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Closed-loop control of propofol anaesthesia

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We describe the use of a closed-loop system to control depth of propofol anaesthesia automatically. We used the auditory evoked potential index (AEP_{index}) as the input signal of this system to validate it as a true measure of depth of anaesthesia. Auditory evoked potentials were acquired and processed in real time to provide the AEP_{index}. The AEP_{index} was used in a proportional integral (PI) controller to determine the target blood concentration of propofol required to induce and maintain general anaesthesia automatically. We studied 100 spontaneously breathing patients. The mean AEP_{index} before induction of anaesthesia was 73.5 (SD 17.6), during surgical anaesthesia 37.8 (4.5) and at recovery of consciousness 89.7 (17.9). Twenty-two patients required assisted ventilation before incision. After incision, ventilation was assisted in four of these 22 patients for more than 5 min. There was no incidence of intraoperative awareness and all patients were prepared to have the same anaesthetic in future. Movement interfering with surgery was minimal. Cardiovascular stability and overall control of anaesthesia were satisfactory.

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Anaesthesia has been defined as 'that state which ensures the suppression of the somatic and visceral sensory components, and thus the perception of pain'.[1] Before the introduction of neuromuscular blocking drugs into anaesthetic practice, movement of the patient provided a clear indication of depth of anaesthesia. However, when neuromuscular blocking drugs are administered, the availability of patient movement as a valuable sign of the inadequacy of anaesthesia is lost and reliance has been placed on indirect signs. There have been many reports of patients being aware during surgery[2–5] and considerable efforts have been made to develop a reliable index of depth of anaesthesia.

Auditory evoked potentials (AEP) have been reported to fulfil many of the requirements for measurement of the level of anaesthesia.[6–10] In particular, the AEP has been shown to provide good discrimination of the transition from asleep to awake and *vice versa*.[10 11] We have developed a system to obtain a single index which represents the morphology of the AEP[12–15] and used this index as the input signal for closed-loop anaesthesia (CLAN) during surgery in patients who did not receive neuromuscular blocking drugs.

Patients and methods

After obtaining approval from the Hospital Ethics Committee for evaluation of the CLAN system and written informed consent, we studied 100 ASA I or II patients, mean age 50 (range 19–83) yr and mean weight 66 (40–108) kg, undergoing body surface surgery. All were able to understand the purpose of the study. There were no other exclusion criteria. Patients received temazepam for premedication approximately 1 h before surgery. Young patients received temazepam 30 mg and older patients received temazepam 20 mg. Day-case patients did not receive premedication.

Auditory evoked potential acquisition

In the operating theatre, patients were connected to the CLAN system. AEP were obtained using a system described previously[10–14] from three electrodes placed at the right mastoid (+) and middle forehead (–), with Fp2 as the reference. The amplifier was custom-built with a 5-kV medical grade isolation. It had a common mode rejection ratio (CMRR) of 170 dB with balanced source impedance, input voltage noise of 0.3 μV (10 Hz–1 kHz rms) and current input noise of 4 pA (0.05 Hz–1 kHz rms). A third-order Butterworth analogue band-pass filter with a bandwidth of 1–220 Hz was used. The clicks were 70 dB above the normal hearing level and had a duration of 1 ms. They were presented at a rate of 6.9 s^{-1} to both ears. The amplified EEG was sampled at a frequency of 1778 Hz by a 12-bit analogue-to-digital converter and was processed in real-time by a microcomputer.

Table 1 Induction algorithm. Step 2 was repeated up to three times. The algorithm was interrupted and the system switched to the proportional integral control algorithm when the desired AEP_{index} was obtained

	Premedicated ($n=67$)	**Unpremedicated ($n=33$)**
Step 1		
Initial target propofol concentration	2.0 μg ml^{-1}	4.0 μg ml^{-1}
Wait for	50 s	40 s
Step 2		
Increase target by	1.0 μg ml^{-1}	1.5 μg ml^{-1}
Wait for	50 s	40 s
Repeat up to	3 times	3 times
Step 3		
Thereafter increase target by	1.0 μg ml^{-1}	1.5 μg ml^{-1}
Every	60 s	60 s

AEP were produced by averaging 256 sweeps of 144 ms duration. The time required to have 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. AEP were obtained at 3-s intervals and the AEP index (AEP_{index}), a mathematical derivative reflecting the morphology of the AEP, was calculated automatically. The AEP_{index} is defined as the sum of the square root of the absolute difference between every two successive segments of the AEP waveform.[11–14]

The 3-s running average of the AEP_{index} was entered into a proportional integral (PI) control algorithm. The algorithm calculated the required alteration in the target blood concentration of propofol from the difference between the measured AEP_{index} and the control value of the AEP index ($AEP_{index}^{control}$) selected by the anaesthetist. The new value for the target propofol concentration was transmitted to the target-controlled infusion (TCI) system which used a pharmacokinetic model[16] to achieve and maintain the required target concentration set by the PI control algorithm.

