Anesthesiology 2002; 96:67–73

Closed-loop Control of Anesthesia Using Bispectral Index

Performance Assessment in Patients Undergoing Major Orthopedic Surgery under Combined General and Regional Anesthesia

Anthony R. Absalom, M.B.Ch.B., F.R.C.A., Nicholas Sutcliffe, M.B.Ch.B., M.R.C.P., F.R.C.A.,† Gavin N. Kenny, B.Sc.(Hons), M.D., F.R.C.A., F.A.N.Z.C.A.‡*

Background: **The Bispectral Index (BIS) is an electroencephalogram-derived measure of anesthetic depth. A closed-loop anesthesia system was built using BIS as the control variable, a proportional–integral–differential control algorithm, and a propofol target-controlled infusion system as the control actuator. Closed-loop performance was assessed in 10 adult patients.**

Methods: **Ten adult patients scheduled to undergo elective hip or knee surgery were enrolled. An epidural cannula was inserted, and 0.5% bupivacaine was used to provide anesthesia to T8 before general anesthesia was induced using the propofol target-controlled infusion system under manual control. After the start of surgery, when anesthesia was clinically adequate, automatic control of anesthesia was commenced using the BIS as the control variable. Adequacy of anesthesia during closed-loop control was assessed clinically and by calculating the median performance error, the median absolute performance error, and the mean offset of the control variable.**

Results: **The median performance error and the median absolute performance error were 2.2 and 8.0%, respectively. Mean offset of the BIS from the set point was 0.9. Cardiovascular parameters were stable during closed-loop control. Operating conditions were adequate in all patients but one, who began moving after 45 min of stable anesthesia. No patients reported awareness or recall of intraoperative events. In three patients, there was oscillation of the measured BIS around the set point.**

Conclusions: **The system was able to provide clinically adequate anesthesia in 9 of 10 patients. Further studies are required to determine whether control performance can be improved by alterations to the gain factors or by using an effect site–targeted, target-controlled infusion propofol system.**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

Additional material related to this article can be found on the ANESTHESIOLOGY Web site. Go to the following address, click on Enhancements Index, and then scroll down to find the appropriate article and link. http://www.anesthesiology.org

* Clinical Lecturer, University Department of Anaesthesia, Glasgow Royal Infirmary. Current position: Consultant Anaesthetist, Department of Anaesthesia, Norfolk and Norwich University Hospital, Norwich, United Kingdom. ‡ Professor, University Department of Anaesthesia, Glasgow Royal Infirmary. † Consultant Anaesthetist, Health Care International (Scotland) Ltd., Glasgow, United Kingdom.

Received from the University Department of Anaesthesia, Glasgow Royal Infirmary, Alexandra Parade, Glasgow, United Kingdom. Submitted for publication January 22, 2001. Accepted for publication August 15, 2001. Aspect International, Leiden, The Netherlands, donated the electroencephalographic electrodes and loaned the authors the A-1000 monitor used in the study. Other disposable items and drugs were provided by HCI (Scotland) Ltd., Clydebank, Dumbartonshire, United Kingdom. Presented at the meeting of the European Society for Intravenous Anaesthesia, Amsterdam, The Netherlands, May 28, 1999.

Address reprint requests to Dr. Absalom: Department of Anaesthesia, Norfolk and Norwich University Hospital, Colney Lane, Norwich NR4 7UZ, United Kingdom. Address electronic mail to: tabsalom@compuserve.com.

CURRENTLY, there is no "gold standard" for measuring anesthetic depth, so many clinicians still rely on traditional clinical signs although they are not completely reliable.[1] However, newer parameters, such as the Bispectral Index (BIS)[2] and the auditory evoked potential index (AEP_{Ex}),[3] derived from analysis of the surface electroencephalogram, show promise as objective and reliable measures of anesthetic depth.

The BIS is the weighted average of three subparameters that analyze the phase and frequency relations among the component frequencies in the electroencephalogram.[2] It changes monotonically with increasing depth of anesthesia. BIS correlates well with the hypnotic component of anesthesia[4] but predicts movement in response to surgical stimulation less reliably, especially when different combinations of hypnotic and analgesic drugs are used.[5]

Electroencephalographic parameters can be used to control anesthesia automatically. The median frequency of the power spectrum of the electroencephalogram has been used with limited success,[6–8] whereas the AEP_{Ex} has been used with more success.[9] Closed-loop control offers patients several potential benefits. Because of more frequent sampling of the control variable and more frequent changes to the rate of drug delivery than with manually delivered anesthesia, the stability of the control variable may be greater. At the same time, the dose delivered is customized to meet the exact requirements of each patient, thereby overcoming the problems of interindividual pharmacokinetic and pharmacodynamic differences and differing levels of surgical stimulation. Recovery times and the risk of inadvertent awareness may thereby be decreased.

