Effects of the auditory stimuli of an auditory evoked potential system on levels of consciousness, and on the bispectral index†

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Investigators in the field of depth of anaesthesia monitoring sometimes measure the auditory evoked potential (AEP) and the Bispectral Index (BIS) concurrently. However, the auditory stimuli required to generate an AEP may increase the level of consciousness, and cause an increase in the BIS. They may also alter the BIS by producing phase-locked harmonics in the surface electroencephalogram. The aim of this study was to determine if AEP stimuli have clinically significant effects on levels of consciousness and BIS values during sedation and general anaesthesia. Ten healthy adult patients were studied by measuring and recording the BIS for 6 epochs of 5 min each. The first 3 epochs took place during steady-state sedation, during which time the Observer’s Assessment of Awareness/Sedation (OAA/S) score was also measured. The second 3 epochs took place during steady-state anaesthesia. During alternate epochs, patients were subjected to the auditory stimuli generated by an AEP system. The auditory stimuli were not associated with a change in BIS values (during sedation and anaesthesia) or OAA/S scores (sedation).

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At present there is no ‘gold standard’ measure of anaesthetic depth. The traditional clinical signs are surrogate measures, which assess autonomic activity and are unreliable predictors of conscious perception and recall.1,2 Newer measures derived from analyses of the electrocardiogram (respiratory sinus arrhythmia) and the electroencephalogram (EEG) (Bispectral Index (BIS), auditory evoked potential (AEP) and approximate entropy) are undergoing further evaluation. These studies sometimes involve comparisons of clinical signs with simultaneous measurements of combinations of the newer variables.3–6

Repetitive auditory stimuli are required to generate an AEP. Theoretically, these may alter the BIS by causing sufficient stimulation to increase the level of consciousness. In addition they may cause an indirect effect on the BIS. Bispectral analysis assesses phase relationships among component frequencies in the EEG. By introducing phase-locked harmonics, the repetitive stimuli may cause false alterations in the BIS. We, therefore, evaluated the effect of the AEP clicks on levels of consciousness and BIS values during steady-state sedation and anaesthesia.

Methods and results

After ethics committee approval and informed consent, 10 adult patients, ASA status I–III, presenting for elective plastic or lower limb orthopaedic surgery were studied. Exclusion criteria included a history of deafness, obesity, hiatus hernia, or psychiatric disorders.

A custom-made AEP system was used to generate clicks at a frequency of 6.9 Hz and volume of 70 dB. An A-2000 BIS monitor (Software v3.3, Aspect Medical Systems, Newtown, USA) was used to generate BIS data, which were recorded electronically every 5 s. These data were recorded for 30 min, comprising 6 epochs of 5 min, during which the AEP clicks were alternately switched on or off. Patients 1, 3, 5, 7, and 9 had the clicks on during odd-numbered epochs,
and off during even-numbered epochs, while the reverse applied to the remaining patients. The first three epochs were recorded while patients were sedated before induction of anaesthesia, and the remaining three after induction of anaesthesia. Heart rate, non-invasive arterial pressure, and oxygen saturation were recorded every 5 min.

No sedative pre-medication was given. On arrival in the pre-anaesthetic care unit, routine monitoring was instituted and baseline measurements recorded. An i.v. cannula was inserted into the dorsum of the non-dominant hand and a target-controlled infusion (TCI) of propofol was started at an initial target blood concentration of 1 μg ml⁻¹ using a Diprifusor (AstraZeneca, UK). The three patients undergoing lower limb orthopaedic surgery first had a lumbar epidural catheter inserted. Bupivacaine 0.5%, 10 ml, was injected into the epidural space, and the patient was observed for 20 min before the propofol TCI was started. During this period, 500 ml of modified gelatin solution (Geloflex, Braun Medical, UK) was administered. There were no episodes of hypotension (prospectively defined as systolic arterial pressure <80 mm Hg, or a decrease of >30% from baseline).

During the period of sedation, a single investigator performed the Observer’s Assessment of Awareness/Sedation (OAA/S) every minute. The target propofol concentration was gradually increased until the OAA/S score was 4 (response to name spoken in normal tone), and the patient was lying peacefully, with closed eyes. The target blood concentration was then set to the current estimated effect-site concentration. Once the estimated blood and effect-site concentrations had equilibrated, the first 15 min of BIS recording was started. The amount of background noise was kept to a minimum, and the patient was not disturbed except to assess sedation and measure arterial pressure.