The value for the AEP_{index} was recorded with the patient awake and the anticipated $AEP_{index}^{control}$ for satisfactory anaesthesia was entered into the CLAN system. Previous experience using the AEP_{index} as a monitor of the adequacy of anaesthesia[11 15] suggested a range of 30–40 for the $AEP_{index}^{control}$. Anaesthesia was induced automatically by the CLAN system using a predetermined series of increasing target blood propofol concentrations (Table 1) until the AEP_{index} was equal to the selected $AEP_{index}^{control}+10$. Thereafter, control of anaesthesia was achieved by transmitting the target blood propofol concentration calculated by the PI algorithm to the infusion system and maintaining the measured AEP_{index} close to the selected $AEP_{index}^{control}$.

A target plasma concentration of alfentanil 15 ng ml^{-1} was achieved before induction and was maintained throughout surgery.[17] During maintenance of anaesthesia, patients breathed a mixture of 66% nitrous oxide in oxygen. A laryngeal mask airway was inserted in all patients to maintain a clear airway and to allow monitoring of ventilatory frequency and end-tidal carbon dioxide partial pressure. Arterial oxygen saturation was monitored continuously and arterial pressure, heart rate, degree of sweating and tear formation were recorded at intervals of 5 min and used to calculate PRST scores. [18] Measurements of heart rate, arterial pressure, sweating and tear formation were compared with baseline values and scored to provide an estimate of the amount of sympathetic stimulation.[18]

Data analysis was performed on an IBM-compatible PC using *Minitab for Windows 95* (version 11). Statistical tests used were analysis of variance (ANOVA), *t* test and chi-square test, as appropriate.

Table 2 Anaesthetic and surgical times. Durations are mean (SD) [range] min

Duration of induction	3.7 (1.4) [1.3–8.9]
Start of induction to incision	12.4 (3.8) [5.6–27.9]
Incision to end of surgery	37.9 (26.4) [4.4–123.8]
End of surgery to recovery	6.6 (4.6) [0.0–17.9]
Duration of anaesthesia	56.9 (28.4) [19.7–156.3]

Table 3 Values of AEP_{index} recorded in 100 patients (mean (SD) [range])

Before induction of anaesthesia	73.5 (17.6) [41–134]
During body surface surgery	37.8 (4.5) [31–57]
At recovery of consciousness	89.7 (17.9) [60–147]

Results

Duration of induction (defined as the time required for loss of verbal response and abolition of the eyelash reflex) and other times are shown in Table 2.

The mean AEP_{index} before induction of anaesthesia was 73.5 (SD 17.6) and anaesthesia was induced smoothly in all patients. The mean value required to produce surgical anaesthesia was 37.8 (4.5) (Table 3). The AEP_{index} and the $AEP_{index}^{control}$ were not affected by age or sex.

Propofol concentrations selected by the system are shown in Table 4. The number of changes in the $AEP_{index}^{control}$ is shown in Table 5. Control of the AEP_{index} was maintained within $AEP_{index}^{control}\pm5$ for an average of 65.2% of the duration of anaesthesia (Table 6).

PRST scores recorded during surgery did not exceed 2 in any patient but 15 patients made some movement during surgery (Table 7). These movements were mainly slight and, apart from two patients, did not interfere with surgery. The mean $AEP_{index}^{control}$ was 38.8 for patients who moved and 37.7 for non-movers (ns)–not statistically significant. However, mean the AEP_{index} was significantly different between the two groups (mean 39.9 and 37.4, respectively; $P=0.005$).

AEP_{index} and target blood propofol concentrations recorded from one patient are shown in Figure 1.