Use of a variable in a closed-loop system also provides some information about the validity of that variable. If the variable is able to control the relevant physiologic process, it is probably a valid measure of the state of that system. The BIS has already been used for automatic control of propofol sedation.[10] We wanted to know whether BIS could be used to provide clinically satisfactory anesthesia and developed a computer system for this purpose. The aim of this study was to measure the performance of this system. Because patient movement may indicate inadequate anesthesia,[11] the patients studied did not receive neuromuscular blocking agents and breathed spontaneously. Recently, Struys *et al.*[12] have studied the ability of another system to control anesthesia automatically using the BIS and an adaptive, model-based control algorithm.

Table 1. Overview of Computer Program

Automatic sequential start-up routines
Get patient name and ASA status
Set initial program mode
Set up and open data file
Check communication with peripheral devices
Initialize variables
Set up user interface
Start main loop
User-activated routines
Change screen settings
Change graph scales and settings
Stop and start logging data to disk
Change BIS set point
Change minimum propofol concentration
Change "allowable" BIS error (default 5)
Change mode
Main program loop
Disable timer
Request data update from BIS monitor
Await reply from BIS monitor
Verify validity of reply
If mode = "Automatic" then
Get current propofol concentration from TCI system
Run control algorithm
If mode = "Manual" then get propofol target from user interface
If mode = "Manual" or "Automatic" then send propofol target to TCI system
Plot target and actual BIS ± estimated propofol concentration
If no request to stop then start timer (5 s)

ASA = American Society of Anesthesiologists; BIS = Bispectral Index; TCI = target-controlled infusion.

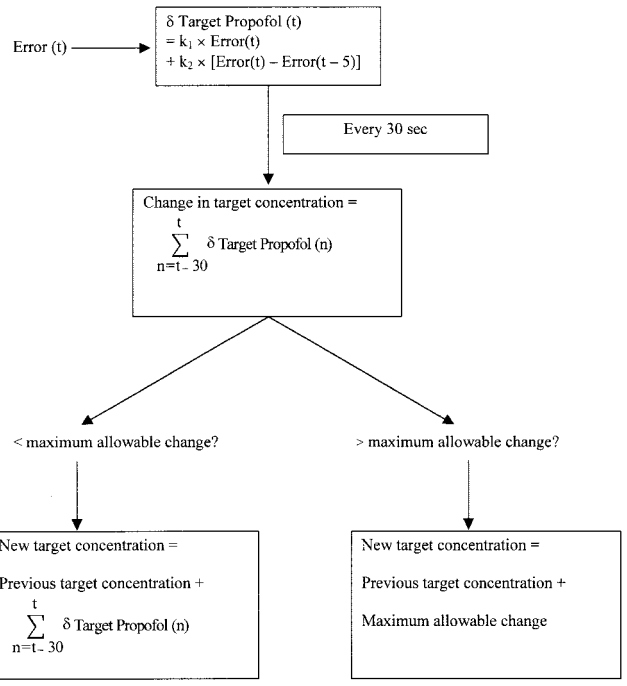

Fig. 1. Overview of control algorithm (t represents time in seconds, k_1 and k_2 are constants, target concentration is the target propofol concentration in μg/ml, and the maximum allowable change is 2.0 for patients with American Society of Anesthesiologists physical status I and II classification and 1.0 for patients with American Society of Anesthesiologists physical status III classification).

Materials and Methods

Description of Closed-loop Anesthesia System

Like all feedback control systems, a closed-loop anesthesia system aims to control the level of a control variable to a user-defined value, using a control algorithm and a control actuator. The control variable is the BIS, which in the current study was obtained from an A-1000 monitor (Aspect Medical Systems, Natick, MA; software version 3.22). A propofol target-controlled infusion (TCI) system served as the control actuator. The TCI system incorporates the pharmacokinetic parameters used in a commercially available propofol TCI system (Diprifusor; AstraZeneca, Macclesfield, England). An IBM-compatible PC (266 MHz processor) was used to implement the control algorithm, to provide a user interface, and to control communication with the A-1000 monitor and the TCI system *via* RS232 serial ports. Custom-made system software was written by one of the authors (A. R. A.) in Borland Delphi 2 (Inprise, Scotts Valley, CA; table 1).

