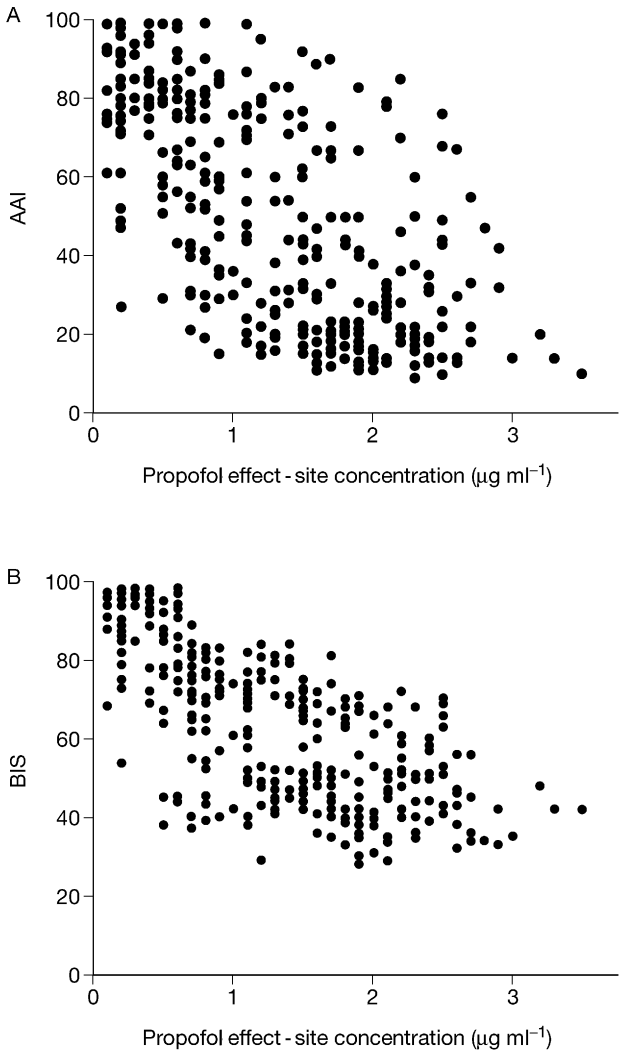

Fig 2 Individual values of AAI (A) and BIS (B) at increasing propofol effect-site concentrations.

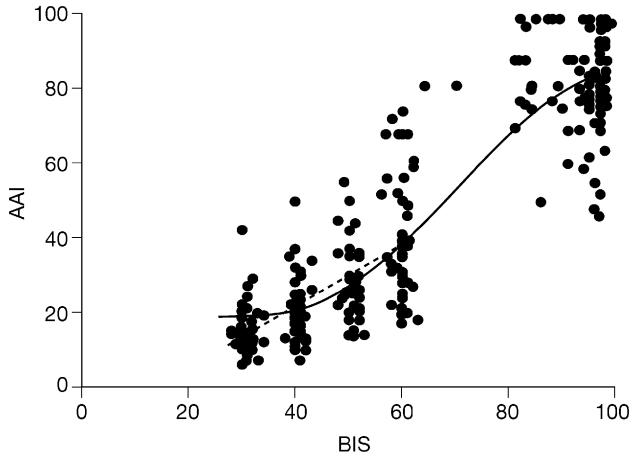

Fig 3 At stepwise increased BIS values of 30, 40, 50, and 60, significantly increasing AAI values (mean (SD)) were measured as 15 (6), 20 (8), 28 (11), and 40 (16). In this range, the regression relationship was AAI=0.82×BIS – 11.1 (dashed line). The correlation coefficient was r=0.63. A sigmoid model (AAI=15.5+70.1/(1+e $^{((BIS - 64.3)/8.5)}$); r=0.92) (solid line) described the correlation between all BIS and AAI values (BIS range 30–100).