At the end of anaesthesia, the CLAN system was set to achieve recovery, and delivery of propofol was stopped automatically. Both nitrous oxide and alfentanil were discontinued. Anaesthesia lasted for a mean duration of 56.9 (SD 28.4) min and the mean time from the end of surgery to recovery, defined as obeying commands, was 6.6 (4.6) min (Table 2). The mean AEP_{index} when patients recovered

Table 4 Target propofol concentrations selected by the CLAN system (μg ml^{-1})

	At the end of induction	Maximum during maintenance	Minimum during maintenance	Average during maintenance	At recovery
Mean (SD)	5.7 (2.1)	6.7 (2.2)	2.6 (1.5)	4.3 (1.8)	1.3 (0.6)
Range	1.0–11.5	2.1–13.0	0.9–6.8	1.3–10.6	0.4–4.2

consciousness was 89.7 (17.9) (Table 3). Each patient regained consciousness at an AEP_{index} which was greater than the value at which consciousness was lost.

Cardiovascular stability

Changes in systolic arterial pressure and heart rate are shown in Figure 2. The mean maximum decrease in systolic arterial pressure was 22% of baseline. The mean maximum decrease in heart rate was 5% of baseline.

Respiratory stability

Before incision, end-tidal carbon dioxide partial pressure increased to more than 8 kPa in 22 patients and ventilation was assisted until spontaneous respiration resulted in end-tidal carbon dioxide values of less than 8 kPa. Fourteen patients required assistance for less than 5 min while eight patients required assistance for 5 min or more. Only four of these patients required assistance for more than 5 min after skin incision. There was no significant difference in the AEP_{index} or the $AEP^{control}_{index}$ between patients who required respiratory assistance and those who did not. Six of the patients who required assistance made some movement during surgery and nine did not. Ventilatory frequency and end-tidal carbon dioxide measurements are given in Figure 3.

Patient assessment

Seventy-seven patients completed a questionnaire on recall and acceptability of the anaesthetic technique (Table 8). There were no occurrences of awareness during anaesthesia in any patient and all were prepared to have the same anaesthetic again. Six patients described the clicks presented to them before induction of anaesthesia as slightly annoying while the remainder were not concerned. Five patients had no recollection of hearing the clicks during the study. Although all patients were awake in the operating theatre, only nine patients remembered waking up in theatre; 49 patients thought they woke in recovery and 19 in the ward.

Table 5 Number of changes in $AEP^{control}_{index}$ indexcontrol during CLAN

	During 1st 15-min period	During 2nd 15-min period	Total number of changes
Median	2	0	3.5
Range	0–9	0–6	0–17

Table 6 Control of AEP_{index} as a percentage of total CLAN time (mean (SD) [range])

Within target value±5%	65.2 (14.1) [10.3–89.0]
Within target value±10%	89.6 (9.5) [46.7–100.0]
Within target value±15%	98.7 (4.6) [74.9–100.0]

Table 7 Adequacy of anaesthesia

Highest PRST scores	0 (0–2)
Movement during surgery (*n*)	15
Disturbance of surgery (*n*)	2
(1) one patient received no drug for 7 min	
(2) surgery stopped for 45 s in one patient	
Awareness or recall (*n*)	0

Table 8 Patient questionnaire.

Where did you awake after your operation?	
Theatre	9
Recovery	49
Ward	19
Do you remember any dreams or noises during your operation?	
Yes	0
No	77
Would you be happy to have the same anaesthetic?	
Yes	77
No	0
Do you remember the clicks before induction?	
Yes	72
No	5
Did the clicks bother you?	
Very much	0
Slightly	6
No	66

Discussion

At present, monitoring of clinical signs is the only routine method for determining depth of anaesthesia. When no neuromuscular blocking drugs are used, skeletal muscle response to surgical stimulation and the frequency and depth of respiration reflect accurately the depth of anaesthesia. If 'adequate anaesthesia' is schematically illustrated as a range of acceptable responses (Fig. 4), its upper limit (i.e. insufficient anaesthesia) is determined by movement to surgical stimuli and the lower limit (i.e. excessive anaesthesia) by respiratory depression.