The system can operate in various modes. In "monitor" mode, it acts as a data management system: it requests an update of the latest electroencephalographic data at user-defined intervals (usually every 5 s), provides a graphic display of current and trend values, and records them on the hard disk of the PC. In "manual" mode, the user can also control the TCI system manually, using the keyboard or the mouse of the PC. The PC displays a graph of the calculated blood propofol concentration and records the target propofol concentrations with the electroencephalographic data. When the system is in "automatic" mode, in addition to the functions already described, it also automatically controls the propofol infusion. The user must enter a target BIS value, a minimum propofol concentration (default value, 1 μg/ml), and the American Society of Anesthesiologists physical status classification of the patient. If the American Society of Anesthesiologists status is IV or V, the system refuses to operate in automatic mode.

In automatic mode, the system requests an update of the electroencephalographic data every 5 s and calculates the BIS "error" (difference between the target and actual BIS value). This value is passed to a proportional–integral–differential control algorithm identical to one used previously in an auditory evoked potential (AEP)–based closed-loop system[9] (fig. 1; for the source code, see Appendix 1 in the Web Enhancement). The algorithm uses the error to calculate an adjustment to the target propofol concentration (δ Target Propofol) but does not apply this immediately. Adjustments to the target propofol concentration are only made every 30 s, using the sum of the previous six δ Target Propofol values. The maximum allowable change depends on the American Society of Anesthesiologists status of the patient (2 μg/ml for status I and II and 1 μg/ml for status

III), whereas the overall maximum target concentration allowed is 15 μg/ml. As a further safety feature, the system automatically reduces the target propofol concentration by 0.2 or 0.3 μg/ml every 3 min.

The constants of the algorithm were previously tuned during laboratory simulations with AEP data from patients undergoing manually-controlled propofol anesthesia and then fine-tuned during live testing in six subjects, using an AEP closed-loop anesthesia system.

Clinical Protocol

After local research ethics committee approval (Health Care International [Scotland] Ltd. Ethics Committee, Glasgow, United Kingdom) and written informed consent, 10 adult patients presenting for elective hip or knee replacement were enrolled. Inclusion criteria were that patients had to be of American Society of Anesthesiologists physical status I or II and aged between 18 and 80 yr. Exclusion criteria included body mass index greater than 30, a history of neurologic disease, and use of psychoactive medication.

Anxious patients were given 20–30 mg oral temazepam 1 h before surgery. Two anesthesiologists were involved with each patient—one was in charge of the clinical management of the patient, and the other took care of the research equipment and manually recorded the BIS, physiologic data, and the blood and effect site propofol concentration every 5 min. After arrival in the preanesthetic care unit, a 16-gauge cannula was inserted into a large forearm vein during local anesthesia, an infusion of lactated Ringer's solution was infused at 500 ml/h, and routine physiologic monitoring was commenced (pulse oximetry, electrocardiography, noninvasive blood pressure monitoring). An epidural catheter was then inserted *via* the L2–L3 or L3–L4 interspace, through which 10 ml bupivacaine, 0.5%, was injected. Hypotension (defined as a systolic blood pressure $<$ 80 mmHg or a decrease of $>$ 30% from baseline) was treated with bolus doses of intravenous ephedrine (3 mg). The patient was observed for approximately 20 min, during which time the upper level of epidural anesthesia was determined by testing for cold sensation. When blockade reached the T8 dermatome, the patient was transferred to the operating room.

In the operating room, the patient was connected to the BIS monitor, and the closed-loop anesthesia system was started in monitor mode. After the patient had breathed 100% oxygen for 3 min, the system was switched to manual mode, and anesthesia was induced using propofol administered by the TCI system. The initial target plasma concentration was 2 μg/ml, and this was increased in steps of 0.5 μg/ml until consciousness was lost. A laryngeal mask airway was inserted, and the patient was allowed to breathe 40% oxygen in air spontaneously *via* a circle breathing system. Episodes of apnea after induction were treated with manual ventilation.

Table 2. Patient Characteristics

Age (yr)	67 (11)
Sex (M/F)	4/6
Weight (kg)	79 (11)
Height (cm)	168 (9)

Values are mean (SD).

The surgeon was then allowed to commence surgery. The BIS value was noted when the investigators judged the level of anesthesia was adequate (hemodynamic stability, regular and adequate spontaneous respiration, absence of signs of autonomic activation). Automatic control of anesthesia was initiated using that BIS value as the set point. When the surgeon began the final skin sutures, the system was switched to manual mode, and the target propofol concentration was set to zero. Patients remained in the operating room until they had regained consciousness, the laryngeal mask airway had been removed, and they had correctly stated their date of birth. The times at which the following events occurred were recorded manually: end of closed-loop control, end of surgery, eye opening, response to command, ability to state the date of birth.