Loss of consciousness

We used the eyelash reflex because this test is widely used clinically to determine transition from consciousness to unconsciousness. Because of a substantial overlap with the awake AAI values, we obtained a smaller prediction probability for consciousness *vs* unconsciousness for AAI (P_K=0.79) than for BIS (P_K=0.99). In contrast, Struys and colleagues[17] found similar prediction probabilities for AAI and BIS while also using the eyelash reflex test. However, these authors used a more gradual increase of the propofol plasma concentration (i.e. an increase of 0.5 μg ml^{-1} every 4 min). This would allow a more accurate determination of the loss of consciousness and also reduce the influence of the calculation time of both monitors while the depth of anaesthesia was changing. The present investigation, with a more rapid induction of anaesthesia and a time to loss of eyelash reflex of 52 s, represents clinical circumstances, and in these conditions, the P_K value for BIS was greater than that for the AAI. In addition, neither the study of Struys,[17] our study, or the study of Barr and co-workers,[20] using loss of response to verbal command, support a study where AEPs gave a better prediction of the transition from unconsciousness to consciousness compared with BIS.[15] This study was done with a different AEP index, described by Kenny and colleagues.[15 22] These measures—although based on the same principle—may involve different computation and cannot easily be compared.

Surgical depth of anaesthesia

During surgery a BIS target value between 40 and 60 is suggested.[2] Adjusting the BIS to this range gives less anaesthetic use and faster and improved recovery.[4–10] Therefore, it is relevant to study the AAI in this BIS range. While increasing the BIS value in steps from 30 to 40, and then 50 and 60, a slight but significant increase of the AAI values was noted with substantial overlap. The slope of the correlation between AAI and BIS in this range was less than 1 (0.82). This accords with the observation that a sigmoid curve fitted the relationship between all AAI and BIS values and this range was in the flat part of the curve for the AAI values. This observation supports Struys and co-workers[17] who found that the AAI reached its minimum early compared with the BIS with no difference for AAI between the OAA/S scores 2, 1, and 0, while BIS discriminated between OAA/S score 2 and 1. In the study of Alpiger and colleagues,[19] the AAI did not change significantly at end-expiratory steady-state sevoflurane concentrations of 2.0, 1.5, and 1.0%. In contrast, in the study of Katoh and co-workers[23] BIS changed substantially between

end-expiratory steady-state sevoflurane concentrations of 1.5 and 1.0%.

The BIS seems to reach a plateau value at around 30–35,[24 25] which is less than the target range of 40–60. In contrast, the AAI might reach these plateau values earlier, possibly just inside a supposed target range. This could explain why guidance from the AAI did not reduce the sevoflurane consumption or the emergence time in the study of Assareh and colleagues.[26]

Conclusion

Wide variation in the awake values, considerable overlap of AAI values between consciousness and unconsciousness, and an apparent plateau of the values in a range of major clinical interest suggest further improvement of the AAI method is needed.

Acknowledgements

The Alaris AEP monitor was provided by the manufacturer. The study itself was solely supported by departmental funding.

References

1 Billard V, Gambus PL, Chamoun N, Stanski DR, Shafer SL. A comparison of spectral edge, delta power, and bispectral index as EEG measures of alfentanil, propofol, and midazolam drug effect. *Clin Pharmacol Ther* 1997; **61**: 45–58

2 Johansen JW, Sebel PS. Development and clinical application of electroencephalographic bispectrum monitoring. *Anesthesiology* 2000; **93**: 1336–44

3 O'Connor MF, Daves SM, Tung A, Cook RI, Thisted R, Apfelbaum J. BIS monitoring to prevent awareness during general anesthesia. *Anesthesiology* 2001; **94**: 520–2

4 Guignard B, Coste C, Menigaux C, Chauvin M. Reduced isoflurane consumption with bispectral index monitoring. *Acta Anaesthesiol Scand* 2001; **45**: 308–14

5 Gan TJ, Glass PS, Windsor A, Payne F, Rosow C, Sebel P, Manberg P. Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. *Anesthesiology* 1997; **87**: 808–15

6 Yli-Hankala A, Vakkuri A, Annila P, Korttila K. EEG bispectral index monitoring in sevoflurane or propofol anaesthesia: analysis of direct costs and immediate recovery. *Acta Anaesthesiol Scand* 1999; **43**: 545–9

7 Bannister CF, Brosius KK, Sigl JC, Meyer BJ, Sebel PS. The effect of bispectral index monitoring on anesthetic use and recovery in children anesthetized with sevoflurane in nitrous oxide. *Anesth Analg* 2001; **92**: 877–81