If the patient's lungs are ventilated mechanically but the patient is not paralysed, the upper limit remains the same but the lower limit is now determined by circulatory depression. When neuromuscular blocking drugs are used, an indication of the depth of anaesthesia is given by the combination of cardiovascular changes, sweating and lacrimation, and pupil signs. The lower limit is still circulatory depression, but there is no clear upper limit as the patient

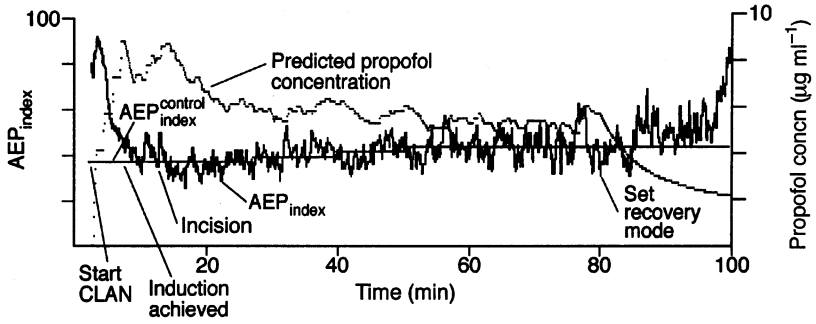

Fig 1 AEP_{index} and predicted target blood concentrations of propofol recorded in one patient.

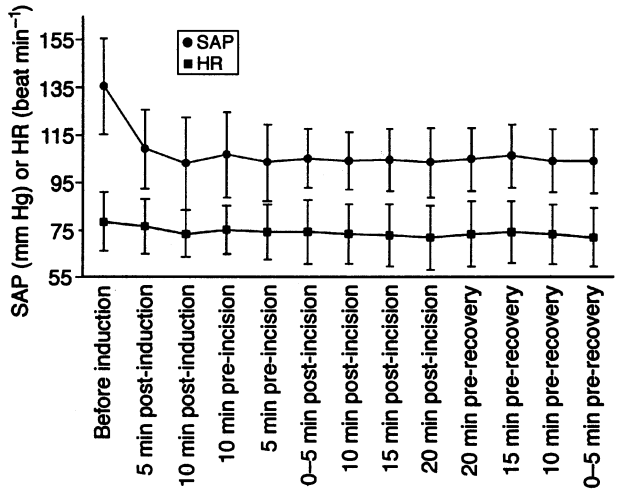

Fig 2 Systolic arterial pressure (SAP) and heart rate (HR) during CLAN (mean, SD).

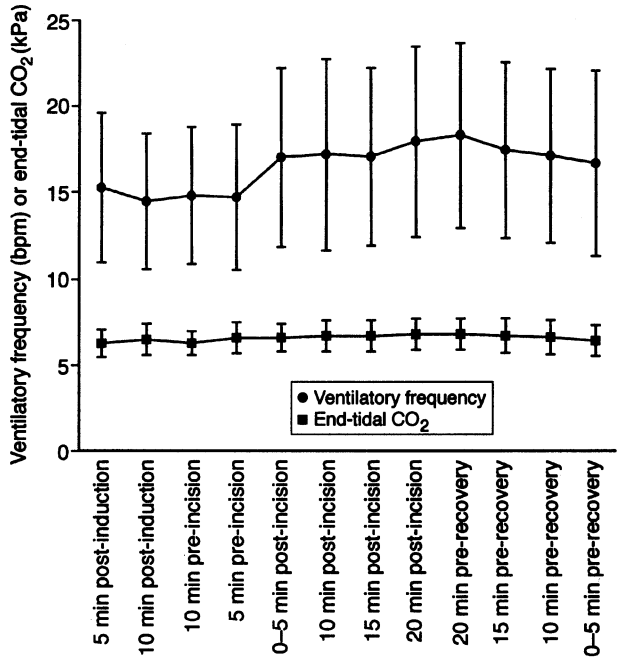

Fig 3 Ventilatory frequency and end-tidal carbon dioxide partial pressure during CLAN (mean, SD).

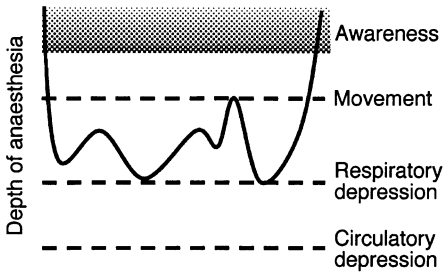

Fig 4 Signs relating to depth of anaesthesia in a spontaneously breathing patient.

cannot move. The only available signs are those which arise from stimulation of the sympathetic nervous system. However, these are not specific and are affected by many drugs used routinely in clinical practice.[1 19–23] Clearly, if for any reason anaesthesia becomes lighter, the patient may regain consciousness without necessarily providing the anaesthetist with any indication, especially if high opioid concentrations are administered.