Data Analysis

Physiologic data are presented as mean (SD), and time intervals are presented as median (range). Performance of the system was assessed using the median prediction error (MDPE), median absolute prediction error (MDAPE), wobble, and the mean offset. These measures were recommended for assessment of the predictive performance of computer-controlled infusion pumps[13] but have recently been used to evaluate the performance of a closed-loop controller for neuromuscular blockade. MDPE and MDAPE are measures of bias and precision, respectively.[14] Wobble measures the intraindividual variability in performance errors. For the ith patient, for whom N_i BIS values were measured during automatic control, performance error, MDPE, MDAPE, and wobble are defined as follows[13]:

PE at the jth BIS measurement,

$$PE_{ij} = (BIS_{measured} - BIS_{setpoint})/BIS_{setpoint} \times 100$$

$$MDPE_i = \text{Median } \{PE_{ij},\ j = 1, \ldots, N_i\}$$

$$MDAPE_i = \text{Median } \{|PE_{ij}|,\ j = 1, \ldots, N_i\}$$

$$Wobble_i = \text{Median } \{|PE_{ij} - MDPE_i|,\ j = 1, N_i\}$$

Results

The patient characteristics are shown in table 2. Median BIS and calculated blood and effect site propofol concentrations at key clinical endpoints before and after the period of automatic control of anesthesia are summarized in table 3. Median duration of automatic control

Table 3. BIS Values and Propofol Concentrations at Key Events

	BIS	Cp_{CALC} (μg/ml)	Ce_{CALC} (μg/ml)
Baseline	97 (94–98)	0	0
Loss of consciousness	74 (53–89)	4 (3.5–7)	1.5 (1.1–3.3)
LOC + 30 s	59 (40–74)	Not recorded	Not recorded
Before intubation	58 (43–66)	4 (3.5–5)	1.9 (1.3–3.6)
Start of surgery	46 (34–67)	3.4 (2.8–4)	3.5 (2.8–4)
Start of automatic control	45 (40–57)	3 (2.5–4.5)	3.1 (2.6–4.5)
Eye opening	80 (67–87)	1.6 (0.7–2.2)	1.8 (0.9–2.9)
Responds to command	80 (79–87)	1.2 (0.7–2.2)	1.3 (0.9–2.9)
States date of birth	87 (80–91)	1.2 (0.7–2.2)	1.3 (0.9–2.5)

Values are median (range).

BIS = Bispectral Index; Cp_{CALC} = calculated plasma propofol concentration; Ce_{CALC} = calculated effect site propofol concentration; LOC = loss of consciousness.

Table 4. BIS Set Point and Performance Parameters for Individual Patients

Patient	Setpoint	MDPE (%)	MDAPE (%)	Wobble (%)	Mean Offset	Premedication
1	45	6.7	8.5	6.1	3.3	Yes
2	50	2.4	4.8	4.8	1.2	Yes
3	40	2.5	5.0	2.5	0.2	Yes
4	47	0.0	11.1	11.1	1.7	Yes
5	45	0.0	6.7	6.7	0.8	Yes
6	49	−1.8	8.2	9.0	−1.5	No
7	45	2.2	4.4	4.4	1.3	Yes
8	50	2.0	8.0	8.0	1.2	No
9	55	3.6	9.1	9.1	1.9	Yes
10	57	1.8	14.5	14.4	−0.7	Yes
Overall	48	2.2	8.0	7.3	0.89	—

BIS = Bispectral Index; MDPE = median performance error; MDAPE = median absolute performance error.

of anesthesia was 72 (40–80) min. The median time interval between end of closed-loop control and eye opening was 10.5 (2–15) min, and the median interval between end of surgery and eye opening was 3 (−6 to 7) min.

During automatic control, the system was able to provide satisfactory operating conditions in all but one patient. In this patient, the system provided adequate anesthesia for 45 min. Eleven minutes before the end of the operation, the surgeon began to manipulate the hip vigorously, causing tugging on the laryngeal mask, which was fixed to the operating table *via* the breathing system. During the subsequent 90 s, the BIS increased from 50 to 84, and the patient began grunting and moving. The system increased the blood propofol concentration from 2.2 to 5 μg/ml, the patient stopped moving, and the BIS decreased sharply to 34. Because the operation was almost completed, the system was switched to manual mode, and the target concentration was reduced to 2 μg/ml. Performance data for this patient up to the point when automatic control was stopped were included in the performance analysis.