8 Song D, Joshi GP, White PF. Titration of volatile anesthetics using bispectral index facilitates recovery after ambulatory anesthesia. *Anesthesiology* 1997; **87**: 842–8

9 Pavlin DJ, Hong JY, Freund PR, Koerschgen ME, Bower JO, Bowdle TA. The effect of bispectral index monitoring on end-tidal gas concentration and recovery duration after outpatient anesthesia. *Anesth Analg* 2001; **93**: 613–9

10 Johansen JW, Sebel PS, Sigl JC. Clinical impact of hypnotic-titration guidelines based on EEG bispectral index (BIS) monitoring during routine anesthetic care. *J Clin Anesth* 2000; **12**: 433–43

11 Heneghan C, Thornton C, Navaratnarajah M, Jones J. Effect of isoflurane on the auditory evoked response in man. *Br J Anaesth* 1987; **59**: 277–82

12 Schwender D, Klasing S, Conzen P, Finsterer U, Pöppel E, Peter K. Effects of anesthesia with increasing endexpiratory concentrations of sevoflurane on mid-latency auditory evoked potentials. *Anesth Analg* 1995; **80**: 499–505

13 Schwender D, Klasing S, Conzen P, Finsterer U, Pöppel E, Peter K. Mid-latency auditory evoked potentials during anaesthesia with increasing endexpiratory concentrations of desflurane. *Acta Anaesthesiol Scand* 1996; **40**: 171–6

14 Thornton C, Konieczko K, Knight A, Kaul B, Jones J, Dore C, White D. Effect of propofol on the auditory evoked response and oesophageal contractility. *Br J Anaesth* 1989; **63**: 411–7

15 Gajraj RJ, Doi M, Mantzaridis H, Kenny GN. 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

16 Smith WD, Dutton RC, Smith NT. Measuring the performance of anesthetic depth indicators. *Anesthesiology* 1996; **84**: 38–51

17 Struys M, Jensen EW, Smith W *et al.* Performance of the ARX-derived auditory evoked potential index as an indicator of anaesthetic depth. *Anesthesiology* 2002; **96**: 803–16

18 Litvan H, Jensen EW, Revuelta M, *et al.* Comparison of auditory evoked potentials and the A-line ARX index for monitoring the hypnotic level during sevoflurane and propofol induction. *Acta Anaesthesiol Scand* 2002; **46**: 245–51

19 Alpiger S, Helbo-Hansen HS, Jensen EW. Effect of sevoflurane on the midlatency auditory evoked potentials measured by a new fast extracting monitor. *Acta Anaesthesiol Scand* 2002; **46**: 252–6

20 Barr G, Anderson RE, Jakobsson JG. A study of bispectral analysis and auditory evoked potential indices during propofol-induced hypnosis in volunteers: the effect of an episode of wakefulness on explicit and implicit memory. *Anaesthesia* 2001; **56**: 888–93

21 Bruhn J, Bouillon TW, Hoeft A, Shafer SL. Artifact robustness, inter- and intraindividual baseline stability, and rational EEG parameter selection. *Anesthesiology* 2002; **96**: 54–9

22 Mantzaridis H, Kenny GN. Auditory evoked potential index: a quantitative measure of changes in auditory evoked potentials during general anaesthesia. *Anaesthesia* 1997; **52**: 1030–6

23 Katoh T, Suzuki A, Ikeda K. Electroencephalographic derivatives as a tool for predicting the depth of sedation and anesthesia induced by sevoflurane. *Anesthesiology* 1998; **88**: 642–50

24 Olofsen E, Dahan A. The dynamic relationship between end-tidal sevoflurane and isoflurane concentrations and bispectral index and spectral edge frequence of the electroencephalogram. *Anesthesiology* 1999; **90**: 1345–53

25 Bruhn J, Bouillon T, Shafer SL. Bispectral index (BIS) and burst suppression: revealing a part of the BIS algorithm. *J Clin Monit Comp* 2001; **16**: 593–6

26 Assareh H, Anderson RE, Usuijarvi J, Jakobsson J. Sevoflurane requirements during ambulatory surgery: a clinical study with and without AEP-index guidance. *Acta Anaesthesiol Scand* 2002; **46**: 495–9