There is no accepted standard by which depth of anaesthesia should be assessed but any signal used to measure depth of anaesthesia must provide sufficient information to enable satisfactory general anaesthesia to be produced during surgery. Any monitor of anaesthetic depth should enable the anaesthetist to provide satisfactory conditions in a patient breathing spontaneously while undergoing a surgical procedure. This form of anaesthesia requires that good control must be maintained throughout the procedure. Satisfactory anaesthesia requires:

- adequate cardiovascular and respiratory stability
- no or minimal patient movement
- no awareness or recall of events during the procedure.

These conditions form the basis of a standard against which any monitor of depth of anaesthesia may be judged. In addition, the monitor should:

- provide similar signals when different anaesthetic agents are used
- alter its signal appropriately during surgical stimulation
- produce a similar signal when the patient has recovered from anaesthesia to that recorded before induction of anaesthesia
- be unaffected by cardioactive drugs

- produce a marked signal difference during the transition from awake to asleep and *vice versa*.

Attempts to provide an accurate assessment of depth of anaesthesia have included scoring systems for arterial pressure, heart rate, sweating and tear formation (PRST)[18]; movement of a non-paralysed hand[24]; measurement of lower oesophageal contractility[25]; and various assessments of the electroencephalogram (EEG).[26–32]

Closed-loop control of propofol anaesthesia in volunteers has been described previously using the median frequency of the EEG as the input signal.[33] However, anaesthesia was not always adequate even to abolish the corneal reflex and this level would not be expected to produce satisfactory conditions for surgery. A similar system was used in 11 patients undergoing surgery to control administration of alfentanil during nitrous oxide–oxygen anaesthesia with neuromuscular blocking drugs.[34] Systolic arterial pressure has also been used to control the level of anaesthesia by altering administration of isoflurane during surgery and to advise on the need for supplementary morphine.[35] Patients were anaesthetized to a satisfactory level before the control system was used and again, the system was evaluated only in patients who had received neuromuscular blocking drugs. In that study, 9% of patients did not have satisfactory control of anaesthesia.

Ours is the first report describing closed-loop control of anaesthesia from induction through surgery to recovery in patients who did not receive neuromuscular blocking drugs and were breathing spontaneously. The PI algorithm controlled the AEP_{index} within acceptable limits during the maintenance phase. The $AEP_{index}^{control}$ was initially set at 35. Thereafter it was changed by the anaesthetist depending on patient response. The aim was to achieve adequate anaesthesia in terms of respiratory and cardiovascular stability and to avoid patient movement to surgical stimulation. All patients had satisfactory PRST scores, while movement interfering with surgery was minimal. Most of the patients had satisfactory values for end-tidal carbon dioxide concentration, although eight required assisted ventilation for more than 5 min. It is possible that excessively low values of the $AEP_{index}^{control}$ were selected in an attempt to avoid patient movement after the initial surgical incision. Electrical interference during diathermy overloaded the EEG amplifier and prevented acquisition of a satisfactory signal. Therefore, during the use of diathermy, the system was set automatically to maintain the target blood propofol concentration at the previous value until a new valid signal was obtained. This did not appear to adversely affect control of depth of anaesthesia.

The first requirement for any closed-loop system is a valid input signal which can be used to alter the output of the controlling agent. AEP has been reported previously to reflect accurately the level of anaesthesia, especially during the transition from awake to asleep and *vice versa*.[10 11] By using the AEP as the input signal for the closed-loop control system in patients undergoing surgery while breathing spontaneously, we believe that we have validated this measurement technique as an assessment of the level of anaesthesia during maintenance with propofol. An important finding was that no patient recovered consciousness at an AEP_{index} which was less than the value at which anaesthesia had been induced. This supports previous reports of the ability of AEP to distinguish clearly between awake and unconscious states.[10 11 13–15] It would appear that if the AEP_{index} is maintained below the value at which consciousness is lost during propofol anaesthesia, awareness should not occur. Clearly, other anaesthetic agents and patients must be assessed to determine if this is a universal finding.

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