For all patients, cardiovascular parameters were stable throughout the period of automatic control (fig. 2). Oxygen saturation was always greater than 95%, mean respiratory rate was 18 (3) breaths/min, and mean end-tidal carbon dioxide was 40 (7) mmHg. The median BIS chosen as the set point was 48 (range, 40–57). Performance of the system in individual patients is summarized in table 4. Intersubject analysis resulted in an MDPE of 2.2%, an MDAPE of 8.0%, median wobble of 7.3%, and mean offset of 0.89. Figure 3 shows the offset values for all patients during feedback control of anesthesia. System performance was similar in the two patients who did not receive a sedative premedication, compared with the remaining patients. Figure 4 shows the target propofol concentrations during closed-loop control of anesthesia. All patients were visited in the ward after surgery, and none had evidence of explicit recall.

Discussion

In the subjects studied, a closed-loop anesthesia system using the BIS as the control variable was able to

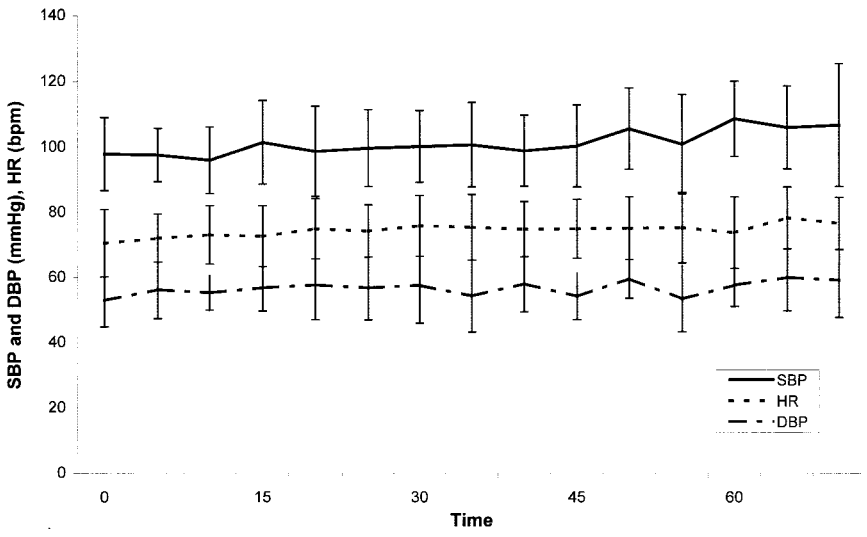

Fig. 2. Hemodynamic parameters during automatic control of anesthesia. Values are mean (SD). SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

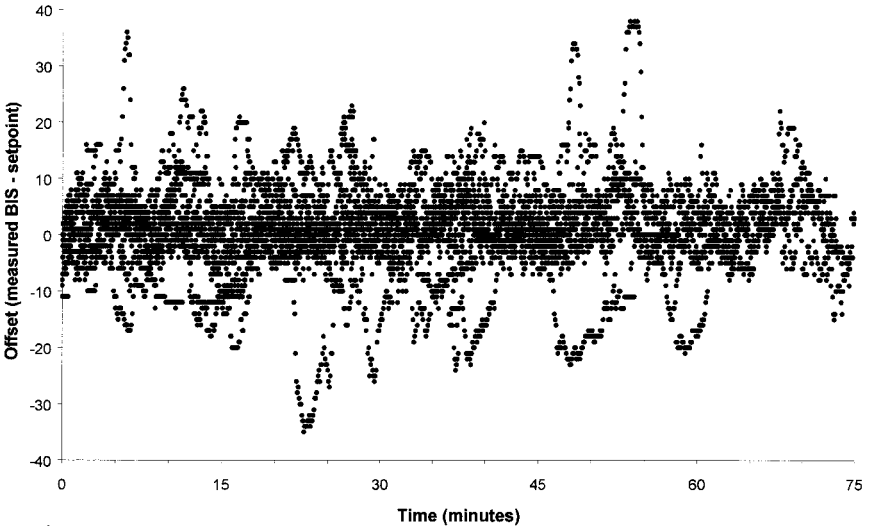

Fig. 3. Individual offset values (measured Bispectral Index [BIS] − set point) during automatic control of anesthesia.

provide clinically adequate anesthesia and satisfactory operating conditions during periods of automatic control of anesthesia lasting from 40 to 80 min. Overall ability of the system to control the BIS to a user-defined value was satisfactory. The MDPE of 2.2% indicates the system had a slight positive bias, *i.e.*, the median measured BIS was 2.2% greater than the target BIS. An MDAPE value of 8.0% indicates that 50% of BIS values were within 8% of the set point. Median wobble was 7.3%. These figures compare favorably with those recently reported by Struys *et al.*,[12] who reported an MDPE of −6.6%, an MDAPE of 7.7%, and median wobble of 5.9%.