At the end of the first 15 min, the propofol TCI was continued at the same target concentration, and the patient was moved into the operating theatre. After he or she had breathed 100% oxygen for 3 min, anaesthesia was induced and maintained using TCI propofol, supplemented with TCI remifentanil or alfentanil in patients undergoing plastic surgery. A laryngeal mask airway (LMA) was inserted, and the patients’ lungs were mechanically ventilated using 40% oxygen in air, except for the orthopaedic patients who breathed the same mixture spontaneously. The target propofol concentration was reduced to a level just above the estimated effect-site concentration required for loss of consciousness and LMA insertion. After equilibration, the target concentrations of propofol and opioid were kept constant, and the second 15 min period of BIS recording began. The study terminated at the end of this period, and the surgeon was allowed to start the operation.

OAA/S scores are presented as median (range), and all other data as mean (SD). For individual patients median OAA/S scores and mean BIS values were derived by combining epochs during which the clicks were, respectively, on and off. All five OAA/S scores for each epoch were included, whereas only the middle (third) minute of BIS data from each epoch was used, to ensure that only BIS values derived from EEG data recorded during the current epoch were included. Within-subject analysis (two-way ANOVA) was used to assess the effect of the clicks on the BIS. OAA/S scores were compared using the Wilcoxon rank-sum test. \( P<0.05 \) was regarded as statistically significant.

Five males and five females were studied. Mean age, weight, and height were 39.8 (20.3) [range 17–69] yr, 68.3 (17.1) kg, and 168 (13.3) cm. The effect-site propofol concentrations required for sedation and maintenance of anaesthesia were 1.6 (0.4) and 3.6 (1.0) μg ml⁻¹, respectively. During sedation, the median OAA/S scores were 4 (3–4) with the clicks on, and 4 (3–5) with the clicks off.

\( ^\text{3} \text{LMA} \) is the property of Intavent Limited.

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**Figure 1.** Mean BIS values for individual patients during 3rd minute of each epoch. Heavy line represents the mean.
There was no difference between OAA/S scores in the first minute after starting the clicks compared with subsequent minutes. During general anaesthesia, stopping or starting of the clicks was not associated with a change in clinical signs of depth of anaesthesia, except in one patient who made some spontaneous movements during epoch 6, soon after the clicks were switched off. These movements stopped without any intervention.

Mean BIS values for individual patients are shown in Figure 1. BIS data were not collected for one patient during epoch 6, as the study was terminated when the surgeon insisted on starting the operation. During sedation, the mean (SD) BIS values were 75.2 (9.8) when the clicks were on and 74.9 (9.8) when the clicks were off. For general anaesthesia the corresponding figures were 46.0 (13.6) and 47.7 (16.2), respectively. ANOVA showed a large between-subject variation but no significant within-subject variability in the BIS associated with the clicks (P = 0.34 for sedation and P = 0.95 for anaesthesia). The mean within-subject difference in the BIS (value with clicks on less value with clicks off) was ±0.96 (95% CI: −3.13 to 1.2) for sedation, and ±0.17 (95% CI: −6.3 to 6.0) for general anaesthesia.

Comment

In this study, AEP clicks did not alter the clinical signs of depth of sedation or anaesthesia, and were not associated with a change in the BIS. There are various reasons why the AEP clicks may not have an effect on the BIS. The first is that even if the AEP clicks are initially rather loud, the stapedius reflex quickly causes accommodation. This reflex attenuates the amplitude of the electrical impulses passing along the auditory pathways. The second is that the amplitude of the AEP arriving at the cortex of the brain is many orders of magnitude smaller than the background EEG. This is why signal averaging techniques are necessary to extract the AEP waveform from the EEG. The A-2000 monitor utilizes a combination of time domain, frequency domain, and bispectral analyses, none of which is likely to be sensitive to very small amplitude signals.

It is possible that our result is falsely negative. With 10 subjects, and an α level of 0.05, our study can only accept the null hypothesis with power >80% for a mean within-subject difference in BIS of 2.7 during sedation and 7.7 during anaesthesia (the SD of the within-patient differences in the current study were 3.0 and 8.6, respectively). To exclude a smaller difference between groups with adequate power, a far greater sample size is necessary.

In conclusion, based on the patients we have studied we have not found evidence that the AEP clicks cause an alteration in the level of consciousness or the BIS.

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