Kenny and Mantzaridis[9] have previously developed an AEP-based, closed-loop anesthesia system and evaluated its performance in 100 patients by calculating the proportion of time that the measured AEP was within 5, 10, and 15% of the target AEP value. Table 5 shows these figures for both systems. However, the figures from their study are not directly comparable with the figures from the current study. Obviously, the control variable for the two systems was different, and although the same control algorithm was used in both systems, the constant were tuned for the AEP_{Ex}. The control actuator (TCI propofol system) was the same in both systems, but patient characteristics, type of surgery, and anesthetic technique were all different. Patients in the BIS study were older (mean age, 67 *vs.* 50 yr), were heavier (mean weight, 79 *vs.* 66 kg), and were undergoing major orthopedic surgery as opposed to body surface surgery. With regard to anesthetic technique, patients received TCI propofol for induction and maintenance of anesthesia in both studies. However, for induction in the BIS study, the TCI propofol system was under manual control, whereas in the AEP study it was controlled automatically by the closed-loop system using an algorithm of stepwise increases in propofol concentration. Propofol anesthesia was maintained automatically in both studies, but in the BIS study, it was supplemented by epidural analgesia to T8, whereas patients in the AEP closed-loop study received target-controlled infusions of propofol and alfentanil and breathed 66% nitrous oxide.

How do the input signals differ? The BIS evaluates spontaneous cortical electrical activity, whereas the AEP reflects activity throughout the electrical pathway from the cochlea to the cortex. Moreover, as an evoked potential, the AEP is in effect a test of response to stimulation. In two studies, the AEP was able, whereas the BIS,

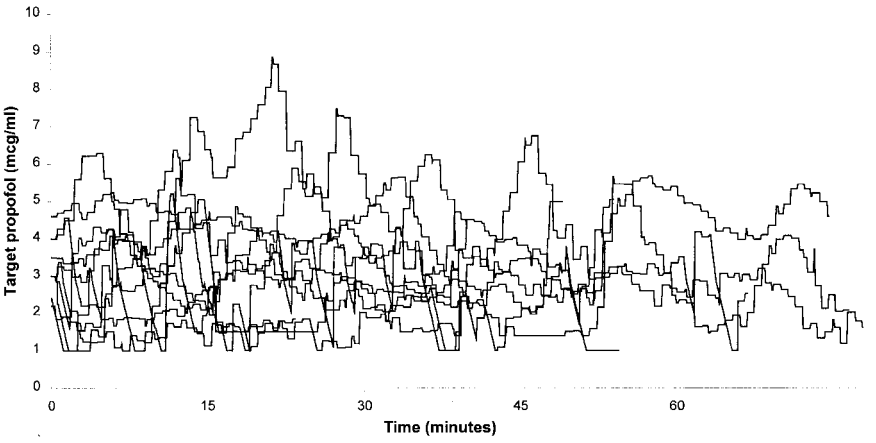

Fig. 4. Target blood propofol concentrations (μg/ml) during automatic control of anesthesia.

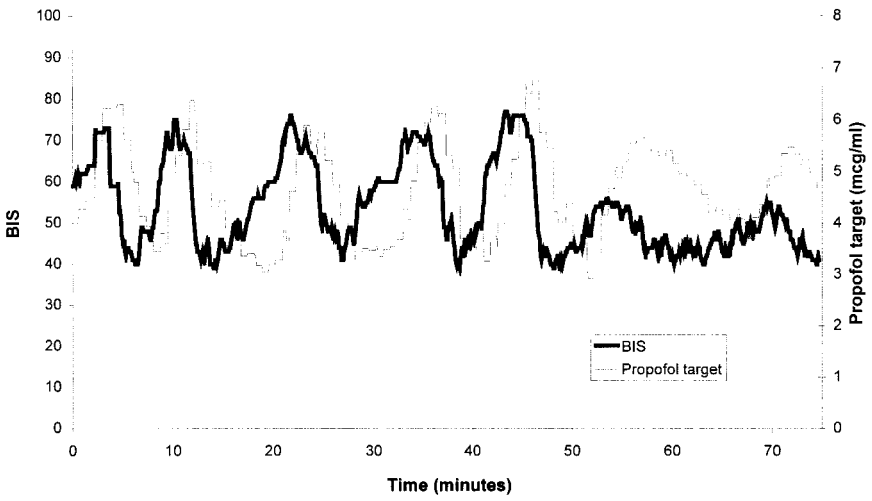

Fig. 5. Bispectral Index (BIS) and target propofol concentration (μg/ml) in patient 10 during closed-loop control.

spectral edge frequency, and median frequency were unable, to predict movement in response to noxious stimulation significantly better than chance.[15,16] In another study, even at BIS values indicating light anesthesia, it was shown that the effect site opiate concentration is a better predictor of the likelihood of a clinical response to a noxious stimulus than the BIS and the concentration of propofol or isoflurane.[5] Because patients in the current (BIS) study were not given any systemic or inhaled analgesics, they were thus more likely to have short-term fluctuations in their depth of anesthesia and in the BIS when stimulated above the level of epidural blockade.

In three patients (patients 4, 5, and 10 in table 4), there were oscillations of the BIS and target propofol concentrations, although none of these patients showed clinical signs of inadequate anesthesia or cardiovascular instability. The worst oscillations were seen in patient 10, whose MDPE and MDAPE were also the worst of all the patients (fig. 5). In this patient, the initial BIS target was 57. After 46 min, the target was decreased to 45, after which stability increased markedly. There are several possible reasons for this oscillation. The first is that the constants used by the control algorithm were not appropriate for this patient. It is likely that smaller changes made less frequently would have resulted in finer control. The software in use did not allow for adjustment of gain factors. Adaptive algorithms have the benefit of individualizing the control parameters for each patient at run time, and this may lead to improved control.

Table 5. Control of AEP_{Ex} and BIS as a Percentage of Total Closed-loop Anesthesia Time

	AEP System	BIS System
Within target value ± 5%	65	34
Within target value ± 10%	90	57
Within target value ± 15%	99	75

AEP_{Ex} = auditory evoked potential index; AEP = auditory evoked potential; BIS = Bispectral Index.

Another factor that may generate oscillation is the time taken for equilibration between the central compartment and the propofol effect site.[17] Billard *et al.*[18] have estimated that the plasma–effect site equilibration constant, k_{eo}, is 0.2 min^{-1}, whereas Schnider *et al.*[19] have estimated a time to peak effect for propofol of 1.6 min. Therefore, time to peak effect after a change in plasma propofol concentration is of the order of 1.6–4.5 min.[20] A blood-targeted TCI system does not take this delay into account. Thus, there is a lag in effect site concentration and clinical effect when the closed-loop system changes the target blood propofol concentration. Moreover, if after an increase the BIS decreases to below the target (*i.e.*, effect site propofol concentration is now too high), the system gradually decreases the target blood propofol concentration. Until the blood concentration has decreased below that at the effect site, the effect site concentration continues to increase, causing even deeper levels of anesthesia and a lower BIS. Conversely, if the blood propofol concentration is below effect site concentration and the BIS increases above the target BIS level, the system gradually increases the blood propofol target. Before the blood concentration surpasses that at the effect site, the effect site concentration falls, whereas it needs to increase to counteract the increase in BIS. In future studies, we aim to overcome this problem by including effect site "steering" in the control algorithm. Another solution is to use a TCI system that targets the effect site rather than the central compartment.

Instability or oscillation may also occur if the BIS target is too high. In subsequent patient-controlled sedation studies, we have found that some subjects are conscious at BIS values above 55 (unpublished observations, November 1999 to October 2000). Therefore, although displaying the clinical signs of adequate anesthesia, patient 10 may only have been lightly anesthetized at this BIS level. Thus, a small increase in stimulus would cause an arousal response and a large increase in the BIS, leading to some degree of instability in the BIS. This may explain

why stability improved markedly after the BIS target in this patient was reduced to 45.

As mentioned earlier, one patient in the study moved when the surgeon manipulated the hip. At this time, the blood propofol concentration was 2.2 μg/ml. In any patient, depth of anesthesia is a dynamic balance among stimulation, hypnosis, and analgesia. Because there was no analgesia above the T8 dermatome and no systemic opiates had been administered, responses to stimuli above this area could only be attenuated or prevented by the propofol infusion. We believe that the sudden pharyngeal stimulation caused by movement of the laryngeal mask airway when the hip was manipulated caused the patient's conscious level to increase abruptly. It is not always possible to predict when a surgeon will suddenly inflict a noxious stimulus on the patient, and as mentioned previously, with the exception of the AEP_{Ex}, none of the other electroencephalogram-based measures of anesthetic depth are able to predict movement to noxious stimulus significantly better than chance.[15,16,21,22] Ideally, automated systems should be able to limit sudden arousal responses more quickly and with less overshoot than when anesthesia is controlled manually. Again, use of an effect site–targeted TCI system may achieve this more efficiently because they are able to calculate the duration and extent of blood concentration overshoot required to increase the effect site concentration to the new target more quickly and accurately.

In conclusion, a closed-loop computer system using the BIS as the control variable was able to control propofol anesthesia in patients undergoing orthopedic surgery during combined general and epidural anesthesia. Cardiovascular parameters were stable during automatic control, and operating conditions were adequate in all except one patient, who moved in response to sudden stimulation above the level of epidural anesthesia. Overall stability of the control variable was adequate, although there was some oscillation in three further patients. Therefore, there is a requirement for further studies to determine whether control can be improved by alterations to the system, such as using effect site steering or an effect site targeted TCI system, by altering the control constants or by using an adaptive control algorithm.

The authors thank Aspect International (Leiden, The Netherlands), who donated the electroencephalographic electrodes and loaned the authors the A-1000 monitor used in the study.

References

1. Russell IF: Midazolam-alfentanil: An anaesthetic? An investigation using the isolated forearm technique. Br J Anaesth 1993; 70:42–6

2. Rampil IJ: A primer for EEG signal processing in anesthesia. ANESTHESIOLOGY 1998; 89:980–1002

3. 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

4. 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

5. Sebel PS, Lang E, Rampil IJ, White PF, Cork R, Jopling M, Smith NT, Glass PS, Manberg P: A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. Anesth Analg 1997; 84:891–9

6. Schwilden H, Schüttler J, Stoeckel H: Closed-loop feedback control of methohexital anesthesia by quantitative EEG analysis in humans. ANESTHESIOLOGY 1987; 67:341–7

7. Schwilden H, Stoeckel H, Schüttler J: Closed-loop feedback control of propofol anaesthesia by quantitative EEG analysis in humans. Br J Anaesth 1989; 62:290–6

8. Schwilden H, Stoeckel H: Effective therapeutic infusions produced by closed-loop feedback control of methohexital administration during total intravenous anesthesia with fentanyl. ANESTHESIOLOGY 1990; 73:225–9

9. Kenny GN, Mantzaridis H: Closed-loop control of propofol anaesthesia. Br J Anaesth 1999; 83:223–8

10. Mortier E, Struys M, De Smet T, Versichelen L, Rolly G: Closed-loop controlled administration of propofol using bispectral analysis. Anaesthesia 1998; 53:749–54

11. Ghoneim MM: Awareness during anesthesia. ANESTHESIOLOGY 2000; 92:597–602

12. Struys M, De Smet T, van de Velde S, Versichelen L, Mortier E: Accuracy of closed-loop administration of propofol using BIS and a patient-individualized, model-based algorithm (abstract). ANESTHESIOLOGY 2000; 93:A314

13. Varvel JR, Donoho DL, Shafer SL: Measuring the predictive performance of computer-controlled infusion pumps. J Pharmacokinet Biopharm 1992; 20:63–94

14. Kansanaho M, Olkkola KT: Performance assessment of an adaptive model-based feedback controller: comparison between atracurium, mivacurium, rocuronium and vecuronium. Int J Clin Monit Comput 1996; 13:217–24

15. Doi M, Gajraj RJ, Mantzaridis H, Kenny GN: Prediction of movement at laryngeal mask airway insertion: Comparison of auditory evoked potential index, bispectral index, spectral edge frequency and median frequency. Br J Anaesth 1999; 82:203–7

16. Kurita T, Doi M, Katoh T, Kenny GN, Sato K: Auditory Evoked Potential Index predicts movement in response to skin incision during sevoflurane anesthesia (abstract). ANESTHESIOLOGY 1999; 91:A501

17. Jacobs JR, Reves JG: Effect site equilibration time is a determinant of induction dose requirement. Anesth Analg 1993; 76:1–6

18. 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

19. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ: The influence of age on propofol pharmacodynamics. ANESTHESIOLOGY 1999; 90:1502–16

20. Struys MM, De Smet T, Depoorter B, Versichelen LF, Mortier EP, Dumortier FJ, Shafer SL, Rolly G: Comparison of plasma compartment versus two methods for effect compartment-controlled target-controlled infusion for propofol. ANESTHESIOLOGY 2000; 92:399–406

21. 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

22. Kochs E, Kalkman CJ, Thornton C, Newton D, Bischoff P, Kuppe H, Abke J, Konecny E, Nahm W, Stockmanns G: Middle latency auditory evoked responses and electroencephalographic derived variables do not predict movement to noxious stimulation during 1 minimum alveolar anesthetic concentration isoflurane/nitrous oxide anesthesia. Anesth Analg 1999; 88:1412–7